MÁRCIO LORENCINI

AVALIAÇÃO GLOBAL DE TRANSCRITOS ASSOCIADOS AO ENVELHECIMENTO DA EPIDERME HUMANA UTILIZANDO MICROARRANJOS DE DNA

GLOBAL EVALUATION OF TRANSCRIPTS ASSOCIATED TO HUMAN EPIDERMAL AGING WITH DNA MICROARRAYS

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Tese apresentada ao Instituto de Biologia da Universidade Estadual de Campinas como parte dos requisitos exigidos para a obtenção do título de Doutor em Genética e Biologia Molecular, na área de Genética Animal e Evolução.

Thesis presented to the Institute of Biology of the University of Campinas in partial fulfillment of the requirements for the degree of Doctor in Genetics and Molecular Biology, in the area of Animal Genetics and Evolution.

Orientador/Supervisor: PROF. DR. NILSON IVO TONIN ZANCHIN

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RESUMO

Com o aumento do tempo de vida da população humana muitas modalidades médicas, incluindo a dermatologia, deparam-se com uma revolução na forma de garantir saúde e qualidade de vida aos pacientes. Em contato com o ambiente externo, a pele representa um órgão no qual as mudanças com o envelhecimento causam danos funcionais, além de potencial impacto estético e psicossocial. A epiderme, camada mais externa da pele, constitui uma barreira seletiva com destacada capacidade de renovação e manutenção da homeostasia corporal. Entretanto, o entendimento de diversos mecanismos associados à fisiologia e envelhecimento da epiderme permanece como desafio para a comunidade científica. Com base nesse cenário, o objetivo do presente trabalho foi compreender o atual estado da arte no tema de envelhecimento da epiderme e realizar experimentos voltados para lacunas existentes, com foco na integração de aspectos clínicos, fisiológicos, morfológicos, celulares e moleculares. O capítulo de abertura descreve uma avaliação global de transcritos associados ao envelhecimento da epiderme humana, com a técnica de microarranjos de DNA e coleta não invasiva com fitas adesivas. O estudo indica características moleculares específicas do fotoenvelhecimento epidermal, com alterações relevantes e complementares a dados clínicos e morfológicos prévios, como modulação das vias de organização do citoesqueleto de actina e sinalização de cálcio, expressão gênica alterada de proteínas do envelope córneo, e avaliação de um painel segmentado por décadas de vida que sugere aspectos inéditos de regulação homeostática da epiderme, além de genes com modulação contínua ao longo das idades. O segundo capítulo compara o envelhecimento nas regiões folicular e interfolicular da epiderme. Como um sistema biológico de simples obtenção e fácil manuseio, os bulbos dos folículos pilosos representam uma fonte rica de material epidermal distinto, conforme evidencias na ampla modulação gênica diferenciada. O terceiro capítulo inclui uma avaliação *in vitro* do envelhecimento da epiderme, com queratinócitos de indivíduos de diferentes idades cultivados em monocamada e no modelo de pele equivalente. Os

resultados evidenciam diferenças na expressão de marcadores moleculares de proliferação e diferenciação entre queratinócitos neonatais e adultos, mas não entre adultos de diferentes idades. Não houve diferença nas populações de células tronco, entretanto, observou-se aumento de células na fase proliferativa do ciclo celular em neonatos, assim como predominância de células na fase estacionária do ciclo celular em adultos mais velhos. Concluindo, os resultados obtidos no presente trabalho contribuem de forma significativa para o avanço do entendimento dos mecanismos moleculares afetados pelo avanço da idade da epiderme, possilitando a busca de novas alternativas no tratamento do envelhecimento cutâneo.

ABSTRACT

With the increase in lifetime of the human population many medical disciplines, including dermatology, are facing a revolution in the approaches to ensure healthcare and quality of life for patients. In contact with the external environment, the skin is an organ in which the changes of aging cause functional damage, in addition to potential aesthetic and psychosocial impact. Epidermis, the outermost skin layer, is a selective barrier with outstanding capacity for renewal and maintenance of the body homeostasis. However, the understanding of several mechanisms associated with skin physiology and aging remains a challenge for the scientific community. Considering this scenario, the objective of this work was to evaluate the state of the art knowledge on epidermal aging and to conduct experimental approaches to cover gaps that still exist on that theme, focusing on the integration of clinical, physiological, morphological, cellular and molecular aspects of epidermis aging. The opening chapter describes a study based on global transcriptional evaluation associated with aging of the human epidermis, using DNA microarrays and noninvasive tape stripping. This study reveals molecular characteristics specific of epidermal photoaging, with relevant findings complementary to previous clinical and morphological data, such as modulation of the actin cytoskeleton and calcium signaling pathways; altered gene expression of proteins of the cornified envelope; and evaluation of a segmented panel structured by decades of life, which suggests new aspects of homeostatic regulation in the epidermis and unvails genes with continuous modulation throughout different ages. The second chapter compares the gene expression patterns of the follicular and interfollicular regions of epidermis undergoing aging. As a biological system easily sampled and handled, the bulbs of plucked hair follicles represent a rich source of distinct epidermal material, as evidenced by the wide differential gene modulation that was detected. The third chapter includes an experimental *in vitro* evaluation of skin aging using keratinocytes isolated from individuals of different ages and cultured in monolayer and in skin equivalent models. Differences in the expression of proliferation and differentiation molecular markers between neonatal and adult

keratinocytes were observed. No differences were found regarding the stem cell populations, however, neonates showed an increased percentage of cells in the proliferative phase of cell cycle, while older adults presented a predominance of cells in the stationary phase of cell cycle. The results herein presented provide novel insights on the molecular mechanisms affected by epidermal aging, enabling the search of new alternatives in the treatment of aging skin.

SUMÁRIO

Dedico este trabalho a todos que são apaixonados pelo que fazem,
porque procuram e conseguem fazê-lo sempre melhor!

“Knowledge in youth is wisdom in age.” (Old proverb)

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1. INTRODUÇÃO

1.1. Conceituação do envelhecimento humano

A complexidade do envelhecimento humano pode ser analisada a partir de diferentes abordagens conceituais e teóricas. Segundo Santin (2010), a questão do envelhecimento se estende em todos os níveis das ciências humanas, das ciências econômicas, das ciências jurídicas e das políticas sociais. O termo envelhecimento conota movimento, remetendo a um processo de chegar à velhice, ou de se tornar velho. Em relação aos seres vivos, envelhecimento significa aproximar-se do fim da vida. De acordo com Del-Masso (2010), envelhecer é chegar pouco a pouco a um período mais avançado da vida ou perder a jovialidade e a beleza, além das possíveis perdas das habilidades cognitivas. É inquestionável que o processo de envelhecimento provoca no organismo modificações biológicas, psicológicas e sociais. Entretanto, é nas idades mais avançadas que esse processo torna-se mais evidente, o que faz com que a própria velhice seja mais notada do que o processo de envelhecimento. Por isso é mais fácil reconhecer o estágio final do envelhecimento, normalmente com base nas aparências físicas (Santin, 2010).

A constituição do envelhecimento humano, como um objeto distinto de estudo é relativamente recente, incluído como uma parte importante da gerontologia e da geriatria. A gerontologia não trata apenas do velho ou da velhice, ela inclui os fenômenos que levam à velhice. A geriatria, por sua vez, não trata apenas das doenças dos idosos, mas se preocupa, também, com as prevenções destas doenças (Santin, 2010). Do ponto de vista biológico, o envelhecimento é um processo complexo e contínuo que se caracteriza por alterações celulares e moleculares, com diminuição progressiva da capacidade de homeostase do organismo (Bagatin, 2008). Os fatores que interferem no envelhecimento podem ser intrínsecos (determinados pela constituição genética individual) e extrínsecos (exposições ambientais). Embora os mecanismos fundamentais envolvidos na patogênese do envelhecimento ainda necessitem de

mais estudos, uma massa crescente de evidências aponta para o fato de que múltiplas vias e vários elementos estão envolvidos no processo de envelhecimento celular e molecular (Makrantonaki e Zouboulis, 2007; Zouboulis e Makrantonaki, 2011). Sabe-se que o acúmulo de radicais livres e o estresse oxidativo que ocorre com a idade, contribuem para o fenótipo senil provocando alterações no organismo como desenvolvimento de tumores malignos, arteriosclerose, doenças neurodegenerativas e artrite reumatóide (Dröge, 2002). Outra causa descrita para o envelhecimento é o aumento da atividade inflamatória crônica, com o acúmulo de substâncias que desencadeiam uma série de danos teciduais (Caruso *et al.*, 2004).

No que se refere às descrições de processos moleculares associados ao envelhecimento, alguns mecanismos relacionados são: encurtamento e ruptura dos telômeros (Buckingham e Klingelhutz, 2011), perda de metilação no DNA com alteração na taxa de proliferação celular (Richardson, 2003; Bollati, 2009), acúmulo de mutações genéticas (como no gene de p53), alterações hormonais e alterações inflamatórias (Giacomoni, 2005). Johnson (2006) relata marcadores biológicos do envelhecimento que, mesmo na ausência de quadro patológico, representam indicativos da perda de capacidade funcional do organismo. O aumento de citocinas pró-inflamatórias (IL-1, IL-6 e TNF-α), diminuição da testosterona sérica, antioxidantes, alelos da apolipoproteína E, deleções no DNA e sinalizadores de resposta ao estresse são alguns exemplos destes marcadores.

1.2. Envelhecimento populacional

O tempo médio de sobrevida humana tem aumentado consideravelmente nas últimas décadas, sendo que os idosos passam a representar uma parcela significativa da população e o surgimento de indivíduos centenários não representa mais uma raridade (Farage *et al.*, 2010). De acordo com a Organização das Nações Unidas (ONU) (www.onu.org.br), uma transição única e irreversível do processo demográfico deve resultar em populações mais velhas em todos os lugares, sendo que a proporção de pessoas com 60 anos ou mais deve triplicar, e

o número de pessoas acima dos 80 anos deve quadruplicar na maior parte dos países até 2050. As estimativas do Fundo de População das Nações Unidas (UNFPA) (www.unfpa.org.br) também apontam que em 2050 80% das pessoas mais velhas do mundo viverão em países em desenvolvimento e a população com mais de 60 anos de idade será maior que a população com menos de 15.

No Brasil esta não é uma realidade distinta. O envelhecimento da população brasileira apresenta características de um processo acelerado, em ritmo significativamente maior se comparado com aquele já observado em diversos países europeus (Carvalho e Garcia, 2003). Com um perfil estável até os anos 60, o Brasil apresentava uma população jovem: 52% abaixo de 20 anos, e menos de 3% acima dos 65. A partir de então, um rápido e generalizado declínio da fecundidade foi o principal fator responsável pelo com estreitamento contínuo da base da pirâmide etária, que torna os grupos etários mais velhos proporcionalmente maiores em relação a toda a população (Carvalho e Garcia, 2003). Embora a menor fecundidade seja a principal responsável pelo envelhecimento populacional, o aumento da longevidade também contribui, de forma secundária, para esse fenômeno. Segundo dados publicados pelo Instituto Brasileiro de Geografia e Estatística (IBGE) em 29 de agosto de 2013 (www.ibge.gov.br/home/estatistica/populacao/projecao_da_populacao/2013/default.shtm), a esperança de vida ao nascer, que em 2013 chegou a 71,3 anos para homens e 78,5 anos para mulheres, em 2060, deve atingir 78,0 e 84,4 anos, respectivamente, o que representa um ganho de 6,7 anos médios de vida para os homens e 5,9 anos para as mulheres.

Além de representar uma mudança significativa em termos socioeconômicos, o novo perfil populacional impacta na atuação de diversas modalidades médicas, visando promover a saúde e bem-estar de todos. Buscando alternativas multidisciplinares para combater o problema, profissionais de diferentes modalidades agrupam-se, como na Sociedade Brasileira para o Estudo do Envelhecimento (SOBRAE) (www.sobrae.com.br), que inclui dermatologistas, médicos esteticistas, do trabalho, do exercício e do esporte. De fato, os cuidados geriátricos tem se tornado uma questão de saúde mundial (Thapa *et al.*, 2012).

1.3. Dermatologia e o envelhecimento cutâneo

A dermatologia representa uma das áreas médicas mais impactadas pelo envelhecimento populacional, uma vez que o envelhecimento cutâneo pode causar danos funcionais, além de potencial impacto estético e psicossocial. A pele representa um sistema complexo e dinâmico, no qual alguns sinais do processo de envelhecimento natural são notados visivelmente.

Diversas doenças da pele associadas ao envelhecimento não representam condições letais, mas podem comprometer a qualidade de vida dos indivíduos afetados. As erupções pruriginosas crônicas, por exemplo, podem diminuir a autoestima, deixar o portador em situações constrangedoras, interferir no sono, e muitas vezes, provocar depressão, isolamento social e deterioração da aparência, além de representar uma condição desconfortável e, não menos importante, possuir elevado custo de tratamento. Outras características observadas na pele envelhecida são a capacidade reduzida de cicatrização, o enfraquecimento da imunidade local que aumenta o risco de infecções, uma maior lentidão na resposta a tratamentos e um aumento na predisposição a reações adversas (Farage *et al.*, 2010). De impacto mais drástico, a pele envelhecida apresenta maior disposição para o desenvolvimento de tumores, exigindo maiores cuidados principalmente quanto à exposição solar (Tsatsou *et al.*, 2012).

Com o envelhecimento da população mundial, a elevação da qualidade de vida e, portanto, o prolongamento do período ativo e produtivo dos indivíduos, a aparência da pele toma cada vez mais importância para garantir a segurança e confiança dos indivíduos no convívio social. Muitas vezes, a aceitação do envelhecimento humano não é uma das tarefas simples, já que os indivíduos costumam acreditar que só os outros envelhecem e que eles devem permanecer eternamente jovens ou maduros (Del-Masso, 2010). Dessa forma, a busca por tratamentos estéticos para reverter os sinais do envelhecimento cutâneo, como a formação de rugas ou o aparecimento de manchas, tem aumentado muito em consultórios dermatológicos ou mesmo no mercado cosmético (Wollina *et al.*, 2008). Entretanto, apesar das diversas opções terapêuticas disponíveis, muitas

delas carecem de legitimidade científica, levando ao questionamento sobre a real fundamentação da abordagem dermatológica anti-idade (Kreyden, 2005).

1.4. Funções, estrutura e tipos de pele

A pele é o maior órgão do corpo humano, representando 15% do peso total, e responsável por seu revestimento e proteção. Apesar de amplamente descrita, a estrutura básica da pele foi revisada no Anexo 1 devido à sua importância no tema central deste trabalho. Além disso, uma revisão detalhada abrangendo diversos aspectos anatômicos, histológicos e imunohistoquímicos da pele humana normal pode ser conferida no trabalho de Kanitakis (2002). Em decorrência de sua arquitetura e propriedades físicas, químicas e biológicas, a pele é responsável por diversas atividades, tais como proteção imunológica, termorregulação, percepção sensorial, secreção e proteção contra radiação solar (Mota, 2006).

A estrutura da pele é formada por duas camadas principais: epiderme e derme. Adjacente, encontra-se o tecido subcutâneo ou tecido adiposo, algumas vezes descrito na literatura como uma terceira camada cutânea (Figura 1).

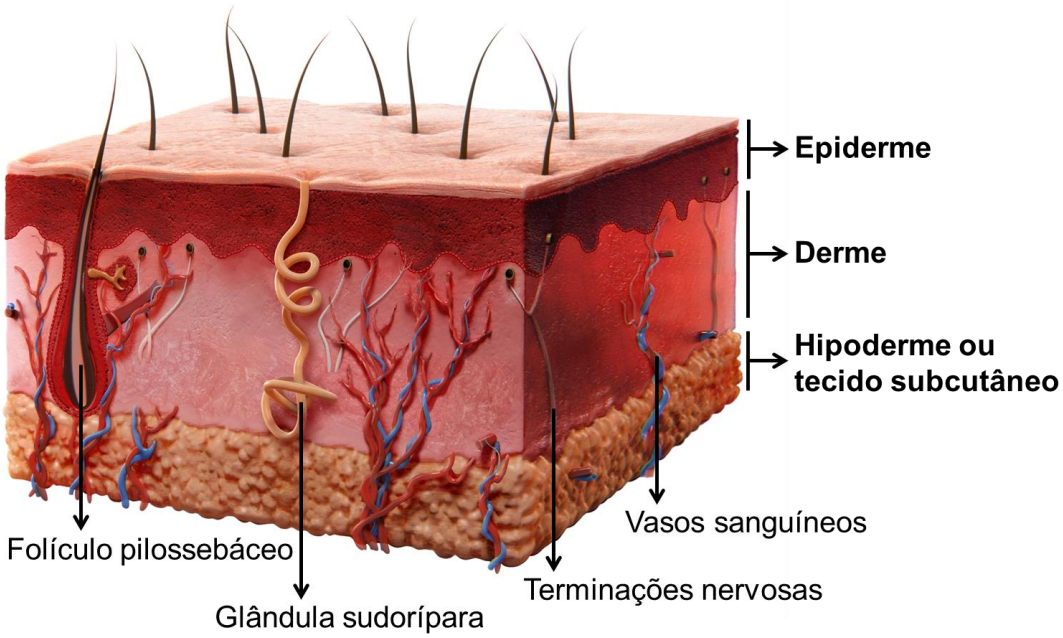

Figura 1. Estrutura morfológica da pele, indicando suas camadas e os principais elementos presentes em cada uma delas.

A epiderme representa a porção mais externa da pele, formada por diversas camadas celulares justapostas e organizadas em uma estrutura multilamelar. Compondo uma verdadeira barreira seletiva, a epiderme controla as trocas de moléculas entre o interior do corpo e o ambiente externo. Majoritariamente formada por queratinócitos (~85% das células totais), possui também melanócitos, células de Langerhans e células de Merkel. Por sofrer um constante processo de descamação, a epiderme precisa ser renovada continuamente (Milstone, 2004). A renovação inicia-se com a multiplicação de células proliferativas (epidermopoiese) na porção mais interna da epiderme, a camada basal, originando os queratinócitos que passam por um processo de diferenciação à medida que são empurrados para a superfície epidermal pela ocorrência de novas divisões celulares na camada basal, em um processo que leva em torno de quatro semanas para se completar (Figura 2) (Fuchs e Raghavan, 2002). A diferenciação dos queratinócitos é marcada por mudanças de cunho molecular, estrutural e funcional, dando origem a uma epiderme estratificada do interior à superfície corporal, composta por camada basal, camada espinhosa, camada granulosa e estrato córneo (Fuchs e Raghavan, 2002; Simpson *et al.*, 2011). Em algumas áreas, como palmas das mãos e solas dos pés, é possível observar uma camada extra, conhecida como estrato lúcido, entre a camada granulosa e o estrato córneo (Brohem *et al.*, 2011). No estrato córneo, os queratinócitos atingem seu ponto máximo de diferenciação, podendo ser chamados de corneócitos: células mortas, anucleadas e de morfologia achatada, que representam blocos de proteínas e lipídios, unidos entre si e mergulhados em uma matriz lipídica (Eckhart *et al.*, 2013). Muito mais que um elemento de proteção mecânica, a epiderme representa um tecido metabolicamente ativo que passa periodicamente por ciclos de renovação completa, em constante equilíbrio dinâmico (Fuchs e Raghavan, 2002). Alguns autores consideram o funcionamento da epiderme como paradoxal, exibindo grande estabilidade para proteção do organismo contra agressões externas ao mesmo tempo em que mantém considerável flexibilidade de seus componentes celulares para garantir regeneração tecidual e capacidade de resposta a diferentes estímulos (Simpson *et al.*, 2011). Devido a tal capacidade, a

epiderme representa um componente decisivo na manutenção da homeostasia corporal, com funções de: 1) barreira de proteção contra insultos mecânicos e químicos (Lulevich *et al.*, 2010; Kirschner *et al.*, 2013), 2) manutenção do equilíbrio hidro-iônico do organismo (Proksch *et al.*, 2008; Kirschner *et al.*, 2013), 3) defesa imunológica contra patógenos e eliminação de toxinas (Geusau *et al.*, 2001; Baroni *et al.*, 2012; Polak *et al.*, 2013), e 4) proteção contra radiação solar e atividade antioxidante (Shindo *et al.*, 1994; Yamaguchi *et al.*, 2006).

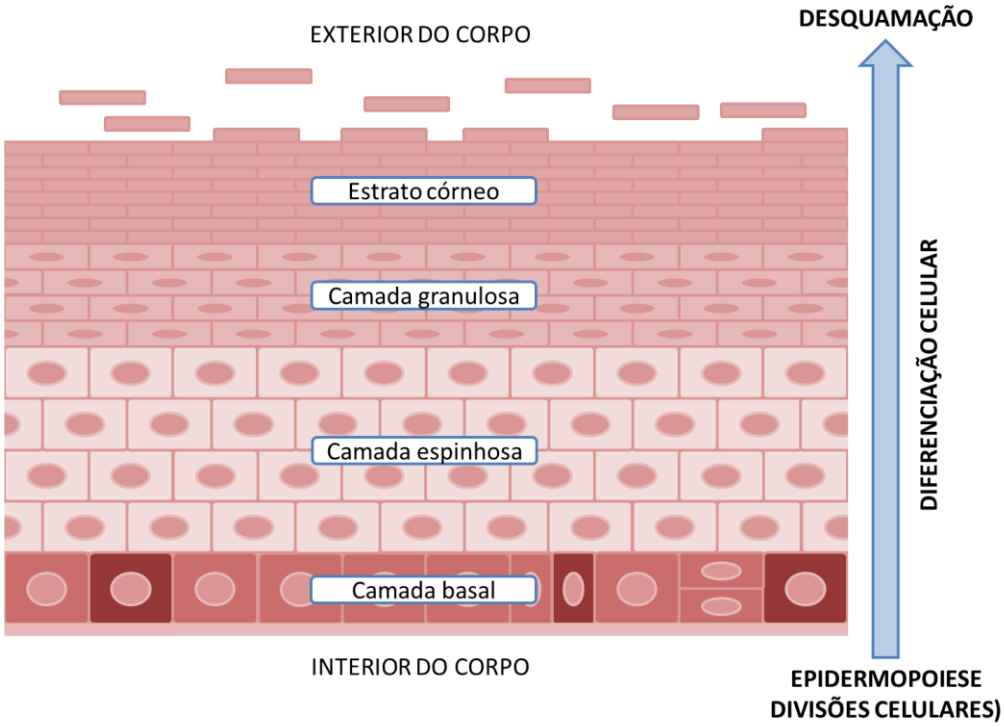

Figura 2. Esquema representativo do processo de renovação epidermal.

A derme representa a porção interna da pele, cuja estrutura é rica em elementos de matriz extracelular, como as fibras de colágeno e elastina, apresentando também vasos sanguíneos, vasos linfáticos e terminações nervosas. Basicamente, a derme é responsável por todo o tipo de sustentação da pele, em termos físicos e nutricionais, representando cerca de 90% da espessura cutânea. A derme apresenta espessura variável de acordo com a região do corpo observada, apresentando duas regiões distintas: a papilar (superficial, delgada e composta de tecido conjuntivo frouxo com fibras mais esparsas) e a reticular (mais

profunda, espessa e composta de tecido conjuntivo denso com estrutura fibrilar mais compactas). Os fribroblastos representam o principal tipo celular residente na derme, responsáveis pela síntese de diversos componentes da matriz extracelular, incluindo proteínas e outros elementos da substância fundamental amorfa (tais como fluido intersticial e complexos de glicosaminoglicanos e proteínas, denominados proteoglicanos e glicoproteínas). Além disso, a derme também apresenta células relacionadas à defesa imunológica, incluindo células dendríticas e diversos outros tipos celulares não permanentes que migram para derme a partir dos vasos sanguíneos em situações específicas como no caso das respostas inflamatórias (incluindo macrófagos e neutrófilos) (Farage *et al.*, 2010).

Para uma correta funcionalidade da pele, a comunicação entre suas duas principais camadas é essencial. Ao captar sinais do ambiente externo, a epiderme aciona mecanismos específicos, como no caso da produção de citocinas frente à radiação ultravioleta, que atingem a derme e estimulam uma resposta biológica. A ativação desta cascata de sinalizações intra e intercelulares, pode gerar estímulos em *feedback* para a epiderme, formando um ciclo de interações contínuas e regulação mútua entre as camadas (Brohem e Lorencini, 2014). Ainda, a derme com sua rica estruturação fibrosa e a presença de vasos sanguíneos, fornece constante suporte e garante o abastecimento de nutrientes para manutenção viável da epiderme. A manutenção do equilíbrio hidro-iônico é mais um exemplo funcional das interações entre epiderme e derme. As trocas de água entre os diferentes compartimentos da pele e o meio externo, dependem de três fatores: 1) umidade do meio externo, 2) capacidade de substituir a perda de água por evaporação (movimento de água de dentro para fora, a partir dos vasos sanguíneos) e 3) habilidade intrínseca do estrato córneo de impedir ou reduzir a perda de água transepidérmica (Bouwstra *et al.*, 2008). Para que tudo isso ocorra, são estabelecidas redes de sinalizações complexas formadas entre os dois componentes celulares principais da pele: queratinócitos e fibroblastos. Essas interações têm se demonstrado fundamentais para inúmeros processos, tais como crescimento e diferenciação de células, reparação tecidual, cicatrização de feridas,

além do desenvolvimento e tratamento de diversas doenças (Brohem e Lorencini, 2014).

Complementando as atribuições funcionais da epiderme e derme, o tecido subcutâneo ou adiposo representa uma camada de células com elevada capacidade de armazenamento energético na forma de lipídeos, além de exercer papel de proteção mecânica e auxílio no controle da temperatura. Além das camadas, a pele também apresenta seus anexos, como as glândulas sudoríparas e os folículos pilossebáceos (unidades compostas pela associação de folículos pilosos e glândulas sebáceas) (Farage *et al.*, 2010).

A pele pode ser classificada em diferentes tipos com base em critérios como: 1) produção de sebo e hidratação ou 2) coloração. Considerando a produção de sebo e hidratação, a Sociedade Brasileira de Dermatologia (SBD) (www.sbd.org.br) define quatro tipos de pele:

- Normal, tipo de pele menos frequente com textura saudável e aveludada, elasticidade ideal e quantidade adequada de gordura natural, aspecto rosado, com poros pequenos e pouco visíveis, pouco propensa ao desenvolvimento de espinhas e manchas;
- Seca, caracterizada pela perda de água em excesso, normalmente com poros poucos visíveis, pouca luminosidade e mais propensa à descamação e vermelhidão, maior tendência ao aparecimento de pequenas rugas e fissuras, podendo ser causada por fatores genéticos e hormonais, assim como condições ambientais (tempo frio ou seco, vento, radiação ultravioleta ou até mesmo banhos demorados e com água quente);
- Oleosa, com aspecto mais brilhante, úmido e espesso por causa da produção de sebo maior do que o normal, poros dilatados e maior tendência à formação de acne, cravos e espinhas, podendo ser causada por fatores genéticos, alterações hormonais, excesso de sol, estresse e dieta rica em alimentos com alto teor de gordura;
- Mista, tipo de pele mais frequente, com aspecto oleoso e poros dilatados na “zona T” (testa, nariz e queixo) e seco nas bochechas e extremidades, tem

espessura mais fina, com tendência à descamação e ao surgimento de rugas finas e precoces.

A coloração da pele resulta de uma combinação de fatores como a espessura das camadas celulares e a quantidade de pigmentos, com destaque para a melanina produzida pelos melanócitos da epiderme. A quantidade de melanina sintetizada tem forte influência de componentes genéticos, mas também pode ser modulada por fatores como idade, ocorrência de resposta inflamatória, variações hormonais e influências ambientais como tabagismo, alcoolismo, poluição e exposição à radiação solar. Além disso, a produção de melanina pode ser regulada em diferentes estágios biomoleculares como o nível de atividade da tirosinase nos melanócitos (principal enzima envolvida na síntese de melanina), mudanças na rota biossintética (podendo originar pigmentos mais claros de feomelanina ou pigmentos mais escuros de eumelanina) e na transferência de pigmentos produzidos para os queratinócitos (Mota, 2006). Com base na coloração da pele e sua reação à exposição solar, a SBD adota a escala Fitzpatrick (Figura 3) para classificação dos fototipos cutâneos, criada em 1976 pelo dermatologista e diretor do departamento de Dermatologia da Escola de Medicina de Harvard: Thomas B. Fitzpatrick. Tal escala considera seis fototipos cutâneos, sendo eles:

- Fototipo I, com pele branca que sempre queima, nunca bronzeia e é muito sensível ao sol;
- Fototipo II, com pele branca que sempre queima, bronzeia muito pouco e é sensível ao sol;
- Fototipo III, com pele morena clara que queima (moderadamente), bronzeia (moderadamente) e tem sensibilidade normal ao sol;
- Fototipo IV, com pele morena moderada que queima (pouco), sempre bronzeia e tem sensibilidade normal ao sol;
- Fototipo V, com pele morena escura que queima (raramente), sempre bronzeia e é pouco sensível ao sol;
- Fototipo VI, com pele negra que nunca queima, totalmente pigmentada e é insensível ao sol.

Figura 3. Escala de Fitzpatrick para classificação dos seis fototipos cutâneos. Adaptado de www.laserdocs.co.uk.

1.5. Mudanças cutâneas com o envelhecimento

Por representar um órgão em contato direto com o ambiente externo, a pele está frequentemente exposta à ação de agentes agressores. Essa exposição ao longo do tempo pode refletir diretamente na velocidade de envelhecimento cutâneo, caracterizado pela formação de rugas e além de perda de resistência e elasticidade. Em pessoas com exposição constante à radiação solar, por exemplo, tais efeitos tendem a ser mais pronunciados ou acelerados (Scharffetter-Kochanek *et al.*, 2000). Waller e Maibach (2005 e 2006) fizeram um compilado das principais modificações que afetam a estrutura da pele com o avanço da idade, incluindo tendência de diminuição do fluxo sanguíneo, redução da espessura de derme e epiderme, alterações na organização das fibras colagênicas e elásticas, diminuição na atividade de enzimas que atuam em processos de modificação pós-traducional, formação de agregados proteicos, modificações na deposição de glicosaminoglicanos que tendem a interagir menos com moléculas de água e mudanças no conteúdo lipídico.

Quanto aos aspectos clínicos, o envelhecimento da pele é caracterizado por atrofia tecidual e rugas finas, com comprometimento de fibras elásticas e surgimento de elastose na derme reticular. A exposição constante à radiação solar promove o aparecimento de sinais intensificados, ocorrendo formação de rugas mais profundas, espessamento da pele, amarelamento, ressecamento, surgimento de melanoses, telangiectasias, poiquilodermia, queratoses actínicas e aumento da

probabilidade de ocorrência de câncer. Ainda, as rugas derivadas de efeito direto da ação excessiva da radiação solar podem corresponder a até 85% daquelas presentes na pele envelhecida (Bagatin, 2008). Intrinsicamente, ao longo dos anos, a pele também apresenta mudanças que podem ser observadas em suas diferentes camadas (Figura 4). Ocorrem alterações como redução de gordura no tecido subcutâneo, aumento de substância elastolítica na derme superior, destruição da estrutura fibrilar, aumento da quantidade de substância intercelular e infiltrado inflamatório moderado. Em um trabalho amplo, que avaliou 45 amostras de pele distintas de homens e mulheres com idades entre 17 e 81 anos, foi observado que, com o envelhecimento há uma diminuição na espessura e na quantidade de camadas de células viáveis na epiderme, aumento na quantidade de grânulos querato-hialinos, achatamento da junção dermo-epidermal, maior presença de material elastolítico na derme, aumento de infiltrado inflamatório com presença de trabéculas fibrosas mais espessas e atrofia da hipoderme. O envelhecimento cronológico também afeta o metabolismo de fibroblastos, reduzindo seu tempo de vida, capacidade de divisão celular e potencial de produção de colágeno. Ainda, durante o envelhecimento, o aumento da espessura das fibrilas de colágeno diminui a elasticidade da pele (Levakov *et al.*, 2012).

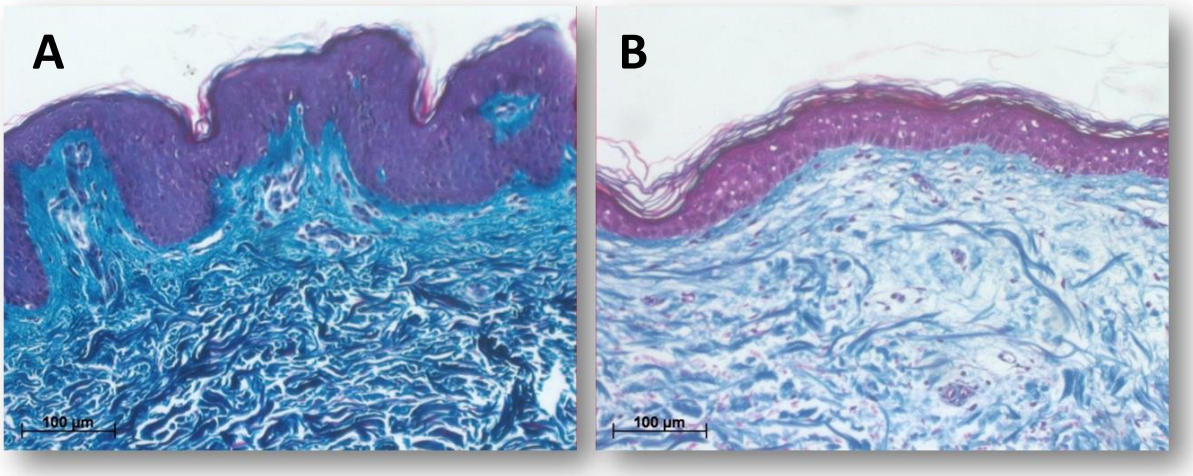

Figura 4. Análise histológica do envelhecimento cutâneo, com destaque para características como redução da espessura epidermal, achatamento da junção dermo-epidermal e desestruturação de fibras na derme. (A) Pele jovem (indivíduo de aproximadamente 30 anos). (B) Pele envelhecida (indivíduo de aproximadamente 60 anos).

Trabalhos relacionados ao estudo de síndromes de envelhecimento precoce ou síndromes progeróides também têm contribuído com o entendimento da importância de alguns genes no avanço do envelhecimento cutâneo, como no caso das síndromes de Hutchinson-Gilford, Werner, Bloom, Cockayne etc. Estes estudos, particularmente no caso da síndrome de Hutchinson-Gilford, que representa a forma mais dramática de envelhecimento prematuro, têm apontado para processos chave no avanço do envelhecimento cutâneo, incluindo mecanismos de transcrição, replicação e reparo do DNA, instabilidade genômica, senescência celular, ciclo celular, apoptose, função mitocondrial, proteólise mediada por ubiquitina, matriz extracelular, síntese de lipídeos, metabolismo celular e diferenciação de células-tronco (Makrantonaki e Zouboulis, 2007; Capell *et al.*, 2009; Zouboulis e Makrantonaki, 2011).

Apesar das diversas descrições de efeitos do envelhecimento sobre a pele, a maioria dos trabalhos permanece focada na derme e na desorganização de sua estrutura rica em matriz extracelular (Luebberding *et al.*, 2012).

1.6. Mudanças funcionais e moleculares da epiderme com o envelhecimento

Há diversas mudanças que acometem a função de barreira da epiderme com o envelhecimento (Ramos-e-Silva *et al.*, 2012). Um estudo recente realizado com 150 mulheres entre 18 e 80 anos observou que, com o aumento da idade, há uma queda contínua na produção de sebo e diminuição no valor de pH, com significativo aumento detectado em mulheres de 50 a 60 anos, período típico da ocorrência de menopausa, mas sem mudanças na perda de água transepidermal ou no nível de hidratação do estrato córneo (Luebberding *et al.*, 2012). Alguns trabalhos apontam a redução da espessura da epiderme que surge com o envelhecimento como decorrente da diminuição da quantidade e/ou atividade de células tronco na camada basal ou na região dos folículos pilosos. Este tema é bastante discutido na comunidade científica e há concordância quanto ao fato de que a homeostase das células-tronco da epiderme pode mudar com o

envelhecimento, embora os mecanismos específicos relacionados a este processo ainda não sejam bem esclarecidos. No trabalho de Lock-Andersen *et al.* (1997) é evidenciado que a espessura do estrato córneo não varia entre grupos de jovens e idosos, mas há uma redução na chamada epiderme celular, formada pelos estratos que apresentam células viáveis. Outros trabalhos também apontam evidências de um aumento no número de células-tronco com a idade, embora descrevam a ocorrência, em paralelo, de um decréscimo na função e atividade metabólica das mesmas. Um estudo demonstrou que há um desequilíbrio na via de sinalização Jak-Stat e na produção de citocinas das células-tronco epidermais, de forma que o declínio em sua funcionalidade poderia ser compreendido como um mecanismo para a supressão de tumores que poderiam surgir com o avanço da idade (Doles *et al.*, 2012). Outros trabalhos evidenciam o afinamento da epiderme com o avanço da idade associado à redução na capacidade proliferativa das células e ao aumento na taxa de apoptose, sendo este último mecanismo reforçado pela observação do aumento na expressão de Fas (Gilhar *et al.*, 2004; El-Aal *et al.*, 2012). Ainda, há observações demonstrando que, com a idade, não há alterações na atividade das células-tronco da epiderme, sendo que as mesmas mantêm suas características ao longo do envelhecimento cutâneo, diferentemente do que ocorre com as chamadas células amplificadoras transientes. Neste caso, o aumento da quantidade destas células pode ser interpretado como um mecanismo compensatório para a queda de sua atividade, buscando uma manutenção das funções da epiderme (Liang *et al.*, 2004; Stern e Bickenbach, 2007; Charruyer *et al.*, 2009).

Um estudo desenvolvido por Schmuth *et al.* (2005) demonstrou que existem diferenças na produção de proteínas transportadoras de ácidos graxos na epiderme quando comparados tecidos de origem embrionária e adulta, indicando uma regulação dinâmica destes constituintes ao longo do desenvolvimento. A atividade de esfingomielinase também é reduzida, sendo que indivíduos de 80 anos apresentam 25% da atividade encontrada em indivíduos de 20 anos, reforçando como o envelhecimento compromete o metabolismo de lipídeos na epiderme (Yamamura e Tezuka, 1990). Como um elemento essencial para a

diferenciação dos queratinócitos e manutenção da homeostase da barreira cutânea, a distribuição de cálcio entre as camadas da epiderme na face também parece variar com a idade. Na pele jovem e saudável, há um gradiente de cálcio caracterizado por uma baixa concentração nas camadas mais internas (camada basal e estrato espinhoso) com um aumento na disponibilidade extra e intracelular de cálcio que atinge um pico de maior concentração no estrato granuloso. Em amostras de pele de indivíduos mais velhos, entretanto, o cálcio apresenta-se distribuído igualmente entre todas as camadas da epiderme, sem a formação do gradiente observado na pele jovem, sugerindo uma disfunção em bombas ou canais iônicos que pode culminar com as alterações morfológicas tipicamente observadas com o avanço do envelhecimento cutâneo (Denda *et al.*, 2003).

Outros achados apontam para diferenças na eliminação de danos provocados por radiação na epiderme quando amostras de indivíduos de diferentes idades são comparadas. No estudo de Yamada *et al.* (2006) foi verificado por imunohistoquímica e immunoblotting que a remoção de dímeros de pirimidina induzidos por UVB acontece de forma mais lenta na epiderme de indivíduos mais velhos. No grupo de 22 a 26 anos, o tempo de remoção completa dos dímeros foi de 4 dias, frente a 14 dias no grupo de 70 a 78 anos. Os resultados indicaram que a idade é um fator mais importante que a dose de radiação para a remoção dos dímeros de pirimidina da epiderme. Além das modificações que acometem os queratinócitos, estudos também apontam para mudanças associadas ao envelhecimento que afetam outros tipos celulares presentes na epiderme, como uma redução no número de melanócitos (com redução de 10 a 20% a cada década depois dos 25-30 anos) e células de Langerhans, comprometendo as funções de proteção contra radiação ou imunológica da pele (Ortonne, 1990; Wulf *et al.*, 2004). Assim como em outros tecidos ou outras doenças, os estudos baseados em biologia molecular e expressão dos genes ainda precisam ser mais bem explorados para explicar os fenômenos que acometem a epiderme ao longo do envelhecimento. Sabe-se, por exemplo, que o nível de detecção da filagrina por imunohistoquímica diminui em amostras de epiderme com idades mais avançadas. Entretanto, o nível de

expressão gênica da filagrina não parece ser afetado pela idade. Ainda, avaliando a disponibilidade de aminoácidos derivados da degradação enzimática da filagrina para a formação dos fatores naturais de hidratação (NMF), foi verificado que a quantidade total de aminoácidos no estrato córneo de indivíduos mais velhos foi maior que nos jovens, sugerindo que a redução na disponibilidade de filagrina preconizada pelo avanço da idade pode ser derivada de sua proteólise nas camadas superiores do estrato espinhoso e não de alterações referentes à diminuição na expressão gênica (Takahashi e Tezuka, 2004). Este exemplo ilustra bem a necessidade de se esclarecer mecanismos moleculares para a melhor compreensão e talvez até para o desenvolvimento de terapias específicas para o tratamento da epiderme.

1.7. Evolução contínua em biologia molecular impacta na dermatologia

Com a conclusão do Projeto Genoma Humano, novas perspectivas foram abertas para ajudar as gerações futuras a viver melhor e atingir idades superiores aos 100 anos com a dignidade almejada. Assim como nas outras áreas, a dermatologia também foi impactada pelos avanços científicos da revolução genética. Nos últimos anos o número de publicações científicas abordando o tema "expressão gênica" aplicado aos cuidados da pele aumentou consideravelmente. Além disso, a biologia molecular tem estado mais presente na abordagem do envelhecimento cutâneo, que, como um processo altamente complexo, envolve a ação simultânea e contínua de diversos fatores que desencadeiam uma diminuição progressiva da capacidade homeostática da pele. Considerando tudo isso associado à própria complexidade histológica da pele, os estudos nesta área vêm sendo muito favorecidos pela aplicação de tecnologias de avaliação global dos fenômenos biológicos. A utilização destas tecnologias deu origem ao termo "skinomics", referindo-se à avaliação global de moléculas biológicas associadas ao desenvolvimento e funcionalidade cutânea (Blumenberg, 2005).

Aliada ao avanço dos estudos da pele e suas alterações, a biologia molecular também oferece vantagens para o desenvolvimento de tratamentos

mais eficazes no combate ao envelhecimento cutâneo. A farmacogenômica representa uma nova área que surgiu a partir destes conceitos, envolvendo a aplicação de tecnologias como o sequenciamento de DNA, análise da expressão gênica e técnicas estatísticas em pesquisas e testes relacionados a fármacos ou ingredientes. Um dos princípios defendidos pela farmacogenômica é o desenvolvimento da chamada medicina personalizada, onde fármacos e suas combinações são otimizados em uma composição única para cada indivíduo (Squassina *et al.*, 2010). Esta nova perspectiva permite levar em consideração as variações individuais tanto na identificação das necessidades, como na escolha dos ativos e acompanhamento da resposta de um indivíduo ao tratamento escolhido na busca da máxima assertividade e eficácia. Mais uma vez, as tecnologias inovadoras derivadas da revolução genética têm favorecido ainda mais o avanço e detalhamento dos conceitos de farmacogenômica aplicados à dermatologia (Rizzo e Maibach, 2012).

1.8. Justificativa e estrutura do trabalho

De fato, as mudanças nas propriedades físicas de diversos tecidos do corpo humano com o avanço da idade vêm sendo descritas há algumas décadas. Muitos trabalhos já avaliaram as mudanças que acometem a organização da matriz extracelular dérmica, associando a perda da integridade da pele a tais fenômenos. A importância destes estudos é indiscutível uma vez que a perda da configuração estrutural original da matriz extracelular pode ter impactos diretos na função dérmica (Bailey, 2001). De acordo com Cristofalo e Pignolo (1996), embora alterações na natureza dos contatos de células senescentes sejam normalmente atribuídas a mudanças na composição da matriz extracelular, ainda permanecem dúvidas quanto à produção de proteínas específicas não relacionadas à matriz ou de moléculas associadas à membrana. Paralelo a isso, diversas dúvidas permanecem com relação às mudanças provocadas pelo envelhecimento que podem afetar os queratinócitos na epiderme. Poucos trabalhos têm sido desenvolvidos no que se refere especificamente à avaliação dos efeitos do

envelhecimento na epiderme, mesmo em termos de avaliação de sinais clínicos da função de barreira (Luebberding *et al.*, 2012). Tendo em vista a falta de conhecimento científico específico sobre o envelhecimento da epiderme humana, alguns estudos começam a surgir focados em biologia molecular, embora não focados na compreensão global dos mecanismos associados ao envelhecimento da epiderme e, geralmente, baseados em ensaios de cultivo celular *in vitro* (Gilchrest *et al.*, 1994; Baek *et al.*, 2003; Brégégère *et al.*, 2003; Perera *et al.*, 2006). Gromov *et al.* (2003) desenvolveram um trabalho bastante interessante e complementar o que está sendo proposto na abordagem deste estudo, porém com análise global de proteínas associadas ao envelhecimento da epiderme. Além de seus achados interessantes, os autores concordam quanto às limitações encontradas na literatura atual para mecanismos moleculares associados ao envelhecimento cutâneo: a maioria dos estudos globais está concentrada em análises de fibroblastos, a complexidade do tecido cutâneo dificulta a interpretação de estudos globais (como os já realizados para tecido muscular, cerebral e hepático) e muitas vezes há utilização de modelos animais com baixa reprodutibilidade para tecido correspondente humano.

O entendimento dos mecanismos moleculares de envelhecimento cutâneo pode abrir novas estratégias para o tratamento de diversas doenças que surgem com o avanço da idade, incluindo câncer (Makrantonaki e Zouboulis, 2007), além de auxiliar na busca de tratamentos estéticos intensamente procurados nas clínicas dermatológicas atualmente, como no caso da eliminação de rugas sem a necessidade de procedimentos cirúrgicos ou altamente invasivos. Apesar da maioria dos estudos apontar para a derme e a composição de sua matriz extracelular como o principal componente na determinação do envelhecimento cutâneo, uma redução na hidratação do estrato córneo da epiderme pode contribuir com a formação de rugas de 25 a 85% maiores (Flynn e Mccormack, 2010). Além disso, uma grande parte das doenças que acometem a pele estão associadas a células específicas da epiderme, como no caso dos melanomas. Estas características fazem da epiderme um alvo rico para novos estudos

moleculares de espectro global, visando elucidar aspectos ainda pouco explorados sobre a biologia desta camada cutânea.

O presente trabalho contém três capítulos no formato de artigos científicos elaborados no tema de envelhecimento epidermal. O primeiro capítulo descreve uma avaliação global de transcritos modulados de acordo com o envelhecimento da epiderme humana, utilizando a técnica de microarranjos de DNA e coleta não invasiva da epiderme com fitas adesivas. O segundo capítulo contém uma comparação dos estudos realizados sobre o envelhecimento nas regiões folicular e interfolicular da epiderme. O terceiro capítulo inclui uma avaliação *in vitro* do envelhecimento da epiderme, com queratinócitos de indivíduos de diferentes idades cultivados em monocamada e no modelo de pele equivalente. Nos documentos anexos, são apresentados também dois trabalhos de revisão da literatura, um deles representando uma análise aprofundada e abrangente, descrevendo os recentes avanços em biologia celular e molecular com modelos tradicionais da função e envelhecimento da epiderme. O outro trabalho apresenta uma revisão de ordem prática no tema, contemplando as alternativas terapêuticas possíveis para tratamento do envelhecimento epidermal.

2. OBJETIVOS

2.1. Objetivo geral

Realizar avaliação global de transcritos da epiderme humana utilizando a técnica de microarranjo de DNA, e buscando identificar marcadores moleculares, vias metabólicas ou agrupamentos gênicos diferencialmente expressos com o avanço da idade.

2.2. Objetivos específicos

- A partir de coletas de amostras de epiderme humana de mulheres de diferentes faixas etárias, avaliar a expressão gênica associada ao envelhecimento utilizando microarranjos de DNA;
- Identificar os principais conjuntos de genes diferencialmente expressos, associados a processos biológicos ou a vias metabólicas moduladas pelo envelhecimento da epiderme;
- Realizar análise comparativa da expressão gênica com o envelhecimento da epiderme obtida por técnicas distintas de coleta: fita adesiva e pelos de sobrancelha;
- Estabelecer modelos experimentais *in vitro* com o cultivo de células epidermais para avaliar o efeito da idade do doador.

3. EXPERIMENTOS E RESULTADOS

3.1. Capítulo I (Artigo experimental I)

Title: Transcriptome of *in vivo* human epidermal aging in sun-exposed skin

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Running title: Transcriptome of human epidermal aging

Abstract

Skin is a complex system formed by the dermis and epidermis, which both comprise a variety of cell types. As the outer layer of skin, the epidermis forms a barrier on the surface of the body to protect against external aggressions and maintain its balance of fluids and ions. In addition to the action of external factors, the skin undergoes the intrinsic aging process, which governs the entire body of an organism. Single-target and large-scale studies have been used extensively to try to understand the mechanisms that underlie the skin damage caused by intrinsic and extrinsic factors. Nevertheless, most molecular processes remain to be understood. In this study, we assessed human epidermal aging in sun-exposed skin using non-invasive tape stripping and DNA microarrays analysis for ~20,000 genes. To better understand the mechanisms of aging as a continuous and gradual process, traditional young versus old analysis was complemented by different strategies to evaluate a broad panel of volunteers from each decade of life between 20 and 80 years old, representing an unprecedented approach for epidermal aging evaluation. By adopting a minimal fold change (FC) value of 1.5 and a p-value cut-off of 0.05, statistically significant differences were observed for 3,247 distinct human genes, with 4,146 up-regulated and 717 down-regulated. Although the number of up-regulated genes was higher than down-regulated genes, 63 gene ontology (GO) terms were associated with down-regulation, and only 24 were associated with up-regulation. Down-regulated genes were predominant at FC 3.0 with a 0.05 p-value cut-off, indicating that in terms of significant biological process enrichment and the intensity of FC expression, down-regulation is a critical condition for epidermal aging of sun-exposed skin. Relevant pathways comprising differentially expressed genes (DEGs) include the actin cytoskeleton (37 DEGs) and calcium signaling pathways (31 DEGs). Clustering analysis was performed using more stringent criteria (FC: 2.0, p-value cut-off: 0.01) to separate the young (20-40 years) and old groups (50-80 years). However, this clustering did not order the groups in a continuous and crescent sequence of ages, and the old group showed clear segregation into two distinct blocks, indicating that age-associated changes should not be interpreted as part of a linear process.

Analysis of specific gene expression profiles associated with each decade evidenced a dynamic and oscillating pattern of epidermal transcription with aging. A cluster with a single member, the SPRR2G gene, showed continuous increased expression, and a cluster with 20 members showed continuous reduced expression throughout a lifetime. In conclusion, the data presented in this article contribute to the understanding of the dramatic molecular changes that the epidermis experiences during aging.

Introduction

Skinomics represents a set of global biological techniques that are applied to skin studies, such as genomics, transcriptomics, proteomics, and metabolomics (Blumenberg, 2005). Because of its accessibility, skin was one of the first targets analyzed by DNA microarrays, and dermatology embraced this approach early (Blumemberg, 2012 and 2013). Currently, several investigative strategies have been used to understand the molecular networks modulating skin function, covering aspects of health and disease and the occurrence of multifactorial processes such as aging (Robinson *et al.*, 2009; Villaseñor-Park and Ortega-Loayza, 2013). However, considering the inherent complexity of skin and the limitations of whole-tissue analysis, e.g., that it is not able to localize messenger RNAs to specific cell types, reducing the variables used in an experimental design may sometimes be recommended instead of extrapolating generalized conclusions (Mitsui *et al.*, 2012). The epidermis and dermis are distinct skin layers in terms of their function, cellular and molecular composition, and even embryonic origin. This biological heterogeneity challenges the correct interpretation of skinomics because global analysis reflects a mixture of signaling pathways and molecular responses that occur simultaneously in different biological compartments. To avoid such complexity problems, some groups have worked with isolated skin layers or cells to achieve comprehensive results without traces of confounding material (Jansen and Schalkwijk, 2003; Mitsui *et al.*, 2012).

If skin biology studies have significant sophistication per se, the elucidation of skin aging-related mechanisms adds several pieces to this intricate research puzzle (Jansen and Schalkwijk, 2003). As a highly complex biological process involving cumulative deterioration, aging impairs homeostasis over a lifetime in different tissues and organs (Kirkwood, 2005). Although the impact of age on cutaneous functionality and organization has been extensively studied, little is known about the aging of the human epidermis, despite its essential role as the main functional barrier of the body where the symptoms of aging can be visually perceived with significant aesthetic and psychosocial implications (Farage *et al.*,

2010; Sotoodian and Maibach, 2012). In fact, some “omics”-oriented studies have addressed the aspects of aging that affect the most abundant epidermal cell type, keratinocytes, by applying experimental *in vitro* models (Baek *et al.*, 2003; Darbro *et al.*, 2005; Perera *et al.*, 2006; Sprenger *et al.*, 2010). However, it is important to remember the differences between cultured cells and their *in vivo* counterparts. Cultured keratinocytes are less differentiated than those *in vivo*, and some points must be considered when comparing the cell biological mechanisms of *in vitro* senescence with those taking place in *in vivo* aging (Hwang *et al.*, 2009; Mitsui *et al.*, 2012). In addition, the dynamics of *in vivo* skin aging can be even more complex if the simultaneous influence of intrinsic factors (physiological components and genetic predisposition) and extrinsic factors (external insults, particularly from solar radiation) is considered (El-Domyati *et al.*, 2002; Farage *et al.*, 2008). Therefore, representative *in vivo* studies of epidermal aging are lacking, particularly those that employ “omics” approaches and include intrinsic and extrinsic age-related components.

In this study, we assessed the *in vivo* transcriptome of human epidermal aging in sun-exposed skin using non-invasive tape stripping and DNA microarrays analysis for ~20,000 genes. To better understand the mechanisms of aging as a continuous and gradual process, traditional young versus old analysis was complemented by different strategies to evaluate a broad panel of volunteers from each decade of life between 20 and 80 years old. This study represents an unprecedented approach for epidermal aging evaluation.

Materials and methods

Volunteers and samples

The Research Ethics Committee institutional review board from Universidade Positivo, Curitiba, Brazil, approved this study, and written informed consent was obtained before enrolling volunteers for participation in this study, which was performed in compliance with the Declaration of Helsinki Principles.

Epidermal samples were obtained using Q-Squames Skin Sampling Discs (CuDerm, Dallas, TX, USA) applied to the back of the left or right hand (random choice) of women of different ages and skin phototype II or III according to the Fitzpatrick scale. Twenty-five adhesive tapes were collected from the same area of each volunteer; the first five were discarded, and the remaining 20 were stored in RNAlater solution (Ambion, Austin, TX, USA). Samples from 62 healthy women were used for microarray analysis (Table S1), and an independent panel of 20 healthy women was used for real-time qPCR validation (Table S3).

RNA extraction and processing

RNA extraction was performed using the RNeasy Mini Kit (Qiagen, Hilden, Germany). Tape strips, two at a time, were agitated in Tissuelyser LT (Qiagen) for 5 minutes at 50 Hz with lysis buffer and two 7-mm magnetic beads (Qiagen). The procedure was repeated until all 20 tape strips from each volunteer were processed, followed by the subsequent steps for total RNA extraction. Purified RNAs were quantified with a 2000c NanoDrop spectrometer (Thermo Scientific, Wilmington, NC, USA), and the quality was checked using a 2100 Bioanalyzer (Agilent Technologies, Santa Clara, CA, USA) and a Agilent RNA 6000 Pico Kit (Agilent Technologies). Because of the low total RNA yields, the samples were amplified with the Arcturus RiboAmp PLUS HS Kit (Applied Biosystems, Carlsbad, CA, USA) and SuperScript III Reverse Transcriptase (Applied Biosystems). All procedures were performed according to manufacturers' instructions.

RNA labeling, hybridization and microarray scanning

Amplified RNAs were processed using the Turbo Arcturus Labelling Kit (Applied Biosystems), and samples were labeled with Cy5. Universal Human Reference RNA (Agilent Technologies) from a unique batch was labeled with Cy3 for use in the data normalization of different arrays (Novoradovskaya *et al.*, 2004). The use of exogenous RNA from the Agilent RNA Spike-in Kit (Agilent

Technologies) was also used for the further calibration of the microarray measurements (Yang, 2006). After fragmentation with the Gene Expression Hybridization Kit (Agilent Technologies), 1:1 ratio mixtures of Cy5-labeled RNA from each volunteer and Cy3-labeled Universal Human Reference RNA (Agilent Technologies) were co-hybridized to two-color Agilent Whole Human Genome Oligo 44K microarrays (Agilent Technologies) to evaluate ~44,000 probe sets, which target 19,596 genes. Scanning and image analysis were performed using the Agilent DNA Microarray Scanner (Agilent Technologies). All procedures were performed according to manufacturers' instructions.

cDNA synthesis and real-time qPCR

To validate the gene expression patterns in the RNA samples, cDNA was obtained using a ReverAid First Strand cDNA Synthesis Kit (Thermo Scientific). cDNA from three or four volunteers in the same age group was pooled in equal quantities, resulting in three samples for analysis for each group (young and old), and real-time qPCR was performed in duplicate for each sample using the ViiA 7 Real Time PCR System (Applied Biosystems) with the TaqMan Fast Advanced Master Mix (Applied Biosystems) and TaqMan Gene Expression Assays (Applied Biosystems) for the following target genes: beta actin (ACTB, Hs99999903_m1); CCAAT/enhancer binding protein, alpha (CEBPA, Hs00269972_s1); fibroblast growth factor 5 (FGF5, Hs03676587_s1); forkhead box Q1 (FOXQ1, Hs00536425_s1); frizzled-related protein (FRZB, Hs00173503_m1); growth arrest-specific 7 (GAS7, Hs00932959_m1); melanoma antigen family A, 10 (MAGEA10, Hs00253298_s1); olfactory receptor, family 11, subfamily G, member 2 (OR11G2, Hs02340403_s1); olfactory receptor, family 4, subfamily F, member 4 (OR4F4, Hs03406040_gH); and olfactory receptor, family 7, subfamily D, member 2 (OR7D2, Hs01089409_s1). Glyceraldehyde-3-phosphate dehydrogenase (GAPDH, Hs03929097_g1) was used as an endogenous control. All procedures were performed according to manufacturers' instructions.

Data analysis

Microarray raw data were extracted using the Agilent Feature Extraction v8.1 software (Agilent Technologies, Santa Clara, CA, USA). Data visualization and analysis were performed using the GeneSpring v12.5 software (Agilent Technologies). Data normalization was performed within and across the arrays using per gene, per chip normalization, according to Agilent's recommendation. To detect the differentially expressed genes (DEGs) between experimental conditions, the following analyses were performed: 1) unpaired t-test with a corrected p-value (Benjamini Hochberg FDR) and a cut-off of 0.05 for young versus old comparisons; 2) unpaired t-test with a corrected p-value (Benjamini Hochberg FDR) and a cut-off of 0.01 for segmentation according to different decades of life (each group compared to the immediately preceding younger group); and 3) one-way ANOVA with post-hoc Tukey's HSD with a corrected p-value (Benjamini Hochberg FDR) and a cut-off of 0.01 for continuous gene expression analysis throughout aging (all groups compared to the youngest condition, i.e., ~20 years old). Hierarchical clustering was performed using the Euclidean distance metric and Ward's linkage rule. K-means clustering analysis was used for DEGs identified when all groups were compared to the youngest condition (~20 years old). The minimal FC, p-values and specific statistical tests were defined according to each analysis. For real-time qPCR experiments, the FC was calculated using the ddCt technique (Livak and Schmittgen, 2001). The DAVID database was used to conduct functional enrichment analysis (Huang *et al.*, 2009a and 2009b). The human genome was used as a reference, and regulated GO terms were ranked according to their p-values (or called EASE score, a modified Fisher's exact test) with a cut-off of 0.01; Benjamini correction was also considered for ranking but not elimination (www.david.abcc.ncifcrf.gov). The KEGG database was used for the analysis of modulated pathways (Kanehisa and Goto, 2000; Kanehisa *et al.*, 2014), considering the human genome as a reference and an adjusted p-value cut-off of 0.01 (www.genome.jp/kegg). Network connectivity was analyzed using STRING

v9.1 (Franceschini *et al.*, 2013), a database of known and predicted protein interactions (www.string-db.org).

Results

Panel of volunteers and sample considerations

To cover a broad spectrum of the aging process, we recruited a panel of volunteers comprising 62 women who were distributed according to different decades of age i.e., 20 ± 1 years old (12 volunteers), 30 ± 1 years old (9 volunteers), 40 ± 1 years old (9 volunteers), 50 ± 1 years old (9 volunteers), 60 ± 1 years old (8 volunteers), 70 ± 1 years old (8 volunteers) and 80 ± 1 years old (7 volunteers) (Table S1). Using non-invasive adhesive tape stripping, our analysis focused on the outer viable layers of epidermis, including the granular (mainly) and spinous layers. Most of the stratum corneum was discarded with the first five tapes collected because its dead cell components are not suitable for RNA extraction. The basal layer was likely not accessible due to its deeper position. Thus, epidermal differentiation and keratinocyte activity/structure are that biological processes that are most likely to be revealed by this approach. Moreover, tapes were collected from sun-exposed areas, providing samples with particular clinical and morphological interests with regards to epidermal aging.

Young versus old epidermis microarray analysis and technical validation using real-time qPCR

To establish comparisons with previous skin aging studies, young versus old analyses were initially performed by dividing the volunteers into two groups: 20-40 years old (30 volunteers) and 50-80 years old (32 volunteers) (Table S1). By adopting a minimal fold change (FC) value of 1.5 and a p-value cut-off of 0.05, statistically significant differences were observed for 4,863 probe sets (3,416 recognized HGNC mapped probe sets representing 3,247 distinct human genes),

with 4,146 up-regulated and 717 down-regulated (Table S2). Technical validation of the microarray results was performed using real-time qPCR in an independent young versus old panel including 10 volunteers who were 25 ± 3 years old and 10 volunteers who were 55 ± 4 years old (Table S3). Similar results were found for the expression of 10 randomly selected genes (up-, down- or non-regulated) (Figure 1).

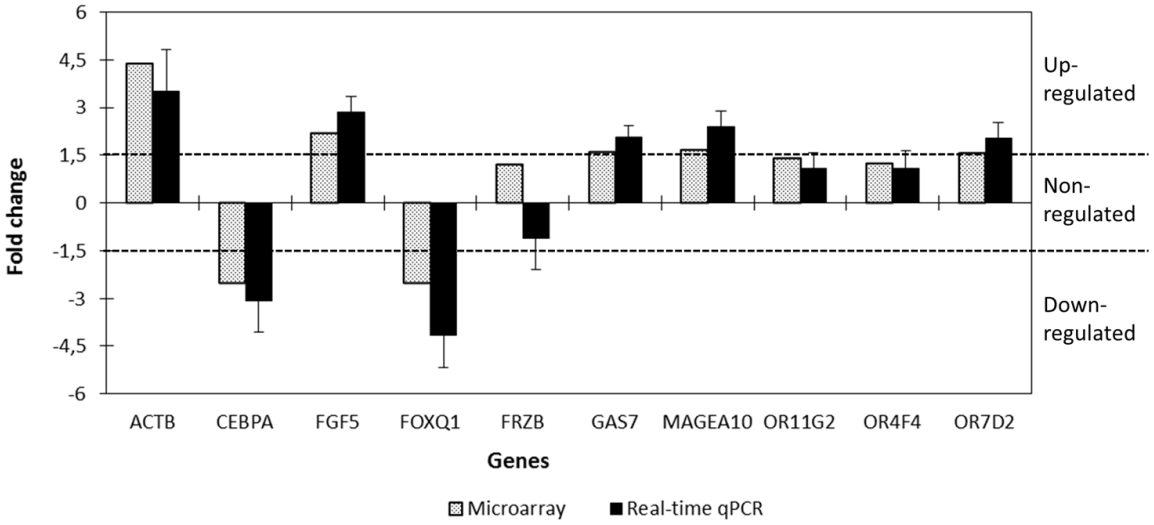

Figure 1. Real-time qPCR validation of microarray results. These qPCR results represent the median (± SD) of triplicate analyses using an independent secondary panel of volunteers (10 young, 10 old). GAPDH was used as an endogenous control. A complete list of regulated genes can be found in Table S2.

Separate lists of the up- and down-regulated genes (Table S2) were analyzed in the DAVID database to identify significantly up- and down-modulated biological processes, respectively, ranked according to p-value (cut-off 0.01) (Table 1). Although the number of up-regulated genes was higher than that of down-regulated genes, the opposite trend was found for biological processes, i.e., 63 gene ontology (GO) terms were associated with down-regulated gene expression, and 24 were associated with up-regulated gene expression. Filtering data with distinct FC values of 1.5, 2.0 and 3.0 and maintaining the p-value cut-off of 0.05 demonstrated that the ratio between the up- and down-regulated genes decreased with an increase in FC criteria (Table S4). Notably, the down-regulated genes were predominant in the 3.0 FC dataset. Therefore, one may conclude that despite the

higher number of up-regulated genes in terms of significant biological processes enrichment and FC expression intensity, the down-regulation of gene expression is critical for the epidermal aging of sun-exposed skin.

Table 1. Gene ontology (GO) terms associated with sun-exposed epidermal aging.

GO term	GO code	Number of DEGs[1]	p-value
Up-regulated biological processes			
Translational elongation	GO:0006414	30	0.000160
Negative regulation of protein metabolic process	GO:0051248	44	0.001159
Negative regulation of protein modification process	GO:0031400	31	0.001371
Multi-organism process	GO:0051704	127	0.001785
Negative regulation of cellular protein metabolic process	GO:0032269	42	0.001801
Interspecies interaction between organisms	GO:0044419	60	0.002109
Induction of apoptosis by extracellular signals	GO:0008624	29	0.002222
Negative regulation of response to stimulus	GO:0048585	26	0.003719
Positive regulation of programmed cell death	GO:0043068	84	0.003956
Positive regulation of cell death	GO:0010942	84	0.004483
Positive regulation of apoptosis	GO:0043065	83	0.004805
Carbohydrate transport	GO:0008643	18	0.004839
Glucose transport	GO:0015758	11	0.005714
Regulation of apoptosis	GO:0042981	143	0.005774
Regulation of programmed cell death	GO:0043067	144	0.006142
Regulation of glucose transport	GO:0010827	12	0.006592
Positive regulation of cellular process	GO:0048522	304	0.006815
Response to peptide hormone stimulus	GO:0043434	35	0.007001
Regulation of cell death	GO:0010941	144	0.007087
Hexose transport	GO:0008645	11	0.007479
Cellular protein metabolic process	GO:0044267	380	0.007861
Regulation of synaptic plasticity	GO:0048167	18	0.008135
Protein metabolic process	GO:0019538	449	0.008462
Monosaccharide transport	GO:0015749	11	0.009636
Down-regulated biological processes			
Organ development	GO:0048513	69	0.000001
System development	GO:0048731	81	0.000019
Anatomical structure development	GO:0048856	84	0.000066
Multicellular organismal development	GO:0007275	92	0.000090
Cell fate commitment	GO:0045165	12	0.000254
Cell differentiation	GO:0030154	58	0.000289
Regulation of transcription from RNA polymerase II promoter	GO:0006357	32	0.000331
Keratinization	GO:0031424	7	0.000334
Negative regulation of programmed cell death	GO:0043069	20	0.000391
Developmental process	GO:0032502	96	0.000403
Negative regulation of cell death	GO:0060548	20	0.000404
Regulation of programmed cell death	GO:0043067	34	0.000502
Regulation of system process	GO:0044057	18	0.000511
Epithelium development	GO:0060429	15	0.000518

Regulation of cell death	GO:0010941	34	0.000540
Tissue development	GO:0009888	29	0.000790
Cellular developmental process	GO:0048869	58	0.000810
Epithelial cell differentiation	GO:0030855	11	0.000907
Anatomical structure morphogenesis	GO:0009653	44	0.000957
Positive regulation of cellular process	GO:0048522	61	0.001163
Regulation of cellular process	GO:0050794	178	0.001284
Regulation of biological process	GO:0050789	184	0.001431
Ectoderm development	GO:0007398	13	0.001545
Organ morphogenesis	GO:0009887	25	0.001610
Regulation of apoptosis	GO:0042981	32	0.001746
Negative regulation of biological process	GO:0048519	59	0.002009
Regulation of RNA metabolic process	GO:0051252	59	0.002035
Regulation of neurological system process	GO:0031644	11	0.002087
Negative regulation of apoptosis	GO:0043066	18	0.002244
Biological regulation	GO:0065007	191	0.002249
Epidermis development	GO:0008544	12	0.002574
Positive regulation of biological process	GO:0048518	64	0.002744
Multicellular organismal process	GO:0032501	118	0.003216
Regulation of transcription, DNA-dependent	GO:0006355	57	0.003250
Keratinocyte differentiation	GO:0030216	7	0.003266
Regulation of gene expression	GO:0010468	84	0.003317
Regulation of metabolic process	GO:0019222	102	0.003860
Regulation of primary metabolic process	GO:0080090	94	0.004054
Regulation of localization	GO:0032879	25	0.004503
Epidermal cell differentiation	GO:0009913	7	0.005033
Regulation of transmission of nerve impulse	GO:0051969	10	0.005283
Angiogenesis	GO:0001525	10	0.005520
Notch signaling pathway	GO:0007219	6	0.005603
Cell fate determination	GO:0001709	5	0.005715
Myeloid leukocyte differentiation	GO:0002573	5	0.006366
Regulation of macromolecule metabolic process	GO:0060255	92	0.006416
Regulation of transcription	GO:0045449	76	0.006710
Positive regulation of apoptosis	GO:0043065	19	0.007115
Regulation of nucleobase, nucleoside, nucleotide and nucleic acid metabolic process	GO:0019219	81	0.007177
Positive regulation of programmed cell death	GO:0043068	19	0.007589
Regulation of cellular biosynthetic process	GO:0031326	84	0.007758
Positive regulation of cell death	GO:0010942	19	0.008003
Immune system development	GO:0002520	14	0.008370
Leukocyte differentiation	GO:0002521	9	0.008471
Negative regulation of cellular process	GO:0048523	52	0.008553
Regulation of cellular metabolic process	GO:0031323	96	0.008743
Regulation of nitrogen compound metabolic process	GO:0051171	81	0.008975
Cell death	GO:0008219	27	0.009011
Regulation of multicellular organismal process	GO:0051239	33	0.009012
Signal transduction	GO:0007165	81	0.009054
Regulation of biosynthetic process	GO:0009889	84	0.009157
Regulation of anatomical structure morphogenesis	GO:0022603	12	0.009370
Death	GO:0016265	27	0.009837

1. DEGs, differentially expressed genes.

To identify the modulated pathways, the complete list of modulated genes was analyzed using the KEGG database (Table S2). Forty pathways showed significant modulation and were ranked according to their p-values (cut-off: 0.01) (Table S5). In addition to statistical significance, biological interpretation is essential for meaningful pathway analysis. Of the identified pathways, ~50% were associated with human diseases and organismal systems not necessarily related to skin. Other pathways could be linked to key aspects of epidermal aging, such as focal adhesion, cytokine-cytokine receptor interaction, Wnt signaling pathway, MAPK signaling pathway, cell adhesion molecules, Jak-STAT signaling pathway and Hedgehog signaling pathway, which helps explain the clinical, morphological and/or functional alterations of aged epidermis. The actin cytoskeleton pathway has 37 DEGs in common with our results, and 32 of these genes are up-regulated, which corresponds to significant ACTB up-regulation according to the microarray and qPCR techniques and might help explain the clinical observations of solar keratosis in sun-exposed skin (Figure 2a). The calcium signaling pathway has 31 DEGs in common with our results, which likely contribute to the impaired calcium gradient observed in aged epidermises (Figure 2b).

Comparison to previous studies

To verify the alignment of our findings with key previous aging-related studies, specific comparisons were established. A recent transcriptome analysis of intrinsic epidermal aging reported only 75 DEGs between five young and five old donors (18-24 and 70-75 years old, respectively) (Raddatz *et al.*, 2013). Despite the noted biological and technical variations and population specificities, 15 common DEGs were shared by our studies (Table S6), including cross-linked envelope proteins in keratinocytes, adhesion molecules and components of signal transduction pathways.

Figure 2 **A**

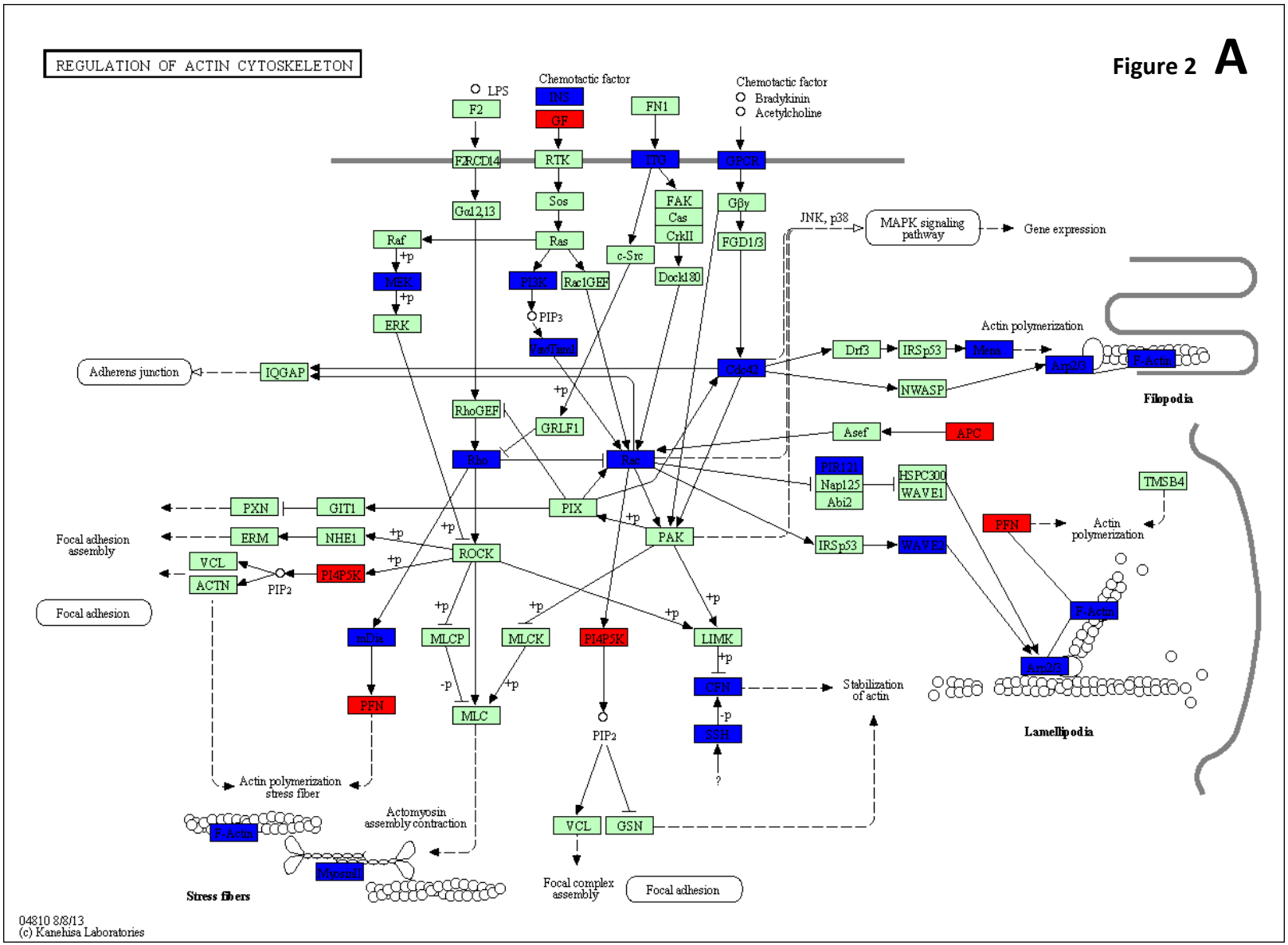
REGULATION OF ACTIN CYTOSKELETON
LPS
F2
Chemotactic factor
INS
GF
FN1
Chemotactic factor
Bradykinin
Acetylcholine
F2RCD14
RTK
ITG
GPCR
Gα12,13
Sos
FAK
Cas
CrkII
Gβγ
JNK, p38
MAPK signaling pathway
Gene expression
Raf
+p
MEK
+p
ERK
Ras
c-Src
FGD1/3
PI3K
Rac1GEF
Dock180
PIP3
Vav/Tiam1
Actin polymerization
Drf3
IRSp53
Mena
Arp2/3
F-Actin
Filopodia
Adherens junction
IQGAP
Cdc42
NWASP
RhoGEF
+p
GRLF1
Asef
APC
Rho
Rac
PIR121
Nap125
Abi2
HSPC300
WAVE1
TMSB4
PXN
GIT1
PIX
+p
PFN
Actin polymerization
Focal adhesion assembly
ERM
NHE1
+p
+p
ROCK
PAK
IRSp53
WAVE2
VCL
ACTN
PIP2
+p
PI4P5K
Focal adhesion
mDia
MLCP
MLCK
PI4P5K
LIMK
+p
F-Actin
Arp2/3
PFN
-p
+p
CFN
Stabilization of actin
MLC
PIP2
SSH
-p
?
Lamellipodia
Actin polymerization stress fiber
Actomyosin assembly contraction
F-Actin
Myosin II
VCL
GSN
Stress fibers
Focal complex assembly
Focal adhesion
04810 8/8/13
(c) Kanehisa Laboratories

Figure 2 **B**

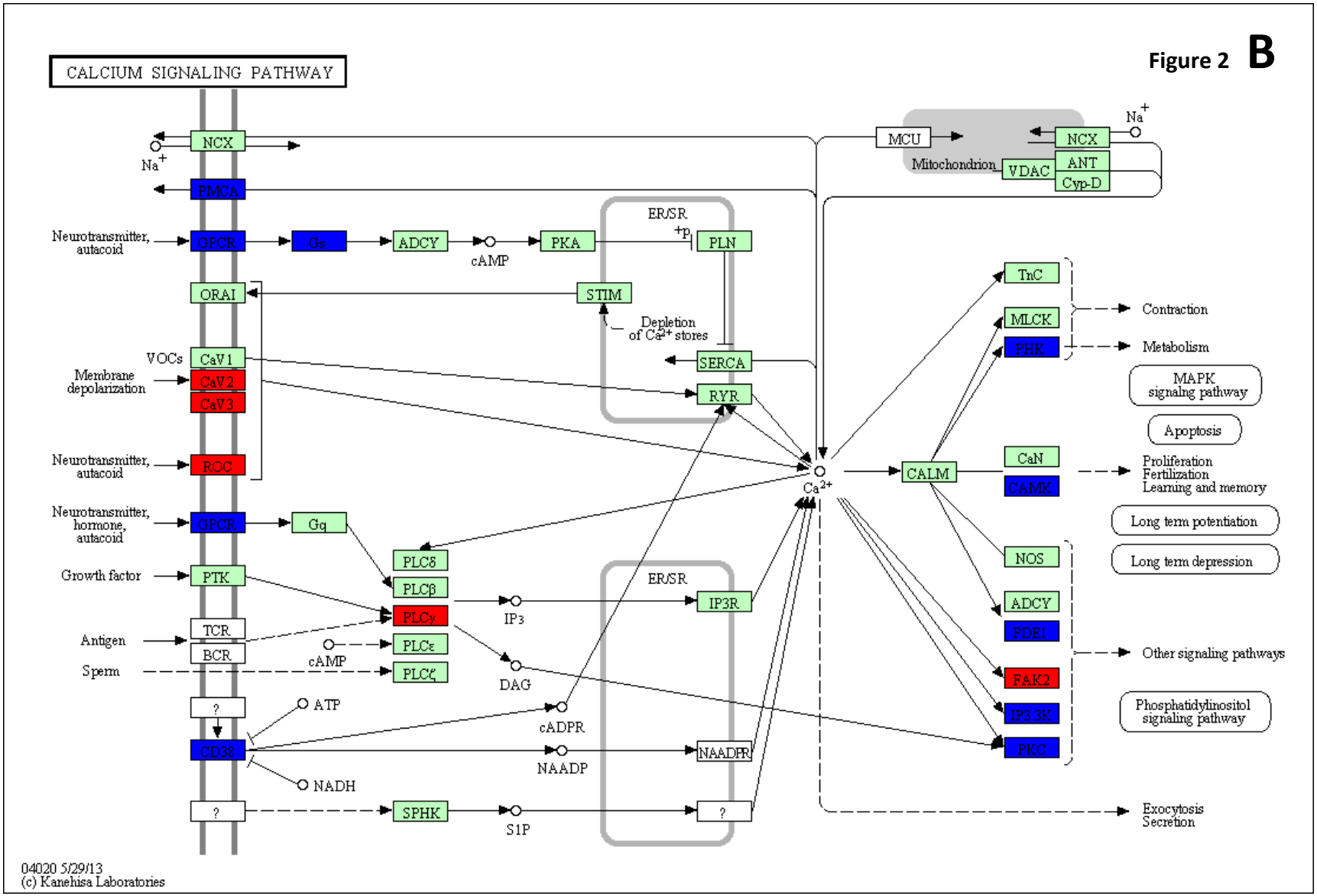
CALCIUM SIGNALING PATHWAY
NCX
Na+
PMCA
Neurotransmitter, autacoid
GPCR
Gs
ADCY
cAMP
PKA
ER/SR
+p
PLN
ORAI
STIM
Depletion of Ca2+ stores
VOCs
CaV1
Membrane depolarization
CaV2
CaV3
SERCA
RYR
Neurotransmitter, autacoid
ROC
Neurotransmitter, hormone, autacoid
GPCR
Gq
Growth factor
PTK
PLCδ
PLCβ
PLCγ
PLCε
PLCζ
IP3
DAG
Antigen
TCR
BCR
Sperm
cAMP
ER/SR
IP3R
?
ATP
cADPR
CD38
NAADP
NAADPR
NADH
?
SPHK
S1P
?
Ca2+
MCU
Mitochondrion
NCX
Na+
VDAC
ANT
Cyp-D
CALM
TnC
MLCK
PHK
Contraction
Metabolism
MAPK signaling pathway
Apoptosis
CaN
CAMK
Proliferation
Fertilization
Learning and memory
Long term potentiation
Long term depression
NOS
ADCY
PDE1
FAK2
IP3 3K
PKC
Other signaling pathways
Phosphatidylinositol signaling pathway
Exocytosis
Secretion
04020 5/29/13
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Figure 2. Biological pathways modulated by sun-exposed epidermal aging from the KEGG database. (A) Actin cytoskeleton pathway. (B) Calcium signaling pathway. A complete list of regulated genes can be found in Table S2. White boxes represent species independent genes from the reference pathway map that were not differentially expressed in our study; green boxes represent human genes from the pathway that were not differentially expressed in our study; blue and red boxes represent human genes from the pathway that were respectively up- or down-regulated in our study. Graphic representations: ▭ gene product; ○ other molecules (mostly chemical compounds); ▭ another map; → activation; ⊣ inhibition; ⇢ indirect effect; ⇢▷ indirect link to another map; +p phosphorylation; -p dephosphorylation.

With a representative sample size for better analyzing intergroup changes despite intragroup variability, an elegant study was performed by Glass *et al.* (2013) as part of the MuTHER (Multiple Tissue Human Expression Resource) project. Using a linear mixed model and a large panel of 856 female twins ranging in age from 39 to 85 years old, 1,672 probe sets were differentially expressed in photo-protected skin throughout a lifetime, of which 273 were also detected in our analysis (Table S7). Yan *et al.* (2013) conducted a skin photoaging evaluation with paired analysis of sun-exposed and sun-protected samples from 21 Chinese women ranging from 34-55 years old. A total of 1,621 modulated probe sets were identified, and 250 also present in our data (Table S8). If considered together, the Glass *et al.* (2013) and Yan *et al.* (2013) studies had 42 DEGs in common with our results, including significant epidermal markers such as keratins and keratin associated proteins. To determine broader aging aspects, we checked whether known aging-related genes from Human Ageing Genomic Resources (HAGR) were present in our dataset (de Magalhães *et al.*, 2009; Tacutu *et al.*, 2013). GenAge is a database within HAGR that consists of 298 genes potentially associated with human aging, and 43 of these genes are correlated with our study (Table S9), including markers of actin filament organization, regulation of cell growth and progression through the cell cycle as well as genes related to protein modification and apoptosis. The two lists of ~40 shared DEGs, which were obtained from the comparison of our results with those of Glass and Yan or the HAGR data, were evaluated using the DAVID and STRING databases and revealed distinct profiles (Figure 3), which are detailed in the discussion section.

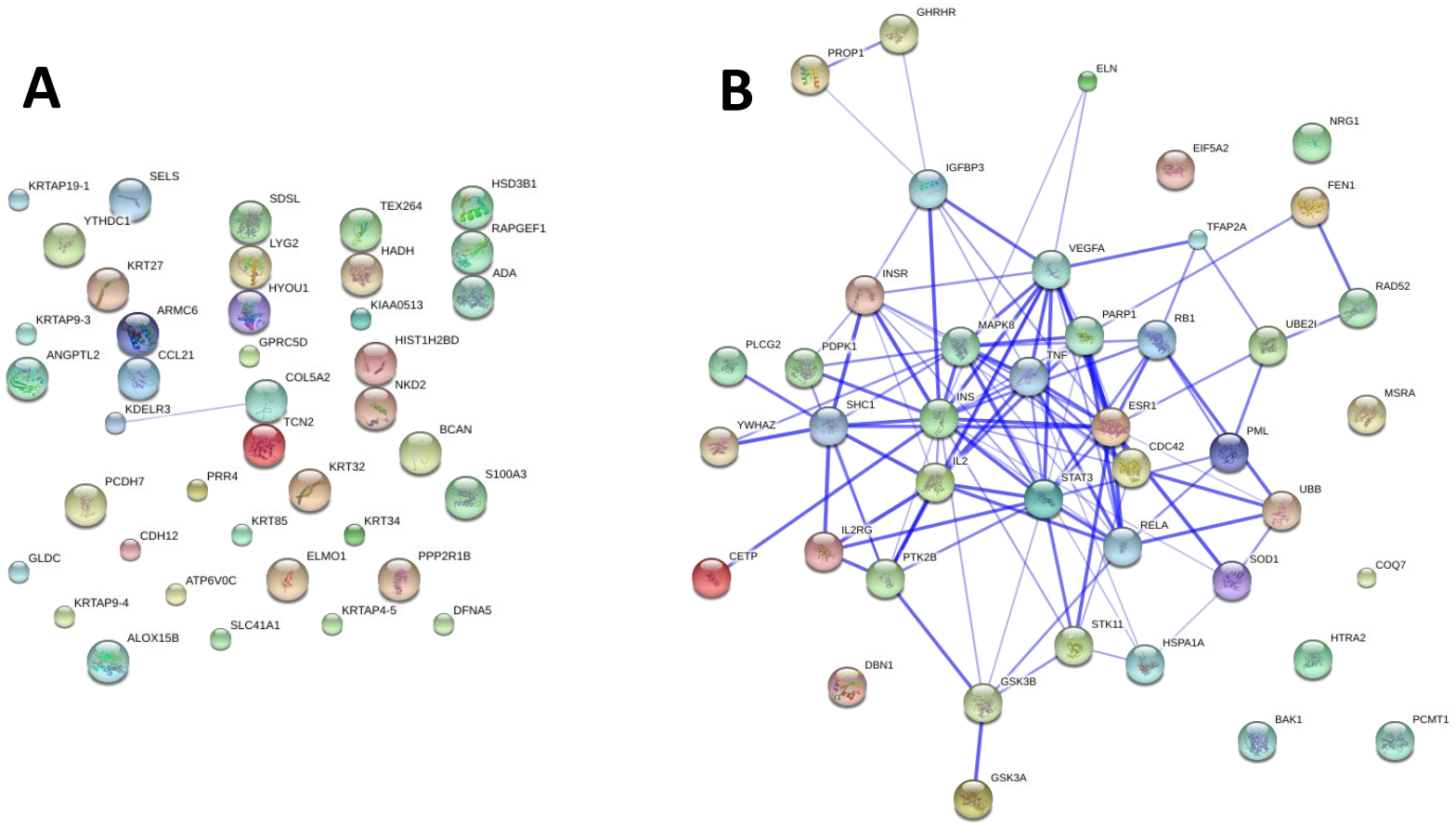

Figure 3. Associations between modulated biomarkers of sun-exposed epidermal aging. Analyses were performed with differentially expressed genes (DEGs) by comparing our dataset with other studies. (A) DEGs in common with Glass *et al.* (2013) and Yan *et al.* (2013), sun-protected and sun-exposed skin aging studies, respectively, showing genes mainly related to tissue-specific biological processes and only one association. (B) DEGs in common with Human Ageing Genomic Resources (HAGR), a study of aging not restricted to skin, showing genes related to broad biological processes and many molecular associations. Complete lists of genes are found in Tables S7-S9. Different node colors are used only as a visual aid. Big nodes indicate proteins with available structural information. Stronger associations are represented by thicker lines.

Epidermal aging transcriptome segmentation according to different decades of life

As previously stated, our panel of volunteers whose DNA was used for microarray analysis comprised women distributed across different age decades. Because the number of volunteers per experimental group was significantly reduced by panel segmentation, more restrictive criteria were adopted for the selection of DEGs, i.e., considering a minimal FC of 2.0 and a p-value cut-off of 0.01. Clustering analysis was performed to evaluate the consistency of traditional grouping, i.e., young versus old, in reflecting the evolution of epidermal aging (Figure 4a). Indeed, the young (20-40 years) and old groups (50-80 years) were separated, but at least two specific observations are notable from the analysis. First, clustering did not order the groups into a continuous and crescent sequence of ages, indicating that the age-associated changes should not be interpreted as part of a linear process. Second, the old group showed clear segregation into two distinct blocks. Together, these findings exposed critical limitations of the traditional young versus old polarizing analyses, based on a single comparison of extreme phenotypic aging conditions. The next step was identifying DEGs in each decade of life by comparing each age group with the immediately preceding younger one. Following this rational, six lists of DEGs were generated to represent each decade of life between 20 and 80 years of age (Table S10). Though specific gene expression profiles are associated with each decade, one of the most interesting findings related to such an overall analysis is evidence of a dynamic and pattern of epidermal transcription that oscillates with age (Figure 4b).

Continuous gene expression analysis throughout aging

To better understand the continuous gene regulation in sun-exposed epidermal aging, each group was compared to the youngest group (~20 years old). Significant DEGs should present a minimal FC of 1.5 in at least four of the six total comparisons and a minimal FC of 3.0 between the 20- and 80-year-old groups. The p-value cut-off considered was 0.01. Genes complying with those criteria were

subjected to K-means clustering analysis. Several clusters were found, and the most representative clusters were selected for further evaluation, considering a continuous tendency toward an increase or decrease gene expression with age (Figure 5). One cluster evinced the isolated gene SPRR2G as an example of increased expression throughout life (Table S11). Regarding the continuous tendency to reduce gene expression with age, the selected cluster demonstrated 20 modulated probe sets (11 HGNC identified genes), including the keratinization marker LCE1A and the transcription factor CEBPA (also identified in our young versus old analysis and confirmed by qPCR) (Table S11).

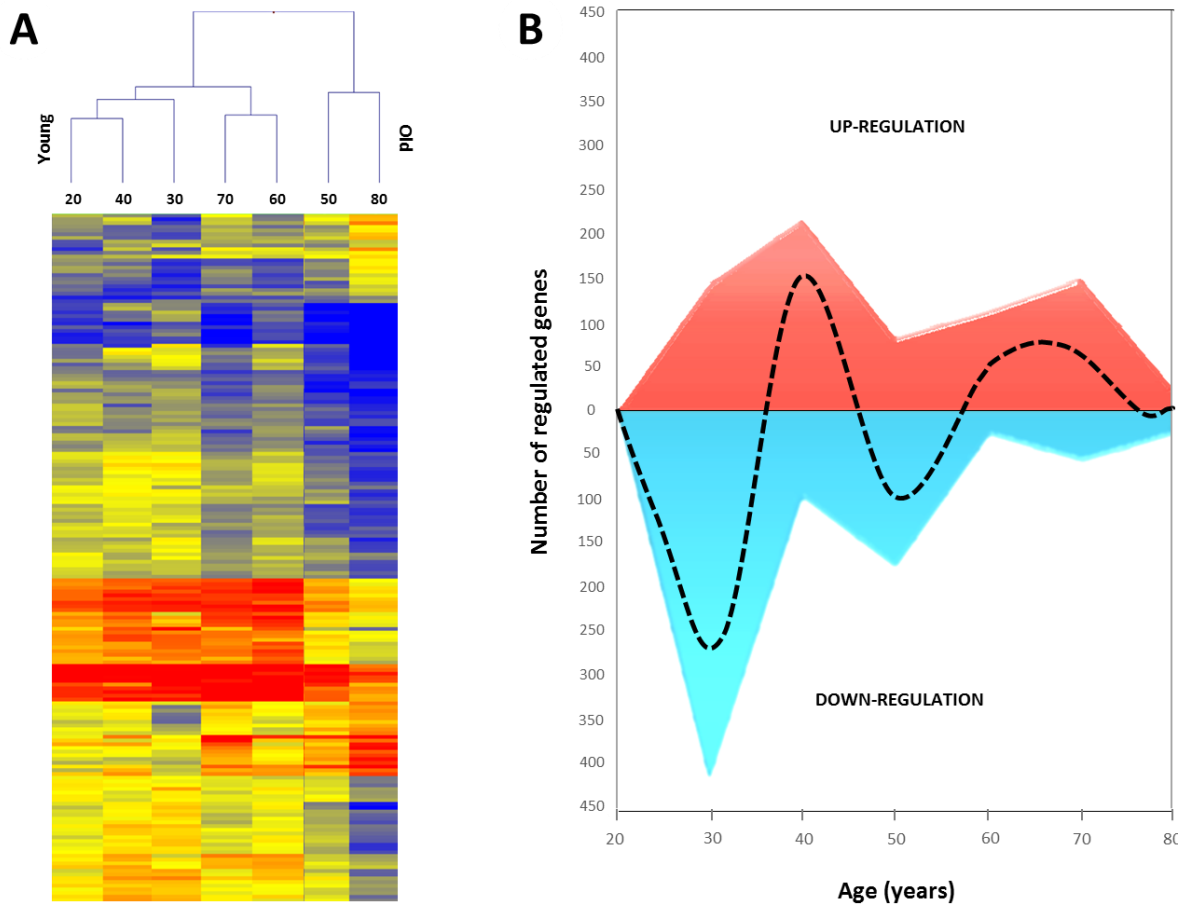

Figure 4. Overall analysis of gene expression during sun-exposed epidermal aging using a segmented panel of different decades of life. (A) Hierarchical clustering analysis showing different age groups organized according to similarities in gene expression profile (branches at top). The colored boxes indicate a distribution of decades in preliminary young (blue) versus old (rose) classification. (B) Oscillating transcriptional profile along a lifetime, as indicated by a dashed line

(tendency in the difference between the numbers of up- and down-regulated genes). Each age group was compared to its preceding younger group.

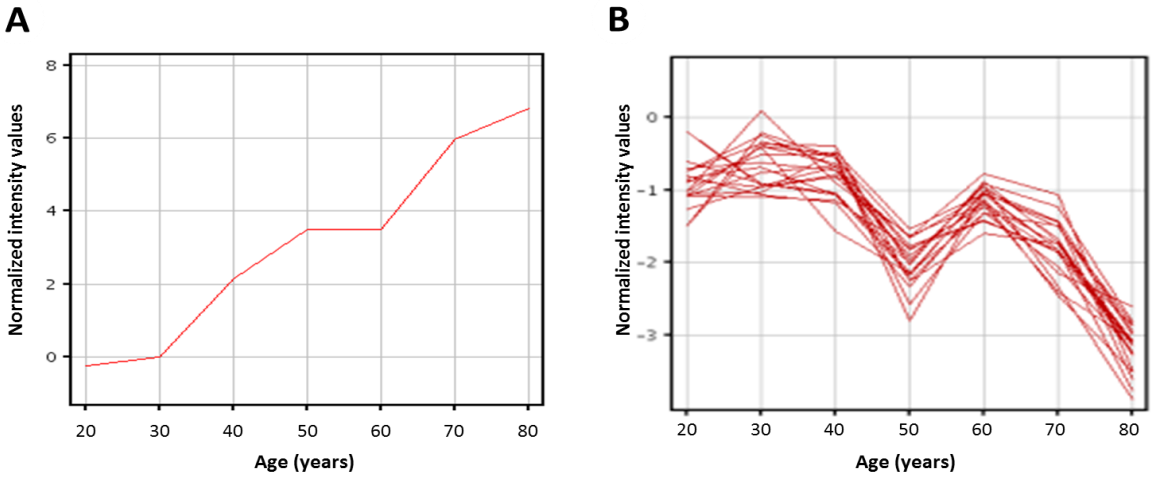

Figure 5. Clustering analysis of genes with similar expression profiles throughout life. (A) Genes with a tendency toward a continuous increase in sun-exposed epidermal aging. (B) Genes with tendency toward continuous decrease in sun-exposed epidermal aging. Each age group was compared with the youngest age group (~20 years old). A complete list of genes can be found in Table S11.

Discussion

In accordance with Rinnerthaler *et al.* (2013) and based on the adoption of different strategies for analysis, this study contributes to the understanding of the dramatic changes that occur in the epidermis during aging. As expected, the main findings were related to modifications in epidermal differentiation and keratinocyte activity/structure. Processes such as cell proliferation were not enriched in our data, possibly because cells from the basal epidermal layer were not likely to be sampled by tape stripping. Considering the fact that samples were collected from the back of hands, this report represents the first study focused on the transcriptome of sun-exposed human epidermal aging.

A comparison of our data with skin-based transcriptome studies (Glass *et al.*, 2013; Yan *et al.*, 2013) indicated the regulation of tissue-specific biological processes, such as epidermis and ectoderm development. However, a comparison

with HAGR data predominantly demonstrated changes in broader biological processes, such as the regulation of cell death and response to chemical stimulus. The high level of interaction between the biomarkers of HAGR cross-analysis – 44 in total – indicates the coordinated regulation of key genes that may simultaneously impact several processes (Figure 3b). Therefore, the epidermis appears to be affected by aging at different levels of molecular regulation, involving impaired broad and tissue-specific biological processes. Mitogen-activated protein kinase 8 (MAPK8) represents a gene that affects the expression of other genes in a cascade effect. This gene responds to activation by environmental stress and pro-inflammatory cytokines by phosphorylating a number of transcription factors. In addition to the MAPK8 gene, the MAPK signaling pathway was enriched in our analyses, suggesting an epidermal response to constant sun exposition. Akasaka *et al.* (2010) showed that MAPK8 protein accumulates in sunlight-exposed human epidermises, thereby promoting oxidative stress. Moreover, the MAPK signaling pathway has an indirect link with the Wnt signaling pathway, which was also enriched in our data. Aberrant Wnt signaling contributes to cancerous growth (Castilho *et al.*, 2009), and our findings suggest that it could be related to increase predisposition to cancer development in photoaged skin (Mouret *et al.*, 2011).

It is important to note that several studies have evaluated the effects of aging on the entire skin, but most of these studies have proven to be difficult due to the heterogeneous nature of specimens (Gromov *et al.*, 2003). The extensive list of DEGs presented here reflects our experimental composition (i.e., isolation of the epidermis plus a representative sample size) in association with the simultaneous effects of the intrinsic and extrinsic aging factors on the skin. Interestingly, despite the predominance of up-regulated genes in our data, down-regulated genes had the highest FC values and resulted in a higher number of significantly enriched biological processes (Table 1). Regarding the biological meaning of modulated processes in the comparison between young and old epidermises, seven of the top 10 up-regulated GO terms were related to the deleterious effects on epidermal functions, such as the negative regulation of cellular protein metabolic process, negative regulation of response to stimulus and positive regulation of cell death

(including programmed cell death and apoptosis). The top 10 down-regulated GO terms included processes related to cell differentiation, keratinization and negative regulation of cell death. Some of these results complement or help elucidate the molecular mechanisms behind clinical or morphological epidermal changes. Moreover, establishing comprehensive parallels to other analyses adds significant insight to our data. Apoptosis induction in the photoaged epidermis was previously described as being marked by the presence of sunburn cells or apoptotic keratinocytes (Leyden, 2001; Van Laethem *et al.*, 2005). Such an observation could be supported by our findings of either the induced positive regulation of cell death or the reduced negative regulation of cell death.

According to López-Otín *et al.* (2013), the rate of aging is controlled, at least to some extent, by genetic pathways and biochemical processes that have been conserved throughout evolution, such as the nine emphasized mammalian hallmarks of aging: genomic instability, telomere attrition, epigenetic alterations, loss of proteostasis, deregulated nutrient sensing, mitochondrial dysfunction, cellular senescence, stem cell exhaustion, and altered intercellular communication. A study by Raddatz *et al.* (2013) highlighted the destabilization of the epigenome as a significant component of epidermal aging, but in contrast with our study, they found that young and old epidermis transcriptomes were similar overall. Because the results of this group were characterized by high expression levels of epidermis-specific genes, we assumed that technical and/or biological limitations did not allow the authors to draw conclusions about broad and conserved regulatory processes. Our identification of DEGs shared with HAGR and the definitions López-Otín *et al.* (2013) suggest that the age-related modulation of epidermis-specific genes might be accompanied by overall impaired pathways that represent general hallmarks of aging in the entire organism.

A recent study evaluated age-related changes in the composition of the cornified envelope (CE) in human skin (Rinnerthaler *et al.*, 2013). Despite not applying an “omics”-related technique, the expression of 46 genes related to CE formation was evaluated in photo-protected epidermises that were isolated from nine individuals from each of the following age groups: 1-10, 17-44 and 59-74

years. Consistent with our findings, the authors observed no significant changes in the expression of the genes involved in the initial steps of CE assembly, including envoplakin, periplakin and involucrin. Of the five types of transglutaminases (TGMs), the authors identified only a slight increase in TGM1 expression, while we detected a similar result for TGM3. In both studies, the DEGs were mainly related to the processes occurring after scaffold formation, predominantly affecting loricrin (LOR) and the small proline-rich proteins (SPRRs), which correspond to 80% of the CE constitution (Kalinin *et al.*, 2001). Rinnerthaler's group verified the down-regulation of LOR and the up-regulation of SPRRs, with the exception of SPRR2G. Increased SPPRs, which function as small bridges between LOR and themselves, were suggested to function in a compensatory mechanism for decreased LOR. In contrast, our data showed increased expression for LOR and some SPPRs, mainly SPPR2G, suggesting that LOR/SPRR expression has distinct patterns of regulation in photo-protected and photo-exposed skin. Nevertheless, inverse LOR regulation could be related to the presence of a thicker epidermis in photoaged skin (Leyden, 2001; El-Domyati *et al.*, 2002), contrary to epidermal thinning in photo-protected areas (Lock-Andersen *et al.*, 1997; Makrantonaki and Zouboulis, 2007). The opposite regulation of LOR expression in photo-protected and photo-exposed epidermises resembles elastin regulation in the dermis, whose production is reduced by aging in photo-protected skin, while it is over-expressed in photoaging conditions in the same tissue and leads to elastosis (Uitto, 2008). To date, there is no evidence for SPRR2G regulation with epidermal aging, but several studies have suggested that SPRRs are related to increased epithelial proliferation and the development of malignant processes (Carregaro *et al.*, 2013). Our findings suggest a specific mechanism for epidermal photoaging related to impaired CE formation, which has not been previously described and has potential for further studies in the future.

Because the ionic distribution of calcium drives keratinocytes into differentiation and is inevitable for CE synthesis, Rinnerthaler *et al.* (2013) also evaluated the influence of aging on this biological process and showed that the calcium distribution is different in aged skin, confirming a previous study performed

with facial sun-exposed epidermis (Denda *et al.*, 2003). Our results showed a significant modulation of the calcium signaling pathway in aged epidermises, which is represented by 31 DEGs (Figure 2b). These results represent the first evidence of the molecular mechanisms that are involved in the impairment of the calcium gradient upon epidermal aging, which should be better explored in future studies.

The effects of epidermal photoaging also appear to impair some aspects of the cellular structure, as demonstrated by our findings of modulation of the beta actin (ACTB) gene and the actin cytoskeleton pathway (Figure 2a). Interestingly, ACTB, which is widely used as an endogenous control gene, was up-regulated by epidermal aging in our microarray and qPCR analyses (Figure 1). ACTB modulation might be related to morphological changes in aged keratinocytes in photo-exposed skin areas in which the higher incidence of solar keratosis is associated with diffuse epidermal hyperplasia (Koehler *et al.*, 2011). Previous reports have stated that senescent keratinocytes are irregularly shaped, enlarged and flattened (Soroka *et al.*, 2008), strongly suggesting the impaired regulation of key cytoskeleton components, such as ACTB. Furthermore, actin microfilaments from keratinocytes were shown to be depolymerized by UV radiation (Provost *et al.*, 2003); thus, increased ACTB gene expression could be interpreted as a compensatory mechanism or chronic attempt at damage repair. From a morphological perspective, the regulation of the actin cytoskeletal pathway could be related to the thicker epidermis observed in association with photoaging (Leyden, 2001; El-Domyati *et al.*, 2002).

The young versus old approach used in our study was important for obtaining interesting results and permitting comparisons with relevant previous findings in the literature. However, based on the proposition that aging is a continuous and cumulative process throughout life, we also performed analyses using a segmented panel of volunteers grouped according to different decades of life to understand the real dynamics of sun-exposed epidermal aging. Hierarchical clustering showed that epidermal aging does not appear to represent a linear biological process because different decades of life were not organized in a sequence of crescent age (Figure 4a). The group of 50-year-olds was allocated

closer to the 80-year-old group; however, menopause could help explain this phenomenon because it has already been noted as causing accelerated skin aging (Thornton, 2013). Moreover, the impaired gene expression at 50 years of age appears to be slightly recovered by 60 and 70 years of age, which likely occurs because these groups are clustered closer to the younger group, but they become impaired again at 80 years. Unfortunately, we could not identify clear reasons for this phenomenon, but it suggested an oscillatory pattern of gene expression in the epidermis throughout aging, which has likely been widely neglected because of the number of polarized young versus old analyses. By calculating the difference between the up-regulated and down-regulated genes in each decade, an intriguing profile was revealed, with alternate fluctuations throughout life (Figure 4b). In addition to being a barrier for mechanical protection, the epidermis has been described to be a metabolically active tissue in constant dynamic balance that periodically undergoes complete renewal cycles (Fuchs and Raghavan, 2002). The idea of a constant epidermal dynamic balance suggests the concept of a homeostasis that is characterized by fluctuations requiring readjustment (O'Neill, 2004). López-Otín *et al.* (2013) stated that several critical questions have arisen in the field of aging regarding, among other factors, the compensatory responses that attempt to reestablish homeostasis. Thus, we have interpreted the molecular behavior of the epidermis throughout aging as a continuous attempt at homeostatic regulation based on successive rounds of feedback response. The highest oscillation in terms of gene expression occurs at approximately 30 years of age, which is in accordance with the publication of Kuwazuru *et al.* (2012), who stated that skin wrinkling morphology suddenly changes in the early 30s based on the evaluation of facial skin from 102 women aged 25–56 years. However, the amplitude of the fluctuation appears to decrease over a lifetime (which means a lower number of regulated genes), possibly suggesting that homeostatic mechanisms deteriorate with epidermal aging (O'Neill, 2004). According to Kirkwood (2005), aging involves cumulative changes that affect the ability to adaptively respond to stress. Notably, a ten-year interval between two sequential groups may be too large to infer causal relationships, which was not our intention.

Nevertheless, the use of segmented intervals appears to represent an advantage for the continuous evaluation of aging, thereby enriching data interpretation.

An additional analysis, which used the panel of volunteers segregated by decades of age, was conducted to identify genes that tend to change continuously throughout life. SPPR2G represented the most significant up-regulated gene (Figure 5a). Because SPPR2G was not modulated in the study of Rinnerthaler *et al.* (2013), we believe that it represents a strong candidate for epidermal aging specifically associated with photoaged conditions. Additionally, the homologous family of SPRRs appears to have the greatest age-related changes in the CE occurring as a life-long process (Rinnerthaler *et al.*, 2013). In the continuously down-regulated genes (Figure 5b), we identified the keratinization marker LCE1A. This gene represents a protein that is involved in the last step of CE assembly and was found to be down-regulated during epidermal aging in the study by Rinnerthaler *et al.* (2013). In this case, in addition to differences related to photo-exposed or photo-protected areas, decreased levels of LCE1 members can be expected to be a result of reduced calcium levels in the aged epidermis. Another continuously down-regulated gene was the transcription factor CEBPA, which was also identified in the young versus old analysis and confirmed by qPCR. CEBPA is a basic leucine zipper transcription factor that is abundantly expressed in keratinocytes and whose function in skin is poorly characterized. Under UVB radiation, CEBPA is induced in keratinocytes, participates in cell cycle checkpoints that arrest cell cycle progression and prevents the replication of damaged DNA (Yoon K and Smart, 2004). Our evidences of gene expression reduction in the epidermis upon aging, using different analysis and techniques, suggests that CEBPA is an important element that is associated with an increased predisposition to cancer development in photoaged skin (Mouret *et al.*, 2011).

Given the functional importance of the epidermis to the homeostasis of an organism and the necessity of better understanding of the molecular mechanisms underlying epidermal aging, this study critically evaluated the changes affecting the epidermis throughout life, including intrinsic and extrinsic factors. With the main objective of this study being to open new perspectives for skin aging evaluation, we

presented alternative analyses that consider aging to be a continuous process. Future perspectives could include elucidating the specific mechanisms associated with epidermal aging to allow for the development of potential therapeutic approaches.

Conflict of Interests

Each author certifies that all affiliations with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the article are completely disclosed.

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Supplemental material

Table S1. Characterization of the main volunteer panel for microarray analyses.

Volunteer Number	Age (Years Old)	Skin Phototype [1]	Skin Type [2]	Ethnic Group [3]
1	19	II	Normal	Italian/Portuguese
2	19	II	Combination	Italian/Polish
3	19	II	Combination	Indigenous/Italian/Japanese
4	20	II	Oily	Italian
5	20	III	Oily	German/Indigenous
6	20	II	Oily	Italian/Polish
7	20	II	Oily	Portuguese
8	21	III	Oily	Italian/Portuguese
9	21	III	Oily	German/Italian
10	21	III	Oily	European
11	21	III	Oily	European
12	21	II	Normal	Italian
13	29	II	Combination	German/Italian
14	30	III	Dry	Asiatic
15	30	II	Combination	Indigenous/Spanish
16	30	III	Combination	Indigenous
17	31	III	Oily	Italian
18	31	II	Dry	Indigenous
19	31	II	Oily	Ukrainian
20	31	III	Combination	Lebanese/Portuguese
21	31	II	Oily	Italian/Spanish
22	40	II	Combination	German
23	40	III	Dry	Not declared
24	40	III	Combination	Not declared
25	40	II	Combination	Italian
26	41	II	Normal	European
27	41	II	Combination	German/Indigenous
28	41	II	Combination	German
29	41	III	Combination	Not declared
30	41	III	Combination	Italian
31	49	III	Combination	Japonese
32	49	III	Dry	Portuguese
33	50	II	Dry	Polish
34	50	III	Combination	German/Italian
35	50	III	Combination	German
36	51	II	Combination	German/Russian
37	51	III	Dry	Portuguese
38	51	II	Normal	Italian
39	51	II	Oily	Portuguese
40	59	II	Combination	Portuguese
41	59	II	Dry	Italian/Polish
42	59	II	Oily	Asiatic
43	60	III	Combination	Indigenous/Spanish
44	60	II	Oily	Polish
45	60	II	Dry	Italian
46	61	II	Dry	Spanish
47	61	II	Normal	Italian
48	69	II	Normal	Italian
49	69	II	Dry	Ukrainian
50	69	II	Oily	German
51	71	II	Normal	Indigenous/Russian
52	71	II	Combination	German
53	71	III	Oily	Dutch/Indigenous/Portuguese/Swiss
54	71	II	Dry	Danish/Portuguese
55	71	II	Combination	Not declared
56	79	II	Not declared	Caucasian
57	79	II	Dry	Ukrainian
58	79	II	Combination	Japonese
59	81	II	Not declared	Polish
60	81	II	Normal	Portuguese
61	81	II	Dry	Italian
62	81	II	Combination	German/Portuguese

1 Classification according to Fitzpatrick phototyping scale

2. Personal declaration of predominant skin type in the body according to sebum production

3. Personal declaration of ethnic groups

Table S2. Probe sets modulated in the epidermis of young versus old volunteers with a minimal fold change of 1.5 and a p-value cut-off of 0.05 (only one long list).

HGNC Approved Symbol [1]	HGNC Approved Name [1]	FC	Reg. [2]
RBFOX1	RNA binding protein, fox-1 homolog (C. elegans) 1	1,52	Up
A4GALT	alpha 1,4-galactosyltransferase	2,09	Down
NCEH1	neutral cholesterol ester hydrolase 1	1,52	Up
AATF	apoptosis antagonizing transcription factor	1,98	Up
AATK	apoptosis-associated tyrosine kinase	1,51	Down
ABAT	4-aminobutyrate aminotransferase	2,15	Up
MTSS1L	metastasis suppressor 1-like	1,95	Up
MTSS1L	metastasis suppressor 1-like	1,91	Down
ABCC2	ATP-binding cassette, sub-family C (CFTR/MRP), member 2	1,62	Up
ABCC6	ATP-binding cassette, sub-family C (CFTR/MRP), member 6	1,68	Up
ABCD3	ATP-binding cassette, sub-family D (ALD), member 3	1,61	Up
ABCE1	ATP-binding cassette, sub-family E (OABP), member 1	1,85	Up
ABCF2	ATP-binding cassette, sub-family F (GCN20), member 2	1,52	Up
ABCG1	ATP-binding cassette, sub-family G (WHITE), member 1	1,73	Up
ABCG5	ATP-binding cassette, sub-family G (WHITE), member 5	1,52	Up
ABHD1	abhydrolase domain containing 1	1,70	Up
ABHD2	abhydrolase domain containing 2	1,93	Up
ABHD4	abhydrolase domain containing 4	1,75	Up
ABI3BP	ABI family, member 3 (NESH) binding protein	1,65	Up
ABI3BP	ABI family, member 3 (NESH) binding protein	1,69	Up
ABLIM2	actin binding LIM protein family, member 2	1,58	Up
ABR	active BCR-related	1,67	Up
ACAD9	acyl-CoA dehydrogenase family, member 9	1,86	Up
ACAT1	acetyl-CoA acetyltransferase 1	1,55	Up
ACBD4	acyl-CoA binding domain containing 4	3,06	Down
ACN9	ACN9 homolog (S. cerevisiae)	1,54	Up
ACOT11	acyl-CoA thioesterase 11	1,67	Up
ACOT12	acyl-CoA thioesterase 12	1,57	Up
ACOX2	acyl-CoA oxidase 2, branched chain	1,51	Up
ACP6	acid phosphatase 6, lysophosphatidic	1,56	Up
ACR	acrosin	1,63	Up
ACTA1	actin, alpha 1, skeletal muscle	1,95	Up
ACTB	actin, beta	4,39	Up
ACTG1	actin, gamma 1	2,23	Up
ACTG1	actin, gamma 1	3,13	Up
ACTL8	actin-like 8	2,23	Down
ACTR1B	ARP1 actin-related protein 1 homolog B, centractin beta (yeast)	1,76	Down
ADA	adenosine deaminase	1,69	Up
ADAM12	ADAM metallopeptidase domain 12	1,91	Up
ADAM20	ADAM metallopeptidase domain 20	1,64	Up
ADAM22	ADAM metallopeptidase domain 22	1,54	Up
ADAM22	ADAM metallopeptidase domain 22	1,78	Up
ADAM33	ADAM metallopeptidase domain 33	1,55	Up
ADAMTS10	ADAM metallopeptidase with thrombospondin type 1 motif, 10	1,65	Down
ADAMTS2	ADAM metallopeptidase with thrombospondin type 1 motif, 2	1,58	Up
ADAMTS7	ADAM metallopeptidase with thrombospondin type 1 motif, 7	2,45	Down
ADAR	adenosine deaminase, RNA-specific	1,52	Up
ADCYAP1R1	adenylate cyclase activating polypeptide 1 (pituitary) receptor type I	1,53	Up
ADD1	adducin 1 (alpha)	1,74	Up
ADD2	adducin 2 (beta)	1,81	Up
ADD3	adducin 3 (gamma)	1,76	Up
ADH1A	alcohol dehydrogenase 1A (class I), alpha polypeptide	1,54	Up
ADH1C	alcohol dehydrogenase 1C (class I), gamma polypeptide	1,92	Up
ADHFE1	alcohol dehydrogenase, iron containing, 1	1,51	Up
ADIPOQ	adiponectin, C1Q and collagen domain containing	1,57	Up
ADIPOR1	adiponectin receptor 1	1,75	Up
ADNP	activity-dependent neuroprotector homeobox	2,27	Up
ADPRH	ADP-ribosylarginine hydrolase	1,69	Up
ADRBK1	adrenergic, beta, receptor kinase 1	1,76	Up
ADRBK2	adrenergic, beta, receptor kinase 2	1,52	Up
AEBP1	AE binding protein 1	1,61	Up
AES	amino-terminal enhancer of split	1,83	Up
AKR7L	aldo-keto reductase family 7-like	1,65	Up
AFF1	AF4/FMR2 family, member 1	1,51	Up
AFG3L1P	AFG3-like AAA ATPase 1, pseudogene	1,92	Up
AGBL2	ATP/GTP binding protein-like 2	1,68	Up
AGBL4	ATP/GTP binding protein-like 4	1,66	Down
AGBL5	ATP/GTP binding protein-like 5	1,85	Up
AGPAT4	1-acylglycerol-3-phosphate O-acyltransferase 4	1,53	Up
PHYKPL	5-phosphohydroxy-L-lysine phospho-lyase	1,92	Up
AHI1	Abelson helper integration site 1	1,78	Up
AIM1L	absent in melanoma 1-like	1,66	Up
AIRE	autoimmune regulator	1,50	Down
AK5	adenylate kinase 5	1,64	Up
AK7	adenylate kinase 7	1,60	Up
AKAP14	A kinase (PRKA) anchor protein 14	1,57	Up
AKAP5	A kinase (PRKA) anchor protein 5	1,68	Up
AKAP8L	A kinase (PRKA) anchor protein 8-like	1,51	Up
AKT1S1	AKT1 substrate 1 (proline-rich)	1,80	Up
AKTIP	AKT interacting protein	1,67	Up
ALAS2	aminolevulinate, delta-, synthase 2	1,62	Up
ALCAM	activated leukocyte cell adhesion molecule	1,60	Down
ALDH18A1	aldehyde dehydrogenase 18 family, member A1	1,61	Up
ALDH1A3	aldehyde dehydrogenase 1 family, member A3	1,51	Up
ALDH1B1	aldehyde dehydrogenase 1 family, member B1	1,54	Up
ALDH2	aldehyde dehydrogenase 2 family (mitochondrial)	2,00	Up
ALDH8A1	aldehyde dehydrogenase 8 family, member A1	1,62	Up
ALDOA	aldolase A, fructose-bisphosphate	1,68	Down
ALG3	ALG3, alpha-1,3- mannosyltransferase	1,93	Up
ALG3	ALG3, alpha-1,3- mannosyltransferase	1,60	Up
ALKBH8	alkB, alkylation repair homolog 8 (E. coli)	1,54	Up
ALOX12	arachidonate 12-lipoxygenase	1,72	Up
ALOX15B	arachidonate 15-lipoxygenase, type B	2,74	Up
ALOX5AP	arachidonate 5-lipoxygenase-activating protein	3,85	Down
FAM117B	family with sequence similarity 117, member B	2,09	Up
TMEM237	transmembrane protein 237	1,62	Up
ALX4	ALX homeobox 4	1,74	Up
AMDHD1	amidohydrolase domain containing 1	1,80	Up
AMFR	autocrine motility factor receptor, E3 ubiquitin protein ligase	1,81	Up
AMMECR1L	AMMECR1-like	1,60	Up
AMN	amnion associated transmembrane protein	1,70	Up
AMN	amnion associated transmembrane protein	2,28	Down
AMPH	amphiphysin	1,71	Up
ANAPC10	anaphase promoting complex subunit 10	1,67	Up
ANAPC4	anaphase promoting complex subunit 4	1,51	Up
ANAPC5	anaphase promoting complex subunit 5	1,69	Up
ANGPT2	angiopoietin 2	1,53	Down
ANGPTL2	angiopoietin-like 2	1,58	Up
ANK2	ankyrin 2, neuronal	1,62	Up
ANKFY1	ankyrin repeat and FYVE domain containing 1	1,67	Up
ANKMY2	ankyrin repeat and MYND domain containing 2	1,80	Up
ANKRD23	ankyrin repeat domain 23	1,65	Up
ANKRD27	ankyrin repeat domain 27 (VPS9 domain)	1,90	Up
ANKRD53	ankyrin repeat domain 53	1,79	Down
ANKRD7	ankyrin repeat domain 7	1,74	Up
ANKRD9	ankyrin repeat domain 9	1,53	Down
ANPEP	alanyl (membrane) aminopeptidase	1,65	Up
ANXA13	annexin A13	1,85	Up
ANXA3	annexin A3	1,65	Up
ANXA8	annexin A8	1,71	Up
KDM1A	lysine (K)-specific demethylase 1A	1,69	Up
AP1G2	adaptor-related protein complex 1, gamma 2 subunit	1,62	Up
AP1S1	adaptor-related protein complex 1, sigma 1 subunit	1,51	Up
AP2A2	adaptor-related protein complex 2, alpha 2 subunit	1,69	Up
AP3S1	adaptor-related protein complex 3, sigma 1 subunit	1,56	Up
NECAB3	N-terminal EF-hand calcium binding protein 3	1,86	Up
APBB1	amyloid beta (A4) precursor protein-binding, family B, member 1 (Fe65)	2,39	Down
APC	adenomatous polyposis coli	2,10	Up

APC2	adenomatosis polyposis coli 2	2,23	Down
APCS	amyloid P component, serum	1,82	Up
APH1B	APH1B gamma secretase subunit	1,67	Up
API5	apoptosis inhibitor 5	1,63	Up
APLP2	amyloid beta (A4) precursor-like protein 2	1,56	Up
APOBEC3F	apolipoprotein B mRNA editing enzyme, catalytic polypeptide-like 3F	1,63	Up
APOL1	apolipoprotein L, 1	4,06	Down
APOL1	apolipoprotein L, 1	1,60	Down
APPBP2	amyloid beta precursor protein (cytoplasmic tail) binding protein 2	1,69	Up
AQP10	aquaporin 10	1,85	Up
AQP2	aquaporin 2 (collecting duct)	1,76	Down
AQP5	aquaporin 5	1,67	Up
ARC	activity-regulated cytoskeleton-associated protein	1,59	Up
ARCN1	archain 1	1,71	Up
NAA11	N(alpha)-acetyltransferase 11, NatA catalytic subunit	1,64	Up
ARF1	ADP-ribosylation factor 1	2,06	Up
ARF3	ADP-ribosylation factor 3	1,62	Up
ARHGAP17	Rho GTPase activating protein 17	1,53	Up
ARHGAP19	Rho GTPase activating protein 19	1,56	Up
ARHGAP26	Rho GTPase activating protein 26	1,69	Up
ARHGEF10	Rho guanine nucleotide exchange factor (GEF) 10	1,58	Up
ARHGEF16	Rho guanine nucleotide exchange factor (GEF) 16	1,57	Up
ARHGEF18	Rho/Rac guanine nucleotide exchange factor (GEF) 18	1,51	Up
ARHGEF19	Rho guanine nucleotide exchange factor (GEF) 19	1,99	Up
ARHGEF3	Rho guanine nucleotide exchange factor (GEF) 3	1,61	Up
ARID4B	AT rich interactive domain 4B (RBP1-like)	1,76	Up
ARID5B	AT rich interactive domain 5B (MRF1-like)	1,77	Up
ARIH1	ariadne RBR E3 ubiquitin protein ligase 1	1,58	Up
ARIH2	ariadne RBR E3 ubiquitin protein ligase 2	2,40	Down
ARL3	ADP-ribosylation factor-like 3	1,61	Up
ARL6IP1	ADP-ribosylation factor-like 6 interacting protein 1	1,53	Up
ARL6IP4	ADP-ribosylation-like factor 6 interacting protein 4	1,58	Up
ARL6IP6	ADP-ribosylation-like factor 6 interacting protein 6	1,51	Up
ARMC5	armadillo repeat containing 5	1,58	Down
ARMC6	armadillo repeat containing 6	1,53	Down
ARPC5	actin related protein 2/3 complex, subunit 5, 16kDa	2,13	Up
ARRDC1	arrestin domain containing 1	2,06	Up
ARV1	ARV1 homolog (S. cerevisiae)	1,59	Up
ARV1	ARV1 homolog (S. cerevisiae)	1,52	Up
ACER1	alkaline ceramidase 1	1,69	Up
ASB2	ankyrin repeat and SOCS box containing 2	1,50	Up
ASB8	ankyrin repeat and SOCS box containing 8	1,57	Up
ASCC3	activating signal cointegrator 1 complex subunit 3	1,80	Up
ATMIN	ATM interactor	1,66	Up
ASGR1	asialoglycoprotein receptor 1	1,57	Up
ASMTL	acetylserotonin O-methyltransferase-like	1,53	Up
ASNS	asparagine synthetase (glutamine-hydrolyzing)	1,84	Up
ASXL3	additional sex combs like 3 (Drosophila)	1,50	Up
ATCAY	ataxia, cerebellar, Cayman type	3,93	Down
ATF5	activating transcription factor 5	1,67	Up
ATF7IP	activating transcription factor 7 interacting protein	1,55	Up
ATG16L1	autophagy related 16-like 1 (S. cerevisiae)	1,70	Up
ATG9B	autophagy related 9B	1,76	Up
ATOH7	atonal homolog 7 (Drosophila)	1,90	Up
ATP11A	ATPase, class VI, type 11A	1,58	Down
ATP13A1	ATPase type 13A1	1,72	Up
ATP13A2	ATPase type 13A2	1,51	Up
ATP13A3	ATPase type 13A3	1,67	Up
ATP1A4	ATPase, Na+/K+ transporting, alpha 4 polypeptide	1,81	Up
ATP2B4	ATPase, Ca++ transporting, plasma membrane 4	1,63	Up
ATP5H	ATP synthase, H+ transporting, mitochondrial Fo complex, subunit d	2,05	Up
ATP5L	ATP synthase, H+ transporting, mitochondrial Fo complex, subunit G	2,17	Up
ATP6V0A1	ATPase, H+ transporting, lysosomal V0 subunit a1	1,58	Up
ATP6V0A2	ATPase, H+ transporting, lysosomal V0 subunit a2	1,52	Up
ATP6V0C	ATPase, H+ transporting, lysosomal 16kDa, V0 subunit c	1,78	Up
ATP6V1A	ATPase, H+ transporting, lysosomal 70kDa, V1 subunit A	1,65	Up
ATP6V1B2	ATPase, H+ transporting, lysosomal 56/58kDa, V1 subunit B2	1,58	Up
ATP6V1D	ATPase, H+ transporting, lysosomal 34kDa, V1 subunit D	1,55	Up
ATP7B	ATPase, Cu++ transporting, beta polypeptide	1,75	Down
DPH6	diphthamine biosynthesis 6	1,78	Up

ATXN1	ataxin 1	1,77	Up
ATXN7L1	ataxin 7-like 1	1,54	Up
AURKB	aurora kinase B	2,32	Up
AUTS2	autism susceptibility candidate 2	1,77	Up
AVPR1A	arginine vasopressin receptor 1A	1,53	Up
AVPR2	arginine vasopressin receptor 2	1,92	Up
LPCAT2	lysophosphatidylcholine acyltransferase 2	1,54	Up
B2M	beta-2-microglobulin	1,61	Up
B3GALT1	UDP-Gal:betaGlcNAc beta 1,3-galactosyltransferase, polypeptide 1	1,52	Up
B3GALT2	UDP-Gal:betaGlcNAc beta 1,3-galactosyltransferase, polypeptide 2	1,59	Up
B3GALT4	UDP-Gal:betaGlcNAc beta 1,3-galactosyltransferase, polypeptide 4	1,73	Up
B3GAT1	beta-1,3-glucuronyltransferase 1 (glucuronosyltransferase P)	1,68	Up
B3GNT2	UDP-GlcNAc:betaGal beta-1,3-N-acetylglucosaminyltransferase 2	1,50	Up
B3GNT4	UDP-GlcNAc:betaGal beta-1,3-N-acetylglucosaminyltransferase 4	2,13	Up
B3GNTL1	UDP-GlcNAc:betaGal beta-1,3-N-acetylglucosaminyltransferase-like 1	1,64	Up
BACE2	beta-site APP-cleaving enzyme 2	1,73	Up
BACE2	beta-site APP-cleaving enzyme 2	1,87	Up
BACH2	BTB and CNC homology 1, basic leucine zipper transcription factor 2	1,51	Up
BAG1	BCL2-associated athanogene	1,58	Up
BAGE4	B melanoma antigen family, member 4	1,58	Up
BAK1	BCL2-antagonist/killer 1	2,06	Down
BAMBI	BMP and activin membrane-bound inhibitor	1,77	Up
BASP1	brain abundant, membrane attached signal protein 1	1,63	Up
DDX39B	DEAD (Asp-Glu-Ala-Asp) box polypeptide 39B	1,50	Up
PRRC2A	proline-rich coiled-coil 2A	1,55	Down
BBS1	Bardet-Biedl syndrome 1	1,51	Down
BCAM	basal cell adhesion molecule (Lutheran blood group)	1,54	Down
BCAN	brevican	1,64	Up
BCAR3	breast cancer anti-estrogen resistance 3	2,41	Up
BCAS4	breast carcinoma amplified sequence 4	1,78	Up
BCAT1	branched chain amino-acid transaminase 1, cytosolic	1,91	Up
BCKDK	branched chain ketoacid dehydrogenase kinase	1,60	Up
BCL11A	B-cell CLL/lymphoma 11A (zinc finger protein)	1,50	Up
BCL11B	B-cell CLL/lymphoma 11B (zinc finger protein)	1,63	Up
BCL2L14	BCL2-like 14 (apoptosis facilitator)	1,81	Up
BCL7A	B-cell CLL/lymphoma 7A	1,77	Up
BCORL1	BCL6 corepressor-like 1	1,51	Up
BDH2	3-hydroxybutyrate dehydrogenase, type 2	2,04	Down
BDKRB1	bradykinin receptor B1	1,62	Up
BEX2	brain expressed X-linked 2	1,84	Up
BFSP1	beaded filament structural protein 1, filensin	1,97	Up
BFSP2	beaded filament structural protein 2, phakinin	1,57	Up
BHLHE23	basic helix-loop-helix family, member e23	1,98	Down
BICD2	bicaudal D homolog 2 (Drosophila)	1,79	Up
BID	BH3 interacting domain death agonist	1,65	Up
BIVM	basic, immunoglobulin-like variable motif containing	1,67	Up
BLCAP	bladder cancer associated protein	1,59	Up
BLMH	bleomycin hydrolase	1,88	Up
BLOC1S2	biogenesis of lysosomal organelles complex-1, subunit 2	1,51	Up
BLVRA	biliverdin reductase A	1,65	Up
BMP1	bone morphogenetic protein 1	1,78	Up
BMP7	bone morphogenetic protein 7	1,63	Up
BMP8A	bone morphogenetic protein 8a	1,52	Up
BMP8A	bone morphogenetic protein 8a	1,91	Down
BNIP3	BCL2/adenovirus E1B 19kDa interacting protein 3	1,90	Up
BNIP3L	BCL2/adenovirus E1B 19kDa interacting protein 3-like	1,55	Up
BOLA1	bolA family member 1	1,76	Up
BOLA2B	bolA family member 2B	1,77	Up
BPI	bactericidal/permeability-increasing protein	1,91	Up
BPIFC	BPI fold containing family C	1,60	Up
BPTF	bromodomain PHD finger transcription factor	1,53	Up
MPC1	mitochondrial pyruvate carrier 1	1,54	Up
BRS3	bombesin-like receptor 3	1,50	Up
CELF4	CUGBP, Elav-like family member 4	1,83	Up
BRWD1	bromodomain and WD repeat domain containing 1	1,60	Down
BTBD9	BTB (POZ) domain containing 9	2,02	Up
BTF3	basic transcription factor 3	1,94	Up
BTG1	B-cell translocation gene 1, anti-proliferative	2,13	Up
BTG2	BTG family, member 2	2,01	Up
BTNL9	butyrophilin-like 9	1,53	Down

BZW2	basic leucine zipper and W2 domains 2	1,79	Up
C10orf11	chromosome 10 open reading frame 11	1,93	Up
WBP1L	WW domain binding protein 1-like	1,74	Up
BEND7	BEN domain containing 7	1,52	Down
JAKMIP3	Janus kinase and microtubule interacting protein 3	1,62	Up
FRA10AC1	fragile site, folic acid type, rare, fra(10)(q23.3) or fra(10)(q24.2) candidate 1	1,78	Up
C10orf62	chromosome 10 open reading frame 62	1,67	Up
MORN4	MORN repeat containing 4	1,59	Up
FAM204A	family with sequence similarity 204, member A	1,69	Up
C11orf16	chromosome 11 open reading frame 16	3,55	Down
C11orf21	chromosome 11 open reading frame 21	1,55	Down
KIAA1549L	KIAA1549-like	2,43	Down
DNHD1	dynein heavy chain domain 1	1,70	Up
C11orf49	chromosome 11 open reading frame 49	1,73	Up
ANAPC15	anaphase promoting complex subunit 15	1,51	Down
C11orf57	chromosome 11 open reading frame 57	1,63	Up
IFT46	intraflagellar transport 46 homolog (Chlamydomonas)	1,52	Up
MSANTD2	Myb/SANT-like DNA-binding domain containing 2	1,70	Up
LINC00301	long intergenic non-protein coding RNA 301	1,51	Up
C11orf70	chromosome 11 open reading frame 70	1,86	Up
C11orf72	chromosome 11 open reading frame 72	2,20	Up
C11orf72	chromosome 11 open reading frame 72	1,91	Up
SHANK2-AS3	SHANK2 antisense RNA 3	2,42	Down
SDHAF2	succinate dehydrogenase complex assembly factor 2	1,57	Up
HNF1A-AS1	HNF1A antisense RNA 1	1,58	Up
C12orf29	chromosome 12 open reading frame 29	1,82	Up
RHNO1	RAD9-HUS1-RAD1 interacting nuclear orphan 1	1,73	Up
C12orf5	chromosome 12 open reading frame 5	1,96	Up
LACC1	laccase (multicopper oxidoreductase) domain containing 1	1,66	Up
MEDAG	mesenteric estrogen-dependent adipogenesis	1,53	Up
C14orf1	chromosome 14 open reading frame 1	1,68	Up
JKAMP	JNK1/MAPK8-associated membrane protein	1,70	Up
C14orf113~withdrawn	entry withdrawn	1,97	Up
DTD2	D-tyrosyl-tRNA deacylase 2 (putative)	1,52	Up
GSKIP	GSK3B interacting protein	1,62	Up
ZNF839	zinc finger protein 839	1,64	Up
ZC2HC1C	zinc finger, C2HC-type containing 1C	1,69	Up
C14orf144	chromosome 14 open reading frame 144	1,54	Up
CEP128	centrosomal protein 128kDa	1,74	Up
INF2	inverted formin, FH2 and WH2 domain containing	1,68	Up
NOP9	NOP9 nucleolar protein	1,57	Up
ELMSAN1	ELM2 and Myb/SANT-like domain containing 1	2,71	Down
CCDC176	coiled-coil domain containing 176	1,58	Up
HMGN2P46	high mobility group nucleosomal binding domain 2 pseudogene 46	1,72	Up
ANP32A-IT1	ANP32A intronic transcript 1 (non-protein coding)	1,85	Up
KATNBL1	katanin p80 subunit B-like 1	2,02	Up
C15orf41	chromosome 15 open reading frame 41	1,61	Up
LINC00593	long intergenic non-protein coding RNA 593	2,14	Up
FAM195A	family with sequence similarity 195, member A	1,89	Up
C16orf3	chromosome 16 open reading frame 3	2,04	Down
C16orf45	chromosome 16 open reading frame 45	1,54	Up
CMC2	C-x(9)-C motif containing 2	1,59	Up
C16orf70	chromosome 16 open reading frame 70	1,60	Up
C16orf71	chromosome 16 open reading frame 71	1,74	Up
C16orf74	chromosome 16 open reading frame 74	1,51	Up
LINC00304	long intergenic non-protein coding RNA 304	2,51	Down
TEFM	transcription elongation factor, mitochondrial	1,95	Up
SPATA32	spermatogenesis associated 32	1,84	Up
C17orf59	chromosome 17 open reading frame 59	1,72	Up
TMEM256	transmembrane protein 256	1,54	Up
CTC1	CTS telomere maintenance complex component 1	1,52	Up
C17orf75	chromosome 17 open reading frame 75	1,62	Up
C17orf77	chromosome 17 open reading frame 77	1,57	Up
COPRS	coordinator of PRMT5, differentiation stimulator	1,80	Up
TPGS2	tubulin polyglutamylase complex subunit 2	1,77	Up
C18orf15	chromosome 18 open reading frame 15	1,57	Up
RBFA	ribosome binding factor A (putative)	1,99	Up
C18orf54	chromosome 18 open reading frame 54	1,73	Up
MFSD12	major facilitator superfamily domain containing 12	1,57	Up
C19orf31~withdrawn	entry withdrawn	1,75	Up
C19orf33	chromosome 19 open reading frame 33	2,11	Up
C19orf44	chromosome 19 open reading frame 44	4,15	Down
C19orf47	chromosome 19 open reading frame 47	1,57	Up
KXD1	KxDL motif containing 1	1,63	Up
WDR83OS	WD repeat domain 83 opposite strand	1,65	Up
DDA1	DET1 and DDB1 associated 1	1,78	Up
C19orf59	chromosome 19 open reading frame 59	1,95	Up
SMG9	SMG9 nonsense mediated mRNA decay factor	1,52	Up
ZC3H4	zinc finger CCCH-type containing 4	2,05	Up
C1orf100	chromosome 1 open reading frame 100	1,95	Up
C1orf101	chromosome 1 open reading frame 101	1,59	Up
C1orf106	chromosome 1 open reading frame 106	1,59	Up
DIEXF	digestive organ expansion factor homolog (zebrafish)	2,17	Up
SH3D21	SH3 domain containing 21	1,52	Up
CCDC181	coiled-coil domain containing 181	1,90	Up
CCDC181	coiled-coil domain containing 181	1,51	Up
C1orf116	chromosome 1 open reading frame 116	1,51	Up
TMEM167B	transmembrane protein 167B	1,82	Up
DESI2	desumoylating isopeptidase 2	1,55	Up
AUNIP	aurora kinase A and ninein interacting protein	1,56	Up
SNAP47	synaptosomal-associated protein, 47kDa	1,93	Up
MAB21L3	mab-21-like 3 (C. elegans)	2,26	Up
RNF220	ring finger protein 220	1,51	Up
RNF220	ring finger protein 220	1,53	Up
TSACC	TSSK6 activating co-chaperone	3,17	Up
C1orf198	chromosome 1 open reading frame 198	2,74	Up
FAM189B	family with sequence similarity 189, member B	1,51	Up
C1orf204	chromosome 1 open reading frame 204	1,51	Down
C1orf210	chromosome 1 open reading frame 210	1,57	Down
STMN1	stathmin 1	1,64	Up
TRMT1L	tRNA methyltransferase 1 homolog (S. cerevisiae)-like	2,02	Up
C1orf43	chromosome 1 open reading frame 43	1,81	Up
C1orf53	chromosome 1 open reading frame 53	1,61	Up
C1orf63	chromosome 1 open reading frame 63	1,61	Up
SZT2	seizure threshold 2 homolog (mouse)	1,59	Up
RSG1	REM 2 and RAB-like small GTPase 1	1,88	Up
C1orf95	chromosome 1 open reading frame 95	2,91	Down
C1QTNF2	C1q and tumor necrosis factor related protein 2	1,62	Up
C1QTNF2	C1q and tumor necrosis factor related protein 2	1,79	Up
C1R	complement component 1, r subcomponent	1,99	Up
C2	complement component 2	1,58	Up
C2	complement component 2	1,78	Up
C2	complement component 2	1,75	Up
VSTM2L	V-set and transmembrane domain containing 2 like	1,64	Up
SOGA1	suppressor of glucose, autophagy associated 1	1,64	Up
SOGA1	suppressor of glucose, autophagy associated 1	1,61	Down
PABPC1L	poly(A) binding protein, cytoplasmic 1-like	1,61	Up
PPDPF	pancreatic progenitor cell differentiation and proliferation factor	2,56	Up
C20orf195	chromosome 20 open reading frame 195	3,18	Down
ZFAS1	ZNFX1 antisense RNA 1	1,91	Up
C20orf26	chromosome 20 open reading frame 26	1,58	Up
AAR2	AAR2 splicing factor homolog (S. cerevisiae)	1,53	Up
FERMT1	fermitin family member 1	1,54	Up
RTFDC1	replication termination factor 2 domain containing 1	1,57	Up
BPIFA3	BPI fold containing family A, member 3	1,89	Up
ISM1	isthmin 1, angiogenesis inhibitor	1,55	Up
C20orf85	chromosome 20 open reading frame 85	1,81	Up
ZNF295-AS1	ZNF295 antisense RNA 1	1,52	Up
CYP4F29P	cytochrome P450, family 4, subfamily F, polypeptide 29, pseudogene	2,05	Up
C21orf33	chromosome 21 open reading frame 33	1,72	Up
MIS18A	MIS18 kinetochore protein A	1,86	Up
YBEY	ybeY metallopeptidase (putative)	1,55	Up
C21orf58	chromosome 21 open reading frame 58	1,55	Down
LINC00334	long intergenic non-protein coding RNA 334	1,84	Up
GUCD1	guanylyl cyclase domain containing 1	1,53	Up
C22orf29	chromosome 22 open reading frame 29	1,56	Down
SMDT1	single-pass membrane protein with aspartate-rich tail 1	1,97	Up
TMEM184B	transmembrane protein 184B	1,76	Up
KIAA0930	KIAA0930	2,81	Up
CNPPD1	cyclin Pas1/PHO80 domain containing 1	1,91	Up

MMADHC	methylmalonic aciduria (cobalamin deficiency) cblD type, with homocystinuria	1,71	Up
DRC1	dynein regulatory complex subunit 1 homolog (Chlamydomonas)	1,64	Down
MAATS1	MYCBP-associated, testis expressed 1	1,80	Up
C3orf27	chromosome 3 open reading frame 27	1,74	Up
SSUH2	ssu-2 homolog (C. elegans)	1,78	Up
HMCES	5-hydroxymethylcytosine (hmC) binding, ES cell-specific	1,65	Up
C3orf38	chromosome 3 open reading frame 38	1,78	Up
FAM194A	family with sequence similarity 194, member A	1,96	Up
PP2D1	protein phosphatase 2C-like domain containing 1	1,59	Up
C3orf58	chromosome 3 open reading frame 58	2,19	Down
MB21D2	Mab-21 domain containing 2	1,62	Up
NDUFAF3	NADH dehydrogenase (ubiquinone) complex I, assembly factor 3	1,55	Up
C3orf62	chromosome 3 open reading frame 62	1,57	Up
WDFY3-AS2	WDFY3 antisense RNA 2	1,59	Up
NOA1	nitric oxide associated 1	1,66	Up
C4orf17	chromosome 4 open reading frame 17	1,77	Up
TRMT44	tRNA methyltransferase 44 homolog (S. cerevisiae)	1,50	Up
PACRGL	PARK2 co-regulated-like	1,51	Down
C5AR1	complement component 5a receptor 1	1,61	Up
C5orf20	chromosome 5 open reading frame 20	3,28	Down
FAM172A	family with sequence similarity 172, member A	1,52	Down
GAPT	GRB2-binding adaptor protein, transmembrane	1,51	Up
SETD9	SET domain containing 9	1,50	Up
FAM13B	family with sequence similarity 13, member B	1,75	Up
C6orf106	chromosome 6 open reading frame 106	1,64	Up
UHRF1BP1	UHRF1 binding protein 1	1,89	Up
CCDC167	coiled-coil domain containing 167	1,50	Up
OARD1	O-acyl-ADP-ribose deacylase 1	1,67	Up
ATAT1	alpha tubulin acetyltransferase 1	1,62	Up
AKIRIN2	akirin 2	1,83	Up
FAXC	failed axon connections homolog (Drosophila)	1,57	Up
SLC18B1	solute carrier family 18, subfamily B, member 1	1,74	Up
C6orf203	chromosome 6 open reading frame 203	1,52	Up
RSPH9	radial spoke head 9 homolog (Chlamydomonas)	1,61	Up
VWA7	von Willebrand factor A domain containing 7	1,98	Down
C6orf47	chromosome 6 open reading frame 47	2,31	Up
C6orf62	chromosome 6 open reading frame 62	1,87	Up
BEND6	BEN domain containing 6	1,60	Up
GINM1	glycoprotein integral membrane 1	1,82	Up
BRAT1	BRCA1-associated ATM activator 1	1,51	Up
BRAT1	BRCA1-associated ATM activator 1	1,67	Up
C7orf34	chromosome 7 open reading frame 34	1,66	Up
COA1	cytochrome c oxidase assembly factor 1 homolog (S. cerevisiae)	1,56	Up
FAM167A	family with sequence similarity 167, member A	1,75	Down
C8orf15--withdrawn	entry withdrawn	1,64	Up
C8orf31	chromosome 8 open reading frame 31	1,82	Up
C8orf34	chromosome 8 open reading frame 34	1,63	Up
UTP23	UTP23, small subunit (SSU) processome component, homolog (yeast)	1,65	Up
UTP23	UTP23, small subunit (SSU) processome component, homolog (yeast)	1,54	Down
FER1L6-AS1	FER1L6 antisense RNA 1	1,77	Up
C8orf60	chromosome 8 open reading frame 60	1,79	Up
ARHGEF39	Rho guanine nucleotide exchange factor (GEF) 39	1,87	Up
ERCC6L2	excision repair cross-complementing rodent repair deficiency, complementation group 6-like 2	1,89	Up
EQTN	equatorin, sperm acrosome associated	1,51	Up
C9orf114	chromosome 9 open reading frame 114	1,62	Up
LINC00476	long intergenic non-protein coding RNA 476	1,70	Up
C9orf135	chromosome 9 open reading frame 135	1,88	Up
C9orf139	chromosome 9 open reading frame 139	1,63	Down
MORN5	MORN repeat containing 5	1,73	Up
LINC00474	long intergenic non-protein coding RNA 474	1,54	Up
GSN-AS1	GSN antisense RNA 1	1,55	Up
C9orf37	chromosome 9 open reading frame 37	1,60	Up
C9orf37	chromosome 9 open reading frame 37	1,84	Up
C9orf53	chromosome 9 open reading frame 53	2,03	Up
C9orf57	chromosome 9 open reading frame 57	1,66	Up
AIF1L	allograft inflammatory factor 1-like	1,86	Up
C9orf62	chromosome 9 open reading frame 62	1,99	Down
C9orf66	chromosome 9 open reading frame 66	1,82	Up
TMEM252	transmembrane protein 252	1,66	Up
RABL6	RAB, member RAS oncogene family-like 6	1,52	Up

CA11	carbonic anhydrase XI	1,58	Up
CABIN1	calcineurin binding protein 1	2,85	Up
CABLES2	Cdk5 and Abl enzyme substrate 2	1,73	Up
CACNA1B	calcium channel, voltage-dependent, N type, alpha 1B subunit	1,80	Down
CACNA1I	calcium channel, voltage-dependent, T type, alpha 1I subunit	2,48	Down
CACNA2D1	calcium channel, voltage-dependent, alpha 2/delta subunit 1	1,65	Up
CACNB1	calcium channel, voltage-dependent, beta 1 subunit	1,61	Up
CACNG7	calcium channel, voltage-dependent, gamma subunit 7	1,74	Up
CALCR	calcitonin receptor	2,00	Down
CALU	calumenin	1,66	Up
CAMK1D	calcium/calmodulin-dependent protein kinase ID	1,99	Up
CAMK2D	calcium/calmodulin-dependent protein kinase II delta	1,56	Up
CAMK2G	calcium/calmodulin-dependent protein kinase II gamma	1,62	Up
CAMTA1	calmodulin binding transcription activator 1	1,96	Up
CAMTA1	calmodulin binding transcription activator 1	1,87	Up
CANT1	calcium activated nucleotidase 1	1,59	Down
CAPN3	calpain 3, (p94)	1,57	Up
CAPN6	calpain 6	1,51	Up
CAPN9	calpain 9	1,77	Up
CAPRIN1	cell cycle associated protein 1	1,67	Up
CAPRIN1	cell cycle associated protein 1	1,90	Down
SHPK	sedoheptulokinase	2,22	Up
CASD1	CAS1 domain containing 1	1,71	Up
CASKIN2	CASK interacting protein 2	1,52	Down
CASKIN2	CASK interacting protein 2	1,98	Down
CASP10	caspase 10, apoptosis-related cysteine peptidase	1,51	Up
CASP4	caspase 4, apoptosis-related cysteine peptidase	1,56	Up
CASP4	caspase 4, apoptosis-related cysteine peptidase	4,11	Down
CASP5	caspase 5, apoptosis-related cysteine peptidase	1,85	Up
CASP8	caspase 8, apoptosis-related cysteine peptidase	3,85	Down
CAV1	caveolin 1, caveolae protein, 22kDa	1,70	Up
CAV3	caveolin 3	1,68	Up
CBS	cystathionine-beta-synthase	2,13	Up
CBX4	chromobox homolog 4	1,63	Up
CCBE1	collagen and calcium binding EGF domains 1	1,60	Up
CCDC102B	coiled-coil domain containing 102B	2,05	Up
CCDC108	coiled-coil domain containing 108	2,06	Down
PRIMPOL	primase and polymerase (DNA-directed)	1,77	Up
CCDC114	coiled-coil domain containing 114	1,88	Up
CCDC12	coiled-coil domain containing 12	1,71	Up
CCDC13	coiled-coil domain containing 13	1,51	Up
CCDC134	coiled-coil domain containing 134	1,79	Up
CCDC137	coiled-coil domain containing 137	1,55	Down
CCDC26	coiled-coil domain containing 26	1,76	Up
CCDC50	coiled-coil domain containing 50	1,54	Down
SPICE1	spindle and centriole associated protein 1	1,63	Up
COA3	cytochrome c oxidase assembly factor 3	1,84	Up
TMA7	translation machinery associated 7 homolog (S. cerevisiae)	1,83	Up
CCDC79	coiled-coil domain containing 79	1,51	Up
CCDC86	coiled-coil domain containing 86	1,82	Up
CCDC90B	coiled-coil domain containing 90B	1,68	Up
CCDC96	coiled-coil domain containing 96	1,54	Up
CCIN	calicin	1,71	Up
CCKAR	cholecystokinin A receptor	1,57	Up
CCL2	chemokine (C-C motif) ligand 2	1,55	Up
CCL21	chemokine (C-C motif) ligand 21	1,55	Up
CCL3L3	chemokine (C-C motif) ligand 3-like 3	1,58	Up
CCL4	chemokine (C-C motif) ligand 4	1,64	Up
CCNB1IP1	cyclin B1 interacting protein 1, E3 ubiquitin protein ligase	1,70	Up
CCND2	cyclin D2	1,99	Up
CCND3	cyclin D3	1,99	Up
CCPG1	cell cycle progression 1	1,73	Up
ACKR4	atypical chemokine receptor 4	1,64	Up
CCT2	chaperonin containing TCP1, subunit 2 (beta)	1,59	Up
CCT4	chaperonin containing TCP1, subunit 4 (delta)	1,82	Up
CD109	CD109 molecule	1,65	Up
CD151	CD151 molecule (Raph blood group)	1,68	Up
CD163	CD163 molecule	1,84	Up
CD177	CD177 molecule	1,81	Up
CD177	CD177 molecule	1,88	Up

CD19	CD19 molecule	1,70	Up
CD1E	CD1e molecule	1,65	Up
CD2	CD2 molecule	1,78	Up
CD207	CD207 molecule, langerin	1,77	Up
CD244	CD244 molecule, natural killer cell receptor 2B4	1,85	Up
CD276	CD276 molecule	1,60	Down
CD2AP	CD2-associated protein	1,62	Up
CD302	CD302 molecule	1,53	Down
CD38	CD38 molecule	1,64	Up
CD46	CD46 molecule, complement regulatory protein	1,51	Up
CD59	CD59 molecule, complement regulatory protein	1,63	Up
CD6	CD6 molecule	1,61	Up
CD63	CD63 molecule	2,56	Up
CD83	CD83 molecule	1,60	Up
CDA	cytidine deaminase	1,52	Up
CDK11B	cyclin-dependent kinase 11B	1,95	Up
CDK13	cyclin-dependent kinase 13	1,70	Up
CDC37	cell division cycle 37	1,53	Down
CDC42	cell division cycle 42	1,87	Up
CDC42BPA	CDC42 binding protein kinase alpha (DMPK-like)	1,66	Up
CDC42EP1	CDC42 effector protein (Rho GTPase binding) 1	3,50	Down
CDC42EP1	CDC42 effector protein (Rho GTPase binding) 1	1,60	Down
CDC42EP4	CDC42 effector protein (Rho GTPase binding) 4	1,70	Up
CDCA3	cell division cycle associated 3	1,53	Up
CDCA7L	cell division cycle associated 7-like	1,73	Up
CDCA8	cell division cycle associated 8	1,57	Up
CDH12	cadherin 12, type 2 (N-cadherin 2)	1,61	Up
CDH22	cadherin 22, type 2	2,51	Down
CDH24	cadherin 24, type 2	1,75	Down
CDH3	cadherin 3, type 1, P-cadherin (placental)	2,22	Up
CDH4	cadherin 4, type 1, R-cadherin (retinal)	1,51	Up
CDIPT	CDP-diacylglycerol--inositol 3-phosphatidyltransferase	1,64	Up
CDK2AP1	cyclin-dependent kinase 2 associated protein 1	1,70	Up
CDK5R2	cyclin-dependent kinase 5, regulatory subunit 2 (p39)	1,80	Up
CDKAL1	CDK5 regulatory subunit associated protein 1-like 1	1,64	Up
CDR1	cerebellar degeneration-related protein 1, 34kDa	1,60	Up
CDSN	corneodesmosin	1,73	Up
CEACAM1	carcinoembryonic antigen-related cell adhesion molecule 1 (biliary glycoprotein)	1,68	Up
CEACAM4	carcinoembryonic antigen-related cell adhesion molecule 4	1,79	Down
CEACAM5	carcinoembryonic antigen-related cell adhesion molecule 5	1,70	Up
CEBPA	CCAAT/enhancer binding protein (C/EBP), alpha	2,50	Down
CEND1	cell cycle exit and neuronal differentiation 1	1,84	Up
CEND1	cell cycle exit and neuronal differentiation 1	1,58	Down
ADAP1	ArfGAP with dual PH domains 1	2,13	Up
AGAP3	ArfGAP with GTPase domain, ankyrin repeat and PH domain 3	2,47	Down
CEP135	centrosomal protein 135kDa	1,74	Up
CEP250	centrosomal protein 250kDa	1,91	Up
CEP55	centrosomal protein 55kDa	1,62	Up
CEP57	centrosomal protein 57kDa	1,70	Up
CEP63	centrosomal protein 63kDa	1,51	Up
CEP76	centrosomal protein 76kDa	1,65	Up
CERK	ceramide kinase	1,67	Up
CETP	cholesteryl ester transfer protein, plasma	1,68	Up
CFL2	cofilin 2 (muscle)	1,81	Up
CGA	glycoprotein hormones, alpha polypeptide	1,89	Up
CGB1	chorionic gonadotropin, beta polypeptide 1	1,69	Down
TRMT6	tRNA methyltransferase 6 homolog (S. cerevisiae)	1,67	Up
CGN	cingulin	1,99	Up
CHAC2	ChaC, cation transport regulator homolog 2 (E. coli)	1,61	Up
CHAD	chondroadherin	1,63	Up
CHAF1B	chromatin assembly factor 1, subunit B (p60)	1,59	Up
CHCHD5	coiled-coil-helix-coiled-coil-helix domain containing 5	1,51	Up
CHCHD5	coiled-coil-helix-coiled-coil-helix domain containing 5	2,06	Up
CHCHD7	coiled-coil-helix-coiled-coil-helix domain containing 7	1,69	Up
CHD2	chromodomain helicase DNA binding protein 2	1,53	Up
CHD6	chromodomain helicase DNA binding protein 6	1,79	Up
CHDH	choline dehydrogenase	1,87	Up
CHDH	choline dehydrogenase	1,70	Up
CHIA	chitinase, acidic	1,64	Up
CHM	choroideremia (Rab escort protein 1)	1,67	Up
CHML	choroideremia-like (Rab escort protein 2)	1,70	Up
CHMP4A	charged multivesicular body protein 4A	1,53	Up
CHMP7	charged multivesicular body protein 7	1,56	Up
CHP1	calcineurin-like EF-hand protein 1	2,64	Up
CHRAC1	chromatin accessibility complex 1	1,75	Up
CHRDL1	chordin-like 1	6,09	Down
CHRM2	cholinergic receptor, muscarinic 2	1,90	Up
CHRM3	cholinergic receptor, muscarinic 3	1,60	Up
CHRNA1	cholinergic receptor, nicotinic, alpha 1 (muscle)	1,60	Up
CHRNA4	cholinergic receptor, nicotinic, alpha 4 (neuronal)	2,25	Down
CHST11	carbohydrate (chondroitin 4) sulfotransferase 11	1,51	Up
CHST13	carbohydrate (chondroitin 4) sulfotransferase 13	2,54	Down
CHST3	carbohydrate (chondroitin 6) sulfotransferase 3	1,64	Up
CHST4	carbohydrate (N-acetylglucosamine 6-O) sulfotransferase 4	1,74	Up
CHTF18	CTF18, chromosome transmission fidelity factor 18 homolog (S. cerevisiae)	1,77	Up
CHURC1	churchill domain containing 1	2,29	Up
CIAO1	cytosolic iron-sulfur protein assembly 1	1,66	Up
CIB4	calcium and integrin binding family member 4	1,60	Up
CIDECP	cell death-inducing DFFA-like effector c pseudogene	1,79	Up
CIDEB	cell death-inducing DFFA-like effector b	1,91	Up
CIITA	class II, major histocompatibility complex, transactivator	2,09	Up
CIRBP	cold inducible RNA binding protein	1,84	Up
CIRH1A	cirrhosis, autosomal recessive 1A (cirhin)	1,57	Up
CIZ1	CDKN1A interacting zinc finger protein 1	1,56	Up
CKAP2	cytoskeleton associated protein 2	1,60	Up
CKAP5	cytoskeleton associated protein 5	1,62	Up
CKB	creatine kinase, brain	1,53	Down
CKLF	chemokine-like factor	1,67	Up
CLCA4	chloride channel accessory 4	1,68	Up
CLCC1	chloride channel CLIC-like 1	1,57	Up
CLCF1	cardiotrophin-like cytokine factor 1	1,52	Down
CLDN11	claudin 11	3,09	Up
CLDN12	claudin 12	1,69	Up
CLDN12	claudin 12	1,74	Up
CLEC14A	C-type lectin domain family 14, member A	1,71	Up
CLEC2B	C-type lectin domain family 2, member B	2,08	Up
CLEC4G	C-type lectin domain family 4, member G	1,52	Up
CLINT1	clathrin interactor 1	1,91	Up
CLN3	ceroid-lipofuscinosis, neuronal 3	1,73	Up
CLNS1A	chloride channel, nucleotide-sensitive, 1A	1,53	Up
CLPTM1	cleft lip and palate associated transmembrane protein 1	1,56	Up
CLPTM1L	CLPTM1-like	2,68	Down
CLTC	clathrin, heavy chain (Hc)	1,52	Up
CMIP	c-Maf inducing protein	3,90	Down
CMTM7	CKLF-like MARVEL transmembrane domain containing 7	1,57	Up
XIRP1	xin actin-binding repeat containing 1	1,78	Up
XIRP2	xin actin-binding repeat containing 2	1,55	Up
CNDP2	CNDP dipeptidase 2 (metallopeptidase M20 family)	1,53	Up
CNFN	cornifelin	1,96	Up
CNNM2	cyclin M2	1,71	Up
CNNM4	cyclin M4	1,68	Up
CNOT2	CCR4-NOT transcription complex, subunit 2	1,76	Up
CNOT4	CCR4-NOT transcription complex, subunit 4	1,87	Up
CNOT6	CCR4-NOT transcription complex, subunit 6	1,93	Up
CNR2	cannabinoid receptor 2 (macrophage)	1,56	Up
CNR2	cannabinoid receptor 2 (macrophage)	1,71	Up
CNTN4	contactin 4	1,60	Up
CNTNAP5	contactin associated protein-like 5	1,52	Up
CNTROB	centrobin, centrosomal BRCA2 interacting protein	1,59	Up
COG5	component of oligomeric golgi complex 5	1,70	Up
COG6	component of oligomeric golgi complex 6	1,55	Up
COIL	coilin	1,97	Up
COL18A1	collagen, type XVIII, alpha 1	1,64	Down
COL21A1	collagen, type XXI, alpha 1	1,64	Up
COL3A1	collagen, type III, alpha 1	1,63	Up
COL4A2	collagen, type IV, alpha 2	1,76	Up
COL5A1	collagen, type V, alpha 1	1,70	Up
COL5A2	collagen, type V, alpha 2	1,82	Up
COL6A1	collagen, type VI, alpha 1	1,82	Up
COLEC10	collectin sub-family member 10 (C-type lectin)	1,51	Up

COMMD1	copper metabolism (Murr1) domain containing 1	1,62	Up
COMMD4	COMM domain containing 4	2,68	Up
COMMD6	COMM domain containing 6	2,41	Up
COPA	coatomer protein complex, subunit alpha	1,59	Up
COPE	coatomer protein complex, subunit epsilon	1,59	Up
COPS8	COP9 signalosome subunit 8	1,61	Up
COQ7	coenzyme Q7 homolog, ubiquinone (yeast)	1,78	Up
COQ9	coenzyme Q9	1,59	Up
CORIN	corin, serine peptidase	1,55	Up
CORO2A	coronin, actin binding protein, 2A	1,54	Up
CORO2A	coronin, actin binding protein, 2A	1,53	Up
CORO2B	coronin, actin binding protein, 2B	1,58	Up
CORT	cortistatin	2,31	Up
COTL1	coactosin-like 1(Dictyostelium)	1,51	Up
COX4I1	cytochrome c oxidase subunit IV isoform 1	1,61	Up
COX7A2L	cytochrome c oxidase subunit VIIa polypeptide 2 like	1,65	Up
CPAMD8	C3 and PZP-like, alpha-2-macroglobulin domain containing 8	1,89	Up
CPLX3	complexin 3	1,99	Down
CPN2	carboxypeptidase N, polypeptide 2	1,69	Up
CPNE7	copine VII	1,53	Up
CPNE8	copine VIII	1,55	Down
CPSF1	cleavage and polyadenylation specific factor 1, 160kDa	1,57	Up
CPXM2	carboxypeptidase X (M14 family), member 2	1,94	Up
CR1	complement component (3b/4b) receptor 1(Knops blood group)	1,85	Up
CR2	complement component (3d/Epstein Barr virus) receptor 2	1,72	Up
CRABP1	cellular retinoic acid binding protein 1	2,56	Down
CRCT1	cysteine-rich C-terminal 1	3,76	Up
CRCT1	cysteine-rich C-terminal 1	1,67	Down
CREB3L3	cAMP responsive element binding protein 3-like 3	1,55	Down
CREB3L4	cAMP responsive element binding protein 3-like 4	1,75	Up
ATF6B	activating transcription factor 6 beta	2,14	Up
CREG1	cellular repressor of E1A-stimulated genes 1	1,68	Up
CRELD2	cysteine-rich with EGF-like domains 2	1,75	Down
CRHR1	corticotropin releasing hormone receptor 1	2,47	Down
CRIP1	cysteine-rich protein 1(intestinal)	6,95	Down
CRIP3	cysteine-rich protein 3	1,88	Up
CRISPLD2	cysteine-rich secretory protein LCCL domain containing 2	1,67	Up
CRTC1	CREB regulated transcription coactivator 1	1,52	Up
CRTC2	CREB regulated transcription coactivator 2	1,60	Up
CRYBB2	crystallin, beta B2	1,79	Up
CRYGD	crystallin, gamma D	1,69	Up
CRYL1	crystallin, lambda 1	1,58	Up
CSAD	cysteine sulfinic acid decarboxylase	1,80	Down
CSAG2	CSAG family, member 2	1,77	Up
CSF1R	colony stimulating factor 1receptor	1,67	Up
CSF3R	colony stimulating factor 3 receptor (granulocyte)	1,66	Up
CSK	c-src tyrosine kinase	2,10	Up
CSMD3	CUB and Sushi multiple domains 3	1,63	Up
CSN2	casein beta	1,77	Up
CSNK1G2	casein kinase 1, gamma 2	1,98	Up
CSTA	cystatin A (stefin A)	2,22	Up
CSTB	cystatin B (stefin B)	1,87	Up
CSTF1	cleavage stimulation factor, 3' pre-RNA, subunit 1, 50kDa	1,58	Up
CSTL1	cystatin-like 1	1,51	Up
CTAGE1	cutaneous T-cell lymphoma-associated antigen 1	1,59	Up
CTCF	CCCTC-binding factor (zinc finger protein)	1,58	Up
CTDSP2	CTD (carboxy-terminal domain, RNA polymerase II, polypeptide A) small phosphatase 2	1,55	Up
CTDSPL2	CTD (carboxy-terminal domain, RNA polymerase II, polypeptide A) small phosphatase like 2	1,54	Up
CTF1	cardiotrophin 1	1,70	Up
CTNNA3	catenin (cadherin-associated protein), alpha 3	1,71	Up
CTNND2	catenin (cadherin-associated protein), delta 2	1,83	Up
CTPS2	CTP synthase 2	1,54	Up
CTRB2	chymotrypsinogen B2	2,89	Down
CTRL	chymotrypsin-like	1,51	Up
CTSB	cathepsin B	1,57	Up
CTSF	cathepsin F	1,59	Up
CTSH	cathepsin H	1,53	Up
CTSK	cathepsin K	2,05	Up
CUL3	cullin 3	1,65	Up
CUX1	cut-like homeobox 1	1,57	Up
CWF19L2	CWF19-like 2, cell cycle control (S. pombe)	1,78	Up
CXCL12	chemokine (C-X-C motif) ligand 12	1,53	Up
TRMT2B	tRNA methyltransferase 2 homolog B (S. cerevisiae)	1,65	Up
CXorf36	chromosome X open reading frame 36	2,23	Up
CXorf36	chromosome X open reading frame 36	1,55	Up
TET1	tet methylcytosine dioxygenase 1	1,62	Up
CYB5R2	cytochrome b5 reductase 2	1,60	Up
CYB5R3	cytochrome b5 reductase 3	1,75	Up
CYB5R3	cytochrome b5 reductase 3	1,83	Down
CYFIP1	cytoplasmic FMR1interacting protein 1	1,68	Up
CYFIP2	cytoplasmic FMR1interacting protein 2	2,33	Up
CYHR1	cysteine/histidine-rich 1	1,50	Up
FAM197Y2	family with sequence similarity 197, Y-linked, member 2	1,71	Up
CYP11B1	cytochrome P450, family 11, subfamily B, polypeptide 1	1,64	Up
CYP24A1	cytochrome P450, family 24, subfamily A, polypeptide 1	1,74	Up
CYP2A13	cytochrome P450, family 2, subfamily A, polypeptide 13	1,56	Up
CYP2B6	cytochrome P450, family 2, subfamily B, polypeptide 6	1,66	Up
CYP2C9	cytochrome P450, family 2, subfamily C, polypeptide 9	1,52	Up
CYP2F1	cytochrome P450, family 2, subfamily F, polypeptide 1	2,10	Up
CYP2S1	cytochrome P450, family 2, subfamily S, polypeptide 1	1,75	Up
CYP3A7	cytochrome P450, family 3, subfamily A, polypeptide 7	1,51	Up
CYP4F2	cytochrome P450, family 4, subfamily F, polypeptide 2	1,59	Up
CYP4F2	cytochrome P450, family 4, subfamily F, polypeptide 2	1,52	Down
DAB2	Dab, mitogen-responsive phosphoprotein, homolog 2 (Drosophila)	1,55	Up
DAB2IP	DAB2 interacting protein	1,70	Up
DACT3	dishevelled-binding antagonist of beta-catenin 3	2,14	Up
DAD1	defender against cell death 1	1,79	Up
DAP3	death associated protein 3	1,68	Up
DBI	diazepam binding inhibitor (GABA receptor modulator, acyl-CoA binding protein)	2,92	Up
DBN1	drebrin 1	1,50	Up
DBNDD2	dysbindin (dystrobrevin binding protein 1) domain containing 2	2,30	Up
DBP	D site of albumin promoter (albumin D-box) binding protein	1,69	Up
DBR1	debranching RNA lariats 1	1,52	Up
DBT	dihydrolipoamide branched chain transacylase E2	1,53	Up
DCAKD	dephospho-CoA kinase domain containing	1,57	Up
DCBLD1	discoidin, CUB and LCCL domain containing 1	1,53	Down
DCBLD2	discoidin, CUB and LCCL domain containing 2	1,61	Up
DCHS2	dachsous cadherin-related 2	1,81	Up
DCST1	DC-STAMP domain containing 1	1,50	Up
DCTN3	dynactin 3 (p22)	1,61	Up
DCX	doublecortin	1,70	Up
DDAH2	dimethylarginine dimethylaminohydrolase 2	1,57	Down
DDB2	damage-specific DNA binding protein 2, 48kDa	1,58	Up
DDN	dendrin	1,71	Up
DDOST	dolichyl-diphosphooligosaccharide--protein glycosyltransferase subunit (non-catalytic)	1,51	Up
DDT	D-dopachrome tautomerase	1,58	Down
DDX19A	DEAD (Asp-Glu-Ala-Asp) box polypeptide 19A	1,80	Down
DDX47	DEAD (Asp-Glu-Ala-Asp) box polypeptide 47	1,71	Up
DDX56	DEAD (Asp-Glu-Ala-Asp) box helicase 56	1,67	Up
DDX56	DEAD (Asp-Glu-Ala-Asp) box helicase 56	1,94	Up
DEDD	death effector domain containing	1,78	Up
DEFA4	defensin, alpha 4, corticostatin	1,64	Up
DEFA6	defensin, alpha 6, Paneth cell-specific	1,75	Up
DEFB106A	defensin, beta 106A	1,72	Up
DEFB123	defensin, beta 123	2,11	Up
DEGS1	delta(4)-desaturase, sphingolipid 1	1,73	Up
DENND1B	DENN/MADD domain containing 1B	1,62	Up
DENND1C	DENN/MADD domain containing 1C	2,10	Up
DENND2C	DENN/MADD domain containing 2C	1,85	Up
DENND2C	DENN/MADD domain containing 2C	1,50	Up
DENND3	DENN/MADD domain containing 3	1,53	Up
DENND4C	DENN/MADD domain containing 4C	1,67	Up
DFFA	DNA fragmentation factor, 45kDa, alpha polypeptide	2,01	Up
DFFB	DNA fragmentation factor, 40kDa, beta polypeptide (caspase-activated DNase)	1,66	Up
DFNA5	deafness, autosomal dominant 5	2,08	Down
DHRS3	dehydrogenase/reductase (SDR family) member 3	1,52	Up
DHX34	DEAH (Asp-Glu-Ala-His) box polypeptide 34	1,52	Up
DHX36	DEAH (Asp-Glu-Ala-His) box polypeptide 36	1,60	Up
DHX37	DEAH (Asp-Glu-Ala-His) box polypeptide 37	1,59	Up
DHX38	DEAH (Asp-Glu-Ala-His) box polypeptide 38	1,73	Up

DIAPH1	diaphanous-related formin 1	1,67	Up
DICER1	dicer 1, ribonuclease type III	1,57	Up
DIRAS3	DIRAS family, GTP-binding RAS-like 3	1,55	Up
DIRC2	disrupted in renal carcinoma 2	1,53	Up
DISP2	dispatched homolog 2 (Drosophila)	1,54	Up
STAG3L1	stromal antigen 3-like 1 (pseudogene)	2,05	Up
POM121L12	POM 121 transmembrane nucleoporin-like 12	1,82	Up
LRRC37BP1	leucine rich repeat containing 37B pseudogene 1	1,51	Up
LINC01011	long intergenic non-protein coding RNA 1011	1,59	Up
NEURL1B	neuralized E3 ubiquitin protein ligase 1B	1,89	Up
DKK2	dickkopf WNT signaling pathway inhibitor 2	1,83	Up
DLEU1	deleted in lymphocytic leukemia 1 (non-protein coding)	1,56	Up
DLEU2	deleted in lymphocytic leukemia 2 (non-protein coding)	1,73	Up
DLGAP3	discs, large (Drosophila) homolog-associated protein 3	2,02	Down
DLX1	distal-less homeobox 1	1,79	Up
DLX2	distal-less homeobox 2	1,74	Up
DLX3	distal-less homeobox 3	1,59	Up
DMAP1	DNA methyltransferase 1 associated protein 1	2,08	Up
DMBX1	diencephalon/mesencephalon homeobox 1	1,57	Up
DMC1	DNA meiotic recombinase 1	1,65	Up
DMRT1	doublesex and mab-3 related transcription factor 1	1,79	Up
DMRTC1	DMRT-like family C1	1,88	Up
DNAH11	dynein, axonemal, heavy chain 11	1,57	Up
DNAH11	dynein, axonemal, heavy chain 11	2,05	Up
DNAH17	dynein, axonemal, heavy chain 17	1,51	Up
DNAH2	dynein, axonemal, heavy chain 2	1,59	Up
DNAH3	dynein, axonemal, heavy chain 3	1,74	Up
DNAH7	dynein, axonemal, heavy chain 7	1,75	Up
DNAI1	dynein, axonemal, intermediate chain 1	1,64	Up
DNAJA3	DnaJ (Hsp40) homolog, subfamily A, member 3	1,81	Up
DNAJA4	DnaJ (Hsp40) homolog, subfamily A, member 4	1,50	Up
DNAJB11	DnaJ (Hsp40) homolog, subfamily B, member 11	1,53	Up
DNAJB4	DnaJ (Hsp40) homolog, subfamily B, member 4	1,70	Up
DNAJC10	DnaJ (Hsp40) homolog, subfamily C, member 10	1,70	Up
DNAJC16	DnaJ (Hsp40) homolog, subfamily C, member 16	1,54	Up
DNASE1L2	deoxyribonuclease I-like 2	1,77	Up
DND1	DND microRNA-mediated repression inhibitor 1	1,52	Up
DNHD1	dynein heavy chain domain 1	1,69	Up
DNM1P35	DNM1 pseudogene 35	1,67	Down
DOC2A	double C2-like domains, alpha	1,68	Up
DOCK10	dedicator of cytokinesis 10	1,65	Up
DOCK10	dedicator of cytokinesis 10	1,87	Up
DOCK3	dedicator of cytokinesis 3	2,31	Down
DOK3	docking protein 3	1,54	Down
DOK5	docking protein 5	2,09	Up
DXO	decapping exoribonuclease	1,78	Up
DPF2	D4, zinc and double PHD fingers family 2	1,61	Up
DPM3	dolichyl-phosphate mannosyltransferase polypeptide 3	1,78	Up
DPP10	dipeptidyl-peptidase 10 (non-functional)	1,69	Up
DPY19L1	dpy-19-like 1 (C. elegans)	1,52	Up
DPYSL2	dihydropyrimidinase-like 2	1,85	Up
DQX1	DEAQ box RNA-dependent ATPase 1	1,79	Up
RBM45	RNA binding motif protein 45	2,37	Up
CALY	calcyon neuron-specific vesicular protein	1,54	Up
DRD4	dopamine receptor D4	1,71	Up
DRD5	dopamine receptor D5	1,53	Up
DRG2	developmentally regulated GTP binding protein 2	1,61	Up
DSC2	desmocollin 2	1,64	Up
DSCAM	Down syndrome cell adhesion molecule	1,59	Up
DSEL	dermatan sulfate epimerase-like	1,51	Up
DSG4	desmoglein 4	1,99	Up
DTD1	D-tyrosyl-tRNA deacylase 1	1,75	Up
DTNBP1	dystrobrevin binding protein 1	1,76	Up
DTX3L	deltex 3-like (Drosophila)	1,58	Up
DUOX1	dual oxidase 1	1,59	Up
DUSP16	dual specificity phosphatase 16	1,87	Up
DUSP3	dual specificity phosphatase 3	1,94	Down
DUSP4	dual specificity phosphatase 4	1,59	Up
DUSP7	dual specificity phosphatase 7	1,64	Up
DUX3	double homeobox 3	1,62	Up
DUX4	double homeobox 4	1,73	Down
DVL3	dishevelled segment polarity protein 3	2,38	Up
E2F6	E2F transcription factor 6	1,55	Up
E2F6	E2F transcription factor 6	1,75	Up
EBAG9	estrogen receptor binding site associated, antigen, 9	2,50	Up
GPR183	G protein-coupled receptor 183	1,93	Up
EBNA1BP2	EBNA1 binding protein 2	1,59	Up
ECD	ecdysoneless homolog (Drosophila)	1,87	Up
ECE2	endothelin converting enzyme 2	1,65	Up
ECHDC3	enoyl CoA hydratase domain containing 3	1,55	Up
ECHS1	enoyl CoA hydratase, short chain, 1, mitochondrial	1,85	Up
EDC3	enhancer of mRNA decapping 3	1,62	Down
EDEM1	ER degradation enhancer, mannosidase alpha-like 1	1,51	Up
LPAR1	lysophosphatidic acid receptor 1	1,60	Up
EEF1G	eukaryotic translation elongation factor 1 gamma	1,85	Up
EEF1G	eukaryotic translation elongation factor 1 gamma	2,09	Up
EEF2K	eukaryotic elongation factor-2 kinase	1,51	Up
EEFSEC	eukaryotic elongation factor, selenocysteine-tRNA-specific	1,50	Up
NECAB2	N-terminal EF-hand calcium binding protein 2	1,77	Up
EFHD1	EF-hand domain family, member D1	1,73	Up
EFHD2	EF-hand domain family, member D2	1,76	Down
EFNA5	ephrin-A5	3,15	Down
EYS	eyes shut homolog (Drosophila)	1,55	Up
EGFLAM	EGF-like, fibronectin type III and laminin G domains	1,54	Up
EHBP1	EH domain binding protein 1	1,59	Up
EI24	etoposide induced 2.4	1,80	Up
EIF1	eukaryotic translation initiation factor 1	3,18	Up
EIF1	eukaryotic translation initiation factor 1	3,37	Up
EIF1AX	eukaryotic translation initiation factor 1A, X-linked	1,81	Up
EIF2A	eukaryotic translation initiation factor 2A, 65kDa	1,71	Up
EIF2AK3	eukaryotic translation initiation factor 2-alpha kinase 3	1,52	Down
AGO1	argonaute RISC catalytic component 1	1,59	Up
AGO3	argonaute RISC catalytic component 3	1,62	Up
EIF3J	eukaryotic translation initiation factor 3, subunit J	2,07	Up
EIF3I	eukaryotic translation initiation factor 3, subunit I	1,55	Up
EIF3C	eukaryotic translation initiation factor 3, subunit C	2,40	Up
EIF4EBP2	eukaryotic translation initiation factor 4E binding protein 2	1,58	Up
EIF5A2	eukaryotic translation initiation factor 5A2	1,80	Up
CELA2B	chymotrypsin-like elastase family, member 2B	1,78	Up
ELAC2	elaC ribonuclease Z 2	1,68	Up
ELF1	E74-like factor 1 (ets domain transcription factor)	1,65	Up
ELF2	E74-like factor 2 (ets domain transcription factor)	1,84	Down
ELL3	elongation factor RNA polymerase II-like 3	1,62	Up
ELMO1	engulfment and cell motility 1	2,14	Up
ELMO1	engulfment and cell motility 1	1,75	Up
ELN	elastin	1,53	Up
ELOVL6	ELOVL fatty acid elongase 6	1,66	Up
ELTD1	EGF, latrophilin and seven transmembrane domain containing 1	1,68	Up
EMCN	endomucin	1,96	Up
EMILIN1	elastin microfibril interfacer 1	2,97	Down
EMP2	epithelial membrane protein 2	1,68	Up
EMR4P	egf-like module containing, mucin-like, hormone receptor-like 4 pseudogene	2,02	Up
ENAH	enabled homolog (Drosophila)	1,50	Up
ENC1	ectodermal-neural cortex 1 (with BTB domain)	1,64	Up
ENG	endoglin	1,55	Up
ENPP1	ectonucleotide pyrophosphatase/phosphodiesterase 1	1,66	Up
ENPP2	ectonucleotide pyrophosphatase/phosphodiesterase 2	1,92	Up
ENPP4	ectonucleotide pyrophosphatase/phosphodiesterase 4 (putative)	1,64	Up
ENPP6	ectonucleotide pyrophosphatase/phosphodiesterase 6	1,67	Up
ENSA	endosulfine alpha	1,84	Up
EPAS1	endothelial PAS domain protein 1	1,58	Up
EPB41L4B	erythrocyte membrane protein band 4.1 like 4B	1,84	Up
EPHA3	EPH receptor A3	1,82	Up
EPHA4	EPH receptor A4	1,60	Up
EPHB6	EPH receptor B6	1,77	Up
EPN3	epsin 3	1,62	Up
B9D1	B9 protein domain 1	1,58	Down
ERG	v-ets avian erythroblastosis virus E26 oncogene homolog	1,50	Up
ERG	v-ets avian erythroblastosis virus E26 oncogene homolog	1,68	Up
ERGIC1	endoplasmic reticulum-golgi intermediate compartment (ERGIC) 1	1,69	Up

ERGIC1	endoplasmic reticulum-golgi intermediate compartment (ERGIC) 1	1,67	Down
ERGIC2	ERGIC and golgi 2	1,58	Up
ERN1	endoplasmic reticulum to nucleus signaling 1	1,64	Down
ERP27	endoplasmic reticulum protein 27	1,57	Up
ESM1	endothelial cell-specific molecule 1	1,67	Up
ESPNL	espin-like	1,54	Up
ESR1	estrogen receptor 1	1,64	Up
ESR2	estrogen receptor 2 (ER beta)	1,57	Up
ESRRG	estrogen-related receptor gamma	1,78	Up
ETNK2	ethanolamine kinase 2	1,76	Up
MECOM	MDS1 and EVI1 complex locus	1,64	Up
EVX1	even-skipped homeobox 1	2,49	Down
EXOC1	exocyst complex component 1	1,53	Up
EXOC2	exocyst complex component 2	1,67	Up
EXOC3L2	exocyst complex component 3-like 2	3,31	Down
ERI2	ERI1 exoribonuclease family member 2	1,52	Up
EXOSC1	exosome component 1	1,85	Up
EXOSC8	exosome component 8	1,55	Up
EYA3	eyes absent homolog 3 (Drosophila)	1,51	Up
F11R	F11 receptor	1,56	Up
F2RL3	coagulation factor II (thrombin) receptor-like 3	1,54	Down
FAAH	fatty acid amide hydrolase	1,56	Up
FABP2	fatty acid binding protein 2, intestinal	1,80	Up
FABP3	fatty acid binding protein 3, muscle and heart (mammary-derived growth inhibitor)	1,56	Up
FADD	Fas (TNFRSF6)-associated via death domain	1,71	Up
FADS2	fatty acid desaturase 2	1,70	Up
FAIM3	Fas apoptotic inhibitory molecule 3	2,30	Down
UBALD1	UBA-like domain containing 1	1,78	Up
FAM101B	family with sequence similarity 101, member B	1,58	Up
FAM104A	family with sequence similarity 104, member A	1,51	Up
FAM104B	family with sequence similarity 104, member B	1,64	Up
FAM110A	family with sequence similarity 110, member A	1,80	Up
GTSF1L	gametocyte specific factor 1-like	1,58	Up
FAM118A	family with sequence similarity 118, member A	1,64	Up
FAM122B	family with sequence similarity 122B	2,00	Up
FAM127B	family with sequence similarity 127, member B	1,72	Up
MZT2B	mitotic spindle organizing protein 2B	1,68	Up
FAM129B	family with sequence similarity 129, member B	1,65	Down
FAM129C	family with sequence similarity 129, member C	1,85	Up
EDDM3B	epididymal protein 3B	1,89	Up
FAM133A	family with sequence similarity 133, member A	1,64	Up
FAM134B	family with sequence similarity 134, member B	1,50	Up
FAM13A	family with sequence similarity 13, member A	1,66	Up
IFI27L1	interferon, alpha-inducible protein 27-like 1	1,50	Up
FAM21C	family with sequence similarity 21, member C	1,75	Up
FAM32A	family with sequence similarity 32, member A	1,68	Up
FAM3B	family with sequence similarity 3, member B	1,65	Up
BOD1L2	biorientation of chromosomes in cell division 1-like 2	1,64	Up
FAM46C	family with sequence similarity 46, member C	1,56	Up
FAM47A	family with sequence similarity 47, member A	1,74	Up
FAM50A	family with sequence similarity 50, member A	1,50	Up
BRINP2	bone morphogenetic protein/retinoic acid inducible neural-specific 2	1,63	Up
FAM60A	family with sequence similarity 60, member A	1,72	Up
ESYT1	extended synaptotagmin-like protein 1	1,56	Up
FAM63A	family with sequence similarity 63, member A	1,67	Up
TMEM255B	transmembrane protein 255B	2,28	Down
FAM74A4	family with sequence similarity 74, member A4	1,53	Up
RIMKLA	ribosomal modification protein rimK-like family member A	1,60	Up
RMDN2	regulator of microtubule dynamics 2	1,53	Up
FAM89B	family with sequence similarity 89, member B	1,84	Up
FAM8A1	family with sequence similarity 8, member A1	1,67	Up
FAM90A1	family with sequence similarity 90, member A1	1,60	Up
FAM91A1	family with sequence similarity 91, member A1	1,93	Up
FAM98A	family with sequence similarity 98, member A	1,52	Up
FANCB	Fanconi anemia, complementation group B	1,51	Up
FANCD2	Fanconi anemia, complementation group D2	1,74	Up
FANCL	Fanconi anemia, complementation group L	2,01	Up
FARSB	phenylalanyl-tRNA synthetase, beta subunit	1,90	Up
FARSB	phenylalanyl-tRNA synthetase, beta subunit	4,77	Down
FASLG	Fas ligand (TNF superfamily, member 6)	1,73	Up

FASTKD1	FAST kinase domains 1	1,71	Up
FAT2	FAT atypical cadherin 2	1,88	Up
FBLIM1	filamin binding LIM protein 1	1,92	Up
FBLN5	fibulin 5	1,73	Up
FBXL12	F-box and leucine-rich repeat protein 12	2,08	Up
FBXL17	F-box and leucine-rich repeat protein 17	1,60	Down
FBXL5	F-box and leucine-rich repeat protein 5	1,69	Up
FBXL7	F-box and leucine-rich repeat protein 7	1,76	Up
FBXL7	F-box and leucine-rich repeat protein 7	2,40	Up
FBXL8	F-box and leucine-rich repeat protein 8	1,57	Down
FBXO16	F-box protein 16	1,63	Up
FBXO17	F-box protein 17	1,97	Down
FBXO25	F-box protein 25	2,40	Down
FBXO3	F-box protein 3	1,53	Up
FBXO9	F-box protein 9	1,57	Up
FBXO9	F-box protein 9	1,90	Up
FBXW11	F-box and WD repeat domain containing 11	1,59	Up
FCAR	Fc fragment of IgA, receptor for	1,71	Up
FCER1A	Fc fragment of IgE, high affinity I, receptor for; alpha polypeptide	1,55	Up
FCF1	FCF1 rRNA-processing protein	1,51	Up
FCGR2B	Fc fragment of IgG, low affinity IIb, receptor (CD32)	1,80	Up
FCGR3A	Fc fragment of IgG, low affinity IIIa, receptor (CD16a)	1,73	Up
FCGRT	Fc fragment of IgG, receptor, transporter, alpha	1,86	Up
FCN1	ficolin (collagen/fibrinogen domain containing) 1	3,58	Down
FCRL5	Fc receptor-like 5	1,68	Up
FCRLA	Fc receptor-like A	1,58	Up
FCRLB	Fc receptor-like B	1,54	Up
FDPSP2	farnesyl diphosphate synthase pseudogene 2	1,63	Up
FEM1C	fem-1 homolog c (C. elegans)	1,54	Up
FEN1	flap structure-specific endonuclease 1	1,52	Up
FETUB	fetuin B	1,52	Up
FFAR2	free fatty acid receptor 2	1,99	Up
FGA	fibrinogen alpha chain	1,60	Up
FGB	fibrinogen beta chain	1,82	Up
FGD6	FYVE, RhoGEF and PH domain containing 6	1,86	Up
FGF19	fibroblast growth factor 19	1,60	Up
FGF3	fibroblast growth factor 3	2,91	Down
FGF5	fibroblast growth factor 5	2,19	Up
FGL1	fibrinogen-like 1	2,13	Up
FGR	feline Gardner-Rasheed sarcoma viral oncogene homolog	1,79	Up
FHIT	fragile histidine triad	1,55	Up
FIGF	c-fos induced growth factor (vascular endothelial growth factor D)	1,67	Up
FILIP1	filamin A interacting protein 1	1,78	Up
FKBP1A	FK506 binding protein 1A, 12kDa	1,61	Up
FKBP4	FK506 binding protein 4, 59kDa	1,61	Up
FLAD1	flavin adenine dinucleotide synthetase 1	1,57	Up
LRRC37A4P	leucine rich repeat containing 37, member A4, pseudogene	1,65	Up
MAGOHB	mago-nashi homolog B (Drosophila)	1,85	Up
C19orf73	chromosome 19 open reading frame 73	1,81	Down
EPB41L4A-AS2	EPB41L4A antisense RNA 2 (head to head)	1,99	Up
STAG3L4	stromal antigen 3-like 4 (pseudogene)	1,62	Up
DNAJC22	DnaJ (Hsp40) homolog, subfamily C, member 22	2,28	Up
FAM161A	family with sequence similarity 161, member A	1,91	Up
VWDE	von Willebrand factor D and EGF domains	1,61	Up
TMEM209	transmembrane protein 209	1,55	Up
DENND1B	DENN/MADD domain containing 1B	1,63	Up
TMEM214	transmembrane protein 214	1,54	Up
RBM47	RNA binding motif protein 47	1,81	Up
ACSS3	acyl-CoA synthetase short-chain family member 3	1,65	Up
EFCAB6	EF-hand calcium binding domain 6	1,69	Up
C16orf92	chromosome 16 open reading frame 92	1,63	Up
TTC23L	tetratricopeptide repeat domain 23-like	1,54	Up
UBN2	ubinuclein 2	1,56	Up
LINC00889	long intergenic non-protein coding RNA 889	1,59	Up
PUS10	pseudouridylate synthase 10	1,72	Up
LINC00896	long intergenic non-protein coding RNA 896	1,61	Up
DLX6-AS1	DLX6 antisense RNA 1	1,55	Up
ADORA2A-AS1	ADORA2A antisense RNA 1	1,60	Up
LINC00094	long intergenic non-protein coding RNA 94	1,63	Up
C17orf104	chromosome 17 open reading frame 104	1,53	Up

KCNJ2-AS1	KCNJ2 antisense RNA 1 (head to head)	1,64	Up
TAPT1-AS1	TAPT1 antisense RNA 1 (head to head)	1,72	Up
CCDC168	coiled-coil domain containing 168	1,92	Up
C2orf73	chromosome 2 open reading frame 73	1,77	Up
ARHGEF37	Rho guanine nucleotide exchange factor (GEF) 37	1,50	Up
TMEM232	transmembrane protein 232	1,52	Up
C15orf52	chromosome 15 open reading frame 52	1,66	Up
MROH5	maestro heat-like repeat family member 5	1,62	Up
C1orf229	chromosome 1 open reading frame 229	1,69	Down
C11orf88	chromosome 11 open reading frame 88	1,56	Up
FLNB	filamin B, beta	2,05	Down
FLRT1	fibronectin leucine rich transmembrane protein 1	1,90	Down
FMO5	flavin containing monooxygenase 5	1,76	Up
FOXB1	forkhead box B1	1,54	Down
FOXC1	forkhead box C1	1,91	Up
FOXC2	forkhead box C2 (MFH-1, mesenchyme forkhead 1)	1,76	Down
FOXD2	forkhead box D2	1,62	Up
FOXE1	forkhead box E1 (thyroid transcription factor 2)	2,43	Down
FOXG1	forkhead box G1	1,57	Up
FOXJ1	forkhead box J1	1,89	Up
FOXK2	forkhead box K2	1,70	Up
FOXN3	forkhead box N3	1,94	Up
FOXN4	forkhead box N4	1,72	Up
FOXP1	forkhead box P1	1,57	Up
FOXP3	forkhead box P3	1,51	Up
FOXQ1	forkhead box Q1	2,52	Down
FOXRED1	FAD-dependent oxidoreductase domain containing 1	1,59	Up
FPR2	formyl peptide receptor 2	1,53	Up
ATAD5	ATPase family, AAA domain containing 5	1,72	Up
FRG1	FSHD region gene 1	1,76	Up
FRG2	FSHD region gene 2	1,52	Up
FRMD4A	FERM domain containing 4A	1,55	Up
FRMD4A	FERM domain containing 4A	1,55	Down
FSCN1	fascin homolog 1, actin-bundling protein (Strongylocentrotus purpuratus)	1,77	Up
FSD1	fibronectin type III and SPRY domain containing 1	1,60	Up
FSHR	follicle stimulating hormone receptor	1,63	Up
FST	follistatin	1,62	Down
FSTL4	follistatin-like 4	1,78	Up
FTCD	formimidoyltransferase cyclodeaminase	1,52	Up
FTH1	ferritin, heavy polypeptide 1	3,63	Down
FTL	ferritin, light polypeptide	1,72	Up
FTMT	ferritin mitochondrial	1,66	Up
FUBP3	far upstream element (FUSE) binding protein 3	1,67	Up
FUBP3	far upstream element (FUSE) binding protein 3	1,97	Up
FUNDC1	FUN14 domain containing 1	1,89	Up
FUNDC2	FUN14 domain containing 2	1,55	Down
FUT10	fucosyltransferase 10 (alpha (1,3) fucosyltransferase)	1,51	Up
FUT6	fucosyltransferase 6 (alpha (1,3) fucosyltransferase)	1,70	Up
FXN	frataxin	2,26	Down
FYN	FYN oncogene related to SRC, FGR, YES	1,87	Up
FZD10	frizzled family receptor 10	1,85	Up
FZR1	fizzy/cell division cycle 20 related 1 (Drosophila)	1,62	Down
GAB2	GRB2-associated binding protein 2	1,72	Up
GABARAPL3	GABA(A) receptors associated protein like 3, pseudogene	2,84	Up
GABPB2	GA binding protein transcription factor, beta subunit 2	1,53	Up
GABRA1	gamma-aminobutyric acid (GABA) A receptor, alpha 1	1,88	Up
GABRA2	gamma-aminobutyric acid (GABA) A receptor, alpha 2	1,51	Up
GABRB1	gamma-aminobutyric acid (GABA) A receptor, beta 1	1,66	Up
GAD2	glutamate decarboxylase 2 (pancreatic islets and brain, 65kDa)	1,54	Up
GADD45B	growth arrest and DNA-damage-inducible, beta	1,57	Up
GAL	galanin/GMAP prepropeptide	1,61	Up
GAL3ST2	galactose-3-O-sulfotransferase 2	1,68	Up
CSGALNACT2	chondroitin sulfate N-acetylgalactosaminyltransferase 2	1,62	Up
GALNT2	UDP-N-acetyl-alpha-D-galactosamine:polypeptide N-acetylgalactosaminyltransferase 2 (GalNAc-T2)	1,68	Up
GALNT6	UDP-N-acetyl-alpha-D-galactosamine:polypeptide N-acetylgalactosaminyltransferase 6 (GalNAc-T6)	1,79	Up
GALR3	galanin receptor 3	1,68	Down
GAMT	guanidinoacetate N-methyltransferase	1,82	Up
GARNL3	GTPase activating Rap/RanGAP domain-like 3	2,12	Up
RAP1GAP2	RAP1 GTPase activating protein 2	1,76	Up
GART	phosphoribosylglycinamide formyltransferase, phosphoribosylglycinamide synthetase, phosphoribosylaminoimidazole synthetase	1,53	Up
GAS7	growth arrest-specific 7	1,63	Up
GCNT3	glucosaminyl (N-acetyl) transferase 3, mucin type	1,52	Up
MOGS	mannosyl-oligosaccharide glucosidase	4,35	Down
GDA	guanine deaminase	1,55	Up
GDF3	growth differentiation factor 3	1,66	Up
GDNF	glial cell derived neurotrophic factor	1,61	Down
GDPD4	glycerophosphodiester phosphodiesterase domain containing 4	1,62	Up
ARHGEF25	Rho guanine nucleotide exchange factor (GEF) 25	1,57	Up
GFOD1	glucose-fructose oxidoreductase domain containing 1	1,55	Up
GFRA3	GDNF family receptor alpha 3	1,89	Up
GGA2	golgi-associated, gamma adaptin ear containing, ARF binding protein 2	2,20	Up
GGCX	gamma-glutamyl carboxylase	1,78	Up
GGT1	gamma-glutamyltransferase 1	1,74	Up
GGT3P	gamma-glutamyltransferase 3 pseudogene	2,02	Up
GGTLC2	gamma-glutamyltransferase light chain 2	1,76	Up
GHITM	growth hormone inducible transmembrane protein	1,72	Up
GHRHR	growth hormone releasing hormone receptor	1,58	Up
GHRL	ghrelin/obestatin prepropeptide	1,74	Up
GIP	gastric inhibitory polypeptide	1,82	Up
GIPC2	GIPC PDZ domain containing family, member 2	1,92	Up
GIT2	G protein-coupled receptor kinase interacting ArfGAP 2	1,62	Up
GJC2	gap junction protein, gamma 2, 47kDa	1,51	Down
GJA3	gap junction protein, alpha 3, 46kDa	1,52	Up
GJA4	gap junction protein, alpha 4, 37kDa	1,91	Up
GJA5	gap junction protein, alpha 5, 40kDa	1,53	Up
GJB2	gap junction protein, beta 2, 26kDa	1,67	Up
GJE1	gap junction protein, epsilon 1, 23kDa	1,95	Up
GLDC	glycine dehydrogenase (decarboxylating)	1,50	Up
GLIS3	GLIS family zinc finger 3	1,64	Up
GLRX	glutaredoxin (thioltransferase)	1,83	Up
GXYLT2	glucoside xylosyltransferase 2	1,55	Up
GLTP	glycolipid transfer protein	1,71	Down
GLYAT	glycine-N-acyltransferase	1,52	Up
GM2A	GM2 ganglioside activator	1,62	Up
GNAS	GNAS complex locus	2,00	Up
GNAZ	guanine nucleotide binding protein (G protein), alpha z polypeptide	1,58	Down
GNB4	guanine nucleotide binding protein (G protein), beta polypeptide 4	1,79	Down
GNG13	guanine nucleotide binding protein (G protein), gamma 13	1,73	Down
GNG8	guanine nucleotide binding protein (G protein), gamma 8	1,78	Up
GNGT2	guanine nucleotide binding protein (G protein), gamma transducing activity polypeptide 2	1,54	Up
GNPDA2	glucosamine-6-phosphate deaminase 2	1,63	Up
GOLGA1	golgin A1	1,59	Up
GOLGA3	golgin A3	1,74	Up
GOLGA7	golgin A7	2,01	Down
GOLGB1	golgin B1	1,59	Up
GOLM1	golgi membrane protein 1	1,53	Down
GOLT1A	golgi transport 1A	1,75	Up
GOT2	glutamic-oxaloacetic transaminase 2, mitochondrial	1,58	Up
GP1BA	glycoprotein Ib (platelet), alpha polypeptide	2,13	Up
GPBAR1	G protein-coupled bile acid receptor 1	1,86	Up
GPBP1L1	GC-rich promoter binding protein 1-like 1	1,61	Up
GPC4	glypican 4	1,60	Up
GPD1L	glycerol-3-phosphate dehydrogenase 1-like	1,91	Up
GPI	glucose-6-phosphate isomerase	2,27	Down
GPM6A	glycoprotein M6A	1,88	Down
GPR112	G protein-coupled receptor 112	1,71	Up
GPR115	G protein-coupled receptor 115	1,52	Up
GPR116	G protein-coupled receptor 116	1,78	Up
GPR150	G protein-coupled receptor 150	1,81	Down
GPR153	G protein-coupled receptor 153	2,05	Down
GPR156	G protein-coupled receptor 156	2,49	Down
TPRA1	transmembrane protein, adipocyte asscociated 1	1,50	Up
GPR20	G protein-coupled receptor 20	1,56	Down
GPR35	G protein-coupled receptor 35	2,13	Down
GPR55	G protein-coupled receptor 55	1,94	Up
GPR61	G protein-coupled receptor 61	1,71	Up
GPR62	G protein-coupled receptor 62	1,63	Up
GPR64	G protein-coupled receptor 64	1,84	Up
GPR82	G protein-coupled receptor 82	1,74	Up
GPR89A	G protein-coupled receptor 89A	1,78	Up

GPRC5A	G protein-coupled receptor, family C, group 5, member A	1,71	Up
GPRC5B	G protein-coupled receptor, family C, group 5, member B	1,79	Up
GPRC5D	G protein-coupled receptor, family C, group 5, member D	1,93	Up
GPS2	G protein pathway suppressor 2	1,85	Up
GPSM1	G-protein signaling modulator 1	1,60	Up
GPX2	glutathione peroxidase 2 (gastrointestinal)	1,63	Up
GRAMD1A	GRAM domain containing 1A	1,51	Up
GRAMD3	GRAM domain containing 3	1,58	Up
GREM2	gremlin 2, DAN family BMP antagonist	1,62	Up
GRHL1	grainyhead-like 1(Drosophila)	1,51	Up
GRHL3	grainyhead-like 3 (Drosophila)	1,61	Up
GRIN1	glutamate receptor, ionotropic, N-methyl D-aspartate 1	1,65	Down
GRIN2A	glutamate receptor, ionotropic, N-methyl D-aspartate 2A	1,72	Up
GRIN2D	glutamate receptor, ionotropic, N-methyl D-aspartate 2D	1,85	Down
GRIN3A	glutamate receptor, ionotropic, N-methyl-D-aspartate 3A	1,75	Up
GRINA	glutamate receptor, ionotropic, N-methyl D-aspartate-associated protein 1(glutamate binding)	1,75	Up
GRINA	glutamate receptor, ionotropic, N-methyl D-aspartate-associated protein 1(glutamate binding)	1,86	Up
ARHGAP35	Rho GTPase activating protein 35	1,83	Up
GRM5	glutamate receptor, metabotropic 5	1,51	Up
GRWD1	glutamate-rich WD repeat containing 1	1,54	Up
GSC2	goosecoid homeobox 2	1,55	Up
GSDMA	gasdermin A	1,74	Up
GSG2	germ cell associated 2 (haspin)	2,31	Up
GSK3A	glycogen synthase kinase 3 alpha	2,02	Up
GSK3B	glycogen synthase kinase 3 beta	1,66	Up
GSTM3	glutathione S-transferase mu 3 (brain)	1,51	Up
GSTM5	glutathione S-transferase mu 5	1,53	Up
GSTO2	glutathione S-transferase omega 2	1,69	Up
GSTT2	glutathione S-transferase theta 2	2,16	Up
GTF3C4	general transcription factor IIIC, polypeptide 4, 90kDa	1,64	Up
GTPBP10	GTP-binding protein 10 (putative)	2,01	Up
OLA1	Obg-like ATPase 1	1,51	Up
GUCA1A	guanylate cyclase activator 1A (retina)	1,79	Up
GUCA2A	guanylate cyclase activator 2A (guanylin)	1,73	Up
GUCY1A2	guanylate cyclase 1, soluble, alpha 2	1,57	Up
GUCY1A3	guanylate cyclase 1, soluble, alpha 3	1,91	Up
GUK1	guanylate kinase 1	1,63	Up
GULP1	GULP, engulfment adaptor PTB domain containing 1	1,55	Up
GVINP1	GTPase, very large interferon inducible pseudogene 1	1,86	Up
GYPC	glycophorin C (Gerbich blood group)	1,69	Up
GYS2	glycogen synthase 2 (liver)	1,60	Up
H2AFJ	H2A histone family, member J	2,03	Down
H2AFY	H2A histone family, member Y	1,80	Up
H2AFY2	H2A histone family, member Y2	1,86	Up
H2AFZ	H2A histone family, member Z	1,57	Up
H6PD	hexose-6-phosphate dehydrogenase (glucose 1-dehydrogenase)	1,55	Up
HABP2	hyaluronan binding protein 2	1,57	Up
HADH	hydroxyacyl-CoA dehydrogenase	1,70	Up
HAGH	hydroxyacylglutathione hydrolase	1,61	Up
HAGHL	hydroxyacylglutathione hydrolase-like	1,71	Down
HAPLN2	hyaluronan and proteoglycan link protein 2	1,50	Down
HAPLN4	hyaluronan and proteoglycan link protein 4	1,63	Up
HAS2	hyaluronan synthase 2	1,71	Up
HAVCR1	hepatitis A virus cellular receptor 1	1,72	Up
HAX1	HCLS1associated protein X-1	1,66	Up
HBE1	hemoglobin, epsilon 1	1,97	Up
HCN4	hyperpolarization activated cyclic nucleotide-gated potassium channel 4	1,98	Down
HCP5	HLA complex P5 (non-protein coding)	1,73	Up
HTT	huntingtin	2,06	Up
HDAC5	histone deacetylase 5	1,59	Up
HDAC7	histone deacetylase 7	1,86	Down
HDAC9	histone deacetylase 9	1,53	Up
HDAC9	histone deacetylase 9	2,10	Up
HDDC2	HD domain containing 2	2,27	Up
HDHD1	haloacid dehalogenase-like hydrolase domain containing 1	1,60	Up
HEATR2	HEAT repeat containing 2	1,54	Up
HECA	headcase homolog (Drosophila)	1,91	Up
HECTD3	HECT domain containing E3 ubiquitin protein ligase 3	1,58	Up
HEPACAM	hepatic and glial cell adhesion molecule	1,84	Up
HERC2	HECT and RLD domain containing E3 ubiquitin protein ligase 2	1,53	Up
HERC6	HECT and RLD domain containing E3 ubiquitin protein ligase family member 6	1,53	Up
HES7	hes family bHLH transcription factor 7	1,66	Down
HEXA	hexosaminidase A (alpha polypeptide)	1,96	Up
HGD	homogentisate 1,2-dioxygenase	1,74	Up
HGF	hepatocyte growth factor (hepapoietin A; scatter factor)	1,66	Up
HGFAC	HGF activator	1,65	Up
HGS	hepatocyte growth factor-regulated tyrosine kinase substrate	1,65	Up
HGS	hepatocyte growth factor-regulated tyrosine kinase substrate	1,81	Down
HHIP	hedgehog interacting protein	1,63	Up
HIF3A	hypoxia inducible factor 3, alpha subunit	1,53	Up
HINT2	histidine triad nucleotide binding protein 2	1,60	Up
HIP1	huntingtin interacting protein 1	1,54	Down
HIPK1	homeodomain interacting protein kinase 1	1,95	Up
HIST1H2AH	histone cluster 1, H2ah	2,19	Down
HIST1H2AJ	histone cluster 1, H2aj	1,50	Up
HIST1H2AM	histone cluster 1, H2am	1,53	Up
HIST1H2BD	histone cluster 1, H2bd	1,65	Down
HIST1H2BE	histone cluster 1, H2be	1,74	Up
HIST1H2BK	histone cluster 1, H2bk	1,80	Up
HIST1H3D	histone cluster 1, H3d	1,56	Up
HIST1H3J	histone cluster 1, H3j	1,84	Up
HIST1H4A	histone cluster 1, H4a	1,53	Up
HIST1H4B	histone cluster 1, H4b	1,82	Up
HIST1H4E	histone cluster 1, H4e	1,79	Up
HIST1H4J	histone cluster 1, H4j	1,63	Up
HIST2H2AA3	histone cluster 2, H2aa3	1,54	Up
HIST3H2BB	histone cluster 3, H2bb	1,61	Down
HIVEP3	human immunodeficiency virus type I enhancer binding protein 3	2,23	Up
HLA-B	major histocompatibility complex, class I, B	1,51	Up
HLA-DMA	major histocompatibility complex, class II, DM alpha	1,59	Up
HLA-DOA	major histocompatibility complex, class II, DO alpha	1,51	Up
HLA-DOA	major histocompatibility complex, class II, DO alpha	1,53	Up
HLA-DOB	major histocompatibility complex, class II, DO beta	2,00	Up
HLA-DPA1	major histocompatibility complex, class II, DP alpha 1	2,86	Up
HLA-DPB1	major histocompatibility complex, class II, DP beta 1	1,97	Up
HLA-DPB2	major histocompatibility complex, class II, DP beta 2 (pseudogene)	1,56	Up
HLA-DQA1	major histocompatibility complex, class II, DQ alpha 1	1,64	Up
HLA-DQA1	major histocompatibility complex, class II, DQ alpha 1	1,76	Up
HLA-DQB1	major histocompatibility complex, class II, DQ beta 1	1,56	Up
HMCN1	hemicentin 1	1,60	Up
HMGXB4	HMG box domain containing 4	1,61	Up
HMGA1	high mobility group AT-hook 1	1,60	Up
HMGCLL1	3-hydroxymethyl-3-methylglutaryl-CoA lyase-like 1	2,08	Up
HMGCS2	3-hydroxy-3-methylglutaryl-CoA synthase 2 (mitochondrial)	1,83	Up
HMGN1	high mobility group nucleosome binding domain 1	1,98	Up
HMGN2	high mobility group nucleosomal binding domain 2	2,37	Up
HMGN2	high mobility group nucleosomal binding domain 2	1,94	Up
HMHB1	histocompatibility (minor) HB-1	1,56	Up
HMMR	hyaluronan-mediated motility receptor (RHAMM)	1,99	Up
HMOX1	heme oxygenase (decycling) 1	1,89	Down
HMX2	H6 family homeobox 2	1,67	Up
HNF4G	hepatocyte nuclear factor 4, gamma	1,65	Up
HNRNPC	heterogeneous nuclear ribonucleoprotein C (C1/C2)	2,29	Down
HNRNPUL1	heterogeneous nuclear ribonucleoprotein U-like 1	2,64	Up
HOMER2	homer homolog 2 (Drosophila)	1,98	Up
IFFO1	intermediate filament family orphan 1	2,37	Up
HOOK1	hook microtubule-tethering protein 1	1,58	Up
HOXA10	homeobox A10	1,89	Up
HOXA6	homeobox A6	1,65	Up
HOXB3	homeobox B3	1,60	Up
HOXC10	homeobox C10	2,17	Up
HOXC11	homeobox C11	1,59	Up
HOXC5	homeobox C5	1,55	Up
HOXD1	homeobox D1	1,67	Up
HOXD10	homeobox D10	1,61	Up
HOXD13	homeobox D13	1,51	Down
HOXD8	homeobox D8	1,82	Up
HPSE	heparanase	1,89	Up
HPSE2	heparanase 2	1,77	Up
HRH3	histamine receptor H3	1,73	Up

HRK	harakiri, BCL2 interacting protein (contains only BH3 domain)	1,85	Down
HS1BP3	HCLS1 binding protein 3	1,80	Up
HS2ST1	heparan sulfate 2-O-sulfotransferase 1	1,83	Up
HS3ST3B1	heparan sulfate (glucosamine) 3-O-sulfotransferase 3B1	1,85	Up
HSD17B1	hydroxysteroid (17-beta) dehydrogenase 1	2,27	Down
HSD17B14	hydroxysteroid (17-beta) dehydrogenase 14	1,55	Down
HSD17B7P2	hydroxysteroid (17-beta) dehydrogenase 7 pseudogene 2	1,68	Up
HSD3B1	hydroxy-delta-5-steroid dehydrogenase, 3 beta- and steroid delta-isomerase 1	1,91	Up
HSDL2	hydroxysteroid dehydrogenase like 2	1,99	Up
HSFY2	heat shock transcription factor, Y linked 2	1,57	Up
HSH2D	hematopoietic SH2 domain containing	1,85	Up
HSPA1A	heat shock 70kDa protein 1A	1,60	Up
HSPA2	heat shock 70kDa protein 2	1,52	Up
HSPB6	heat shock protein, alpha-crystallin-related, B6	1,66	Up
HSPBP1	HSPA (heat shock 70kDa) binding protein, cytoplasmic cochaperone 1	2,14	Up
CWC15	CWC15 spliceosome-associated protein homolog (S. cerevisiae)	3,02	Down
TRMT112	tRNA methyltransferase 11-2 homolog (S. cerevisiae)	1,88	Up
TRMT2A	tRNA methyltransferase 2 homolog A (S. cerevisiae)	1,58	Down
HTR1A	5-hydroxytryptamine (serotonin) receptor 1A, G protein-coupled	1,83	Up
HTR3C	5-hydroxytryptamine (serotonin) receptor 3C, ionotropic	1,56	Up
HTR7	5-hydroxytryptamine (serotonin) receptor 7, adenylate cyclase-coupled	1,51	Up
HTRA2	HtrA serine peptidase 2	1,70	Up
HYDIN	HYDIN, axonemal central pair apparatus protein	1,79	Up
HYOU1	hypoxia up-regulated 1	1,82	Up
FICD	FIC domain containing	1,57	Up
ID4	inhibitor of DNA binding 4, dominant negative helix-loop-helix protein	1,54	Up
IDI2	isopentenyl-diphosphate delta isomerase 2	1,92	Up
IER5	immediate early response 5	2,37	Down
IFI27	interferon, alpha-inducible protein 27	1,57	Up
IFI30	interferon, gamma-inducible protein 30	2,18	Up
IFIT1	interferon-induced protein with tetratricopeptide repeats 1	1,85	Up
IFIT5	interferon-induced protein with tetratricopeptide repeats 5	1,68	Up
IFITM3	interferon induced transmembrane protein 3	1,56	Up
IFITM5	interferon induced transmembrane protein 5	3,21	Down
IFT122	intraflagellar transport 122 homolog (Chlamydomonas)	1,76	Up
IFT80	intraflagellar transport 80 homolog (Chlamydomonas)	1,77	Up
IGF2BP3	insulin-like growth factor 2 mRNA binding protein 3	1,68	Up
IGFBP3	insulin-like growth factor binding protein 3	1,63	Up
IGFBP4	insulin-like growth factor binding protein 4	1,87	Up
IGH	immunoglobulin heavy locus	1,54	Up
IGHA1	immunoglobulin heavy constant alpha 1	1,62	Up
IGHV1-69	immunoglobulin heavy variable 1-69	2,24	Down
IGKV1-5	immunoglobulin kappa variable 1-5	1,50	Down
IGKV2-24	immunoglobulin kappa variable 2-24	1,75	Up
IGSF11	immunoglobulin superfamily, member 11	1,61	Up
IGSF11	immunoglobulin superfamily, member 11	1,90	Up
IGSF21	immunoglobin superfamily, member 21	1,61	Up
IGSF3	immunoglobulin superfamily, member 3	1,66	Up
IGSF6	immunoglobulin superfamily, member 6	1,51	Up
IGSF8	immunoglobulin superfamily, member 8	1,59	Up
IKZF1	IKAROS family zinc finger 1 (Ikaros)	1,92	Up
IL10	interleukin 10	1,54	Up
IL10RA	interleukin 10 receptor, alpha	1,53	Up
IL15	interleukin 15	1,62	Up
IL17A	interleukin 17A	2,02	Up
IL17RA	interleukin 17 receptor A	1,62	Up
IL18BP	interleukin 18 binding protein	1,56	Up
IL18BP	interleukin 18 binding protein	1,73	Down
IL1B	interleukin 1, beta	1,54	Up
IL36A	interleukin 36, alpha	1,55	Up
IL36G	interleukin 36, gamma	1,81	Up
IL1RAP	interleukin 1 receptor accessory protein	1,51	Up
IL1RN	interleukin 1 receptor antagonist	1,68	Up
IL2	interleukin 2	1,68	Up
IL23A	interleukin 23, alpha subunit p19	1,58	Down
IL24	interleukin 24	1,51	Up
IFNL2	interferon, lambda 2	1,87	Up
IL2RG	interleukin 2 receptor, gamma	1,79	Up
IL3RA	interleukin 3 receptor, alpha (low affinity)	1,70	Up
IL4I1	interleukin 4 induced 1	2,48	Up

ILDR1	immunoglobulin-like domain containing receptor 1	1,60	Down
ILF2	interleukin enhancer binding factor 2	2,19	Up
IMMP1L	IMP1 inner mitochondrial membrane peptidase-like (S. cerevisiae)	1,56	Up
IMP4	IMP4, U3 small nucleolar ribonucleoprotein, homolog (yeast)	1,53	Up
IMPA1	inositol(myo)-1(or 4)-monophosphatase 1	1,75	Up
IMPA2	inositol(myo)-1(or 4)-monophosphatase 2	1,97	Up
ING2	inhibitor of growth family, member 2	1,82	Up
INHBC	inhibin, beta C	1,77	Up
INS	insulin	1,51	Up
INSR	insulin receptor	1,53	Up
INTS1	integrator complex subunit 1	1,52	Up
INTS6	integrator complex subunit 6	1,67	Up
IQSEC1	IQ motif and Sec7 domain 1	1,80	Up
IQSEC2	IQ motif and Sec7 domain 2	2,56	Down
IREB2	iron-responsive element binding protein 2	1,96	Up
IRF5	interferon regulatory factor 5	1,67	Up
IRX4	iroquois homeobox 4	1,54	Down
IRX6	iroquois homeobox 6	1,51	Up
IRX6	iroquois homeobox 6	1,61	Up
ISCA2	iron-sulfur cluster assembly 2	1,55	Up
ISG15	ISG15 ubiquitin-like modifier	1,56	Up
ISG20	interferon stimulated exonuclease gene 20kDa	1,72	Up
ISOC2	isochorismatase domain containing 2	1,50	Down
ITGA2B	integrin, alpha 2b (platelet glycoprotein IIb of IIb/IIIa complex, antigen CD41)	1,53	Up
ITGA5	integrin, alpha 5 (fibronectin receptor, alpha polypeptide)	1,53	Up
ITGA7	integrin, alpha 7	2,04	Up
ITGA8	integrin, alpha 8	1,74	Up
ITGA9	integrin, alpha 9	2,17	Up
ITGAL	integrin, alpha L (antigen CD11A (p180), lymphocyte function-associated antigen 1; alpha polypeptide)	1,51	Up
ITGAL	integrin, alpha L (antigen CD11A (p180), lymphocyte function-associated antigen 1; alpha polypeptide)	1,62	Up
ITGB4	integrin, beta 4	1,51	Up
ITIH5	inter-alpha-trypsin inhibitor heavy chain family, member 5	1,76	Up
ITK	IL2-inducible T-cell kinase	1,56	Down
ITPA	inosine triphosphatase (nucleoside triphosphate pyrophosphatase)	1,56	Up
ITPKA	inositol-trisphosphate 3-kinase A	1,53	Up
ITSN1	intersectin 1 (SH3 domain protein)	1,52	Down
MED29	mediator complex subunit 29	1,62	Up
JAG2	jagged 2	2,57	Down
KDM5D	lysine (K)-specific demethylase 5D	2,04	Up
KDM6B	lysine (K)-specific demethylase 6B	1,56	Up
JOSD1	Josephin domain containing 1	1,69	Up
JPH2	junctophilin 2	1,51	Up
JPH2	junctophilin 2	1,99	Up
JPH2	junctophilin 2	1,71	Up
JPH3	junctophilin 3	1,50	Up
KALRN	kalirin, RhoGEF kinase	1,82	Up
KATNAL1	katanin p60 subunit A-like 1	1,62	Up
KBTBD2	kelch repeat and BTB (POZ) domain containing 2	1,61	Up
KBTBD2	kelch repeat and BTB (POZ) domain containing 2	1,74	Up
KBTBD4	kelch repeat and BTB (POZ) domain containing 4	1,63	Up
KCMF1	potassium channel modulatory factor 1	1,56	Up
KCNA10	potassium voltage-gated channel, shaker-related subfamily, member 10	1,94	Up
KCNA6	potassium voltage-gated channel, shaker-related subfamily, member 6	1,70	Up
KCNAB1	potassium voltage-gated channel, shaker-related subfamily, beta member 1	1,50	Up
KCNAB1	potassium voltage-gated channel, shaker-related subfamily, beta member 1	1,54	Up
KCNAB1	potassium voltage-gated channel, shaker-related subfamily, beta member 1	1,54	Up
KCND3	potassium voltage-gated channel, Shal-related subfamily, member 3	1,65	Up
KCNE1L	KCNE1-like	1,60	Up
KCNG1	potassium voltage-gated channel, subfamily G, member 1	1,68	Up
KCNG3	potassium voltage-gated channel, subfamily G, member 3	2,09	Up
KCNG4	potassium voltage-gated channel, subfamily G, member 4	1,52	Up
KCNH1	potassium voltage-gated channel, subfamily H (eag-related), member 1	1,55	Up
KCNH2	potassium voltage-gated channel, subfamily H (eag-related), member 2	1,98	Up
KCNH5	potassium voltage-gated channel, subfamily H (eag-related), member 5	1,53	Up
KCNIP2	Kv channel interacting protein 2	1,50	Up
KCNIP2	Kv channel interacting protein 2	1,80	Up
KCNIP4	Kv channel interacting protein 4	1,62	Up
KCNJ1	potassium inwardly-rectifying channel, subfamily J, member 1	1,59	Up
KCNJ12	potassium inwardly-rectifying channel, subfamily J, member 12	1,56	Up
KCNK10	potassium channel, subfamily K, member 10	1,67	Up

KCNK7	potassium channel, subfamily K, member 7	2,39	Down
KCNMA1	potassium large conductance calcium-activated channel, subfamily M, alpha member 1	1,69	Up
KCNMA1	potassium large conductance calcium-activated channel, subfamily M, alpha member 1	3,79	Down
KCNN3	potassium intermediate/small conductance calcium-activated channel, subfamily N, member 3	1,67	Up
KCNQ2	potassium voltage-gated channel, KQT-like subfamily, member 2	1,54	Up
KCNQ5	potassium voltage-gated channel, KQT-like subfamily, member 5	1,99	Up
KCTD13	potassium channel tetramerization domain containing 13	1,77	Up
KCTD14	potassium channel tetramerization domain containing 14	1,61	Up
KCTD16	potassium channel tetramerization domain containing 16	1,59	Up
KCTD16	potassium channel tetramerization domain containing 16	1,65	Up
KCTD2	potassium channel tetramerization domain containing 2	1,86	Up
KCTD21	potassium channel tetramerization domain containing 21	1,68	Up
KDELC2	KDEL (Lys-Asp-Glu-Leu) containing 2	1,62	Up
KDELR3	KDEL (Lys-Asp-Glu-Leu) endoplasmic reticulum protein retention receptor 3	1,81	Up
KERA	keratocan	1,79	Up
KIAA0141	KIAA0141	1,66	Up
MLEC	malectin	1,53	Up
MLEC	malectin	1,71	Up
KIAA0247	KIAA0247	1,68	Up
TMEM194A	transmembrane protein 194A	1,56	Up
TTC37	tetratricopeptide repeat domain 37	1,54	Up
RPRD2	regulation of nuclear pre-mRNA domain containing 2	1,87	Up
SZT2	seizure threshold 2 homolog (mouse)	1,58	Up
KIAA0513	KIAA0513	1,59	Up
KIAA0513	KIAA0513	1,87	Up
PRRC2B	proline-rich coiled-coil 2B	1,56	Up
KIAA0586	KIAA0586	1,70	Up
KIAA0753	KIAA0753	1,61	Up
AHCYL2	adenosylhomocysteinase-like 2	1,62	Up
MAU2	MAU2 sister chromatid cohesion factor	1,65	Up
KIAA0907	KIAA0907	1,96	Up
ZSWIM8	zinc finger, SWIM-type containing 8	1,83	Down
FAM149B1	family with sequence similarity 149, member B1	1,88	Down
SIK3	SIK family kinase 3	1,58	Up
KIAA1033	KIAA1033	1,82	Up
PALD1	phosphatase domain containing, paladin 1	1,83	Up
KIAA1328	KIAA1328	2,62	Down
KIAA1377	KIAA1377	1,54	Up
KIAA1462	KIAA1462	1,54	Up
ERV3-2	endogenous retrovirus group 3, member 2	2,14	Up
NYAP2	neuronal tyrosine-phosphorylated phosphoinositide-3-kinase adaptor 2	1,76	Up
CCDC146	coiled-coil domain containing 146	1,56	Up
KIAA1524	KIAA1524	1,58	Up
FAM214B	family with sequence similarity 214, member B	1,72	Up
TLDC1	TBC/LysM-associated domain containing 1	1,60	Up
TLDC1	TBC/LysM-associated domain containing 1	2,25	Up
KIAA1614	KIAA1614	1,53	Up
EPG5	ectopic P-granules autophagy protein 5 homolog (C. elegans)	1,87	Up
ANKRD36B	ankyrin repeat domain 36B	1,58	Up
KIAA1715	KIAA1715	2,33	Up
ZNF518B	zinc finger protein 518B	1,56	Down
KIAA1751	KIAA1751	1,53	Up
TNRC18	trinucleotide repeat containing 18	1,69	Down
KIAA1875	KIAA1875	2,27	Down
TMEM200A	transmembrane protein 200A	1,54	Up
TMEM200A	transmembrane protein 200A	1,52	Up
KIAA1919	KIAA1919	1,62	Up
KIAA1919	KIAA1919	1,61	Up
PEAK1	pseudopodium-enriched atypical kinase 1	2,00	Up
KIAA2013	KIAA2013	1,69	Up
KIF1C	kinesin family member 1C	2,14	Down
KIF23	kinesin family member 23	1,60	Up
KIF24	kinesin family member 24	1,53	Up
KIF26B	kinesin family member 26B	1,95	Up
KIF5A	kinesin family member 5A	1,94	Up
KIR2DS1	killer cell immunoglobulin-like receptor, two domains, short cytoplasmic tail, 1	1,67	Up
KISS1R	KISS1 receptor	1,66	Down
KLC2	kinesin light chain 2	1,97	Up
KLC4	kinesin light chain 4	1,61	Up
KLF13	Kruppel-like factor 13	1,75	Up
KLF3	Kruppel-like factor 3 (basic)	1,60	Up
KLF8	Kruppel-like factor 8	1,57	Up
KLHDC1	kelch domain containing 1	1,52	Up
KLHDC3	kelch domain containing 3	1,67	Up
KLHL12	kelch-like family member 12	1,54	Up
KLHL15	kelch-like family member 15	1,53	Up
KLHL18	kelch-like family member 18	2,33	Up
KLHL20	kelch-like family member 20	1,52	Down
KLHL24	kelch-like family member 24	1,61	Up
KLHL5	kelch-like family member 5	1,53	Up
KLHL9	kelch-like family member 9	1,58	Up
KLK10	kallikrein-related peptidase 10	1,74	Up
KLK15	kallikrein-related peptidase 15	1,61	Up
KLK2	kallikrein-related peptidase 2	1,53	Up
KLK5	kallikrein-related peptidase 5	1,73	Up
KLK7	kallikrein-related peptidase 7	1,67	Up
KNG1	kininogen 1	1,94	Up
KRBA1	KRAB-A domain containing 1	1,50	Up
KREMEN1	kringle containing transmembrane protein 1	1,57	Up
KRT10	keratin 10	2,57	Up
KRT18P16	keratin 18 pseudogene 16	2,02	Up
KRT18P21	keratin 18 pseudogene 21	1,54	Up
KRT23	keratin 23 (histone deacetylase inducible)	2,49	Up
KRT27	keratin 27	1,59	Up
KRT3	keratin 3	1,90	Down
KRT31	keratin 31	3,90	Up
KRT32	keratin 32	1,86	Up
KRT34	keratin 34	4,58	Up
KRT35	keratin 35	1,99	Up
KRT37	keratin 37	1,81	Down
KRT38	keratin 38	2,11	Up
KRT5	keratin 5	1,96	Up
KRT76	keratin 76	1,86	Up
KRT8	keratin 8	1,55	Up
KRT85	keratin 85	2,02	Up
KRT86	keratin 86	3,43	Up
KRTAP1-3	keratin associated protein 1-3	3,32	Up
KRTAP1-3	keratin associated protein 1-3	1,69	Down
KRTAP13-2	keratin associated protein 13-2	1,74	Up
KRTAP13-4	keratin associated protein 13-4	2,20	Down
KRTAP15-1	keratin associated protein 15-1	2,00	Up
KRTAP19-1	keratin associated protein 19-1	2,14	Up
KRTAP2-4	keratin associated protein 2-4	1,68	Up
KRTAP2-4	keratin associated protein 2-4	2,28	Up
KRTAP2-4	keratin associated protein 2-4	2,21	Down
KRTAP2-4	keratin associated protein 2-4	1,83	Down
KRTAP3-1	keratin associated protein 3-1	5,35	Up
KRTAP3-2	keratin associated protein 3-2	3,18	Up
KRTAP4-1	keratin associated protein 4-1	2,56	Up
KRTAP4-1	keratin associated protein 4-1	1,84	Down
KRTAP4-2	keratin associated protein 4-2	1,83	Up
KRTAP4-5	keratin associated protein 4-5	4,40	Up
KRTAP4-7	keratin associated protein 4-7	3,02	Up
KRTAP4-8	keratin associated protein 4-8	4,07	Up
KRTAP4-9	keratin associated protein 4-9	3,38	Up
KRTAP5-9	keratin associated protein 5-9	1,57	Down
KRTAP9-2	keratin associated protein 9-2	3,86	Up
KRTAP9-3	keratin associated protein 9-3	2,79	Up
KRTAP9-4	keratin associated protein 9-4	5,60	Up
KSR1	kinase suppressor of ras 1	1,61	Up
POGLUT1	protein O-glucosyltransferase 1	1,60	Up
TMEM189-UBE2V1	TMEM189-UBE2V1 readthrough	1,83	Up
L1CAM	L1 cell adhesion molecule	1,66	Down
L2HGDH	L-2-hydroxyglutarate dehydrogenase	1,73	Up
L3MBTL1	l(3)mbt-like 1 (Drosophila)	1,50	Up
L3MBTL2	l(3)mbt-like 2 (Drosophila)	1,83	Up
LAGE3	L antigen family, member 3	1,81	Up
LAMA1	laminin, alpha 1	1,50	Up
LANCL3	LanC lantibiotic synthetase component C-like 3 (bacterial)	1,56	Up
LAPTM4B	lysosomal protein transmembrane 4 beta	1,73	Up

LARP1B	La ribonucleoprotein domain family, member 1B	1,54	Up
LAT2	linker for activation of T cells family, member 2	1,60	Up
LAT2	linker for activation of T cells family, member 2	1,70	Up
LATS2	large tumor suppressor kinase 2	1,73	Up
LAYN	layilin	1,51	Up
LBH	limb bud and heart development	1,81	Down
LBX2	ladybird homeobox 2	2,02	Up
LCE1A	late cornified envelope 1A	2,70	Down
LCE1C	late cornified envelope 1C	3,42	Down
LCE1D	late cornified envelope 1D	2,15	Down
LCE2B	late cornified envelope 2B	2,95	Up
LCE2B	late cornified envelope 2B	7,29	Up
LCE2C	late cornified envelope 2C	4,35	Up
LCE2D	late cornified envelope 2D	1,60	Down
LCE3D	late cornified envelope 3D	2,26	Up
LCE3E	late cornified envelope 3E	1,98	Down
LCN12	lipocalin 12	1,77	Up
LCN8	lipocalin 8	1,57	Up
LDB3	LIM domain binding 3	1,77	Up
LDHA	lactate dehydrogenase A	1,95	Up
LEMD2	LEM domain containing 2	1,66	Up
MBOAT7	membrane bound O-acyltransferase domain containing 7	1,58	Up
LFNG	LFNG O-fucosylpeptide 3-beta-N-acetylglucosaminyltransferase	2,21	Down
LGALS1	lectin, galactoside-binding, soluble, 1	1,86	Up
LGALS14	lectin, galactoside-binding, soluble, 14	1,54	Up
LGALS2	lectin, galactoside-binding, soluble, 2	2,42	Up
LGALS3	lectin, galactoside-binding, soluble, 3	2,04	Up
LGALS7	lectin, galactoside-binding, soluble, 7	1,51	Up
LGALS8	lectin, galactoside-binding, soluble, 8	2,00	Down
LGI4	leucine-rich repeat LGI family, member 4	1,84	Up
LHCGR	luteinizing hormone/choriogonadotropin receptor	1,51	Up
LHX1	LIM homeobox 1	1,70	Down
LHX2	LIM homeobox 2	2,12	Up
LIG3	ligase III, DNA, ATP-dependent	2,31	Down
LIMD2	LIM domain containing 2	1,51	Up
LIN7B	lin-7 homolog B (C. elegans)	1,62	Up
LINGO4	leucine rich repeat and Ig domain containing 4	1,51	Down
LLGL2	lethal giant larvae homolog 2 (Drosophila)	1,80	Up
LMAN2	lectin, mannose-binding 2	1,81	Up
LMBRD1	LMBR1 domain containing 1	2,00	Up
LMO1	LIM domain only 1 (rhombotin 1)	1,54	Up
LMO4	LIM domain only 4	1,69	Up
LMOD1	leiomodin 1 (smooth muscle)	1,61	Up
LNX1	ligand of numb-protein X 1, E3 ubiquitin protein ligase	1,63	Up
ZNF841	zinc finger protein 841	1,76	Up
C2orf74	chromosome 2 open reading frame 74	1,51	Down
SMCO2	single-pass membrane protein with coiled-coil domains 2	1,76	Up
C19orf68	chromosome 19 open reading frame 68	1,80	Down
TRNP1	TMF1-regulated nuclear protein 1	1,52	Up
NPIPB15	nuclear pore complex interacting protein family, member B15	1,88	Up
UBXN1	UBX domain protein 1	1,63	Up
FAM178B	family with sequence similarity 178, member B	1,77	Up
VWA5A	von Willebrand factor A domain containing 5A	1,52	Up
LONRF1	LON peptidase N-terminal domain and ring finger 1	1,52	Up
LOR	loricrin	3,57	Up
LOXL2	lysyl oxidase-like 2	1,56	Up
LPA	lipoprotein, Lp(a)	1,55	Up
LPAL2	lipoprotein, Lp(a)-like 2, pseudogene	1,93	Up
LRAT	lecithin retinol acyltransferase (phosphatidylcholine--retinol O-acyltransferase)	1,95	Up
LRCH2	leucine-rich repeats and calponin homology (CH) domain containing 2	1,94	Up
LRCH3	leucine-rich repeats and calponin homology (CH) domain containing 3	1,84	Up
LRFN2	leucine rich repeat and fibronectin type III domain containing 2	1,67	Up
LRFN5	leucine rich repeat and fibronectin type III domain containing 5	2,04	Up
LRP10	low density lipoprotein receptor-related protein 10	1,53	Up
LRP10	low density lipoprotein receptor-related protein 10	1,65	Down
LRP3	low density lipoprotein receptor-related protein 3	1,70	Down
LRP5	low density lipoprotein receptor-related protein 5	1,94	Up
LRRC18	leucine rich repeat containing 18	1,94	Up
LRRC2	leucine rich repeat containing 2	1,55	Up
NRROS	negative regulator of reactive oxygen species	1,83	Up
LRRC34	leucine rich repeat containing 34	1,75	Up
LRRC39	leucine rich repeat containing 39	1,51	Up
LRRC41	leucine rich repeat containing 41	1,75	Up
LRRC49	leucine rich repeat containing 49	1,70	Up
LRTOMT	leucine rich transmembrane and O-methyltransferase domain containing	1,57	Up
CEP97	centrosomal protein 97kDa	1,51	Up
LSAMP	limbic system-associated membrane protein	2,07	Up
PLIN5	perilipin 5	1,59	Up
LSG1	large 60S subunit nuclear export GTPase 1	1,75	Up
LSS	lanosterol synthase (2,3-oxidosqualene-lanosterol cyclase)	1,63	Up
LSS	lanosterol synthase (2,3-oxidosqualene-lanosterol cyclase)	1,93	Up
LSS	lanosterol synthase (2,3-oxidosqualene-lanosterol cyclase)	1,53	Up
LTBP3	latent transforming growth factor beta binding protein 3	1,63	Up
LRRC2-AS1	LRRC2 antisense RNA 1	1,74	Up
LY6H	lymphocyte antigen 6 complex, locus H	1,51	Down
LY6K	lymphocyte antigen 6 complex, locus K	1,58	Up
LYG2	lysozyme G-like 2	1,53	Up
LYN	v-yes-1 Yamaguchi sarcoma viral related oncogene homolog	1,51	Up
LYNX1	Ly6/neurotoxin 1	2,34	Down
LYPD3	LY6/PLAUR domain containing 3	2,20	Up
LYRM1	LYR motif containing 1	1,59	Up
LYZL2	lysozyme-like 2	2,25	Up
SEC16B	SEC16 homolog B (S. cerevisiae)	1,58	Up
MAEA	macrophage erythroblast attacher	1,58	Up
MAF	v-maf avian musculoaponeurotic fibrosarcoma oncogene homolog	2,04	Up
MAFF	v-maf avian musculoaponeurotic fibrosarcoma oncogene homolog F	1,81	Up
MAGEA10	melanoma antigen family A, 10	1,66	Up
MAGEA8	melanoma antigen family A, 8	1,73	Up
MAGEB1	melanoma antigen family B, 1	1,65	Up
MAGEC3	melanoma antigen family C, 3	1,54	Up
MAGI3	membrane associated guanylate kinase, WW and PDZ domain containing 3	1,65	Up
MAK	male germ cell-associated kinase	1,63	Up
MALAT1	metastasis associated lung adenocarcinoma transcript 1 (non-protein coding)	2,00	Up
MAML1	mastermind-like 1 (Drosophila)	1,71	Up
MAN1A2	mannosidase, alpha, class 1A, member 2	2,06	Up
MAN2A1	mannosidase, alpha, class 2A, member 1	2,50	Up
MAN2A2	mannosidase, alpha, class 2A, member 2	2,18	Up
MAN2A2	mannosidase, alpha, class 2A, member 2	1,79	Up
MAN2C1	mannosidase, alpha, class 2C, member 1	1,63	Down
MAP1A	microtubule-associated protein 1A	2,13	Up
MAP1B	microtubule-associated protein 1B	2,00	Up
MAP2K1	mitogen-activated protein kinase kinase 1	1,72	Up
MAP2K3	mitogen-activated protein kinase kinase 3	3,08	Up
MAP2K4	mitogen-activated protein kinase kinase 4	1,52	Up
MAP2K6	mitogen-activated protein kinase kinase 6	1,56	Up
MAP2K6	mitogen-activated protein kinase kinase 6	1,51	Up
MAP3K13	mitogen-activated protein kinase kinase kinase 13	1,59	Up
MAP3K3	mitogen-activated protein kinase kinase kinase 3	1,53	Up
MAP6D1	MAP6 domain containing 1	1,64	Up
MAP7D1	MAP7 domain containing 1	1,55	Up
MAP7D2	MAP7 domain containing 2	1,63	Up
MAPK15	mitogen-activated protein kinase 15	1,69	Up
MAPK8	mitogen-activated protein kinase 8	1,72	Up
MAPK8	mitogen-activated protein kinase 8	1,52	Down
MAPK8IP1	mitogen-activated protein kinase 8 interacting protein 1	1,61	Up
MAPKBP1	mitogen-activated protein kinase binding protein 1	1,71	Up
MARCKS	myristoylated alanine-rich protein kinase C substrate	1,73	Up
MARK4	MAP/microtubule affinity-regulating kinase 4	1,54	Up
MARVELD2	MARVEL domain containing 2	2,07	Down
MAST1	microtubule associated serine/threonine kinase 1	3,02	Down
MATN1	matrilin 1, cartilage matrix protein	1,58	Up
MBD5	methyl-CpG binding domain protein 5	1,66	Up
MBL2	mannose-binding lectin (protein C) 2, soluble	2,13	Up
MC1R	melanocortin 1 receptor (alpha melanocyte stimulating hormone receptor)	1,50	Up
MC3R	melanocortin 3 receptor	1,74	Up
MC5R	melanocortin 5 receptor	1,60	Up
MCAM	melanoma cell adhesion molecule	1,69	Up
MCAM	melanoma cell adhesion molecule	1,51	Up
SLC25A52	solute carrier family 25, member 52	1,60	Down
MCF2L	MCF.2 cell line derived transforming sequence-like	1,56	Up

MCFD2	multiple coagulation factor deficiency 2	1,53	Up
MCL1	myeloid cell leukemia sequence 1 (BCL2-related)	1,53	Down
MCM3AP-AS1	MCM3AP antisense RNA 1	2,49	Up
MCM3AP-AS1	MCM3AP antisense RNA 1	1,61	Up
MCPH1	microcephalin 1	1,72	Up
MCTP2	multiple C2 domains, transmembrane 2	1,60	Up
MECOM	MDS1 and EVI1 complex locus	1,54	Up
ME1	malic enzyme 1, NADP(+)-dependent, cytosolic	1,62	Up
MEA1	male-enhanced antigen 1	1,69	Up
MECP2	methyl CpG binding protein 2 (Rett syndrome)	1,82	Up
MEF2B	myocyte enhancer factor 2B	3,39	Down
MEGF11	multiple EGF-like-domains 11	1,52	Up
MEP1A	meprin A, alpha (PABA peptide hydrolase)	1,62	Up
METAP1	methionyl aminopeptidase 1	1,96	Up
METTL15	methyltransferase like 15	1,71	Up
METTL4	methyltransferase like 4	2,33	Up
MFAP1	microfibrillar-associated protein 1	2,15	Up
MFHAS1	malignant fibrous histiocytoma amplified sequence 1	1,68	Up
MFI2	antigen p97 (melanoma associated) identified by monoclonal antibodies 133.2 and 96.5	1,54	Up
MFN1	mitofusin 1	1,58	Up
MFNG	MFNG O-fucosylpeptide 3-beta-N-acetylglucosaminyltransferase	1,61	Up
MFSD3	major facilitator superfamily domain containing 3	1,55	Up
MFSD5	major facilitator superfamily domain containing 5	1,59	Up
MFSD8	major facilitator superfamily domain containing 8	1,61	Up
MGA	MGA, MAX dimerization protein	1,58	Up
DLGAP1-AS2	DLGAP1 antisense RNA 2	1,77	Up
TMEM216	transmembrane protein 216	1,70	Up
MIR22HG	MIR22 host gene (non-protein coding)	3,27	Down
MIR503HG	MIR503 host gene (non-protein coding)	1,75	Up
C16orf62	chromosome 16 open reading frame 62	1,55	Up
C5orf46	chromosome 5 open reading frame 46	2,21	Up
FNDC9	fibronectin type III domain containing 9	1,51	Up
RPS2P32	ribosomal protein S2 pseudogene 32	1,54	Up
GABPB2	GA binding protein transcription factor, beta subunit 2	1,52	Down
SLC22A24	solute carrier family 22, member 24	1,64	Up
CYP1B1-AS1	CYP1B1 antisense RNA 1	1,51	Up
PRR18	proline rich 18	1,64	Down
LINC00663	long intergenic non-protein coding RNA 663	1,77	Down
LINC00626	long intergenic non-protein coding RNA 626	1,97	Up
C6orf223	chromosome 6 open reading frame 223	1,65	Up
COA5	cytochrome c oxidase assembly factor 5	1,57	Up
CCDC144NL	coiled-coil domain containing 144 family, N-terminal like	1,81	Up
MICALL1	MICAL-like 1	2,66	Down
MICB	MHC class I polypeptide-related sequence B	2,00	Up
MIDN	midnolin	2,34	Up
MINA	MYC induced nuclear antigen	1,72	Up
MINK1	misshapen-like kinase 1	1,80	Up
HINFP	histone H4 transcription factor	1,55	Up
MLANA	melan-A	1,91	Up
MLF1	myeloid leukemia factor 1	1,71	Up
KMT2C	lysine (K)-specific methyltransferase 2C	1,77	Down
MLLT6	myeloid/lymphoid or mixed-lineage leukemia (trithorax homolog, Drosophila); translocated to, 6	1,98	Up
MLLT6	myeloid/lymphoid or mixed-lineage leukemia (trithorax homolog, Drosophila); translocated to, 6	1,99	Up
MLN	motilin	1,62	Up
MLNR	motilin receptor	1,81	Up
MLPH	melanophilin	1,65	Up
MLXIP	MLX interacting protein	1,60	Up
MLXIPL	MLX interacting protein-like	1,91	Down
MLYCD	malonyl-CoA decarboxylase	1,50	Down
MMAB	methylmalonic aciduria (cobalamin deficiency) cblB type	1,58	Up
MMAB	methylmalonic aciduria (cobalamin deficiency) cblB type	1,76	Up
MME	membrane metallo-endopeptidase	1,56	Up
MMP17	matrix metallopeptidase 17 (membrane-inserted)	3,29	Down
MMRN1	multimerin 1	1,65	Up
MMRN2	multimerin 2	1,78	Up
MOB1A	MOB kinase activator 1A	1,67	Up
MOB3C	MOB kinase activator 3C	1,56	Down
MOCS1	molybdenum cofactor synthesis 1	1,95	Up
MOGAT1	monoacylglycerol O-acyltransferase 1	1,51	Up
MON1B	MON1 secretory trafficking family member B	1,93	Down
MORF4	mortality factor 4	1,51	Up
MORF4L2	mortality factor 4 like 2	1,78	Up
MARC2	mitochondrial amidoxime reducing component 2	1,66	Up
MPDZ	multiple PDZ domain protein	2,47	Down
MPEG1	macrophage expressed 1	1,93	Up
MPHOSPH9	M-phase phosphoprotein 9	2,15	Up
MPND	MPN domain containing	1,60	Up
MPP7	membrane protein, palmitoylated 7 (MAGUK p55 subfamily member 7)	1,60	Up
MPPE1	metallophosphoesterase 1	1,67	Up
MPV17	MpV17 mitochondrial inner membrane protein	2,06	Up
MPV17L	MPV17 mitochondrial membrane protein-like	1,54	Up
MR1	major histocompatibility complex, class I-related	1,95	Up
MRAP	melanocortin 2 receptor accessory protein	1,93	Up
MRGPRX1	MAS-related GPR, member X1	1,59	Up
MPRIP	myosin phosphatase Rho interacting protein	1,70	Up
MYL12B	myosin, light chain 12B, regulatory	1,69	Up
MRPL10	mitochondrial ribosomal protein L10	2,07	Up
MRPL16	mitochondrial ribosomal protein L16	1,96	Up
MRPL24	mitochondrial ribosomal protein L24	1,68	Up
MRPL35	mitochondrial ribosomal protein L35	1,50	Up
MRPL4	mitochondrial ribosomal protein L4	1,87	Up
MRPL42	mitochondrial ribosomal protein L42	1,89	Up
MRPS12	mitochondrial ribosomal protein S12	1,52	Up
MRPS18B	mitochondrial ribosomal protein S18B	1,76	Up
MRPS24	mitochondrial ribosomal protein S24	2,00	Up
MRPS25	mitochondrial ribosomal protein S25	1,72	Up
MRPS27	mitochondrial ribosomal protein S27	1,54	Up
MRPS31	mitochondrial ribosomal protein S31	1,58	Up
MRPS36	mitochondrial ribosomal protein S36	1,58	Up
MRVI1	murine retrovirus integration site 1 homolog	1,55	Up
MS4A3	membrane-spanning 4-domains, subfamily A, member 3 (hematopoietic cell-specific)	1,84	Up
MS4A4A	membrane-spanning 4-domains, subfamily A, member 4A	1,82	Up
MSH2	mutS homolog 2	1,54	Up
MSI2	musashi RNA-binding protein 2	1,65	Up
MSMB	microseminoprotein, beta-	1,68	Up
MSRA	methionine sulfoxide reductase A	2,93	Down
MSX1	msh homeobox 1	1,70	Down
MSX2	msh homeobox 2	1,74	Up
MT1JP	metallothionein 1J, pseudogene	1,60	Up
MTA1	metastasis associated 1	2,28	Down
MTA2	metastasis associated 1 family, member 2	1,94	Up
TC2N	tandem C2 domains, nuclear	1,71	Up
MTCH1	mitochondrial carrier 1	1,60	Up
MTF1	metal-regulatory transcription factor 1	1,54	Up
MTMR2	myotubularin related protein 2	1,63	Up
MTMR6	myotubularin related protein 6	1,85	Up
MTMR9	myotubularin related protein 9	1,81	Up
MTMR9	myotubularin related protein 9	1,68	Up
MTNR1A	melatonin receptor 1A	1,63	Up
MTPN	myotrophin	1,54	Up
MTRF1L	mitochondrial translational release factor 1-like	1,62	Up
MTX1	metaxin 1	1,60	Up
MUC16	mucin 16, cell surface associated	1,69	Up
MUC20	mucin 20, cell surface associated	1,81	Up
MUC4	mucin 4, cell surface associated	1,75	Up
MUC5AC	mucin 5AC, oligomeric mucus/gel-forming	1,74	Up
MUC5B	mucin 5B, oligomeric mucus/gel-forming	1,51	Up
MUC5B	mucin 5B, oligomeric mucus/gel-forming	1,56	Up
MUS81	MUS81 structure-specific endonuclease subunit	1,53	Up
MX2	myxovirus (influenza virus) resistance 2 (mouse)	1,56	Up
MXRA5	matrix-remodelling associated 5	1,66	Up
MXRA8	matrix-remodelling associated 8	1,59	Down
MYADM	myeloid-associated differentiation marker	1,75	Up
MYADM	myeloid-associated differentiation marker	1,69	Up
MYBL1	v-myb avian myeloblastosis viral oncogene homolog-like 1	1,52	Up
MYBPC2	myosin binding protein C, fast type	1,69	Up
MYCBP	MYC binding protein	1,68	Up
MYCN	v-myc avian myelocytomatosis viral oncogene neuroblastoma derived homolog	1,60	Down
MYD88	myeloid differentiation primary response 88	1,66	Up
MYH10	myosin, heavy chain 10, non-muscle	2,59	Up

MYL3	myosin, light chain 3, alkali; ventricular, skeletal, slow	1,65	Up
MYL4	myosin, light chain 4, alkali; atrial, embryonic	1,69	Up
MYL4	myosin, light chain 4, alkali; atrial, embryonic	1,52	Up
MYO10	myosin X	1,84	Up
MYO15B	myosin XVB pseudogene	1,59	Up
MYO15B	myosin XVB pseudogene	1,51	Up
MYO1B	myosin IB	1,76	Up
MYO1C	myosin IC	1,51	Up
MYO1G	myosin IG	1,59	Up
MYO6	myosin VI	1,60	Up
MYO7A	myosin VIIA	1,63	Up
MYOD1	myogenic differentiation 1	1,55	Down
MYOG	myogenin (myogenic factor 4)	1,81	Up
MYOM1	myomesin 1	1,59	Up
MYRIP	myosin VIIA and Rab interacting protein	1,52	Up
KAT8	K(lysine) acetyltransferase 8	1,71	Up
N4BP3	NEDD4 binding protein 3	1,62	Down
NADSYN1	NAD synthetase 1	1,70	Up
SND1-IT1	SND1 intronic transcript 1 (non-protein coding)	2,88	Up
NAGS	N-acetylglutamate synthase	1,75	Up
NANOGP1	Nanog homeobox pseudogene 1	1,96	Up
NANP	N-acetylneuraminic acid phosphatase	1,58	Up
NAPSB	napsin B aspartic peptidase, pseudogene	1,53	Up
NARFL	nuclear prelamin A recognition factor-like	1,68	Up
NAT10	N-acetyltransferase 10 (GCN5-related)	1,71	Up
NAT6	N-acetyltransferase 6 (GCN5-related)	1,78	Up
NAV2	neuron navigator 2	1,81	Up
NAV2	neuron navigator 2	1,57	Up
NBPF11	neuroblastoma breakpoint family, member 11	1,62	Up
NBR2	neighbor of BRCA1 gene 2 (non-protein coding)	1,89	Up
NCKIPSD	NCK interacting protein with SH3 domain	1,52	Down
NCKIPSD	NCK interacting protein with SH3 domain	1,53	Down
NCL	nucleolin	1,59	Up
NCR3	natural cytotoxicity triggering receptor 3	1,53	Up
MT-ND3	mitochondrially encoded NADH dehydrogenase 3	6,46	Up
NDFIP1	Nedd4 family interacting protein 1	2,07	Up
NDOR1	NADPH dependent diflavin oxidoreductase 1	2,61	Down
NDP	Norrie disease (pseudoglioma)	1,57	Up
NDRG1	N-myc downstream regulated 1	1,75	Up
NDRG2	NDRG family member 2	1,52	Down
NDST1	N-deacetylase/N-sulfotransferase (heparan glucosaminyl) 1	1,52	Up
NDST2	N-deacetylase/N-sulfotransferase (heparan glucosaminyl) 2	1,62	Up
NDST4	N-deacetylase/N-sulfotransferase (heparan glucosaminyl) 4	1,70	Up
NDUFA10	NADH dehydrogenase (ubiquinone) 1 alpha subcomplex, 10, 42kDa	1,56	Up
NDUFA13	NADH dehydrogenase (ubiquinone) 1 alpha subcomplex, 13	1,59	Up
NDUFA3	NADH dehydrogenase (ubiquinone) 1 alpha subcomplex, 3, 9kDa	2,39	Down
NDUFA8	NADH dehydrogenase (ubiquinone) 1 alpha subcomplex, 8, 19kDa	1,71	Up
NDUFB2	NADH dehydrogenase (ubiquinone) 1 beta subcomplex, 2, 8kDa	1,61	Up
NDUFB4	NADH dehydrogenase (ubiquinone) 1 beta subcomplex, 4, 15kDa	2,75	Up
NDUFB7	NADH dehydrogenase (ubiquinone) 1 beta subcomplex, 7, 18kDa	3,47	Down
NDUFB8	NADH dehydrogenase (ubiquinone) 1 beta subcomplex, 8, 19kDa	2,10	Up
NDUFS1	NADH dehydrogenase (ubiquinone) Fe-S protein 1, 75kDa (NADH-coenzyme Q reductase)	1,73	Up
NDUFS7	NADH dehydrogenase (ubiquinone) Fe-S protein 7, 20kDa (NADH-coenzyme Q reductase)	3,30	Down
NDUFV2	NADH dehydrogenase (ubiquinone) flavoprotein 2, 24kDa	1,54	Up
NDUFV3	NADH dehydrogenase (ubiquinone) flavoprotein 3, 10kDa	1,85	Up
NEFL	neurofilament, light polypeptide	1,57	Up
NEK9	NIMA-related kinase 9	1,50	Up
NENF	neudesin neurotrophic factor	1,54	Up
NEO1	neogenin 1	2,74	Down
NES	nestin	1,69	Up
NETO1	neuropilin (NRP) and tolloid (TLL)-like 1	2,13	Up
NEUROD2	neuronal differentiation 2	1,54	Up
NEUROG1	neurogenin 1	2,72	Down
NEUROG3	neurogenin 3	1,70	Down
NFATC2IP	nuclear factor of activated T-cells, cytoplasmic, calcineurin-dependent 2 interacting protein	1,54	Up
NFATC3	nuclear factor of activated T-cells, cytoplasmic, calcineurin-dependent 3	1,68	Up
NFIA	nuclear factor I/A	1,61	Up
NFIB	nuclear factor I/B	1,56	Up
NFIX	nuclear factor I/X (CCAAT-binding transcription factor)	1,92	Down
NFKBIL1	nuclear factor of kappa light polypeptide gene enhancer in B-cells inhibitor-like 1	2,07	Down
NGB	neuroglobin	1,73	Up
NGFRAP1	nerve growth factor receptor (TNFRSF16) associated protein 1	2,21	Up
BEX5	brain expressed, X-linked 5	1,83	Up
NGLY1	N-glycanase 1	1,74	Up
NHP2L1	NHP2 non-histone chromosome protein 2-like 1 (S. cerevisiae)	1,63	Down
NID1	nidogen 1	1,59	Up
NIN	ninein (GSK3B interacting protein)	1,54	Up
NKD1	naked cuticle homolog 1 (Drosophila)	1,54	Down
NKD2	naked cuticle homolog 2 (Drosophila)	2,35	Down
NKX1-2	NK1 homeobox 2	2,28	Down
NKX2-8	NK2 homeobox 8	1,70	Down
NKX3-1	NK3 homeobox 1	1,91	Up
NLRC3	NLR family, CARD domain containing 3	1,55	Up
NLRC4	NLR family, CARD domain containing 4	1,53	Up
NLRP7	NLR family, pyrin domain containing 7	1,55	Up
NMD3	NMD3 ribosome export adaptor	1,51	Up
NME2P1	NME/NM23 nucleoside diphosphate kinase 2 pseudogene 1	1,79	Up
NME6	NME/NM23 nucleoside diphosphate kinase 6	1,98	Up
NMT1	N-myristoyltransferase 1	1,68	Up
NMU	neuromedin U	1,87	Up
NMUR2	neuromedin U receptor 2	2,05	Up
NOL11	nucleolar protein 11	1,52	Up
NOP14	NOP14 nucleolar protein	1,72	Up
NOL4	nucleolar protein 4	1,64	Up
NOL6	nucleolar protein 6 (RNA-associated)	1,65	Up
NONO	non-POU domain containing, octamer-binding	1,76	Up
NOTCH2	notch 2	1,87	Down
NOTCH4	notch 4	1,58	Down
NOV	nephroblastoma overexpressed	1,73	Up
NOVA1	neuro-oncological ventral antigen 1	1,70	Up
NOX1	NADPH oxidase 1	1,70	Up
NPAS3	neuronal PAS domain protein 3	1,56	Down
NPB	neuropeptide B	1,51	Down
NPC1L1	NPC1-like 1	1,60	Up
NPFF	neuropeptide FF-amide peptide precursor	1,51	Up
NPFFR2	neuropeptide FF receptor 2	2,01	Up
NPHP1	nephronophthisis 1 (juvenile)	1,71	Up
NPHP3	nephronophthisis 3 (adolescent)	1,63	Up
NPHS2	nephrosis 2, idiopathic, steroid-resistant (podocin)	1,66	Up
NPIPA1	nuclear pore complex interacting protein family, member A1	1,52	Up
NPM1	nucleophosmin (nucleolar phosphoprotein B23, numatrin)	3,18	Down
NPTN	neuroplastin	1,52	Up
NPTXR	neuronal pentraxin receptor	1,91	Up
NPVF	neuropeptide VF precursor	1,53	Up
NR1H4	nuclear receptor subfamily 1, group H, member 4	1,92	Up
NR5A1	nuclear receptor subfamily 5, group A, member 1	1,81	Up
NR6A1	nuclear receptor subfamily 6, group A, member 1	1,61	Up
NRAP	nebulin-related anchoring protein	1,57	Down
NRD1	nardilysin (N-arginine dibasic convertase)	1,58	Up
NRG1	neuregulin 1	1,55	Up
NRIP2	nuclear receptor interacting protein 2	1,60	Up
NRN1L	neuritin 1-like	1,58	Up
NRSN2	neurensin 2	2,32	Down
NSFL1C	NSFL1 (p97) cofactor (p47)	1,58	Up
NSMCE1	non-SMC element 1 homolog (S. cerevisiae)	1,53	Up
NT5E	5'-nucleotidase, ecto (CD73)	1,50	Up
NTRK2	neurotrophic tyrosine kinase, receptor, type 2	1,64	Up
NTRK3	neurotrophic tyrosine kinase, receptor, type 3	1,58	Up
NTSR1	neurotensin receptor 1 (high affinity)	1,65	Up
NUCB2	nucleobindin 2	1,74	Up
NUCKS1	nuclear casein kinase and cyclin-dependent kinase substrate 1	1,80	Up
NUCKS1	nuclear casein kinase and cyclin-dependent kinase substrate 1	2,07	Up
NUDT16	nudix (nucleoside diphosphate linked moiety X)-type motif 16	1,78	Up
NUP188	nucleoporin 188kDa	1,82	Up
NUP210L	nucleoporin 210kDa-like	1,52	Up
NUP98	nucleoporin 98kDa	1,75	Up
NUP98	nucleoporin 98kDa	1,55	Up
NUPL1	nucleoporin like 1	1,55	Up
NVL	nuclear VCP-like	1,64	Up
FAM153A	family with sequence similarity 153, member A	1,84	Up

OAZ1	ornithine decarboxylase antizyme 1	2,50	Up
OAZ1	ornithine decarboxylase antizyme 1	1,55	Up
OBSCN	obscurin, cytoskeletal calmodulin and titin-interacting RhoGEF	1,91	Up
OBSCN	obscurin, cytoskeletal calmodulin and titin-interacting RhoGEF	1,55	Up
OCM	oncomodulin	1,67	Up
TENM2	teneurin transmembrane protein 2	1,91	Up
TENM3	teneurin transmembrane protein 3	1,85	Up
OGFOD2	2-oxoglutarate and iron-dependent oxygenase domain containing 2	1,59	Up
OGFR	opioid growth factor receptor	2,32	Down
OGG1	8-oxoguanine DNA glycosylase	1,92	Up
OGN	osteoglycin	1,54	Up
OLFM1	olfactomedin 1	1,57	Up
OLFM2	olfactomedin 2	1,55	Up
OLFML2B	olfactomedin-like 2B	1,58	Up
OLIG3	oligodendrocyte transcription factor 3	1,71	Down
OMA1	OMA1 zinc metallopeptidase	1,57	Up
OPRK1	opioid receptor, kappa 1	1,97	Up
SIGMAR1	sigma non-opioid intracellular receptor 1	1,70	Up
OPTC	opticin	1,54	Up
OR10A5	olfactory receptor, family 10, subfamily A, member 5	1,90	Up
OR10H2	olfactory receptor, family 10, subfamily H, member 2	3,00	Down
OR10J1	olfactory receptor, family 10, subfamily J, member 1	1,70	Up
OR10J3	olfactory receptor, family 10, subfamily J, member 3	1,56	Up
OR10P1	olfactory receptor, family 10, subfamily P, member 1	2,42	Up
OR11H12	olfactory receptor, family 11, subfamily H, member 12	1,51	Up
OR12D3	olfactory receptor, family 12, subfamily D, member 3	1,65	Up
OR1A1	olfactory receptor, family 1, subfamily A, member 1	1,81	Up
OR1A2	olfactory receptor, family 1, subfamily A, member 2	1,61	Up
OR1D2	olfactory receptor, family 1, subfamily D, member 2	1,78	Up
OR1F2P	olfactory receptor, family 1, subfamily F, member 2	1,54	Up
OR1S2	olfactory receptor, family 1, subfamily S, member 2	2,17	Up
OR2A9P	olfactory receptor, family 2, subfamily A, member 9 pseudogene	1,99	Up
OR2H1	olfactory receptor, family 2, subfamily H, member 1	1,95	Down
OR2H2	olfactory receptor, family 2, subfamily H, member 2	1,94	Up
OR2J2	olfactory receptor, family 2, subfamily J, member 2	1,52	Up
OR2M2	olfactory receptor, family 2, subfamily M, member 2	1,67	Up
OR4C46	olfactory receptor, family 4, subfamily C, member 46	1,53	Up
OR4D2	olfactory receptor, family 4, subfamily D, member 2	3,01	Up
OR4X2	olfactory receptor, family 4, subfamily X, member 2	1,64	Up
OR51E1	olfactory receptor, family 51, subfamily E, member 1	1,55	Up
OR51G1	olfactory receptor, family 51, subfamily G, member 1	1,65	Up
OR52A1	olfactory receptor, family 52, subfamily A, member 1	2,04	Up
OR52B2	olfactory receptor, family 52, subfamily B, member 2	1,64	Up
OR52K2	olfactory receptor, family 52, subfamily K, member 2	1,51	Up
OR5AP2	olfactory receptor, family 5, subfamily AP, member 2	1,61	Up
OR5F1	olfactory receptor, family 5, subfamily F, member 1	1,79	Up
OR5T2	olfactory receptor, family 5, subfamily T, member 2	1,83	Up
OR6K2	olfactory receptor, family 6, subfamily K, member 2	2,34	Up
OR6M1	olfactory receptor, family 6, subfamily M, member 1	1,93	Up
OR6N1	olfactory receptor, family 6, subfamily N, member 1	1,59	Up
OR6W1P	olfactory receptor, family 6, subfamily W, member 1 pseudogene	1,75	Up
OR6Y1	olfactory receptor, family 6, subfamily Y, member 1	2,41	Up
OR7D2	olfactory receptor, family 7, subfamily D, member 2	1,57	Up
OR7E13P	olfactory receptor, family 7, subfamily E, member 13 pseudogene	2,13	Up
OR7E156P	olfactory receptor, family 7, subfamily E, member 156 pseudogene	1,84	Up
OR7E24	olfactory receptor, family 7, subfamily E, member 24	1,91	Up
OR7E91P	olfactory receptor, family 7, subfamily E, member 91 pseudogene	1,66	Up
OR8H1	olfactory receptor, family 8, subfamily H, member 1	1,84	Up
OR8U1	olfactory receptor, family 8, subfamily U, member 1	1,71	Up
ORC2	origin recognition complex, subunit 2	1,63	Up
ORMDL3	ORM1-like 3 (S. cerevisiae)	2,21	Up
OSBP	oxysterol binding protein	1,73	Down
OSBPL10	oxysterol binding protein-like 10	1,59	Up
OSBPL10	oxysterol binding protein-like 10	2,19	Up
OSBPL1A	oxysterol binding protein-like 1A	1,55	Up
OSBPL8	oxysterol binding protein-like 8	1,75	Up
OSBPL9	oxysterol binding protein-like 9	1,52	Up
OSMR	oncostatin M receptor	1,68	Up
OSR2	odd-skipped related transciption factor 2	1,66	Up
OSTF1	osteoclast stimulating factor 1	1,99	Up
OSTM1	osteopetrosis associated transmembrane protein 1	1,53	Up
OTOF	otoferlin	1,95	Down
OTOP2	otopetrin 2	1,62	Up
OTUD1	OTU domain containing 1	1,69	Up
OTUD7A	OTU domain containing 7A	1,58	Down
OXGR1	oxoglutarate (alpha-ketoglutarate) receptor 1	1,70	Up
OXR1	oxidation resistance 1	2,19	Up
OXSM	3-oxoacyl-ACP synthase, mitochondrial	1,51	Up
RPRD1A	regulation of nuclear pre-mRNA domain containing 1A	1,91	Up
P2RX3	purinergic receptor P2X, ligand-gated ion channel, 3	1,69	Up
P2RX6	purinergic receptor P2X, ligand-gated ion channel, 6	1,94	Down
P4HB	prolyl 4-hydroxylase, beta polypeptide	1,70	Up
TP53AIP1	tumor protein p53 regulated apoptosis inducing protein 1	1,79	Up
PABPC1	poly(A) binding protein, cytoplasmic 1	1,59	Up
PACRG	PARK2 co-regulated	1,81	Up
PACSIN3	protein kinase C and casein kinase substrate in neurons 3	1,50	Up
PADI4	peptidyl arginine deiminase, type IV	1,90	Up
PAG1	phosphoprotein associated with glycosphingolipid microdomains 1	1,61	Up
PAIP1	poly(A) binding protein interacting protein 1	1,79	Up
PAIP2B	poly(A) binding protein interacting protein 2B	1,79	Up
PANX3	pannexin 3	1,59	Up
PAPLN	papilin, proteoglycan-like sulfated glycoprotein	1,66	Up
PAPSS2	3'-phosphoadenosine 5'-phosphosulfate synthase 2	1,76	Up
PAQR8	progestin and adipoQ receptor family member VIII	1,57	Up
PARD3B	par-3 family cell polarity regulator beta	1,89	Up
PARG	poly (ADP-ribose) glycohydrolase	1,84	Up
PARP1	poly (ADP-ribose) polymerase 1	1,81	Up
PARP10	poly (ADP-ribose) polymerase family, member 10	1,55	Down
PARP2	poly (ADP-ribose) polymerase 2	1,52	Up
PATE1	prostate and testis expressed 1	1,66	Up
PAX1	paired box 1	1,65	Up
PAX3	paired box 3	1,80	Up
PAX5	paired box 5	1,77	Up
PAX6	paired box 6	1,55	Up
PAX7	paired box 7	1,96	Up
PBLD	phenazine biosynthesis-like protein domain containing	1,53	Up
PBX2	pre-B-cell leukemia homeobox 2	1,72	Up
PC	pyruvate carboxylase	2,11	Down
PCBP4	poly(rC) binding protein 4	1,52	Up
PCDH10	protocadherin 10	1,81	Up
PCDH7	protocadherin 7	1,75	Up
PCDHA1	protocadherin alpha 1	1,51	Down
PCDHB12	protocadherin beta 12	1,77	Up
PCDHB9	protocadherin beta 9	1,87	Up
PCDHGA7	protocadherin gamma subfamily A, 7	2,14	Down
PCDHGA8	protocadherin gamma subfamily A, 8	2,50	Up
PCDHGA9	protocadherin gamma subfamily A, 9	1,57	Up
PCDHGB1	protocadherin gamma subfamily B, 1	2,12	Up
PCDHGC4	protocadherin gamma subfamily C, 4	1,56	Up
PCGF1	polycomb group ring finger 1	2,26	Up
PCGF5	polycomb group ring finger 5	1,96	Up
PCK2	phosphoenolpyruvate carboxykinase 2 (mitochondrial)	1,63	Up
PCLO	piccolo presynaptic cytomatrix protein	1,55	Up
PCMT1	protein-L-isoaspartate (D-aspartate) O-methyltransferase	2,54	Up
PCNXL3	pecanex-like 3 (Drosophila)	2,18	Up
PCNXL3	pecanex-like 3 (Drosophila)	2,48	Down
PCOLCE	procollagen C-endopeptidase enhancer	1,61	Up
PCSK1N	proprotein convertase subtilisin/kexin type 1 inhibitor	1,62	Down
PCSK1N	proprotein convertase subtilisin/kexin type 1 inhibitor	2,34	Down
PCSK6	proprotein convertase subtilisin/kexin type 6	1,60	Up
CDK16	cyclin-dependent kinase 16	1,53	Up
PDCD1	programmed cell death 1	1,96	Up
PDCD11	programmed cell death 11	1,71	Up
PDCD4	programmed cell death 4 (neoplastic transformation inhibitor)	1,98	Up
PDCL3	phosducin-like 3	1,75	Up
PDE1B	phosphodiesterase 1B, calmodulin-dependent	1,75	Up
PDE1C	phosphodiesterase 1C, calmodulin-dependent 70kDa	1,61	Up
PDE4C	phosphodiesterase 4C, cAMP-specific	2,08	Up
PDE4D	phosphodiesterase 4D, cAMP-specific	1,62	Up
PDE6B	phosphodiesterase 6B, cGMP-specific, rod, beta	1,79	Up

PDIA3	protein disulfide isomerase family A, member 3	1,63	Up
PDIA3	protein disulfide isomerase family A, member 3	1,51	Up
PDIA6	protein disulfide isomerase family A, member 6	1,56	Up
PDK3	pyruvate dehydrogenase kinase, isozyme 3	1,54	Up
PDPK1	3-phosphoinositide dependent protein kinase-1	1,53	Up
PDRG1	p53 and DNA-damage regulated 1	1,63	Up
PDXDC2P	pyridoxal-dependent decarboxylase domain containing 2, pseudogene	1,50	Up
PDXK	pyridoxal (pyridoxine, vitamin B6) kinase	1,89	Up
PDZD11	PDZ domain containing 11	1,53	Up
PDZRN4	PDZ domain containing ring finger 4	1,81	Up
ECI2	enoyl-CoA delta isomerase 2	1,87	Up
PELI2	pellino E3 ubiquitin protein ligase family member 2	1,95	Up
PENK	proenkephalin	1,56	Down
PER2	period circadian clock 2	1,72	Up
PES1	pescadillo ribosomal biogenesis factor 1	1,63	Up
PEX10	peroxisomal biogenesis factor 10	1,68	Up
PF4	platelet factor 4	1,76	Up
PFKFB1	6-phosphofructo-2-kinase/fructose-2,6-biphosphatase 1	1,57	Down
PFKFB2	6-phosphofructo-2-kinase/fructose-2,6-biphosphatase 2	2,00	Up
PFKL	phosphofructokinase, liver	1,52	Down
PFKL	phosphofructokinase, liver	3,04	Down
PFN1	profilin 1	1,51	Down
PFN3	profilin 3	1,58	Down
PGAM5	phosphoglycerate mutase family member 5	1,72	Up
PGAP1	post-GPI attachment to proteins 1	1,50	Up
PGBD1	piggyBac transposable element derived 1	1,52	Down
PGK1	phosphoglycerate kinase 1	1,59	Up
PGLYRP1	peptidoglycan recognition protein 1	1,59	Up
PGLYRP3	peptidoglycan recognition protein 3	1,54	Up
PGRMC2	progesterone receptor membrane component 2	1,84	Up
PGRMC2	progesterone receptor membrane component 2	1,67	Up
PHACTR4	phosphatase and actin regulator 4	2,01	Up
PHF12	PHD finger protein 12	1,78	Up
JADE1	jade family PHD finger 1	1,53	Up
PHF20L1	PHD finger protein 20-like 1	1,65	Up
PHF23	PHD finger protein 23	1,53	Up
PHF7	PHD finger protein 7	2,60	Down
PHKG2	phosphorylase kinase, gamma 2 (testis)	1,74	Up
PHLDB2	pleckstrin homology-like domain, family B, member 2	2,12	Up
PHLPP2	PH domain and leucine rich repeat protein phosphatase 2	2,01	Up
PHOX2A	paired-like homeobox 2a	1,55	Down
PHYHD1	phytanoyl-CoA dioxygenase domain containing 1	1,58	Up
PIAS4	protein inhibitor of activated STAT, 4	1,67	Down
INPP5J	inositol polyphosphate-5-phosphatase J	1,62	Up
PID1	phosphotyrosine interaction domain containing 1	1,69	Up
PIGG	phosphatidylinositol glycan anchor biosynthesis, class G	1,96	Up
PIGN	phosphatidylinositol glycan anchor biosynthesis, class N	1,92	Up
PIGR	polymeric immunoglobulin receptor	1,97	Up
PIGT	phosphatidylinositol glycan anchor biosynthesis, class T	1,60	Up
PIGU	phosphatidylinositol glycan anchor biosynthesis, class U	1,70	Up
PIGX	phosphatidylinositol glycan anchor biosynthesis, class X	1,70	Up
PIGY	phosphatidylinositol glycan anchor biosynthesis, class Y	1,56	Up
PIK3CG	phosphatidylinositol-4,5-bisphosphate 3-kinase, catalytic subunit gamma	1,85	Up
PILRA	paired immunoglobin-like type 2 receptor alpha	1,52	Up
PIP5K1C	phosphatidylinositol-4-phosphate 5-kinase, type I, gamma	2,73	Down
PIKFYVE	phosphoinositide kinase, FYVE finger containing	1,55	Up
PIR	pirin (iron-binding nuclear protein)	1,57	Up
PISD	phosphatidylserine decarboxylase	2,19	Up
PITPNM2	phosphatidylinositol transfer protein, membrane-associated 2	1,61	Up
PITPNM3	PITPNM family member 3	1,89	Up
PKD1L3	polycystic kidney disease 1-like 3	1,65	Up
PKD2L2	polycystic kidney disease 2-like 2	1,58	Up
PKIA	protein kinase (cAMP-dependent, catalytic) inhibitor alpha	1,53	Up
PKN2	protein kinase N2	1,56	Up
PKN2	protein kinase N2	1,87	Up
PKN2	protein kinase N2	1,62	Down
PKNOX1	PBX/knotted 1homeobox 1	1,58	Up
PKNOX1	PBX/knotted 1homeobox 1	1,67	Up
PLA2G1B	phospholipase A2, group IB (pancreas)	1,64	Up
PLA2G4C	phospholipase A2, group IVC (cytosolic, calcium-independent)	1,95	Up
PLA2G4C	phospholipase A2, group IVC (cytosolic, calcium-independent)	1,99	Up
PLA2G4D	phospholipase A2, group IVD (cytosolic)	1,83	Up
PLA2G4F	phospholipase A2, group IVF	1,79	Up
PLA2R1	phospholipase A2 receptor 1, 180kDa	1,55	Up
PLAA	phospholipase A2-activating protein	1,55	Up
PLAC1	placenta-specific 1	1,60	Up
PLB1	phospholipase B1	1,80	Up
PLCG2	phospholipase C, gamma 2 (phosphatidylinositol-specific)	1,59	Down
PLCH1	phospholipase C, eta 1	1,56	Up
PLCH2	phospholipase C, eta 2	1,50	Down
PLD1	phospholipase D1, phosphatidylcholine-specific	1,81	Up
PLEC	plectin	1,53	Down
PLEKHA7	pleckstrin homology domain containing, family A member 7	1,56	Up
PLEKHF1	pleckstrin homology domain containing, family F (with FYVE domain) member 1	1,86	Up
PLEKHG3	pleckstrin homology domain containing, family G (with RhoGef domain) member 3	1,65	Up
PLEKHG3	pleckstrin homology domain containing, family G (with RhoGef domain) member 3	1,75	Up
PLEKHG5	pleckstrin homology domain containing, family G (with RhoGef domain) member 5	1,51	Up
PLEKHM1	pleckstrin homology domain containing, family M (with RUN domain) member 1	1,63	Up
PLEKHO2	pleckstrin homology domain containing, family O member 2	1,75	Up
PLK1	polo-like kinase 1	1,69	Up
PLK3	polo-like kinase 3	1,97	Up
PML	promyelocytic leukemia	1,55	Down
PMS2	PMS2 postmeiotic segregation increased 2 (S. cerevisiae)	1,58	Up
PNMA1	paraneoplastic Ma antigen 1	1,61	Up
PNMA3	paraneoplastic Ma antigen 3	1,57	Up
PNMT	phenylethanolamine N-methyltransferase	1,59	Up
PNPLA5	patatin-like phospholipase domain containing 5	1,86	Up
PNPLA8	patatin-like phospholipase domain containing 8	1,88	Up
PNPO	pyridoxamine 5'-phosphate oxidase	1,68	Up
POF1B	premature ovarian failure, 1B	1,50	Up
POFUT2	protein O-fucosyltransferase 2	1,79	Up
PRSS53	protease, serine, 53	1,74	Up
POLDIP2	polymerase (DNA-directed), delta interacting protein 2	1,52	Up
POLE	polymerase (DNA directed), epsilon, catalytic subunit	1,98	Up
POLR1A	polymerase (RNA) I polypeptide A, 194kDa	1,67	Up
POLR2C	polymerase (RNA) II (DNA directed) polypeptide C, 33kDa	1,53	Up
POLR2L	polymerase (RNA) II (DNA directed) polypeptide L, 7.6kDa	1,56	Up
POLR3D	polymerase (RNA) III (DNA directed) polypeptide D, 44kDa	1,59	Up
POLR3D	polymerase (RNA) III (DNA directed) polypeptide D, 44kDa	1,75	Up
POLRMT	polymerase (RNA) mitochondrial (DNA directed)	1,73	Up
POM121	POM 121 transmembrane nucleoporin	1,64	Up
POMP	proteasome maturation protein	1,61	Up
POMT1	protein-O-mannosyltransferase 1	1,86	Up
PON3	paraoxonase 3	1,62	Up
POP7	processing of precursor 7, ribonuclease P/MRP subunit (S. cerevisiae)	2,10	Up
POU2F1	POU class 2 homeobox 1	1,66	Up
POU4F1	POU class 4 homeobox 1	1,67	Up
POU5F1	POU class 5 homeobox 1	1,51	Up
POU6F2	POU class 6 homeobox 2	1,67	Up
PPAP2C	phosphatidic acid phosphatase type 2C	1,70	Up
PPAPDC1B	phosphatidic acid phosphatase type 2 domain containing 1B	1,65	Up
PPAT	phosphoribosyl pyrophosphate amidotransferase	1,55	Up
PPBP	pro-platelet basic protein (chemokine (C-X-C motif) ligand 7)	1,55	Up
PPEF1	protein phosphatase, EF-hand calcium binding domain 1	1,71	Down
PPFIA1	protein tyrosine phosphatase, receptor type, f polypeptide (PTPRF), interacting protein (liprin), alpha 1	1,59	Down
PPIA	peptidylprolyl isomerase A (cyclophilin A)	1,61	Up
PPIA	peptidylprolyl isomerase A (cyclophilin A)	1,61	Up
PPIF	peptidylprolyl isomerase F	1,60	Up
PPIL1	peptidylprolyl isomerase (cyclophilin)-like 1	1,75	Up
PPIL2	peptidylprolyl isomerase (cyclophilin)-like 2	1,83	Up
PPM1F	protein phosphatase, Mg2+/Mn2+ dependent, 1F	1,87	Down
PPME1	protein phosphatase methylesterase 1	1,71	Up
PPP1R11	protein phosphatase 1, regulatory (inhibitor) subunit 11	3,98	Down
PPP1R16B	protein phosphatase 1, regulatory subunit 16B	1,62	Up
PPP1R1C	protein phosphatase 1, regulatory (inhibitor) subunit 1C	1,53	Up
PPP1R3C	protein phosphatase 1, regulatory subunit 3C	1,76	Up
PPP1R3E	protein phosphatase 1, regulatory subunit 3E	1,63	Down
PPP1R3F	protein phosphatase 1, regulatory subunit 3F	1,57	Up
PPP1R3F	protein phosphatase 1, regulatory subunit 3F	1,60	Down
PPP2CB	protein phosphatase 2, catalytic subunit, beta isozyme	1,56	Up

PPP2R1B	protein phosphatase 2, regulatory subunit A, beta	1,94	Up
PPP2R2C	protein phosphatase 2, regulatory subunit B, gamma	1,51	Up
PPP2R3A	protein phosphatase 2, regulatory subunit B'', alpha	2,02	Up
PPP2R5B	protein phosphatase 2, regulatory subunit B', beta	2,13	Up
PPP2R5C	protein phosphatase 2, regulatory subunit B', gamma	1,72	Up
PPP2R5C	protein phosphatase 2, regulatory subunit B', gamma	1,52	Up
PRAF2	PRA1 domain family, member 2	1,70	Up
PRB4	proline-rich protein BstNI subfamily 4	2,15	Down
PRC1	protein regulator of cytokinesis 1	1,91	Up
PRDM11	PR domain containing 11	1,52	Up
PRDX4	peroxiredoxin 4	1,53	Up
PREPL	prolyl endopeptidase-like	1,78	Up
PRKAG2	protein kinase, AMP-activated, gamma 2 non-catalytic subunit	1,83	Up
PRKCE	protein kinase C, epsilon	1,56	Up
PRKCG	protein kinase C, gamma	1,59	Up
PRKCH	protein kinase C, eta	1,61	Up
PRKCI	protein kinase C, iota	1,65	Up
PRKD1	protein kinase D1	1,55	Up
PRKG1	protein kinase, cGMP-dependent, type I	1,52	Up
PRL	prolactin	1,53	Up
PRLHR	prolactin releasing hormone receptor	1,59	Down
PRM1	protamine 1	1,70	Up
PRMT2	protein arginine methyltransferase 2	1,64	Down
NDUFAF7	NADH dehydrogenase (ubiquinone) complex I, assembly factor 7	1,74	Up
PROKR2	prokineticin receptor 2	1,57	Up
PROL1	proline rich, lacrimal 1	1,73	Up
PROP1	PROP paired-like homeobox 1	3,01	Down
PRPF18	pre-mRNA processing factor 18	1,65	Up
PRPH	peripherin	1,74	Up
PRPS1	phosphoribosyl pyrophosphate synthetase 1	1,67	Up
PRR12	proline rich 12	1,52	Up
PRR13	proline rich 13	2,06	Up
PRR4	proline rich 4 (lacrimal)	1,62	Up
PRR5	proline rich 5 (renal)	2,46	Down
PRR7	proline rich 7 (synaptic)	1,61	Down
PRRT2	proline-rich transmembrane protein 2	1,50	Down
PRRT3	proline-rich transmembrane protein 3	1,68	Up
PRSS16	protease, serine, 16 (thymus)	1,57	Up
PRSS21	protease, serine, 21 (testisin)	1,64	Up
PRTN3	proteinase 3	1,57	Up
CYTH2	cytohesin 2	1,56	Up
CYTIP	cytohesin 1 interacting protein	1,51	Up
PSEN2	presenilin 2 (Alzheimer disease 4)	1,67	Down
PSG11	pregnancy specific beta-1-glycoprotein 11	1,74	Up
PSG2	pregnancy specific beta-1-glycoprotein 2	1,56	Up
PSG4	pregnancy specific beta-1-glycoprotein 4	1,58	Up
PSG7	pregnancy specific beta-1-glycoprotein 7 (gene/pseudogene)	1,61	Up
PSMA1	proteasome (prosome, macropain) subunit, alpha type, 1	1,64	Up
PSMA6	proteasome (prosome, macropain) subunit, alpha type, 6	1,76	Up
PSMA6	proteasome (prosome, macropain) subunit, alpha type, 6	1,91	Up
PSMB1	proteasome (prosome, macropain) subunit, beta type, 1	1,63	Up
PSMB9	proteasome (prosome, macropain) subunit, beta type, 9	1,53	Down
PSMC1	proteasome (prosome, macropain) 26S subunit, ATPase, 1	1,53	Up
PSMC1	proteasome (prosome, macropain) 26S subunit, ATPase, 1	1,53	Up
PSMD10	proteasome (prosome, macropain) 26S subunit, non-ATPase, 10	1,63	Up
PSMD2	proteasome (prosome, macropain) 26S subunit, non-ATPase, 2	1,54	Up
PSMD5	proteasome (prosome, macropain) 26S subunit, non-ATPase, 5	1,70	Up
PSMD5	proteasome (prosome, macropain) 26S subunit, non-ATPase, 5	2,14	Up
PSMD6	proteasome (prosome, macropain) 26S subunit, non-ATPase, 6	1,52	Up
PSORS1C2	psoriasis susceptibility 1 candidate 2	1,66	Up
PSORS1C2	psoriasis susceptibility 1 candidate 2	2,83	Down
PSPH	phosphoserine phosphatase	2,03	Up
PTCD3	pentatricopeptide repeat domain 3	1,52	Down
PTGER1	prostaglandin E receptor 1 (subtype EP1), 42kDa	1,64	Down
PTHLH	parathyroid hormone-like hormone	1,55	Up
PTK2B	protein tyrosine kinase 2 beta	1,53	Down
PTOV1	prostate tumor overexpressed 1	1,52	Up
PTPLAD1	protein tyrosine phosphatase-like A domain containing 1	1,51	Up
PTPN14	protein tyrosine phosphatase, non-receptor type 14	1,94	Up
PTPN23	protein tyrosine phosphatase, non-receptor type 23	1,92	Up
PTPN7	protein tyrosine phosphatase, non-receptor type 7	1,51	Up
PTPN9	protein tyrosine phosphatase, non-receptor type 9	1,65	Up
PTPRC	protein tyrosine phosphatase, receptor type, C	1,58	Up
PTPRK	protein tyrosine phosphatase, receptor type, K	1,64	Up
PTPRU	protein tyrosine phosphatase, receptor type, U	1,51	Up
PTPRZ1	protein tyrosine phosphatase, receptor-type, Z polypeptide 1	1,52	Up
PUM2	pumilio RNA-binding family member 2	2,09	Up
PVR	poliovirus receptor	1,70	Up
PVRL1	poliovirus receptor-related 1 (herpesvirus entry mediator C)	1,68	Up
PXDNL	peroxidasin homolog (Drosophila)-like	1,51	Up
PEX2	peroxisomal biogenesis factor 2	1,84	Up
PXMP4	peroxisomal membrane protein 4, 24kDa	1,62	Up
PYCARD	PYD and CARD domain containing	1,79	Up
PYGO1	pygopus family PHD finger 1	1,83	Up
PYY2	peptide YY, 2 (pseudogene)	2,78	Down
QPRT	quinolinate phosphoribosyltransferase	1,73	Up
QSOX2	quiescin Q6 sulfhydryl oxidase 2	1,84	Up
RAB10	RAB10, member RAS oncogene family	1,61	Up
RAB11A	RAB11A, member RAS oncogene family	1,50	Down
RAB11FIP5	RAB11 family interacting protein 5 (class I)	1,64	Up
RAB15	RAB15, member RAS oncogene family	1,68	Up
RAB22A	RAB22A, member RAS oncogene family	2,04	Up
RAB23	RAB23, member RAS oncogene family	1,86	Up
RAB27B	RAB27B, member RAS oncogene family	1,69	Up
RAB3GAP2	RAB3 GTPase activating protein subunit 2 (non-catalytic)	1,51	Down
RAB40C	RAB40C, member RAS oncogene family	1,85	Up
RAB43	RAB43, member RAS oncogene family	1,63	Up
RAB5C	RAB5C, member RAS oncogene family	1,80	Up
RAB7L1	RAB7, member RAS oncogene family-like 1	1,72	Up
RABIF	RAB interacting factor	1,53	Up
RABL3	RAB, member of RAS oncogene family-like 3	1,58	Up
RABL5	RAB, member RAS oncogene family-like 5	1,53	Up
RAC1	ras-related C3 botulinum toxin substrate 1 (rho family, small GTP binding protein Rac1)	1,80	Up
RAD1	RAD1 homolog (S. pombe)	1,60	Up
RAD23B	RAD23 homolog B (S. cerevisiae)	2,02	Up
RAD51D	RAD51 paralog D	1,55	Up
RAD52	RAD52 homolog (S. cerevisiae)	1,98	Up
RAD54B	RAD54 homolog B (S. cerevisiae)	1,62	Up
RAD9A	RAD9 homolog A (S. pombe)	1,59	Up
RAI14	retinoic acid induced 14	1,52	Up
RALGPS2	Ral GEF with PH domain and SH3 binding motif 2	1,58	Up
RAMP2	receptor (G protein-coupled) activity modifying protein 2	1,53	Down
RAN	RAN, member RAS oncogene family	2,22	Up
RANBP10	RAN binding protein 10	1,84	Up
RAP2C	RAP2C, member of RAS oncogene family	1,86	Up
RAPGEF1	Rap guanine nucleotide exchange factor (GEF) 1	1,98	Up
RAPGEF4	Rap guanine nucleotide exchange factor (GEF) 4	1,71	Up
RAPSN	receptor-associated protein of the synapse	1,51	Up
RARG	retinoic acid receptor, gamma	1,66	Up
RARS	arginyl-tRNA synthetase	1,51	Up
RASEF	RAS and EF-hand domain containing	1,55	Up
RASGEF1A	RasGEF domain family, member 1A	1,85	Up
RASGRP1	RAS guanyl releasing protein 1 (calcium and DAG-regulated)	1,55	Up
RASGRP2	RAS guanyl releasing protein 2 (calcium and DAG-regulated)	1,52	Up
RASGRP4	RAS guanyl releasing protein 4	1,69	Up
RASL11A	RAS-like, family 11, member A	1,61	Up
RAVER1	ribonucleoprotein, PTB-binding 1	1,93	Up
RB1	retinoblastoma 1	1,57	Up
RBBP9	retinoblastoma binding protein 9	1,67	Up
RBKS	ribokinase	1,65	Up
RBM15B	RNA binding motif protein 15B	1,92	Up
RBM18	RNA binding motif protein 18	1,65	Up
RBM23	RNA binding motif protein 23	1,51	Up
ESRP2	epithelial splicing regulatory protein 2	2,42	Up
RBM38	RNA binding motif protein 38	1,55	Up
RBM43	RNA binding motif protein 43	1,56	Up
RBMS3	RNA binding motif, single stranded interacting protein 3	1,73	Up
RBMXL1	RNA binding motif protein, X-linked-like 1	1,63	Up
RBMY2FP	RNA binding motif protein, Y-linked, family 2, member F pseudogene	1,67	Up
RBPJ	recombination signal binding protein for immunoglobulin kappa J region	1,71	Up

RCC2	regulator of chromosome condensation 2	1,77	Up
RCL1	RNA terminal phosphate cyclase-like 1	2,50	Down
CRCP	CGRP receptor component	1,70	Up
RDH8	retinol dehydrogenase 8 (all-trans)	1,54	Up
REEP3	receptor accessory protein 3	1,65	Up
REEP6	receptor accessory protein 6	1,56	Down
REG1B	regenerating islet-derived 1 beta	1,80	Up
RELA	v-rel avian reticuloendotheliosis viral oncogene homolog A	1,58	Up
REPIN1	replication initiator 1	1,67	Up
REPIN1	replication initiator 1	1,76	Up
RETNLB	resistin like beta	1,52	Up
REXO1	REX1, RNA exonuclease 1 homolog (S. cerevisiae)	1,80	Up
REXO2	RNA exonuclease 2	2,20	Up
RFC3	replication factor C (activator 1) 3, 38kDa	1,69	Up
RFK	riboflavin kinase	1,91	Up
RFX2	regulatory factor X, 2 (influences HLA class II expression)	1,72	Up
ARHGEF28	Rho guanine nucleotide exchange factor (GEF) 28	1,80	Up
RGPD1	RANBP2-like and GRIP domain containing 1	1,60	Up
RGS11	regulator of G-protein signaling 11	2,08	Up
RGS2	regulator of G-protein signaling 2, 24kDa	1,50	Up
RGS20	regulator of G-protein signaling 20	1,51	Up
RGS4	regulator of G-protein signaling 4	1,64	Up
RGSL1	regulator of G-protein signaling like 1	1,81	Up
RHBDD1	rhomboid domain containing 1	1,66	Up
RHBDD3	rhomboid domain containing 3	1,58	Down
RHBDL1	rhomboid, veinlet-like 1 (Drosophila)	2,53	Down
RHBDL3	rhomboid, veinlet-like 3 (Drosophila)	1,54	Up
RHCG	Rh family, C glycoprotein	1,77	Up
RHEBL1	Ras homolog enriched in brain like 1	1,94	Up
RHO	rhodopsin	1,80	Up
RHOA	ras homolog family member A	1,67	Up
RHOA	ras homolog family member A	1,54	Up
RHOC	ras homolog family member C	1,94	Up
RHOG	ras homolog family member G	2,35	Up
RHOT1	ras homolog family member T1	1,55	Up
RHPN1	rhophilin, Rho GTPase binding protein 1	2,77	Down
RHPN2	rhophilin, Rho GTPase binding protein 2	1,53	Up
RIF1	RAP1 interacting factor homolog (yeast)	1,56	Up
RIMBP2	RIMS binding protein 2	1,92	Up
RIMS2	regulating synaptic membrane exocytosis 2	1,76	Up
RING1	ring finger protein 1	1,58	Up
RIPK2	receptor-interacting serine-threonine kinase 2	1,56	Up
RIPK4	receptor-interacting serine-threonine kinase 4	1,51	Up
DSTYK	dual serine/threonine and tyrosine protein kinase	2,24	Up
MEX3D	mex-3 RNA binding family member D	2,01	Up
MEX3D	mex-3 RNA binding family member D	2,55	Down
RNASE2	ribonuclease, RNase A family, 2 (liver, eosinophil-derived neurotoxin)	1,55	Up
RNASE3	ribonuclease, RNase A family, 3	1,62	Up
RND1	Rho family GTPase 1	1,66	Up
RND2	Rho family GTPase 2	1,59	Up
RND3	Rho family GTPase 3	1,61	Up
RNF111	ring finger protein 111	1,58	Up
RNF121	ring finger protein 121	1,61	Up
RNF126	ring finger protein 126	1,59	Up
RNF14	ring finger protein 14	2,12	Up
RNF145	ring finger protein 145	1,65	Up
RNF166	ring finger protein 166	1,56	Up
RNF170	ring finger protein 170	1,60	Up
RNF170	ring finger protein 170	1,58	Up
RNF175	ring finger protein 175	1,59	Up
RNF187	ring finger protein 187	1,60	Up
RNF213	ring finger protein 213	1,58	Up
RNF24	ring finger protein 24	1,66	Up
RNF5	ring finger protein 5, E3 ubiquitin protein ligase	1,68	Up
RNF8	ring finger protein 8, E3 ubiquitin protein ligase	1,59	Up
RNH1	ribonuclease/angiogenin inhibitor 1	1,55	Up
RNPC3	RNA-binding region (RNP1, RRM) containing 3	1,67	Up
RNPS1	RNA binding protein S1, serine-rich domain	1,61	Down
ROBO1	roundabout, axon guidance receptor, homolog 1 (Drosophila)	1,71	Up
ROBO4	roundabout, axon guidance receptor, homolog 4 (Drosophila)	1,74	Up

PTBP3	polypyrimidine tract binding protein 3	1,70	Up
ROR1	receptor tyrosine kinase-like orphan receptor 1	1,67	Up
RORB	RAR-related orphan receptor B	1,56	Up
RORC	RAR-related orphan receptor C	1,87	Up
RP2	retinitis pigmentosa 2 (X-linked recessive)	1,64	Up
RPH3AL	rabphilin 3A-like (without C2 domains)	1,66	Up
RPL10A	ribosomal protein L10a	2,62	Up
RPL10L	ribosomal protein L10-like	1,79	Up
RPL13	ribosomal protein L13	2,47	Up
RPL13A	ribosomal protein L13a	1,52	Up
RPL14	ribosomal protein L14	1,52	Up
RPL22	ribosomal protein L22	1,91	Up
RPL22	ribosomal protein L22	1,84	Up
RPL22L1	ribosomal protein L22-like 1	1,59	Up
RPL23	ribosomal protein L23	3,12	Up
RPL23A	ribosomal protein L23a	3,77	Up
RPL26L1	ribosomal protein L26-like 1	1,82	Up
RPL28	ribosomal protein L28	1,84	Up
RPL29	ribosomal protein L29	1,72	Up
RPL29P2	ribosomal protein L29 pseudogene 2	1,62	Up
RPL36A	ribosomal protein L36a	2,85	Up
RPL7A	ribosomal protein L7a	1,69	Up
RPLP2	ribosomal protein, large, P2	2,87	Up
RPP21	ribonuclease P/MRP 21kDa subunit	1,63	Up
RPP25	ribonuclease P/MRP 25kDa subunit	1,74	Down
RPS13	ribosomal protein S13	2,45	Up
RPS14	ribosomal protein S14	1,73	Up
RPS15A	ribosomal protein S15a	1,69	Up
RPS19	ribosomal protein S19	1,62	Up
RPS19	ribosomal protein S19	1,84	Up
RPS26	ribosomal protein S26	2,26	Up
RPS27L	ribosomal protein S27-like	1,54	Up
RPS28	ribosomal protein S28	3,42	Up
RPS28	ribosomal protein S28	2,40	Down
RPS29	ribosomal protein S29	2,64	Up
RPS3A	ribosomal protein S3A	2,09	Up
RPS4X	ribosomal protein S4, X-linked	1,72	Up
RPS6	ribosomal protein S6	2,31	Up
RPS6KA1	ribosomal protein S6 kinase, 90kDa, polypeptide 1	1,72	Up
RPSAP10	ribosomal protein SA pseudogene 10	1,56	Up
RPUSD2	RNA pseudouridylate synthase domain containing 2	2,24	Up
RRAD	Ras-related associated with diabetes	1,57	Up
RRH	retinal pigment epithelium-derived rhodopsin homolog	1,59	Up
RRN3	RRN3 RNA polymerase I transcription factor homolog (S. cerevisiae)	1,92	Up
RRP15	ribosomal RNA processing 15 homolog (S. cerevisiae)	1,73	Up
RSF1	remodeling and spacing factor 1	1,57	Up
RSL1D1	ribosomal L1 domain containing 1	1,73	Up
RSU1	Ras suppressor protein 1	1,79	Up
RTF1	Rtf1, Paf1/RNA polymerase II complex component, homolog (S. cerevisiae)	1,99	Up
RTP1	receptor (chemosensory) transporter protein 1	1,77	Up
RUFY1	RUN and FYVE domain containing 1	1,59	Up
SNX29P1	sorting nexin 29 pseudogene 1	1,89	Up
SGSM1	small G protein signaling modulator 1	1,63	Up
RXFP4	relaxin/insulin-like family peptide receptor 4	1,60	Up
S100A1	S100 calcium binding protein A1	1,59	Down
S100A2	S100 calcium binding protein A2	1,74	Up
S100A3	S100 calcium binding protein A3	1,70	Up
S100A7	S100 calcium binding protein A7	1,56	Up
S100A7A	S100 calcium binding protein A7A	1,54	Up
S100A8	S100 calcium binding protein A8	1,89	Up
S100PBP	S100P binding protein	1,60	Up
UBA2	ubiquitin-like modifier activating enzyme 2	1,53	Up
SALL2	spalt-like transcription factor 2	1,51	Up
SAMD10	sterile alpha motif domain containing 10	1,53	Up
SAMD3	sterile alpha motif domain containing 3	2,48	Down
SAMD4A	sterile alpha motif domain containing 4A	2,23	Up
SAMD4B	sterile alpha motif domain containing 4B	1,90	Up
SAMD4B	sterile alpha motif domain containing 4B	1,84	Down
SAMM50	SAMM50 sorting and assembly machinery component	1,51	Up
PPP6R3	protein phosphatase 6, regulatory subunit 3	1,55	Down

SASH1	SAM and SH3 domain containing 1	1,69	Up
SC5D	sterol-C5-desaturase	1,58	Up
LEPREL4	leprecan-like 4	1,72	Down
SCAND2P	SCAN domain containing 2 pseudogene	1,77	Up
SCARF2	scavenger receptor class F, member 2	1,86	Down
PDS5A	PDS5, regulator of cohesion maintenance, homolog A (S. cerevisiae)	2,05	Up
SCD	stearoyl-CoA desaturase (delta-9-desaturase)	1,51	Up
SCFD1	sec1family domain containing 1	1,60	Up
SCFD2	sec1family domain containing 2	1,77	Up
SCGB1D1	secretoglobin, family 1D, member 1	1,85	Up
SCGB1D2	secretoglobin, family 1D, member 2	1,59	Up
SCLY	selenocysteine lyase	1,98	Up
SCN3A	sodium channel, voltage-gated, type III, alpha subunit	1,51	Up
SCN5A	sodium channel, voltage-gated, type V, alpha subunit	2,02	Up
SHISA5	shisa family member 5	1,53	Up
SHISA5	shisa family member 5	2,83	Down
SDCCAG3	serologically defined colon cancer antigen 3	1,69	Up
SDHD	succinate dehydrogenase complex, subunit D, integral membrane protein	1,51	Up
SDK2	sidekick cell adhesion molecule 2	1,57	Down
SDR9C7	short chain dehydrogenase/reductase family 9C, member 7	1,76	Up
SDSL	serine dehydratase-like	1,52	Up
SEC22A	SEC22 vesicle trafficking protein homolog A (S. cerevisiae)	1,65	Up
SEC22A	SEC22 vesicle trafficking protein homolog A (S. cerevisiae)	1,78	Up
SEC23B	Sec23 homolog B (S. cerevisiae)	1,52	Up
SEC61A2	Sec61alpha 2 subunit (S. cerevisiae)	1,57	Up
SEC61B	Sec61beta subunit	1,80	Up
VIMP	VCP-interacting membrane protein	1,59	Up
SEMA3D	sema domain, immunoglobulin domain (Ig), short basic domain, secreted, (semaphorin) 3D	1,53	Up
SEMA4C	sema domain, immunoglobulin domain (Ig), transmembrane domain (TM) and short cytoplasmic domain, (semaphorin) 4C	1,72	Up
SEMA4C	sema domain, immunoglobulin domain (Ig), transmembrane domain (TM) and short cytoplasmic domain, (semaphorin) 4C	1,78	Up
SEMA4G	sema domain, immunoglobulin domain (Ig), transmembrane domain (TM) and short cytoplasmic domain, (semaphorin) 4G	1,61	Up
SEMA5B	sema domain, seven thrombospondin repeats (type 1 and type 1-like), transmembrane domain (TM) and short cytoplasmic domain, (semaphorin) 5B	1,53	Up
SEMA6D	sema domain, transmembrane domain (TM), and cytoplasmic domain, (semaphorin) 6D	1,54	Up
SENP5	SUMO1/sentrin specific peptidase 5	1,52	Up
SEPN1	selenoprotein N, 1	1,72	Up
SEPT12	septin 12	2,01	Up
SEPT8	septin 8	1,53	Up
MSRB1	methionine sulfoxide reductase B1	1,78	Up
SERF2	small EDRK-rich factor 2	2,07	Up
SERGEF	secretion regulating guanine nucleotide exchange factor	1,50	Up
SERINC1	serine incorporator 1	1,91	Up
SERPINA11	serpin peptidase inhibitor, clade A (alpha-1 antiproteinase, antitrypsin), member 11	1,93	Up
SERPINA4	serpin peptidase inhibitor, clade A (alpha-1 antiproteinase, antitrypsin), member 4	1,58	Up
SERPINA7	serpin peptidase inhibitor, clade A (alpha-1 antiproteinase, antitrypsin), member 7	1,62	Up
SERPINA9	serpin peptidase inhibitor, clade A (alpha-1 antiproteinase, antitrypsin), member 9	1,98	Up
SERPINB10	serpin peptidase inhibitor, clade B (ovalbumin), member 10	1,57	Up
SERPINB11	serpin peptidase inhibitor, clade B (ovalbumin), member 11(gene/pseudogene)	1,69	Up
SERPINB4	serpin peptidase inhibitor, clade B (ovalbumin), member 4	1,69	Up
SERPINB5	serpin peptidase inhibitor, clade B (ovalbumin), member 5	1,65	Up
SERPINB8	serpin peptidase inhibitor, clade B (ovalbumin), member 8	2,32	Up
SERPIND1	serpin peptidase inhibitor, clade D (heparin cofactor), member 1	1,58	Up
SERPINH1	serpin peptidase inhibitor, clade H (heat shock protein 47), member 1, (collagen binding protein 1)	1,51	Up
SERTAD1	SERTA domain containing 1	2,36	Up
SERTAD2	SERTA domain containing 2	1,72	Up
SETBP1	SET binding protein 1	1,58	Up
SETD4	SET domain containing 4	1,76	Up
SETD5	SET domain containing 5	1,69	Up
SETD8	SET domain containing (lysine methyltransferase) 8	1,60	Up
SEZ6	seizure related 6 homolog (mouse)	1,97	Up
SF3A2	splicing factor 3a, subunit 2, 66kDa	2,02	Down
SF3B5	splicing factor 3b, subunit 5, 10kDa	1,55	Up
SFRP5	secreted frizzled-related protein 5	2,09	Down
SRSF11	serine/arginine-rich splicing factor 11	1,52	Up
SRSF6	serine/arginine-rich splicing factor 6	1,57	Up
SFTA2	surfactant associated 2	1,97	Up
SGK1	serum/glucocorticoid regulated kinase 1	1,51	Up
SGPP1	sphingosine-1-phosphate phosphatase 1	1,77	Up
SGPP2	sphingosine-1-phosphate phosphatase 2	1,53	Up
SGTA	small glutamine-rich tetratricopeptide repeat (TPR)-containing, alpha	1,68	Up
SH2B1	SH2B adaptor protein 1	2,10	Up
SH2D4B	SH2 domain containing 4B	1,57	Up
SH2D4B	SH2 domain containing 4B	2,12	Up
SH2D6	SH2 domain containing 6	1,60	Up
SH3BGRL	SH3 domain binding glutamic acid-rich protein like	1,85	Up
SH3BP1	SH3-domain binding protein 1	1,64	Up
SH3BP4	SH3-domain binding protein 4	1,55	Up
SH3BP5	SH3-domain binding protein 5 (BTK-associated)	1,68	Up
SH3GL2	SH3-domain GRB2-like 2	1,95	Up
SH3GL3	SH3-domain GRB2-like 3	1,86	Up
SHANK2	SH3 and multiple ankyrin repeat domains 2	1,72	Up
SHANK3	SH3 and multiple ankyrin repeat domains 3	1,51	Up
SHB	Src homology 2 domain containing adaptor protein B	1,95	Up
SHC1	SHC (Src homology 2 domain containing) transforming protein 1	1,58	Up
SHC2	SHC (Src homology 2 domain containing) transforming protein 2	1,86	Down
SHF	Src homology 2 domain containing F	1,54	Up
SHOX2	short stature homeobox 2	1,69	Down
SHROOM1	shroom family member 1	1,70	Up
SIAE	sialic acid acetylesterase	2,47	Up
SIDT1	SID1transmembrane family, member 1	1,53	Up
SIDT2	SID1transmembrane family, member 2	1,97	Up
SIGLEC11	sialic acid binding Ig-like lectin 11	1,70	Up
SIPA1L1	signal-induced proliferation-associated 1like 1	2,46	Up
SIRPA	signal-regulatory protein alpha	2,25	Down
SIRPB1	signal-regulatory protein beta 1	1,63	Up
SIT1	signaling threshold regulating transmembrane adaptor 1	1,58	Up
SKI	v-ski avian sarcoma viral oncogene homolog	1,63	Up
SKIV2L2	superkiller viralicidic activity 2-like 2 (S. cerevisiae)	1,61	Up
SKP1	S-phase kinase-associated protein 1	1,63	Up
SLAMF8	SLAM family member 8	1,81	Up
SLC10A3	solute carrier family 10, member 3	2,07	Up
SLC11A2	solute carrier family 11(proton-coupled divalent metal ion transporter), member 2	1,62	Up
SLC12A3	solute carrier family 12 (sodium/chloride transporter), member 3	1,55	Up
SLC15A1	solute carrier family 15 (oligopeptide transporter), member 1	1,52	Up
SLC15A4	solute carrier family 15 (oligopeptide transporter), member 4	1,63	Up
SLC15A4	solute carrier family 15 (oligopeptide transporter), member 4	1,61	Up
SLC16A1	solute carrier family 16 (monocarboxylate transporter), member 1	1,83	Up
SLC16A11	solute carrier family 16, member 11	1,91	Up
SLC16A14	solute carrier family 16, member 14	1,51	Up
SLC16A14	solute carrier family 16, member 14	2,13	Up
SLC16A5	solute carrier family 16 (monocarboxylate transporter), member 5	1,78	Up
SLC17A1	solute carrier family 17 (organic anion transporter), member 1	1,80	Up
SLC17A2	solute carrier family 17, member 2	2,12	Up
SLC17A4	solute carrier family 17, member 4	1,57	Up
SLC1A2	solute carrier family 1(glial high affinity glutamate transporter), member 2	1,91	Up
SLC23A3	solute carrier family 23, member 3	1,52	Down
SLC25A1	solute carrier family 25 (mitochondrial carrier; citrate transporter), member 1	1,74	Up
SLC25A17	solute carrier family 25 (mitochondrial carrier; peroxisomal membrane protein, 34kDa), member 17	1,74	Up
SLC25A27	solute carrier family 25, member 27	1,68	Up
SLC25A33	solute carrier family 25 (pyrimidine nucleotide carrier), member 33	1,51	Up
SLC25A37	solute carrier family 25 (mitochondrial iron transporter), member 37	1,71	Up
SLC25A42	solute carrier family 25, member 42	1,72	Up
SLC26A1	solute carrier family 26 (anion exchanger), member 1	1,83	Up
SLC29A1	solute carrier family 29 (equilibrative nucleoside transporter), member 1	1,55	Up
SLC2A10	solute carrier family 2 (facilitated glucose transporter), member 10	1,97	Up
SLC2A2	solute carrier family 2 (facilitated glucose transporter), member 2	1,88	Up
SLC2A5	solute carrier family 2 (facilitated glucose/fructose transporter), member 5	1,67	Up
SLC2A8	solute carrier family 2 (facilitated glucose transporter), member 8	1,61	Up
SLC30A3	solute carrier family 30 (zinc transporter), member 3	1,60	Up
SLC30A4	solute carrier family 30 (zinc transporter), member 4	1,70	Up
SLC31A1	solute carrier family 31(copper transporter), member 1	1,72	Up
SLC32A1	solute carrier family 32 (GABA vesicular transporter), member 1	1,52	Up
SLC35A3	solute carrier family 35 (UDP-N-acetylglucosamine (UDP-GlcNAc) transporter), member A3	1,95	Up
SLC35A5	solute carrier family 35, member A5	2,02	Up
SLC35B1	solute carrier family 35, member B1	1,80	Up
SLC35B2	solute carrier family 35 (adenosine 3'-phospho 5'-phosphosulfate transporter), member B2	2,04	Down
SLC35B4	solute carrier family 35 (UDP-xylose/UDP-N-acetylglucosamine transporter), member B4	1,86	Up
SLC35C1	solute carrier family 35 (GDP-fucose transporter), member C1	1,76	Up
SLC35D1	solute carrier family 35 (UDP-GlcA/UDP-GalNAc transporter), member D1	1,59	Up
SLC35E3	solute carrier family 35, member E3	2,10	Up
SLC35F1	solute carrier family 35, member F1	1,66	Up

SH2D4B	SH2 domain containing 4B	1,57	Up
SH2D4B	SH2 domain containing 4B	2,12	Up
SH2D6	SH2 domain containing 6	1,60	Up
SH3BGRL	SH3 domain binding glutamic acid-rich protein like	1,85	Up
SH3BP1	SH3-domain binding protein 1	1,64	Up
SH3BP4	SH3-domain binding protein 4	1,55	Up
SH3BP5	SH3-domain binding protein 5 (BTK-associated)	1,68	Up
SH3GL2	SH3-domain GRB2-like 2	1,95	Up
SH3GL3	SH3-domain GRB2-like 3	1,86	Up
SHANK2	SH3 and multiple ankyrin repeat domains 2	1,72	Up
SHANK3	SH3 and multiple ankyrin repeat domains 3	1,51	Up
SHB	Src homology 2 domain containing adaptor protein B	1,95	Up
SHC1	SHC (Src homology 2 domain containing) transforming protein 1	1,58	Up
SHC2	SHC (Src homology 2 domain containing) transforming protein 2	1,86	Down
SHF	Src homology 2 domain containing F	1,54	Up
SHOX2	short stature homeobox 2	1,69	Down
SHROOM1	shroom family member 1	1,70	Up
SIAE	sialic acid acetylesterase	2,47	Up
SIDT1	SID1transmembrane family, member 1	1,53	Up
SIDT2	SID1transmembrane family, member 2	1,97	Up
SIGLEC11	sialic acid binding Ig-like lectin 11	1,70	Up
SIPA1L1	signal-induced proliferation-associated 1like 1	2,46	Up
SIRPA	signal-regulatory protein alpha	2,25	Down
SIRPB1	signal-regulatory protein beta 1	1,63	Up
SIT1	signaling threshold regulating transmembrane adaptor 1	1,58	Up
SKI	v-ski avian sarcoma viral oncogene homolog	1,63	Up
SKIV2L2	superkiller viralicidic activity 2-like 2 (S. cerevisiae)	1,61	Up
SKP1	S-phase kinase-associated protein 1	1,63	Up
SLAMF8	SLAM family member 8	1,81	Up
SLC10A3	solute carrier family 10, member 3	2,07	Up
SLC11A2	solute carrier family 11(proton-coupled divalent metal ion transporter), member 2	1,62	Up
SLC12A3	solute carrier family 12 (sodium/chloride transporter), member 3	1,55	Up
SLC15A1	solute carrier family 15 (oligopeptide transporter), member 1	1,52	Up
SLC15A4	solute carrier family 15 (oligopeptide transporter), member 4	1,63	Up
SLC15A4	solute carrier family 15 (oligopeptide transporter), member 4	1,61	Up
SLC16A1	solute carrier family 16 (monocarboxylate transporter), member 1	1,83	Up
SLC16A11	solute carrier family 16, member 11	1,91	Up
SLC16A14	solute carrier family 16, member 14	1,51	Up
SLC16A14	solute carrier family 16, member 14	2,13	Up
SLC16A5	solute carrier family 16 (monocarboxylate transporter), member 5	1,78	Up
SLC17A1	solute carrier family 17 (organic anion transporter), member 1	1,80	Up
SLC17A2	solute carrier family 17, member 2	2,12	Up
SLC17A4	solute carrier family 17, member 4	1,57	Up
SLC1A2	solute carrier family 1(glial high affinity glutamate transporter), member 2	1,91	Up
SLC23A3	solute carrier family 23, member 3	1,52	Down
SLC25A1	solute carrier family 25 (mitochondrial carrier; citrate transporter), member 1	1,74	Up
SLC25A17	solute carrier family 25 (mitochondrial carrier; peroxisomal membrane protein, 34kDa), member 17	1,74	Up
SLC25A27	solute carrier family 25, member 27	1,68	Up
SLC25A33	solute carrier family 25 (pyrimidine nucleotide carrier), member 33	1,51	Up
SLC25A37	solute carrier family 25 (mitochondrial iron transporter), member 37	1,71	Up
SLC25A42	solute carrier family 25, member 42	1,72	Up
SLC26A1	solute carrier family 26 (anion exchanger), member 1	1,83	Up
SLC29A1	solute carrier family 29 (equilibrative nucleoside transporter), member 1	1,55	Up
SLC2A10	solute carrier family 2 (facilitated glucose transporter), member 10	1,97	Up
SLC2A2	solute carrier family 2 (facilitated glucose transporter), member 2	1,88	Up
SLC2A5	solute carrier family 2 (facilitated glucose/fructose transporter), member 5	1,67	Up
SLC2A8	solute carrier family 2 (facilitated glucose transporter), member 8	1,61	Up
SLC30A3	solute carrier family 30 (zinc transporter), member 3	1,60	Up
SLC30A4	solute carrier family 30 (zinc transporter), member 4	1,70	Up
SLC31A1	solute carrier family 31(copper transporter), member 1	1,72	Up
SLC32A1	solute carrier family 32 (GABA vesicular transporter), member 1	1,52	Up
SLC35A3	solute carrier family 35 (UDP-N-acetylglucosamine (UDP-GlcNAc) transporter), member A3	1,95	Up
SLC35A5	solute carrier family 35, member A5	2,02	Up
SLC35B1	solute carrier family 35, member B1	1,80	Up
SLC35B2	solute carrier family 35 (adenosine 3'-phospho 5'-phosphosulfate transporter), member B2	2,04	Down
SLC35B4	solute carrier family 35 (UDP-xylose/UDP-N-acetylglucosamine transporter), member B4	1,86	Up
SLC35C1	solute carrier family 35 (GDP-fucose transporter), member C1	1,76	Up
SLC35D1	solute carrier family 35 (UDP-GlcA/UDP-GalNAc transporter), member D1	1,59	Up
SLC35E3	solute carrier family 35, member E3	2,10	Up
SLC35F1	solute carrier family 35, member F1	1,66	Up
SLC36A1	solute carrier family 36 (proton/amino acid symporter), member 1	1,67	Up
SLC37A4	solute carrier family 37 (glucose-6-phosphate transporter), member 4	1,52	Up
SLC38A3	solute carrier family 38, member 3	1,57	Up
SLC39A11	solute carrier family 39, member 11	1,59	Down
SLC39A12	solute carrier family 39 (zinc transporter), member 12	1,90	Up
SLC3A1	solute carrier family 3 (amino acid transporter heavy chain), member 1	1,70	Up
SLC41A1	solute carrier family 41(magnesium transporter), member 1	1,66	Up
SLC43A3	solute carrier family 43, member 3	1,77	Up
SLC45A1	solute carrier family 45, member 1	1,72	Up
SLC45A2	solute carrier family 45, member 2	1,66	Up
SLC46A1	solute carrier family 46 (folate transporter), member 1	1,75	Up
SLC46A1	solute carrier family 46 (folate transporter), member 1	1,61	Up
SLC47A1	solute carrier family 47 (multidrug and toxin extrusion), member 1	1,59	Up
SLC4A8	solute carrier family 4, sodium bicarbonate cotransporter, member 8	1,54	Up
SLC5A1	solute carrier family 5 (sodium/glucose cotransporter), member 1	1,52	Up
SLC5A2	solute carrier family 5 (sodium/glucose cotransporter), member 2	2,05	Down
SLC6A10P	solute carrier family 6 (neurotransmitter transporter), member 10, pseudogene	1,59	Up
SLC6A2	solute carrier family 6 (neurotransmitter transporter), member 2	1,58	Up
SLC6A20	solute carrier family 6 (proline IMINO transporter), member 20	1,83	Up
SLC6A6	solute carrier family 6 (neurotransmitter transporter), member 6	2,06	Up
SLC7A1	solute carrier family 7 (cationic amino acid transporter, y+ system), member 1	1,69	Up
SLC7A14	solute carrier family 7, member 14	1,63	Up
SLFN11	schlafen family member 11	1,60	Up
SNX20	sorting nexin 20	1,51	Up
SLMO1	slowmo homolog 1(Drosophila)	1,70	Up
SLMO2	slowmo homolog 2 (Drosophila)	1,73	Up
SMAD9	SMAD family member 9	1,69	Up
SMARCC1	SWI/SNF related, matrix associated, actin dependent regulator of chromatin, subfamily c, member 1	1,69	Up
SMARCC1	SWI/SNF related, matrix associated, actin dependent regulator of chromatin, subfamily c, member 1	1,51	Up
SMARCD1	SWI/SNF related, matrix associated, actin dependent regulator of chromatin, subfamily d, member 1	1,77	Up
SMARCD2	SWI/SNF related, matrix associated, actin dependent regulator of chromatin, subfamily d, member 2	1,78	Up
SMC1A	structural maintenance of chromosomes 1A	1,65	Up
MIEF1	mitochondrial elongation factor 1	1,76	Up
SMG1	SMG1phosphatidylinositol 3-kinase-related kinase	2,12	Up
SMPD2	sphingomyelin phosphodiesterase 2, neutral membrane (neutral sphingomyelinase)	1,75	Up
SMPD3	sphingomyelin phosphodiesterase 3, neutral membrane (neutral sphingomyelinase II)	1,68	Up
SMPD3	sphingomyelin phosphodiesterase 3, neutral membrane (neutral sphingomyelinase II)	1,53	Up
SMPDL3B	sphingomyelin phosphodiesterase, acid-like 3B	1,79	Up
SMTN	smoothelin	1,56	Up
SNCA	synuclein, alpha (non A4 component of amyloid precursor)	1,70	Up
SND1	staphylococcal nuclease and tudor domain containing 1	1,78	Up
SIK1	salt-inducible kinase 1	1,61	Down
SNF8	SNF8, ESCRT-II complex subunit	1,85	Up
SNHG7	small nucleolar RNA host gene 7 (non-protein coding)	1,53	Up
SNORD22	small nucleolar RNA, C/D box 22	2,44	Up
SNPH	syntaphilin	2,60	Up
SNRPA	small nuclear ribonucleoprotein polypeptide A	1,66	Up
SNRPC	small nuclear ribonucleoprotein polypeptide C	1,63	Up
SNUPN	snurportin 1	1,58	Down
SNX10	sorting nexin 10	1,70	Up
SNX13	sorting nexin 13	1,72	Up
SNX14	sorting nexin 14	1,90	Up
SNX15	sorting nexin 15	2,00	Up
ARHGAP33	Rho GTPase activating protein 33	2,08	Down
SNX4	sorting nexin 4	1,55	Up
SNX5	sorting nexin 5	1,54	Up
SNX5	sorting nexin 5	1,71	Up
SOCS1	suppressor of cytokine signaling 1	1,76	Up
SOCS3	suppressor of cytokine signaling 3	1,64	Up
SOCS4	suppressor of cytokine signaling 4	1,54	Up
SOCS6	suppressor of cytokine signaling 6	1,67	Up
SOD1	superoxide dismutase 1, soluble	2,03	Up
SOHLH1	spermatogenesis and oogenesis specific basic helix-loop-helix 1	1,51	Up
SOHLH2	spermatogenesis and oogenesis specific basic helix-loop-helix 2	1,52	Up
SORBS1	sorbin and SH3 domain containing 1	1,57	Up
SORBS1	sorbin and SH3 domain containing 1	1,62	Up
SORCS1	sortilin-related VPS10 domain containing receptor 1	1,62	Up
SOST	sclerostin	1,71	Up
SOX10	SRY (sex determining region Y)-box 10	1,50	Up
SOX12	SRY (sex determining region Y)-box 12	1,80	Up

SOX17	SRY (sex determining region Y)-box 17	1,61	Up
SOX17	SRY (sex determining region Y)-box 17	1,53	Down
SOX3	SRY (sex determining region Y)-box 3	1,74	Up
SOX3	SRY (sex determining region Y)-box 3	2,10	Down
SOX8	SRY (sex determining region Y)-box 8	1,94	Down
SP100	SP100 nuclear antigen	1,53	Up
SP100	SP100 nuclear antigen	1,89	Down
SP5	Sp5 transcription factor	1,52	Down
SPACA4	sperm acrosome associated 4	1,59	Up
SPAG9	sperm associated antigen 9	1,65	Up
SPATA16	spermatogenesis associated 16	1,61	Up
SPATA18	spermatogenesis associated 18	2,27	Up
SPATA2L	spermatogenesis associated 2-like	1,66	Up
SPECC1	sperm antigen with calponin homology and coiled-coil domains 1	2,00	Up
SPEN	spen family transcriptional repressor	1,69	Up
SPG11	spastic paraplegia 11 (autosomal recessive)	1,53	Up
SPG21	spastic paraplegia 21 (autosomal recessive, Mast syndrome)	1,85	Up
SPINK1	serine peptidase inhibitor, Kazal type 1	1,69	Up
SPINT2	serine peptidase inhibitor, Kunitz type, 2	1,77	Up
SPOCK2	sparc/osteonectin, cwcv and kazal-like domains proteoglycan (testican) 2	1,74	Up
SPOP	speckle-type POZ protein	2,30	Up
SPPL2B	signal peptide peptidase like 2B	2,01	Down
SPRED1	sprouty-related, EVH1 domain containing 1	1,55	Up
SPRR1A	small proline-rich protein 1A	3,13	Down
SPRR1B	small proline-rich protein 1B	2,96	Up
SPRR2B	small proline-rich protein 2B	2,96	Down
SPRR2D	small proline-rich protein 2D	1,69	Up
SPRR2G	small proline-rich protein 2G	21,17	Up
SPRR3	small proline-rich protein 3	1,71	Up
SPRYD3	SPRY domain containing 3	1,98	Up
SPSB4	splA/ryanodine receptor domain and SOCS box containing 4	4,14	Down
SPTBN2	spectrin, beta, non-erythrocytic 2	1,56	Up
SPTLC3	serine palmitoyltransferase, long chain base subunit 3	1,68	Up
SQRDL	sulfide quinone reductase-like (yeast)	1,58	Up
U2SURP	U2 snRNP-associated SURP domain containing	1,55	Up
U2SURP	U2 snRNP-associated SURP domain containing	1,59	Up
SRBD1	S1 RNA binding domain 1	1,55	Up
SRCAP	Snf2-related CREBBP activator protein	1,52	Down
SRCRB4D	scavenger receptor cysteine rich domain containing, group B (4 domains)	1,90	Up
SRD5A3	steroid 5 alpha-reductase 3	2,01	Up
SREBF1	sterol regulatory element binding transcription factor 1	1,53	Up
SRGAP1	SLIT-ROBO Rho GTPase activating protein 1	1,81	Up
SRP68	signal recognition particle 68kDa	1,62	Up
SRXN1	sulfiredoxin 1	1,57	Up
SSB	Sjogren syndrome antigen B (autoantigen La)	1,60	Up
SSBP2	single-stranded DNA binding protein 2	1,70	Up
SSH3	slingshot protein phosphatase 3	1,63	Up
SSPN	sarcospan	1,92	Up
SSRP1	structure specific recognition protein 1	1,50	Up
SSU72	SSU72 RNA polymerase II CTD phosphatase homolog (S. cerevisiae)	1,59	Up
ST3GAL5	ST3 beta-galactoside alpha-2,3-sialyltransferase 5	1,56	Up
ST7L	suppression of tumorigenicity 7 like	2,28	Up
STARD9	StAR-related lipid transfer (START) domain containing 9	1,89	Up
STAT1	signal transducer and activator of transcription 1, 91kDa	2,12	Up
STAT2	signal transducer and activator of transcription 2, 113kDa	1,68	Up
STAT3	signal transducer and activator of transcription 3 (acute-phase response factor)	1,58	Up
STAU2	staufen double-stranded RNA binding protein 2	1,64	Up
STC1	stanniocalcin 1	1,67	Up
HSPA13	heat shock protein 70kDa family, member 13	1,51	Up
STEAP3	STEAP family member 3, metalloreductase	1,63	Up
STEAP3	STEAP family member 3, metalloreductase	1,51	Up
STK11	serine/threonine kinase 11	2,49	Down
STK11IP	serine/threonine kinase 11 interacting protein	1,53	Up
STK17B	serine/threonine kinase 17b	2,18	Up
STK31	serine/threonine kinase 31	1,54	Up
STK4	serine/threonine kinase 4	1,65	Up
STOM	stomatin	2,21	Up
STOML2	stomatin (EPB72)-like 2	1,75	Up
STRAP	serine/threonine kinase receptor associated protein	2,20	Up
STRN	striatin, calmodulin binding protein	1,65	Up
STRN4	striatin, calmodulin binding protein 4	1,79	Up
STX12	syntaxin 12	1,62	Up
STXBP6	syntaxin binding protein 6 (amisyn)	1,65	Up
SUFU	suppressor of fused homolog (Drosophila)	1,63	Up
ZNF280D	zinc finger protein 280D	1,79	Up
SULT1A3	sulfotransferase family, cytosolic, 1A, phenol-preferring, member 3	1,75	Up
SULT1C2	sulfotransferase family, cytosolic, 1C, member 2	1,61	Up
SULT4A1	sulfotransferase family 4A, member 1	1,75	Up
SUMO2	small ubiquitin-like modifier 2	1,51	Up
SUMO2	small ubiquitin-like modifier 2	1,87	Up
SUMO2	small ubiquitin-like modifier 2	2,80	Down
SUPT16H	suppressor of Ty 16 homolog (S. cerevisiae)	1,59	Up
SUPT5H	suppressor of Ty 5 homolog (S. cerevisiae)	1,71	Up
SUSD2	sushi domain containing 2	1,88	Up
SUSD3	sushi domain containing 3	1,61	Up
SVEP1	sushi, von Willebrand factor type A, EGF and pentraxin domain containing 1	1,63	Up
SVOPL	SVOP-like	1,77	Down
SYF2	SYF2 pre-mRNA-splicing factor	1,55	Up
SYN1	synapsin I	1,88	Down
SYN3	synapsin III	1,59	Up
SYNC	syncoilin, intermediate filament protein	1,51	Up
SYNGR1	synaptogyrin 1	1,94	Up
SYNGR2	synaptogyrin 2	1,54	Up
SYNJ1	synaptojanin 1	1,57	Up
SYNPO	synaptopodin	2,98	Down
SYT3	synaptotagmin III	1,52	Up
T	T, brachyury homolog (mouse)	1,66	Up
TAC4	tachykinin 4 (hemokinin)	1,63	Down
TACC1	transforming, acidic coiled-coil containing protein 1	1,73	Up
TACC1	transforming, acidic coiled-coil containing protein 1	2,40	Up
TACR1	tachykinin receptor 1	1,96	Up
TADA3	transcriptional adaptor 3	1,61	Up
TADA3	transcriptional adaptor 3	1,53	Up
TAF10	TAF10 RNA polymerase II, TATA box binding protein (TBP)-associated factor, 30kDa	1,96	Up
TAF15	TAF15 RNA polymerase II, TATA box binding protein (TBP)-associated factor, 68kDa	1,58	Up
TAGAP	T-cell activation RhoGTPase activating protein	1,63	Up
TANC1	tetratricopeptide repeat, ankyrin repeat and coiled-coil containing 1	1,56	Up
TAP1	transporter 1, ATP-binding cassette, sub-family B (MDR/TAP)	1,74	Up
TAPT1	transmembrane anterior posterior transformation 1	1,57	Up
TARDBP	TAR DNA binding protein	1,67	Up
TAS2R16	taste receptor, type 2, member 16	2,11	Up
TAS2R43	taste receptor, type 2, member 43	1,76	Up
TAS2R19	taste receptor, type 2, member 19	1,52	Up
TASP1	taspase, threonine aspartase, 1	1,78	Up
TAT	tyrosine aminotransferase	2,11	Up
TAT	tyrosine aminotransferase	2,01	Down
TBC1D10A	TBC1 domain family, member 10A	1,90	Up
TBC1D10B	TBC1 domain family, member 10B	1,51	Up
TBC1D2	TBC1 domain family, member 2	1,85	Up
TBC1D20	TBC1 domain family, member 20	2,03	Up
TBC1D20	TBC1 domain family, member 20	1,58	Down
TBC1D25	TBC1 domain family, member 25	1,85	Up
TBC1D5	TBC1 domain family, member 5	1,60	Up
TBL1Y	transducin (beta)-like 1, Y-linked	1,66	Up
TBL2	transducin (beta)-like 2	1,55	Up
TAF8	TAF8 RNA polymerase II, TATA box binding protein (TBP)-associated factor, 43kDa	1,53	Up
TBRG1	transforming growth factor beta regulator 1	1,90	Up
TBX10	T-box 10	1,93	Up
TCEA1	transcription elongation factor A (SII), 1	1,79	Up
TCEA3	transcription elongation factor A (SII), 3	1,73	Up
TCEAL3	transcription elongation factor A (SII)-like 3	1,72	Up
TCEAL4	transcription elongation factor A (SII)-like 4	1,78	Up
TCEB1	transcription elongation factor B (SIII), polypeptide 1 (15kDa, elongin C)	1,66	Up
TCEB2	transcription elongation factor B (SIII), polypeptide 2 (18kDa, elongin B)	2,30	Up
HNF1A	HNF1 homeobox A	2,68	Down
TCF20	transcription factor 20 (AR1)	1,70	Down
TCF23	transcription factor 23	1,84	Up
TCF25	transcription factor 25 (basic helix-loop-helix)	1,84	Up
TCL6	T-cell leukemia/lymphoma 6 (non-protein coding)	1,50	Up
TCN2	transcobalamin II	2,31	Up

TCTE3	t-complex-associated-testis-expressed 3	3,19	Down
TDRD10	tudor domain containing 10	1,51	Up
TDRD10	tudor domain containing 10	1,67	Down
TEAD1	TEA domain family member 1 (SV40 transcriptional enhancer factor)	1,68	Up
TMBIM6	transmembrane BAX inhibitor motif containing 6	1,55	Up
TENC1	tensin like C1 domain containing phosphatase (tensin 2)	1,51	Up
TERF2IP	telomeric repeat binding factor 2, interacting protein	1,66	Up
TESK1	testis-specific kinase 1	1,59	Up
TESK2	testis-specific kinase 2	1,55	Up
PRSS42	protease, serine, 42	1,74	Up
TEX13A	testis expressed 13A	1,52	Up
TEX261	testis expressed 261	1,52	Up
TEX264	testis expressed 264	1,58	Up
TFAM	transcription factor A, mitochondrial	2,08	Up
TFAP2A	transcription factor AP-2 alpha (activating enhancer binding protein 2 alpha)	1,53	Up
TFF1	trefoil factor 1	1,59	Up
TFF3	trefoil factor 3 (intestinal)	1,93	Up
TFPI	tissue factor pathway inhibitor (lipoprotein-associated coagulation inhibitor)	1,75	Up
TFR2	transferrin receptor 2	1,69	Up
TGFBR2	transforming growth factor, beta receptor II (70/80kDa)	1,67	Up
TGFBR2	transforming growth factor, beta receptor II (70/80kDa)	1,95	Up
TGM3	transglutaminase 3	1,66	Up
TGOLN2	trans-golgi network protein 2	1,52	Up
THADA	thyroid adenoma associated	1,65	Up
THOC1	THO complex 1	2,07	Up
THOC2	THO complex 2	1,54	Up
THRA	thyroid hormone receptor, alpha	1,65	Up
MED13L	mediator complex subunit 13-like	2,84	Up
THRAP3	thyroid hormone receptor associated protein 3	1,71	Up
MED24	mediator complex subunit 24	1,66	Up
THRB	thyroid hormone receptor, beta	1,55	Up
ISM2	isthmin 2	1,76	Up
THSD4	thrombospondin, type I, domain containing 4	1,55	Up
THSD7B	thrombospondin, type I, domain containing 7B	1,55	Up
THY1	Thy-1 cell surface antigen	2,71	Down
TIA1	TIA1 cytotoxic granule-associated RNA binding protein	1,59	Up
TIGD1	tigger transposable element derived 1	1,57	Up
TIMM17A	translocase of inner mitochondrial membrane 17 homolog A (yeast)	1,63	Up
TIMM44	translocase of inner mitochondrial membrane 44 homolog (yeast)	1,50	Up
TIMM50	translocase of inner mitochondrial membrane 50 homolog (S. cerevisiae)	1,68	Up
TIMM8A	translocase of inner mitochondrial membrane 8 homolog A (yeast)	1,88	Up
TIMP2	TIMP metallopeptidase inhibitor 2	1,66	Up
PTH2	parathyroid hormone 2	1,88	Down
TJAP1	tight junction associated protein 1 (peripheral)	1,68	Up
TKTL1	transketolase-like 1	1,64	Up
TLE6	transducin-like enhancer of split 6 (E(sp1) homolog, Drosophila)	1,66	Up
TLK1	tousled-like kinase 1	1,50	Up
TLR1	toll-like receptor 1	1,54	Up
TLX1	T-cell leukemia homeobox 1	1,93	Up
TM2D2	TM2 domain containing 2	1,75	Up
TM7SF3	transmembrane 7 superfamily member 3	2,00	Up
TMC2	transmembrane channel-like 2	1,67	Up
TMC2	transmembrane channel-like 2	1,63	Up
TMCO1	transmembrane and coiled-coil domains 1	1,58	Up
TMED1	transmembrane emp24 protein transport domain containing 1	1,80	Up
TMED10	transmembrane emp24-like trafficking protein 10 (yeast)	1,85	Up
TMED2	transmembrane emp24 domain trafficking protein 2	1,71	Up
TMED6	transmembrane emp24 protein transport domain containing 6	1,78	Up
TMEM108	transmembrane protein 108	2,06	Up
TMEM108	transmembrane protein 108	1,83	Up
EMC3	ER membrane protein complex subunit 3	1,52	Up
TMEM126B	transmembrane protein 126B	1,58	Up
TMEM127	transmembrane protein 127	1,81	Up
TMEM131	transmembrane protein 131	2,15	Up
TMEM141	transmembrane protein 141	1,65	Up
ORAI2	ORAI calcium release-activated calcium modulator 2	1,51	Up
CATSPERD	catsper channel auxiliary subunit delta	1,53	Up
TMEM155	transmembrane protein 155	2,16	Up
TMEM159	transmembrane protein 159	1,94	Up
TMEM169	transmembrane protein 169	1,66	Up
TMEM175	transmembrane protein 175	2,90	Down
TMEM178A	transmembrane protein 178A	1,69	Up
TMEM185A	transmembrane protein 185A	1,57	Up
TMEM25	transmembrane protein 25	1,68	Up
TMEM26	transmembrane protein 26	2,05	Up
TMEM27	transmembrane protein 27	1,54	Up
TMEM30B	transmembrane protein 30B	1,51	Up
TMEM31	transmembrane protein 31	1,67	Up
TMEM39B	transmembrane protein 39B	1,80	Up
NDC1	NDC1 transmembrane nucleoporin	1,69	Up
TMEM50B	transmembrane protein 50B	1,63	Up
TMEM55A	transmembrane protein 55A	1,59	Up
TMEM62	transmembrane protein 62	2,05	Up
TMEM63A	transmembrane protein 63A	1,67	Up
TMEM71	transmembrane protein 71	1,70	Up
TMEM86A	transmembrane protein 86A	1,51	Up
TMEM86A	transmembrane protein 86A	1,73	Up
TMEM97	transmembrane protein 97	1,76	Up
TMEM97	transmembrane protein 97	2,44	Up
TMPRSS13	transmembrane protease, serine 13	1,77	Up
TMPRSS5	transmembrane protease, serine 5	1,63	Down
TMPRSS6	transmembrane protease, serine 6	1,54	Up
TMTC1	transmembrane and tetratricopeptide repeat containing 1	1,51	Up
TNF	tumor necrosis factor	1,61	Down
TNFAIP8L1	tumor necrosis factor, alpha-induced protein 8-like 1	1,53	Down
TNFRSF11B	tumor necrosis factor receptor superfamily, member 11b	1,65	Up
TNFRSF14	tumor necrosis factor receptor superfamily, member 14	1,54	Up
TNFRSF21	tumor necrosis factor receptor superfamily, member 21	1,76	Up
TNFRSF25	tumor necrosis factor receptor superfamily, member 25	2,06	Down
TNFRSF8	tumor necrosis factor receptor superfamily, member 8	1,92	Up
TNFRSF9	tumor necrosis factor receptor superfamily, member 9	1,60	Up
TNFSF18	tumor necrosis factor (ligand) superfamily, member 18	1,53	Down
TNFSF8	tumor necrosis factor (ligand) superfamily, member 8	1,62	Up
TNNI1	troponin I type 1 (skeletal, slow)	1,77	Up
TNS1	tensin 1	1,83	Up
TNS3	tensin 3	1,53	Up
TNXB	tenascin XB	1,58	Down
TOM1L1	target of myb1 (chicken)-like 1	2,11	Up
TOMM34	translocase of outer mitochondrial membrane 34	1,64	Up
TOP1P2	topoisomerase (DNA) I pseudogene 2	1,76	Up
TOR1AIP1	torsin A interacting protein 1	2,27	Up
TP53I11	tumor protein p53 inducible protein 11	1,56	Down
TPCN1	two pore segment channel 1	1,81	Up
TPD52	tumor protein D52	1,68	Up
TPD52L1	tumor protein D52-like 1	1,70	Up
TPM1	tropomyosin 1 (alpha)	1,82	Up
TPSG1	tryptase gamma 1	1,83	Down
TRABD	TraB domain containing	2,33	Down
TRAF1	TNF receptor-associated factor 1	1,67	Up
TRAF3IP3	TRAF3 interacting protein 3	1,95	Up
TRAK1	trafficking protein, kinesin binding 1	1,61	Up
TRAPPC1	trafficking protein particle complex 1	1,53	Up
TRAT1	T cell receptor associated transmembrane adaptor 1	1,76	Up
TREM2	triggering receptor expressed on myeloid cells 2	1,56	Up
TREML1	triggering receptor expressed on myeloid cells-like 1	1,52	Up
TREML2	triggering receptor expressed on myeloid cells-like 2	1,92	Up
TRIM14	tripartite motif containing 14	1,69	Up
TRIM14	tripartite motif containing 14	1,58	Up
TRIM2	tripartite motif containing 2	2,07	Up
TRIM33	tripartite motif containing 33	1,85	Up
TRIM35	tripartite motif containing 35	1,90	Up
TRIM41	tripartite motif containing 41	1,62	Up
TRIM42	tripartite motif containing 42	1,74	Up
TRIM62	tripartite motif containing 62	1,55	Up
TRIO	trio Rho guanine nucleotide exchange factor	1,54	Up
TRIP12	thyroid hormone receptor interactor 12	1,54	Up
TRMT11	tRNA methyltransferase 11 homolog (S. cerevisiae)	1,69	Up
TROAP	trophinin associated protein	1,98	Down
TRPC4	transient receptor potential cation channel, subfamily C, member 4	1,79	Up
TRPV1	transient receptor potential cation channel, subfamily V, member 1	1,52	Up

TRPV2	transient receptor potential cation channel, subfamily V, member 2	1,63	Up
TRPV6	transient receptor potential cation channel, subfamily V, member 6	2,57	Up
TSC22D4	TSC22 domain family, member 4	1,65	Up
TSFM	Ts translation elongation factor, mitochondrial	1,55	Up
TSGA10IP	testis specific, 10 interacting protein	1,93	Up
TSHB	thyroid stimulating hormone, beta	2,32	Up
TSPAN10	tetraspanin 10	2,21	Down
TSPAN10	tetraspanin 10	3,46	Down
TSPAN18	tetraspanin 18	1,69	Up
TSPAN4	tetraspanin 4	1,63	Up
TSSK1B	testis-specific serine kinase 1B	1,63	Up
TTC14	tetratricopeptide repeat domain 14	1,79	Up
TRAPPC12	trafficking protein particle complex 12	1,57	Up
TTC18	tetratricopeptide repeat domain 18	1,52	Up
TTC21B	tetratricopeptide repeat domain 21B	1,78	Up
TTC26	tetratricopeptide repeat domain 26	1,84	Up
TTC27	tetratricopeptide repeat domain 27	1,55	Up
TTC4	tetratricopeptide repeat domain 4	2,07	Up
TTC7B	tetratricopeptide repeat domain 7B	1,50	Up
TTLL1	tubulin tyrosine ligase-like family, member 1	1,66	Up
TTLL11	tubulin tyrosine ligase-like family, member 11	1,81	Up
TTTY13	testis-specific transcript, Y-linked 13 (non-protein coding)	1,52	Up
TTYH3	tweety family member 3	2,07	Up
TUBA1C	tubulin, alpha 1c	1,50	Up
TUBB4B	tubulin, beta 4B class IVb	3,46	Up
TUBB4A	tubulin, beta 4A class IVa	1,77	Up
TUBGCP6	tubulin, gamma complex associated protein 6	1,59	Up
TULP1	tubby like protein 1	1,60	Down
TUSC2	tumor suppressor candidate 2	1,61	Up
TWIST2	twist family bHLH transcription factor 2	1,60	Up
NME9	NME/NM23 family member 9	1,55	Up
TXNL1	thioredoxin-like 1	1,52	Up
GLRX3	glutaredoxin 3	1,59	Up
TYR	tyrosinase	1,87	Up
TYW3	tRNA-yW synthesizing protein 3 homolog (S. cerevisiae)	2,25	Up
U2AF1L4	U2 small nuclear RNA auxiliary factor 1-like 4	1,61	Up
UBA52	ubiquitin A-52 residue ribosomal protein fusion product 1	2,04	Up
UBAP1	ubiquitin associated protein 1	2,04	Up
UBB	ubiquitin B	1,62	Up
UBC	ubiquitin C	2,17	Up
UBC	ubiquitin C	2,15	Up
UBA7	ubiquitin-like modifier activating enzyme 7	1,68	Up
UBE2D3	ubiquitin-conjugating enzyme E2D 3	1,58	Up
UBE2D3	ubiquitin-conjugating enzyme E2D 3	1,59	Up
UBE2G1	ubiquitin-conjugating enzyme E2G 1	1,88	Up
UBE2H	ubiquitin-conjugating enzyme E2H	1,64	Up
UBE2I	ubiquitin-conjugating enzyme E2I	2,30	Down
UBE2NL	ubiquitin-conjugating enzyme E2N-like	1,55	Up
UBE2O	ubiquitin-conjugating enzyme E2O	1,59	Up
UBE2Q2	ubiquitin-conjugating enzyme E2Q family member 2	1,65	Up
UBE2S	ubiquitin-conjugating enzyme E2S	2,02	Up
UBE2Z	ubiquitin-conjugating enzyme E2Z	2,37	Down
UBE3A	ubiquitin protein ligase E3A	1,63	Up
UBL4B	ubiquitin-like 4B	1,70	Up
UBOX5	U-box domain containing 5	1,83	Up
UBQLN3	ubiquilin 3	1,64	Up
UBR1	ubiquitin protein ligase E3 component n-recognin 1	1,70	Up
UBTD2	ubiquitin domain containing 2	1,53	Up
UCHL5	ubiquitin carboxyl-terminal hydrolase L5	1,59	Up
UCKL1	uridine-cytidine kinase 1-like 1	1,64	Up
UCN	urocortin	1,60	Down
UCN2	urocortin 2	1,53	Down
UQCR10	ubiquinol-cytochrome c reductase, complex III subunit X	1,75	Up
UQCR10	ubiquinol-cytochrome c reductase, complex III subunit X	1,54	Up
UFD1L	ubiquitin fusion degradation 1 like (yeast)	1,75	Up
UGDH	UDP-glucose 6-dehydrogenase	1,72	Up
UGT3A1	UDP glycosyltransferase 3 family, polypeptide A1	1,82	Up
UHMK1	U2AF homology motif (UHM) kinase 1	1,68	Up
ULK1	unc-51 like autophagy activating kinase 1	1,77	Up
ULK1	unc-51 like autophagy activating kinase 1	1,52	Up

UMOD	uromodulin	1,59	Up
UNC50	unc-50 homolog (C. elegans)	1,58	Up
UNC5C	unc-5 homolog C (C. elegans)	1,68	Up
SUN2	Sad1 and UNC84 domain containing 2	1,68	Down
UNC93A	unc-93 homolog A (C. elegans)	1,73	Up
KRTDAP	keratinocyte differentiation-associated protein	3,91	Up
C2orf66	chromosome 2 open reading frame 66	1,62	Up
FAM150A	family with sequence similarity 150, member A	1,51	Up
UPK2	uroplakin 2	1,77	Up
UPP2	uridine phosphorylase 2	2,07	Up
UQCR11	ubiquinol-cytochrome c reductase, complex III subunit XI	1,88	Up
UROS	uroporphyrinogen III synthase	1,97	Up
USP13	ubiquitin specific peptidase 13 (isopeptidase T-3)	1,54	Up
USP28	ubiquitin specific peptidase 28	1,68	Up
USP32	ubiquitin specific peptidase 32	1,83	Up
USP34	ubiquitin specific peptidase 34	1,87	Up
USP34	ubiquitin specific peptidase 34	1,51	Up
USP41	ubiquitin specific peptidase 41	1,71	Up
USP45	ubiquitin specific peptidase 45	1,67	Up
USP51	ubiquitin specific peptidase 51	1,65	Up
USP54	ubiquitin specific peptidase 54	1,71	Up
USP54	ubiquitin specific peptidase 54	2,32	Up
USP6	ubiquitin specific peptidase 6 (Tre-2 oncogene)	1,59	Up
USP6NL	USP6 N-terminal like	1,79	Up
USPL1	ubiquitin specific peptidase like 1	1,95	Up
UTF1	undifferentiated embryonic cell transcription factor 1	1,93	Down
UTP14A	UTP14, U3 small nucleolar ribonucleoprotein, homolog A (yeast)	2,21	Up
UTS2R	urotensin 2 receptor	2,47	Down
VAC14	Vac14 homolog (S. cerevisiae)	1,63	Up
VAMP2	vesicle-associated membrane protein 2 (synaptobrevin 2)	1,52	Down
VANGL1	VANGL planar cell polarity protein 1	1,51	Up
VAV3	vav 3 guanine nucleotide exchange factor	1,53	Up
VCX2	variable charge, X-linked 2	1,95	Down
VCY	variable charge, Y-linked	2,03	Up
VEGFA	vascular endothelial growth factor A	1,54	Up
VGLL2	vestigial like 2 (Drosophila)	1,55	Up
VGLL3	vestigial like 3 (Drosophila)	1,57	Up
VIM	vimentin	1,60	Up
VIP	vasoactive intestinal peptide	1,72	Up
VIPR2	vasoactive intestinal peptide receptor 2	1,65	Up
VMAC	vimentin-type intermediate filament associated coiled-coil protein	1,87	Up
VN1R5	vomeronasal 1 receptor 5 (gene/pseudogene)	1,94	Up
VPS11	vacuolar protein sorting 11 homolog (S. cerevisiae)	1,84	Up
CHMP3	charged multivesicular body protein 3	1,60	Up
VPS28	vacuolar protein sorting 28 homolog (S. cerevisiae)	1,97	Up
VRK2	vaccinia related kinase 2	2,04	Up
WAC	WW domain containing adaptor with coiled-coil	1,60	Up
WASF2	WAS protein family, member 2	2,11	Up
WBSCR16	Williams-Beuren syndrome chromosome region 16	1,57	Up
WDHD1	WD repeat and HMG-box DNA binding protein 1	1,86	Up
WDR12	WD repeat domain 12	1,81	Up
WDR18	WD repeat domain 18	2,18	Up
DCAF4	DDB1 and CUL4 associated factor 4	1,64	Up
DCAF5	DDB1 and CUL4 associated factor 5	1,59	Up
WDR27	WD repeat domain 27	1,87	Up
DCAF8	DDB1 and CUL4 associated factor 8	1,53	Up
WDR45	WD repeat domain 45	1,60	Up
WDR45B	WD repeat domain 45B	1,52	Up
POC1A	POC1 centriolar protein A	1,56	Up
DCAF7	DDB1 and CUL4 associated factor 7	1,50	Up
DAW1	dynein assembly factor with WDR repeat domains 1	1,51	Down
DPH7	diphthamide biosynthesis 7	1,87	Up
WDR90	WD repeat domain 90	1,62	Up
WFDC5	WAP four-disulfide core domain 5	1,52	Up
WHSC1	Wolf-Hirschhorn syndrome candidate 1	1,96	Up
WIBG	within bgcn homolog (Drosophila)	1,56	Up
WIPF1	WAS/WASL interacting protein family, member 1	1,81	Up
WIPF2	WAS/WASL interacting protein family, member 2	2,01	Up
WIPI1	WD repeat domain, phosphoinositide interacting 1	1,66	Up
WIPI2	WD repeat domain, phosphoinositide interacting 2	1,94	Up

WNK4	WNK lysine deficient protein kinase 4	1,63	Down
WNT10B	wingless-type MMTV integration site family, member 10B	1,50	Up
WNT5B	wingless-type MMTV integration site family, member 5B	1,52	Up
WNT6	wingless-type MMTV integration site family, member 6	2,38	Down
WNT9A	wingless-type MMTV integration site family, member 9A	1,50	Down
WRNIP1	Werner helicase interacting protein 1	1,52	Up
WWC3	WWC family member 3	2,38	Up
WWP2	WW domain containing E3 ubiquitin protein ligase 2	1,85	Up
WWP2	WW domain containing E3 ubiquitin protein ligase 2	1,88	Up
WWP2	WW domain containing E3 ubiquitin protein ligase 2	1,54	Down
WWTR1	WW domain containing transcription regulator 1	1,74	Up
GPN1	GPN-loop GTPase 1	1,59	Up
XCL2	chemokine (C motif) ligand 2	1,61	Up
XKR6	XK, Kell blood group complex subunit-related family, member 6	2,03	Up
XPNPEP3	X-prolyl aminopeptidase (aminopeptidase P) 3, putative	1,72	Up
XPOT	exportin, tRNA	1,60	Up
XRN1	5'-3' exoribonuclease 1	1,53	Up
XYLB	xylulokinase homolog (H. influenzae)	1,61	Up
YBX1	Y box binding protein 1	1,57	Up
YBX2	Y box binding protein 2	1,77	Up
YPEL4	yippee-like 4 (Drosophila)	1,96	Up
YTHDC1	YTH domain containing 1	1,81	Up
YWHAB	tyrosine 3-monooxygenase/tryptophan 5-monooxygenase activation protein, beta	1,69	Up
YWHAE	tyrosine 3-monooxygenase/tryptophan 5-monooxygenase activation protein, epsilon	1,83	Up
YWHAQ	tyrosine 3-monooxygenase/tryptophan 5-monooxygenase activation protein, theta	1,69	Up
YWHAZ	tyrosine 3-monooxygenase/tryptophan 5-monooxygenase activation protein, zeta	1,52	Up
ZBTB39	zinc finger and BTB domain containing 39	1,73	Up
ZBTB40	zinc finger and BTB domain containing 40	1,56	Up
ZBTB5	zinc finger and BTB domain containing 5	1,86	Up
ZC3H11A	zinc finger CCCH-type containing 11A	1,63	Up
ZC3H13	zinc finger CCCH-type containing 13	1,60	Up
CISD1	CDGSH iron sulfur domain 1	2,12	Up
ZDHHC2	zinc finger, DHHC-type containing 2	1,80	Up
ZDHHC21	zinc finger, DHHC-type containing 21	1,63	Up
ZDHHC21	zinc finger, DHHC-type containing 21	1,66	Up
ZDHHC24	zinc finger, DHHC-type containing 24	2,07	Up
ZDHHC4	zinc finger, DHHC-type containing 4	1,88	Up
ZDHHC5	zinc finger, DHHC-type containing 5	1,56	Up
ZDHHC8	zinc finger, DHHC-type containing 8	1,63	Down
ZFAND3	zinc finger, AN1-type domain 3	1,77	Up
ZFAND5	zinc finger, AN1-type domain 5	1,60	Up
ZFAND5	zinc finger, AN1-type domain 5	1,53	Up
ZFP36L1	ZFP36 ring finger protein-like 1	1,98	Up
ZFP91	ZFP91 zinc finger protein	1,64	Up
ZFPL1	zinc finger protein-like 1	1,84	Down
ZFPM1	zinc finger protein, FOG family member 1	1,77	Down
ZFR	zinc finger RNA binding protein	1,55	Up
ZFY	zinc finger protein, Y-linked	1,54	Up
ZFYVE20	zinc finger, FYVE domain containing 20	1,76	Up
ZFYVE26	zinc finger, FYVE domain containing 26	1,59	Up
ZFYVE27	zinc finger, FYVE domain containing 27	1,56	Up
ZG16	zymogen granule protein 16	1,54	Up
ZIC4	Zic family member 4	1,99	Up
ZIM2	zinc finger, imprinted 2	2,04	Up
ZKSCAN2	zinc finger with KRAB and SCAN domains 2	1,66	Up
ZMAT2	zinc finger, matrin-type 2	1,82	Up
ZMAT5	zinc finger, matrin-type 5	1,98	Up
ZMYND12	zinc finger, MYND-type containing 12	1,55	Up
ZNF12	zinc finger protein 12	1,76	Up
ZNF133	zinc finger protein 133	1,52	Up
ZNF141	zinc finger protein 141	1,60	Up
ZNF174	zinc finger protein 174	1,64	Down
ZSCAN26	zinc finger and SCAN domain containing 26	1,51	Up
ZNF213	zinc finger protein 213	1,59	Down
ZNF219	zinc finger protein 219	2,32	Up
ZNF226	zinc finger protein 226	1,66	Up
ZNF234	zinc finger protein 234	1,84	Up
ZNF235	zinc finger protein 235	1,60	Up
ZNF236	zinc finger protein 236	1,57	Up

1. Information from HGNC (HUGO Gene Nomenclature Committee; www.genenames.org).
2. Type of regulation.

ZNF25	zinc finger protein 25	1,53	Up
ZNF277	zinc finger protein 277	1,51	Up
ZNF283	zinc finger protein 283	1,58	Up
SCAPER	S-phase cyclin A-associated protein in the ER	1,63	Up
ZBTB21	zinc finger and BTB domain containing 21	1,54	Up
ZNF320	zinc finger protein 320	1,50	Up
ZNF326	zinc finger protein 326	1,65	Up
ZNF333	zinc finger protein 333	2,02	Up
ZNF296	zinc finger protein 296	1,93	Up
ZNF346	zinc finger protein 346	1,65	Up
ZNF367	zinc finger protein 367	1,55	Up
ZNF396	zinc finger protein 396	1,94	Up
ZFHX2	zinc finger homeobox 2	1,52	Down
ZNF410	zinc finger protein 410	1,89	Up
ZNF415	zinc finger protein 415	1,52	Up
ZNF417	zinc finger protein 417	1,71	Up
ZNF425	zinc finger protein 425	1,68	Up
ZNF429	zinc finger protein 429	1,68	Up
ZNF440	zinc finger protein 440	1,62	Up
ZNF467	zinc finger protein 467	1,81	Down
ZNF468	zinc finger protein 468	1,67	Up
ZNF501	zinc finger protein 501	1,86	Up
ZNF506	zinc finger protein 506	1,93	Up
ZNF518A	zinc finger protein 518A	1,65	Up
ZNF521	zinc finger protein 521	1,70	Up
ZNF525	zinc finger protein 525	1,53	Up
ZNF532	zinc finger protein 532	3,52	Up
ZNF546	zinc finger protein 546	1,67	Up
ZNF551	zinc finger protein 551	1,51	Down
ZNF554	zinc finger protein 554	1,51	Up
ZNF562	zinc finger protein 562	1,51	Up
ZNF578	zinc finger protein 578	1,75	Up
ZNF579	zinc finger protein 579	1,82	Down
ZNF581	zinc finger protein 581	1,58	Up
ZNF589	zinc finger protein 589	1,50	Up
ZNF607	zinc finger protein 607	1,51	Up
ZNF616	zinc finger protein 616	1,85	Up
ZNF618	zinc finger protein 618	1,55	Up
ZNF618	zinc finger protein 618	1,61	Up
ZNF619	zinc finger protein 619	1,74	Down
ZNF625	zinc finger protein 625	1,90	Up
ZNF644	zinc finger protein 644	1,66	Up
UBR3	ubiquitin protein ligase E3 component n-recognin 3 (putative)	1,51	Up
ZNF655	zinc finger protein 655	2,02	Up
ZNF681	zinc finger protein 681	1,51	Up
ZNF695	zinc finger protein 695	1,62	Up
ZNF696	zinc finger protein 696	1,79	Up
ZNF697	zinc finger protein 697	1,63	Down
ZNF704	zinc finger protein 704	2,00	Up
ZNF761	zinc finger protein 761	1,71	Up
ZNF764	zinc finger protein 764	1,85	Up
ZNF767	zinc finger family member 767	1,54	Up
ZNF772	zinc finger protein 772	1,92	Up
ZNF775	zinc finger protein 775	2,23	Down
ZNF777	zinc finger protein 777	2,17	Down
ZNF778	zinc finger protein 778	1,76	Up
ZNF781	zinc finger protein 781	1,57	Up
ZNF80	zinc finger protein 80	1,70	Up
ZNF818P	zinc finger protein 818, pseudogene	1,56	Up
ZNF99	zinc finger protein 99	1,64	Up
ZNRD1	zinc ribbon domain containing 1	1,56	Up
ZRANB1	zinc finger, RAN-binding domain containing 1	1,64	Up
ZSCAN18	zinc finger and SCAN domain containing 18	1,63	Up
ZSCAN2	zinc finger and SCAN domain containing 2	1,95	Up
ZSCAN22	zinc finger and SCAN domain containing 22	1,55	Up
ZSWIM6	zinc finger, SWIM-type containing 6	1,72	Up
ZW10	zw10 kinetochore protein	2,13	Up
ZWILCH	zwilch kinetochore protein	1,62	Up
ZYG11B	zyg-11 family member B, cell cycle regulator	2,01	Up

1. Information from HGNC (HUGO Gene Nomenclature Committee; www.genenames.org).
2. Type of regulation.

Table S3. Characterization of the secondary volunteer panel for real-time qPCR validation.

Volunteer Number	Age (Years Old)	Skin Phototype [1]	Skin Type [2]	Ethnic Group [3]
1	21	II	Normal	Polish
2	24	II	Normal	Germa/Italian
3	27	III	Combination	Indigenous
4	22	II	Oily	Italian
5	27	II	Not declared	Not declared
6	54	II	Oily	Italian/Spanish
7	62	II	Not declared	Not declared
8	27	II	Oily	German/Polish/Portuguese/Spanish
9	24	II	Combination	Portuguese
10	27	II	Oily	Polish
11	25	III	Combination	African/German
12	29	III	Normal	Italian/Libanese/Spanish
13	52	III	Not declared	Not declared
14	51	II	Not declared	Not declared
15	52	III	Not declared	Not declared
16	54	III	Not declared	Not declared
17	54	III	Not declared	Not declared
18	57	II	Seca	Italian
19	56	III	Oily	Spanish
20	62	II	Normal	Italian

1. Classification according to Fitzpatrick phototyping scale

2. Personal declaration of predominant skin type in the body according to sebum production

3. Personal declaration of ethnic groups

Table S4. Number of differentially expressed probe sets in sun-exposed epidermal aging considering different fold-change values and a p-value cut-off of 0.05.

Probe sets account	Fold change values		
	1.5	2.0	3.0
Total	4,863	683	101
Up-regulated	4,146	419	36
Down-regulated	717	264	65
Ratio (up/down)	5.8	1.6	0.6

Table S5. KEGG pathways modulated in sun-exposed epidermal aging with p-value cut-off of 0.01.

KEGG pathway name	KEGG code	Number of DEGs[1]	p-value
Systemic lupus erythematosus	hsa05322	114	5.22E-91
Neuroactive ligand-receptor interaction	hsa04080	69	1.91E-16
Ubiquitin mediated proteolysis	hsa04120	34	1.28E-07
Ribosome	hsa03010	24	2.34E-06
Fc gamma R-mediated phagocytosis	hsa04666	25	6.54E-06
Focal adhesion	hsa04510	40	6.54E-06
Cytokine-cytokine receptor interaction	hsa04060	46	1.36E-05
Wnt signaling pathway	hsa04310	32	2.38E-05
Type I diabetes mellitus	hsa04940	15	2.80E-05
Chemokine signaling pathway	hsa04062	36	3.19E-05
Neurotrophin signaling pathway	hsa04722	27	5.73E-05
Regulation of actin cytoskeleton	hsa04810	37	1.69E-04
Antigen processing and presentation	hsa04612	21	1.69E-04
Alzheimer's disease	hsa05010	31	1.73E-04
Endocytosis	hsa04144	33	1.74E-04
Allograft rejection	hsa05330	13	3.47E-04
MAPK signaling pathway	hsa04010	42	4.04E-04
Vibrio cholerae infection	hsa05110	15	4.09E-04
Cell adhesion molecules (CAMs)	hsa04514	26	4.79E-04
Viral myocarditis	hsa05416	18	4.79E-04
Calcium signaling pathway	hsa04020	31	4.79E-04
Purine metabolism	hsa00230	29	5.79E-04
Graft-versus-host disease	hsa05332	13	6.45E-04
Asthma	hsa05310	11	7.08E-04
Axon guidance	hsa04360	24	8.78E-04
Epithelial cell signaling in Helicobacter pylori infection	hsa05120	16	8.98E-04
Huntington's disease	hsa05016	31	8.98E-04
Autoimmune thyroid disease	hsa05320	14	1.28E-03
Riboflavin metabolism	hsa00740	7	2.64E-03
Natural killer cell mediated cytotoxicity	hsa04650	24	2.64E-03
Hematopoietic cell lineage	hsa04640	17	2.83E-03
Fc epsilon RI signaling pathway	hsa04664	16	3.34E-03
Intestinal immune network for IgA production	hsa04672	12	3.34E-03
Type II diabetes mellitus	hsa04930	12	3.34E-03
ECM-receptor interaction	hsa04512	16	4.89E-03
Oocyte meiosis	hsa04114	20	5.06E-03
Jak-STAT signaling pathway	hsa04630	25	5.06E-03
Butanoate metabolism	hsa00650	10	6.46E-03
Amyotrophic lateral sclerosis (ALS)	hsa05014	12	6.86E-03
Hedgehog signaling pathway	hsa04340	12	9.14E-03

1. DEGs, differentially expressed genes.

Table S6. Epidermal age-modulated genes shared with the study of Raddatz *et al.* (2013).

HGNC Approved Symbol[1]	HGNC Approved Name[1]
ANXA3	annexin A3
CEACAM5	carcinoembryonic antigen-related cell adhesion molecule 5
FABP3	fatty acid binding protein 3, muscle and heart (mammary-derived growth inhibitor)
FBLIM1	filamin binding LIM protein 1
FZD10	frizzled family receptor 10
IFI27	interferon, alpha-inducible protein 27
JPH2	junctophilin 2
MUC16	mucin 16, cell surface associated
OTOP2	otopetrin 2
SAMD4A	sterile alpha motif domain containing 4A
SLC6A2	solute carrier family 6 (neurotransmitter transporter), member 2
SPRR1A	small proline-rich protein 1A
SPRR1B	small proline-rich protein 1B
TRIM2	tripartite motif containing 2
ZDHHC2	zinc finger, DHHC-type containing 2

1. Gene ontology terms identified with GeneSpring version 12.5 software (Agilent Technologies).

Table S7. Epidermal age-modulated genes shared with the study of Glass *et al.* (2013).

HGNC Approved Symbol[1]	HGNC Approved Name[1]
ABI3BP	ABI family, member 3 (NESH) binding protein
ADA	adenosine deaminase
AKR7L	aldo-keto reductase family 7-like
ALOX15B	arachidonate 15-lipoxygenase, type B
ALOX5AP	arachidonate 5-lipoxygenase-activating protein
ANAPC4	anaphase promoting complex subunit 4
ANAPC5	anaphase promoting complex subunit 5
ANGPTL2	angiopoietin-like 2
ANKMY2	ankyrin repeat and MYND domain containing 2
AP1G2	adaptor-related protein complex 1, gamma 2 subunit
APH1B	APH1B gamma secretase subunit
ARHGEF10	Rho guanine nucleotide exchange factor (GEF) 10
ARID4B	AT rich interactive domain 4B (RBP1-like)
ARMC6	armadillo repeat containing 6
ASNS	asparagine synthetase (glutamine-hydrolyzing)
ATP6V0C	ATPase, H+ transporting, lysosomal 16kDa, V0 subunit c
ATP6V1D	ATPase, H+ transporting, lysosomal 34kDa, V1subunit D
AUTS2	autism susceptibility candidate 2
DDX39B	DEAD (Asp-Glu-Ala-Asp) box polypeptide 39B
BCAN	brevican
BCKDK	branched chain ketoacid dehydrogenase kinase
BCL11A	B-cell CLL/lymphoma 11A (zinc finger protein)
BID	BH3 interacting domain death agonist
BLCAP	bladder cancer associated protein
C11orf70	chromosome 11 open reading frame 70
MFSD12	major facilitator superfamily domain containing 12
C1orf63	chromosome 1 open reading frame 63
ZNF295-AS1	ZNF295 antisense RNA 1
C21orf33	chromosome 21 open reading frame 33
MAATS1	MYCBP-associated, testis expressed 1
C6orf106	chromosome 6 open reading frame 106
CCDC167	coiled-coil domain containing 167
CALU	calumenin
CAMK2G	calcium/calmodulin-dependent protein kinase II gamma
COA3	cytochrome c oxidase assembly factor 3
CCDC86	coiled-coil domain containing 86
CCL2	chemokine (C-C motif) ligand 2
CCL21	chemokine (C-C motif) ligand 21
CDA	cytidine deaminase
CDH12	cadherin 12, type 2 (N-cadherin 2)
CEBPA	CCAAT/enhancer binding protein (C/EBP), alpha
AGAP3	ArfGAP with GTPase domain, ankyrin repeat and PH domain 3
CEP135	centrosomal protein 135kDa
CEP63	centrosomal protein 63kDa
CHCHD5	coiled-coil-helix-coiled-coil-helix domain containing 5
CIAO1	cytosolic iron-sulfur protein assembly 1
CLCF1	cardiotrophin-like cytokine factor 1
CNDP2	CNDP dipeptidase 2 (metallopeptidase M20 family)
COL3A1	collagen, type III, alpha 1
COL5A2	collagen, type V, alpha 2
COMMD1	copper metabolism (Murr1) domain containing 1
CORIN	corin, serine peptidase
CREG1	cellular repressor of E1A-stimulated genes 1
CSAD	cysteine sulfinic acid decarboxylase
CSTB	cystatin B (stefin B)
CTSF	cathepsin F
CTSK	cathepsin K
DAB2	Dab, mitogen-responsive phosphoprotein, homolog 2 (Drosophila)
DAD1	defender against cell death 1
DBN1	drebrin 1
DCBLD2	discoidin, CUB and LCCL domain containing 2
DCST1	DC-STAMP domain containing 1
DDB2	damage-specific DNA binding protein 2, 48kDa
DFNA5	deafness, autosomal dominant 5
DIRAS3	DIRAS family, GTP-binding RAS-like 3
DMBX1	diencephalon/mesencephalon homeobox 1
DNAH17	dynein, axonemal, heavy chain 17
DNASE1L2	deoxyribonuclease I-like 2
DOCK3	dedicator of cytokinesis 3
DPM3	dolichyl-phosphate mannosyltransferase polypeptide 3
CALY	calcyon neuron-specific vesicular protein
DUSP16	dual specificity phosphatase 16
DVL3	dishevelled segment polarity protein 3
EEF2K	eukaryotic elongation factor-2 kinase
EI24	etoposide induced 2.4
ELMO1	engulfment and cell motility 1
ERN1	endoplasmic reticulum to nucleus signaling 1
FAM129B	family with sequence similarity 129, member B
FAM46C	family with sequence similarity 46, member C
FAM63A	family with sequence similarity 63, member A
FAM89B	family with sequence similarity 89, member B
FANCD2	Fanconi anemia, complementation group D2
FAT2	FAT atypical cadherin 2
FCN1	ficolin (collagen/fibrinogen domain containing) 1
FETUB	fetuin B
ARHGEF37	Rho guanine nucleotide exchange factor (GEF) 37
FOXQ1	forkhead box Q1
GLDC	glycine dehydrogenase (decarboxylating)

Symbol	
GOLGB1	golgin B1
GPI	glucose-6-phosphate isomerase
GPRC5D	G protein-coupled receptor, family C, group 5, member D
GYPC	glycophorin C (Gerbich blood group)
H2AFJ	H2A histone family, member J
HADH	hydroxyacyl-CoA dehydrogenase
HCP5	HLA complex P5 (non-protein coding)
HIST1H2BD	histone cluster 1, H2bd
HIST1H2BK	histone cluster 1, H2bk
HIVEP3	human immunodeficiency virus type I enhancer binding protein 3
HLA-DPA1	major histocompatibility complex, class II, DP alpha 1
HSD3B1	hydroxy-delta-5-steroid dehydrogenase, 3 beta- and steroid delta-isomerase 1
HYOU1	hypoxia up-regulated 1
IGFBP4	insulin-like growth factor binding protein 4
IL1B	interleukin 1, beta
IRX6	iroquois homeobox 6
ISG20	interferon stimulated exonuclease gene 20kDa
ITGB4	integrin, beta 4
JAG2	jagged 2
KCNIP4	Kv channel interacting protein 4
KCTD13	potassium channel tetramerization domain containing 13
KDELR3	KDEL (Lys-Asp-Glu-Leu) endoplasmic reticulum protein retention receptor 3
KIAA0513	KIAA0513
KIAA0586	KIAA0586
KIAA0753	KIAA0753
MAU2	MAU2 sister chromatid cohesion factor
KIAA0907	KIAA0907
ZSWIM8	zinc finger, SWIM-type containing 8
KLHDC3	kelch domain containing 3
KRT27	keratin 27
KRT32	keratin 32
KRT34	keratin 34
KRT38	keratin 38
KRT5	keratin 5
KRT85	keratin 85
KRT86	keratin 86
KRTAP19-1	keratin associated protein 19-1
KRTAP4-2	keratin associated protein 4-2
KRTAP4-5	keratin associated protein 4-5
KRTAP9-3	keratin associated protein 9-3
KRTAP9-4	keratin associated protein 9-4
POGLUT1	protein O-glucosyltransferase 1
LFNG	LFNG O-fucosylpeptide 3-beta-N-acetylglucosaminyltransferase
LGALS1	lectin, galactoside-binding, soluble, 1
LGALS8	lectin, galactoside-binding, soluble, 8
LRP3	low density lipoprotein receptor-related protein 3
LRRC18	leucine rich repeat containing 18
NRROS	negative regulator of reactive oxygen species
LSS	lanosterol synthase (2,3-oxidosqualene-lanosterol cyclase)
LYG2	lysozyme G-like 2
MAP1A	microtubule-associated protein 1A
MAPKBP1	mitogen-activated protein kinase binding protein 1
MC5R	melanocortin 5 receptor
ME1	malic enzyme 1, NADP(+)-dependent, cytosolic
MEA1	male-enhanced antigen 1
MFSD5	major facilitator superfamily domain containing 5
MIR503HG	MIR503 host gene (non-protein coding)
MLANA	melan-A
MMRN1	multimerin 1
MOCS1	molybdenum cofactor synthesis 1
MOGAT1	monoacylglycerol O-acyltransferase 1
MRPS12	mitochondrial ribosomal protein S12
MRPS24	mitochondrial ribosomal protein S24
MRPS25	mitochondrial ribosomal protein S25
MSRA	methionine sulfoxide reductase A
MSX1	msh homeobox 1
NAPSB	napsin B aspartic peptidase, pseudogene
NDUFA8	NADH dehydrogenase (ubiquinone) 1 alpha subcomplex, 8, 19kDa
NDUFB2	NADH dehydrogenase (ubiquinone) 1 beta subcomplex, 2, 8kDa
NKD2	naked cuticle homolog 2 (Drosophila)
OAZ1	ornithine decarboxylase antizyme 1
OLFML2B	olfactomedin-like 2B
ORC2	origin recognition complex, subunit 2
PADI4	peptidyl arginine deiminase, type IV
PAPLN	papilin, proteoglycan-like sulfated glycoprotein
PARP2	poly (ADP-ribose) polymerase 2
PC	pyruvate carboxylase
PCDH7	protocadherin 7
PCK2	phosphoenolpyruvate carboxykinase 2 (mitochondrial)
PDE4C	phosphodiesterase 4C, cAMP-specific
PGAM5	phosphoglycerate mutase family member 5
PHF12	PHD finger protein 12
PHF7	PHD finger protein 7
PIGN	phosphatidylinositol glycan anchor biosynthesis, class N
PISD	phosphatidylserine decarboxylase
PLCH2	phospholipase C, eta 2
PNPLA5	patatin-like phospholipase domain containing 5
PON3	paraoxonase 3
PPP1R11	protein phosphatase 1, regulatory (inhibitor) subunit 11
PPP2R1B	protein phosphatase 2, regulatory subunit A, beta
PRMT2	protein arginine methyltransferase 2
PRR4	proline rich 4 (lacrimal)

1. Information from HGNC (HUGO Gene Nomenclature Committee; www.genenames.org).

Symbol	
PTPRZ1	protein tyrosine phosphatase, receptor-type, Z polypeptide 1
PXMP4	peroxisomal membrane protein 4, 24kDa
QPRT	quinolinate phosphoribosyltransferase
RAB11FIP5	RAB11 family interacting protein 5 (class I)
RAD54B	RAD54 homolog B (S. cerevisiae)
RANBP10	RAN binding protein 10
RAPGEF1	Rap guanine nucleotide exchange factor (GEF) 1
RASEF	RAS and EF-hand domain containing
RBM18	RNA binding motif protein 18
REEP6	receptor accessory protein 6
REXO2	RNA exonuclease 2
RHOG	ras homolog family member G
RIMBP2	RIMS binding protein 2
RPL29	ribosomal protein L29
RPP25	ribonuclease P/MRP 25kDa subunit
RPS29	ribosomal protein S29
S100A3	S100 calcium binding protein A3
S100PBP	S100P binding protein
SAMM50	SAMM50 sorting and assembly machinery component
SC5D	sterol-C5-desaturase
SDCCAG3	serologically defined colon cancer antigen 3
SDSL	serine dehydratase-like
VIMP	VCP-interacting membrane protein
SEMA5B	sema domain, seven thrombospondin repeats (type 1 and type 1-like), transmembrane domain (TM) and short cytoplasmic domain, (semaphorin) 5B
MSRB1	methionine sulfoxide reductase B1
SERPINH1	serpin peptidase inhibitor, clade H (heat shock protein 47), member 1, (collagen binding protein 1)
SF3B5	splicing factor 3b, subunit 5, 10kDa
SGPP2	sphingosine-1-phosphate phosphatase 2
SHB	Src homology 2 domain containing adaptor protein B
SHF	Src homology 2 domain containing F
SIDT2	SID1 transmembrane family, member 2
SLC10A3	solute carrier family 10, member 3
SLC11A2	solute carrier family 11 (proton-coupled divalent metal ion transporter), member 2
SLC16A5	solute carrier family 16 (monocarboxylate transporter), member 5
SLC25A1	solute carrier family 25 (mitochondrial carrier; citrate transporter), member 1
SLC25A42	solute carrier family 25, member 42
SLC2A5	solute carrier family 2 (facilitated glucose/fructose transporter), member 5
SLC35B1	solute carrier family 35, member B1
SLC35F1	solute carrier family 35, member F1
SLC37A4	solute carrier family 37 (glucose-6-phosphate transporter), member 4
SLC41A1	solute carrier family 41 (magnesium transporter), member 1
SLC45A2	solute carrier family 45, member 2
SLC47A1	solute carrier family 47 (multidrug and toxin extrusion), member 1
SLC7A1	solute carrier family 7 (cationic amino acid transporter, y+ system), member 1
SMG1	SMG1 phosphatidylinositol 3-kinase-related kinase
SND1	staphylococcal nuclease and tudor domain containing 1
ARHGAP33	Rho GTPase activating protein 33
SPEN	spen family transcriptional repressor
SPG11	spastic paraplegia 11 (autosomal recessive)
SPRR1A	small proline-rich protein 1A
SPTLC3	serine palmitoyltransferase, long chain base subunit 3
SREBF1	sterol regulatory element binding transcription factor 1
SSH3	slingshot protein phosphatase 3
STK31	serine/threonine kinase 31
SULT4A1	sulfotransferase family 4A, member 1
SYNGR1	synaptogyrin 1
TAF10	TAF10 RNA polymerase II, TATA box binding protein (TBP)-associated factor, 30kDa
TAP1	transporter 1, ATP-binding cassette, sub-family B (MDR/TAP)
TARDBP	TAR DNA binding protein
TBC1D2	TBC1 domain family, member 2
TCN2	transcobalamin II
TEX264	testis expressed 264
TFF3	trefoil factor 3 (intestinal)
THOC1	THO complex 1
THY1	Thy-1 cell surface antigen
TJAP1	tight junction associated protein 1 (peripheral)
TMEM141	transmembrane protein 141
TMEM178A	transmembrane protein 178A
TMEM31	transmembrane protein 31
TMEM50B	transmembrane protein 50B
TMEM71	transmembrane protein 71
TMEM97	transmembrane protein 97
TNFRSF21	tumor necrosis factor receptor superfamily, member 21
TNFRSF25	tumor necrosis factor receptor superfamily, member 25
TRAK1	trafficking protein, kinesin binding 1
TRPV1	transient receptor potential cation channel, subfamily V, member 1
TRPV2	transient receptor potential cation channel, subfamily V, member 2
TTYH3	tweety family member 3
TUBGCP6	tubulin, gamma complex associated protein 6
UCKL1	uridine-cytidine kinase 1-like 1
UCN2	urocortin 2
UQCR10	ubiquinol-cytochrome c reductase, complex III subunit X
USPL1	ubiquitin specific peptidase like 1
VAV3	vav 3 guanine nucleotide exchange factor
YTHDC1	YTH domain containing 1
ZDHHC24	zinc finger, DHHC-type containing 24
ZDHHC8	zinc finger, DHHC-type containing 8
ZFYVE20	zinc finger, FYVE domain containing 20
ZFYVE26	zinc finger, FYVE domain containing 26
ZNF333	zinc finger protein 333
ZNF525	zinc finger protein 525
ZNF581	zinc finger protein 581

1. Information from HGNC (HUGO Gene Nomenclature Committee; www.genenames.org).

Table S8. Epidermal age-modulated genes shared with the study of Yan *et al.* (2013).

HGNC Approved Symbol[1]	HGNC Approved Name[1]
A4GALT	alpha 1,4-galactosyltransferase
NCEH1	neutral cholesterol ester hydrolase 1
ACAD9	acyl-CoA dehydrogenase family, member 9
ACOT11	acyl-CoA thioesterase 11
ACOX2	acyl-CoA oxidase 2, branched chain
ADA	adenosine deaminase
ADH1A	alcohol dehydrogenase 1A (class I), alpha polypeptide
ADHFE1	alcohol dehydrogenase, iron containing, 1
ADNP	activity-dependent neuroprotector homeobox
AES	amino-terminal enhancer of split
AIM1L	absent in melanoma 1-like
ALDH2	aldehyde dehydrogenase 2 family (mitochondrial)
ALDOA	aldolase A, fructose-bisphosphate
ALKBH8	alkB, alkylation repair homolog 8 (E. coli)
ALOX12	arachidonate 12-lipoxygenase
ALOX15B	arachidonate 15-lipoxygenase, type B
ANGPTL2	angiopoietin-like 2
ANPEP	alanyl (membrane) aminopeptidase
AQP5	aquaporin 5
ARMC6	armadillo repeat containing 6
ARV1	ARV1 homolog (S. cerevisiae)
ATG9B	autophagy related 9B
ATP6V0C	ATPase, H+ transporting, lysosomal 16kDa, V0 subunit c
BCAN	brevican
BLOC1S2	biogenesis of lysosomal organelles complex-1, subunit 2
DTD2	D-tyrosyl-tRNA deacylase 2 (putative)
CCDC176	coiled-coil domain containing 176
CTC1	CTS telomere maintenance complex component 1
MFSD12	major facilitator superfamily domain containing 12
C1orf116	chromosome 1 open reading frame 116
AUNIP	aurora kinase A and ninein interacting protein
C1orf53	chromosome 1 open reading frame 53
ISM1	isthmin 1, angiogenesis inhibitor
MMADHC	methylmalonic aciduria (cobalamin deficiency) cbID type, with homocystinuria
TRMT44	tRNA methyltransferase 44 homolog (S. cerevisiae)
FAM13B	family with sequence similarity 13, member B
ATAT1	alpha tubulin acetyltransferase 1
FAM167A	family with sequence similarity 167, member A
CAMK1D	calcium/calmodulin-dependent protein kinase ID
CCBE1	collagen and calcium binding EGF domains 1
CCL21	chemokine (C-C motif) ligand 21
CCNB1IP1	cyclin B1 interacting protein 1, E3 ubiquitin protein ligase
CCND2	cyclin D2
CCT4	chaperonin containing TCP1, subunit 4 (delta)
CD109	CD109 molecule
CDH12	cadherin 12, type 2 (N-cadherin 2)
CDH4	cadherin 4, type 1, R-cadherin (retinal)
CEACAM1	carcinoembryonic antigen-related cell adhesion molecule 1 (biliary glycoprotein)
CEACAM5	carcinoembryonic antigen-related cell adhesion molecule 5
CGA	glycoprotein hormones, alpha polypeptide
CHAF1B	chromatin assembly factor 1, subunit B (p60)
CHCHD7	coiled-coil-helix-coiled-coil-helix domain containing 7
CKAP5	cytoskeleton associated protein 5
CLN3	ceroid-lipofuscinosis, neuronal 3
CNNM4	cyclin M4
CNOT4	CCR4-NOT transcription complex, subunit 4
CNTN4	contactin 4
COL5A2	collagen, type V, alpha 2
COL6A1	collagen, type VI, alpha 1
COQ9	coenzyme Q9
CRABP1	cellular retinoic acid binding protein 1
CRISPLD2	cysteine-rich secretory protein LCCL domain containing 2
CSF1R	colony stimulating factor 1 receptor
CTDSPL2	CTD (carboxy-terminal domain, RNA polymerase II, polypeptide A) small phosphatase like 2
CTNND2	catenin (cadherin-associated protein), delta 2
CYFIP2	cytoplasmic FMR1 interacting protein 2
DENND3	DENN/MADD domain containing 3
DFNA5	deafness, autosomal dominant 5
LRRC37BP1	leucine rich repeat containing 37B pseudogene 1
DLX1	distal-less homeobox 1
DMC1	DNA meiotic recombinase 1
DNAJA4	DnaJ (Hsp40) homolog, subfamily A, member 4
ECD	ecdysoneless homolog (Drosophila)
ELL3	elongation factor RNA polymerase II-like 3
ELMO1	engulfment and cell motility 1
ENPP1	ectonucleotide pyrophosphatase/phosphodiesterase 1
EPB41L4B	erythrocyte membrane protein band 4.1 like 4B
EPHA3	EPH receptor A3
ESRRG	estrogen-related receptor gamma
MECOM	MDS1 and EVI1 complex locus
FAM101B	family with sequence similarity 101, member B
FAM91A1	family with sequence similarity 91, member A1
FBXO3	F-box protein 3
FCGR2B	Fc fragment of IgG, low affinity IIb, receptor (CD32)
FCGRT	Fc fragment of IgG, receptor, transporter, alpha
FEN1	flap structure-specific endonuclease 1
FKBP4	FK506 binding protein 4, 59kDa
FMO5	flavin containing monooxygenase 5
FRMD4A	FERM domain containing 4A
GAL	galanin/GMAP prepropeptide
GCNT3	glucosaminyl (N-acetyl) transferase 3, mucin type
GJA3	gap junction protein, alpha 3, 46kDa
GLDC	glycine dehydrogenase (decarboxylating)
GNPDA2	glucosamine-6-phosphate deaminase 2
GPD1L	glycerol-3-phosphate dehydrogenase 1-like
GPR115	G protein-coupled receptor 115
GPRC5D	G protein-coupled receptor, family C, group 5, member D
GREM2	gremlin 2, DAN family BMP antagonist
GSTM5	glutathione S-transferase mu 5
GUK1	guanylate kinase 1
GULP1	GULP, engulfment adaptor PTB domain containing 1
HADH	hydroxyacyl-CoA dehydrogenase
HDHD1	haloacid dehalogenase-like hydrolase domain containing 1
HIST1H2BD	histone cluster 1, H2bd
HOXB3	homeobox B3
HOXD10	homeobox D10
HPSE2	heparanase 2
HSD3B1	hydroxy-delta-5-steroid dehydrogenase, 3 beta- and steroid delta-isomerase 1
HYOU1	hypoxia up-regulated 1
IL10RA	interleukin 10 receptor, alpha
ITPKA	inositol-trisphosphate 3-kinase A
JPH2	junctophilin 2
KATNAL1	katanin p60 subunit A-like 1
KCMF1	potassium channel modulatory factor 1
KDELR3	KDEL (Lys-Asp-Glu-Leu) endoplasmic reticulum protein retention receptor 3
MLEC	malectin
KIAA0513	KIAA0513
KIF23	kinesin family member 23
KRT27	keratin 27
KRT32	keratin 32
KRT34	keratin 34
KRT8	keratin 8
KRT85	keratin 85
KRTAP13-2	keratin associated protein 13-2
KRTAP19-1	keratin associated protein 19-1
KRTAP3-1	keratin associated protein 3-1
KRTAP3-2	keratin associated protein 3-2
KRTAP4-5	keratin associated protein 4-5
KRTAP4-7	keratin associated protein 4-7
KRTAP4-8	keratin associated protein 4-8
KRTAP9-3	keratin associated protein 9-3
KRTAP9-4	keratin associated protein 9-4
LCE1A	late cornified envelope 1A
LCE1D	late cornified envelope 1D
LCE2B	late cornified envelope 2B
LCE2C	late cornified envelope 2C
LCE2D	late cornified envelope 2D
LHX2	LIM homeobox 2
LNX1	ligand of numb-protein X 1, E3 ubiquitin protein ligase
LRRC2	leucine rich repeat containing 2
NRROS	negative regulator of reactive oxygen species
LYG2	lysozyme G-like 2
MAP2K1	mitogen-activated protein kinase kinase 1
MAP3K13	mitogen-activated protein kinase kinase kinase 13
MARCKS	myristoylated alanine-rich protein kinase C substrate
METAP1	methionyl aminopeptidase 1
MRAP	melanocortin 2 receptor accessory protein
MS4A4A	membrane-spanning 4-domains, subfamily A, member 4A
MSI2	musashi RNA-binding protein 2
MXRA5	matrix-remodelling associated 5
MYCN	v-myc avian myelocytomatosis viral oncogene neuroblastoma derived homolog
MYH10	myosin, heavy chain 10, non-muscle
MYL4	myosin, light chain 4, alkali; atrial, embryonic
MYO7A	myosin VIIA
NDUFA3	NADH dehydrogenase (ubiquinone) 1 alpha subcomplex, 3, 9kDa
NKD2	naked cuticle homolog 2 (Drosophila)
NOVA1	neuro-oncological ventral antigen 1
NPFFR2	neuropeptide FF receptor 2
NSMCE1	non-SMC element 1 homolog (S. cerevisiae)
NTRK2	neurotrophic tyrosine kinase, receptor, type 2
OMA1	OMA1 zinc metallopeptidase
OXGR1	oxoglutarate (alpha-ketoglutarate) receptor 1
PCDH10	protocadherin 10
PCDH7	protocadherin 7
PCSK1N	proprotein convertase subtilisin/kexin type 1 inhibitor
PDPK1	3-phosphoinositide dependent protein kinase-1
PDXK	pyridoxal (pyridoxine, vitamin B6) kinase
PELI2	pellino E3 ubiquitin protein ligase family member 2
PENK	proenkephalin
JADE1	jade family PHD finger 1
PIGT	phosphatidylinositol glycan anchor biosynthesis, class T
PLA2R1	phospholipase A2 receptor 1, 180kDa
PLEKHG3	pleckstrin homology domain containing, family G (with RhoGef domain) member 3
PNMA3	paraneoplastic Ma antigen 3
PNPO	pyridoxamine 5'-phosphate oxidase
POLR2L	polymerase (RNA) II (DNA directed) polypeptide L, 7.6kDa
PPAPDC1B	phosphatidic acid phosphatase type 2 domain containing 1B
PPP2R1B	protein phosphatase 2, regulatory subunit A, beta
PRR4	proline rich 4 (lacrimal)
PTHLH	parathyroid hormone-like hormone

NKD2	naked cuticle homolog 2 (Drosophila)
NOVA1	neuro-oncological ventral antigen 1
NPFFR2	neuropeptide FF receptor 2
NSMCE1	non-SMC element 1 homolog (S. cerevisiae)
NTRK2	neurotrophic tyrosine kinase, receptor, type 2
OMA1	OMA1 zinc metallopeptidase
OXGR1	oxoglutarate (alpha-ketoglutarate) receptor 1
PCDH10	protocadherin 10
PCDH7	protocadherin 7
PCSK1N	proprotein convertase subtilisin/kexin type 1 inhibitor
PDPK1	3-phosphoinositide dependent protein kinase-1
PDXK	pyridoxal (pyridoxine, vitamin B6) kinase
PELI2	pellino E3 ubiquitin protein ligase family member 2
PENK	proenkephalin
JADE1	jade family PHD finger 1
PIGT	phosphatidylinositol glycan anchor biosynthesis, class T
PLA2R1	phospholipase A2 receptor 1, 180kDa
PLEKHG3	pleckstrin homology domain containing, family G (with RhoGef domain) member 3
PNMA3	paraneoplastic Ma antigen 3
PNPO	pyridoxamine 5'-phosphate oxidase
POLR2L	polymerase (RNA) II (DNA directed) polypeptide L, 7.6kDa
PPAPDC1B	phosphatidic acid phosphatase type 2 domain containing 1B
PPP2R1B	protein phosphatase 2, regulatory subunit A, beta
PRR4	proline rich 4 (lacrimal)
PTHLH	parathyroid hormone-like hormone
QSOX2	quiescin Q6 sulfhydryl oxidase 2
RAPGEF1	Rap guanine nucleotide exchange factor (GEF) 1
RBMS3	RNA binding motif, single stranded interacting protein 3
RBPJ	recombination signal binding protein for immunoglobulin kappa J region
RFC3	replication factor C (activator 1) 3, 38kDa
RGS4	regulator of G-protein signaling 4
RHBDL3	rhomboid, veinlet-like 3 (Drosophila)
RHPN2	rhophilin, Rho GTPase binding protein 2
RNF175	ring finger protein 175
RORB	RAR-related orphan receptor B
RPH3AL	rabphilin 3A-like (without C2 domains)
RSU1	Ras suppressor protein 1
S100A3	S100 calcium binding protein A3
SAMD10	sterile alpha motif domain containing 10
SCARF2	scavenger receptor class F, member 2
SCGB1D2	secretoglobin, family 1D, member 2
SDSL	serine dehydratase-like
SEC23B	Sec23 homolog B (S. cerevisiae)
VIMP	VCP-interacting membrane protein
SETBP1	SET binding protein 1
SH3BGRL	SH3 domain binding glutamic acid-rich protein like
SH3GL3	SH3-domain GRB2-like 3

1. Information from HGNC (HUGO Gene Nomenclature Committee; www.genenames.org).

SHC1	SHC (Src homology 2 domain containing) transforming protein 1
SIDT1	SID1 transmembrane family, member 1
SLC41A1	solute carrier family 41 (magnesium transporter), member 1
SLC6A6	solute carrier family 6 (neurotransmitter transporter), member 6
SLFN11	schlafen family member 11
SMAD9	SMAD family member 9
SMPD3	sphingomyelin phosphodiesterase 3, neutral membrane (neutral sphingomyelinase II)
SNCA	synuclein, alpha (non A4 component of amyloid precursor)
SOX8	SRY (sex determining region Y)-box 8
SPAG9	sperm associated antigen 9
SPINK1	serine peptidase inhibitor, Kazal type 1
SPINT2	serine peptidase inhibitor, Kunitz type, 2
SPRR2B	small proline-rich protein 2B
ST3GAL5	ST3 beta-galactoside alpha-2,3-sialyltransferase 5
STX12	syntaxin 12
SYNC	syncoilin, intermediate filament protein
TASP1	taspase, threonine aspartase, 1
TCN2	transcobalamin II
TDRD10	tudor domain containing 10
TENC1	tensin like C1 domain containing phosphatase (tensin 2)
TEX264	testis expressed 264
TGFBR2	transforming growth factor, beta receptor II (70/80kDa)
THSD7B	thrombospondin, type I, domain containing 7B
TLE6	transducin-like enhancer of split 6 (E(sp1) homolog, Drosophila)
TMCO1	transmembrane and coiled-coil domains 1
TMPRSS6	transmembrane protease, serine 6
TOM1L1	target of myb1 (chicken)-like 1
TPCN1	two pore segment channel 1
TPD52L1	tumor protein D52-like 1
TPSG1	tryptase gamma 1
TSPAN18	tetraspanin 18
TWIST2	twist family bHLH transcription factor 2
UBE2Q2	ubiquitin-conjugating enzyme E2Q family member 2
UBTD2	ubiquitin domain containing 2
VANGL1	VANGL planar cell polarity protein 1
VEGFA	vascular endothelial growth factor A
VIP	vasoactive intestinal peptide
DPH7	diphthamide biosynthesis 7
WFDC5	WAP four-disulfide core domain 5
WNK4	WNK lysine deficient protein kinase 4
WNT5B	wingless-type MMTV integration site family, member 5B
XYLB	xylulokinase homolog (H. influenzae)
YBX2	Y box binding protein 2
YTHDC1	YTH domain containing 1
YWHAQ	tyrosine 3-monooxygenase/tryptophan 5-monooxygenase activation protein, theta
ZMYND12	zinc finger, MYND-type containing 12
ZNF326	zinc finger protein 326

1. Information from HGNC (HUGO Gene Nomenclature Committee; www.genenames.org).

Table S9. Epidermal age-modulated genes shared with Human Ageing Genomic Resources (HAGR).

HGNC Approved Symbol[1]	HGNC Approved Name[1]
BAK1	BCL2-antagonist/killer 1
CDC42	cell division cycle 42
CEBPA	CCAAT/enhancer binding protein (C/EBP), alpha
CETP	cholesteryl ester transfer protein, plasma
COQ7	coenzyme Q7 homolog, ubiquinone (yeast)
DBN1	drebrin 1
EIF5A2	eukaryotic translation initiation factor 5A2
ELN	elastin
ESR1	estrogen receptor 1
FEN1	flap structure-specific endonuclease 1
GHRHR	growth hormone releasing hormone receptor
GSK3A	glycogen synthase kinase 3 alpha
GSK3B	glycogen synthase kinase 3 beta
HSPA1A	heat shock 70kDa protein 1A
HTRA2	HtrA serine peptidase 2
IGFBP3	insulin-like growth factor binding protein 3
IL2	interleukin 2
IL2RG	interleukin 2 receptor, gamma
INS	insulin
INSR	insulin receptor
MAPK8	mitogen-activated protein kinase 8
MSRA	methionine sulfoxide reductase A

1. Information from HGNC (HUGO Gene Nomenclature Committee; www.genenames.org).

HGNC Approved Symbol[1]	HGNC Approved Name[1]
NRG1	neuregulin 1
PARP1	poly (ADP-ribose) polymerase 1
PCMT1	protein-L-isoaspartate (D-aspartate) O-methyltransferase
PDPK1	3-phosphoinositide dependent protein kinase-1
PLCG2	phospholipase C, gamma 2 (phosphatidylinositol-specific)
PML	promyelocytic leukemia
PROP1	PROP paired-like homeobox 1
PTK2B	protein tyrosine kinase 2 beta
RAD52	RAD52 homolog (S. cerevisiae)
RB1	retinoblastoma 1
RELA	v-rel avian reticuloendotheliosis viral oncogene homolog A
SHC1	SHC (Src homology 2 domain containing) transforming protein 1
SOD1	superoxide dismutase 1, soluble
STAT3	signal transducer and activator of transcription 3 (acute-phase response factor)
STK11	serine/threonine kinase 11
TFAP2A	transcription factor AP-2 alpha (activating enhancer binding protein 2 alpha)
TNF	tumor necrosis factor
UBB	ubiquitin B
UBE2I	ubiquitin-conjugating enzyme E2I
VEGFA	vascular endothelial growth factor A
YWHAZ	tyrosine 3-monooxygenase/tryptophan 5-monooxygenase activation protein, zeta

1. Information from HGNC (HUGO Gene Nomenclature Committee; www.genenames.org).

Table S10. Modulated probe sets associated with epidermal aging in each decade of life.

20 versus 30 years old						
Down	Down	Down	Down	Down	Up	Up
AA188598	CAPN10	INHBC	PLAC2	TRIM41	AA627135	MLL3
AA884902	CCDC7	IRAK1	PLCH2	TRPV2	AA805504	MYO1C
ABCA7	CD6	ITGA5	PLD2	TSHB	AA993531	NCAN
ABCE1	CDC2L1	ITGB1	PLEKHG2	TTLL3	AB016902	NECAP1
ACIN1	CDIPT	ITGB4BP	PLG	TUBB8	AB019568	NEUROG3
ACOT11	CHAD	ITIH5	PML	TXNL4B	ACVR1B	PDE3B
ADAM17	CHCHD5	JPH2	PNMT	UBE2L6	ADAMTS4	PDZD7
ADCY4	CHCHD5	KIAA0319L	POLRMT	UNC50	AF076205	PLGLB2
ADCYAP1R1	CHDH	KIF21B	PPAP2C	VDP	AK000809	PREI3
ADRM1	CLDN15	KIT	PPAT	VEGFA	AK022893	PRMT2
AF111848	CLDN6	KLF13	PPP1R15A	VKORC1	AK093036	PRSS2
AF116624	CNTROB	KLHDC7A	PPP1R2	WARS	AK093659	PSEN2
AF343666	COL14A1	KMO	PPP2R5B	WBSCR16	AK095986	PSPH
AFG3L1	CR606969	KRBA1	PPP2R5C	WFDC5	AK127904	PXN
AHI1	CR748243	KRT18P16	PPY	WNT10A	AK128457	RAB11A
AI308948	CRYGS	LAGE3	PRDM11	WNT7A	ANKRD17	RAMP2
AI650285	CSH1	LAIR1	PRELID2	X01147	ASB16	RORC
AJ399872	CX3CL1	LAPTM5	PRKCG	ZDHHC24	AVP	S81524
AK001979	CYHR1	LBX2	PRKD2	ZDHHC5	AW138098	SCRT1
AK025975	CYP24A1	LENG9	PRMT1	ZFP36	AW979273	SCRT2
AK054756	D2HGDH	LILRB5	PROKR2	ZIM2	A_23_P393495	SH2B2
AK055960	DHRS1	LMOD1	PSMA6	ZMYND8	A_24_P110101	SH3BGRL2
AK090442	DIRAS1	LOC116143	PSMD10	ZNF410	A_24_P195749	SPINK7
AK123127	DKFZP434B0335	LOC146429	PTCH2	ZNF552	A_24_P255874	STK11
AK123302	DKFZp434B1231	LOC152663	RAMP3	ZNF607	A_24_P315885	TAF3
AK127156	DMAP1	LOC255783	RARG	ZNF625	A_24_P560431	TH1L
AL036098	DPM3	LOC284926	RARRES3	ZRSR2	A_32_P158543	THC2474831
AMDHD1	DTNB	LOC286467	RASAL1	ZSCAN2	A_32_P80198	THC2482196
ANAPC5	DUX3	LOC348180	RENBP		BC008341	THC2495469
ARD1B	EMX1	LOC402176	REXO1		BC015588	THC2497143
ASPHD1	ENST00000262637	LOC441377	RIPK5		BC034792	THC2509970
ATG16L1	ENST00000299415	LOC441572	RNASE1		BC035669	THC2554498
ATP13A1	ENST00000301701	LOC441623	RPH3AL		BC104421	THC2559651
ATP13A2	ENST00000308384	LOC442211	RPL10		BF436529	THC2563549
ATP5G1	ENST00000327574	LOC442336	RPL29		BQ310837	THC2567636
ATP5G2	ENST00000333131	LOC649375	RPS6KA1		BQ374929	THC2654949
ATP6V0C	ENST00000355629	LOC652147	RPSAP10		BX344068	THC2655842
AW191706	ENST00000358618	LOC652411	SCARF2		C10orf130	THC2689802
AW511634	ENST00000375606	LOC728315	SCC-112		C19orf24	THC2753968
AW978845	ENST00000390596	LOC731183	SCT		C1QTNF3	TMEM142A
AY358103	ENY2	LOC731681	SDS		C1orf172	TMEM33
A_23_P135589	EPAS1	LRP5	SEZ6L2		C1orf210	YPEL1
A_23_P158868	EPN3	LYPD3	SGCA		CACYBP	ZC3H10
A_23_P213468	ETG09_48764	LYPLA1	SGK		CB114618	ZDHHC6
A_23_P21882	ETG10_234183	M6PRBP1	SHB		CB305794	ZNF174
A_24_P247493	FAM100A	M78233	SHBG		CCDC137	ZNF483
A_24_P290214	FAM109B	MAGEA6	SHROOM1		CCDC50	
A_24_P332292	FAM96B	MAN2B1	SIRPB2		CD86	
A_24_P481314	FBLIM1	MAN2C1	SLC16A11		CRIP1	
A_24_P486427	FFAR2	MAPK8	SLC25A17		CTRC	
A_24_P651129	FGD6	MARK2	SLC25A45		CXorf42	
A_24_P75856	FHL3	MCM7	SLC26A6		CYP2B6	
A_24_P903715	FLJ20273	MCOLN1	SLC35C1		DHX9	
A_24_P918926	FLJ20433	MCRS1	SLC37A2		DOCK8	
A_24_P931554	FLJ30403	MFN1	SLC46A1		EDC3	
A_24_P931583	FLJ31958	MFN1	SMEK1		ELOVL7	
A_24_P932270	FLJ41603	MFSD5	SMG1		ENST00000269290	
A_24_P940820	FOXC1	MGC27348	SOD1		ENST00000302932	
A_32_P17615	FOXRED2	MIOX	SPG21		EWSR1	
A_32_P201785	FRMD1	MMP15	SRPK3		EXOC3L2	
A_32_P27558	FUBP3	MMS19L	SSR4		EXOC5	
A_32_P74771	FXYD4	MOCOS	STARD9		FAIM3	
BAIAP2	GAD1	MRPL4	STAT2		FAM120C	
BC009051	GBP4	MRPS18B	STEAP3		FAM18B2	
BC010635	GEFT	MUTYH	STX11		FIP1L1	
BC031973	GGN	MYBL2	SYNGR1		FLJ11710	
BC032451	GIPC3	NARFL	TAAR2		FOS	
BC036435	GOT1	NDOR1	TBXA2R		GGT6	
BC038749	GPR52	NDST4	TCEAL4		GLTSCR1	
BC042649	GPRC5C	NEURL	TELO2		GNAZ	
BCL2L1	GPX2	NGLY1	TFR2		GPR156	
BE064950	GRB7	NOG	TGFB111		H2AFJ	
BF939434	GREM2	NOS2A	TGFBRAP1		HBZ	
BI963219	GRHPR	NOVA1	THC2509446		HDAC7A	
BM973223	GRWD1	NP414444	THC2518594		HIBCH	
BOK	GSCL	NT5M	THC2526647		HRH3	
BQ773021	GTPBP5	NTHL1	THC2538882		HRK	
BSPRY	HAPLN4	NXF3	THC2559123		HSP90B1	
BU616603	HAX1	OBSCN	THC2597403		IGF1R	
C10orf25	HDGFL1	OGG1	THC2643762		IL1R2	
C10orf54	HEATR2	OPRK1	THC2654357		IRS1	
C14orf162	HGS	OR11A1	THC2661063		ITGB1BP2	
C14orf24	HIST1H4E	OR7E91P	THC2681839		JAG2	
C16orf14	HIVEP3	OTOP2	THC2693441		KCNK7	
C17orf86	HLA-B	PCNXL3	THC2703350		KIAA0974	
C19orf16	HMBS	PCSK6	THC2718406		KIAA1632	
C19orf25	HMGN2	PDE4C	THC2724111		KIR2DS4	
C19orf33	HMOX2	PDGFRA	THC2752750		KRT14	
C1QB	HNF4A	PEAR1	THC2758091		LOC283174	
C1orf104	HOXB5	PGM1	TM9SF4		LOC339352	
C1orf88	HRC	PGRMC2	TMED1		LOC387895	
C20orf85	HRNBP3	PHYHD1	TMED10P		LOC400604	
C21orf89	IGF2BP3	PIAS3	TMSB4X		LOC440353	
C5AR1	IGH@	PIGU	TOMM40		LOC651746	
C9orf130	IGHA1	PIK4CA	TP73		LRDD	
C9orf7	IGHD	PKD1	TRAF1		MAP3K7	
CABIN1	IKBKG	PKD1L2	TREML1		MATN1	
CACNB3	IL12RB1	PLA2G4D	TREX2		MGC10814	

30 versus 40 years old					40 versus 50 years old		
Down	Down	Up	Up	Up	Down	Down	Up
AB040974	ZFYVE28	ADAM17	GPR52	THC2681839	AA158952	GDNF	AF086321
ACVR2B	ZNF483	ADAMTS2	GPR61	THC2752750	AA301508	GNAZ	AK024824
AF060170	ZNF488	AF116624	GRWD1	THC2766373	AA372247	GPR52	AK093639
AF132206		AGBL5	H2AFY	TIMM44	AA464246	H64096	AKAP6
AF321778		AHSG	HMG2L1	TMED2	AA604115	HCRT	AW445156
AK091357		AK022479	HTR7P	TRABD	AA627135	HRK	A_23_P392897
AK091555		AK090827	IFITM3	TREM2	AA631847	HSD17B8	A_24_P932270
AL049321		AK091337	IFRD2	TREML1	AA805504	IHPK2	A_32_P104995
ALG5		AK092942	IKBKG	TRIM41	AA854379	ILDR1	A_32_P206391
ANKK1		AK094447	IL2RG	TSC2	AF086436	LOC157860	A_32_P42213
ANKRD17		AK123912	IRF5	TUBGCP6	AF116719	LOC391719	B3GNTL1
AQP2		ANXA2P1	ITIH5	UNQ9433	AF119895	LOC401357	BAX
ASXL1		APC	KIAA1602	USP41	AF187554	LOC441743	BC040420
A_24_P160920		ARD1B	KIAA1609	WDR81	AI206757	LOC442461	BC043527
A_24_P862251		ASTN1	KLF13	ZBTB7C	AI267511	LOC649314	C20orf59
A_24_P943740		ATG16L1	KLF13	ZFAND5	AI652920	LOC728347	C6orf117
A_32_P215745		ATP13A2	KRBA1	ZIC5	AI752947	LOC85391	C6orf15
A_32_P230059		ATP1A4	KRT4	ZNF117	AK000809	LST1	CCND2
BC015588		ATP5G2	LAT2	ZNF226	AK054569	MON1B	CHTF18
BC031939		AT_ssH_PC_3	LOC255783	ZNF342	AK056855	MSRA	COL27A1
BC070091		AY998685	LOC401357		AK057071	ND1	DERL1
BC104421		A_23_P111766	LOC646808		AK093659	NISCH	DKFZP434A0131
BG009439		A_23_P65845	LOC652147		AK098360	NM_001018022	DNAH8
BQ374929		A_23_P89506	LOC652411		AK127378	NPAT	ELN
C20orf117		A_24_P203814	LRAT		AK127904	OR7A17	ELOVL4
C9orf122		A_24_P290214	MAGEC1		AK128457	OSCAR	ENST00000285383
CCDC44		A_24_P467871	MAN2B1		AL517609	PAX4	ENST00000377711
CCDC50		A_24_P541213	MCF2L		ALB	PCDH20	ENST00000379392
CD82		A_24_P575267	MCL1		APC2	PDZD7	ESRRG
CD86		A_24_P632230	MECP2		ATP11A	PPP1R11	FAM101B
CDKN2B		A_24_P651129	MMP15		AW150698	PSMB8	GAD1
DDX52		A_24_P903715	MR1		AW178774	RAXL1	GPR3
DEAF1		A_24_P919340	MTHFD1		AW378392	RGMA	HPCAL1
DERL1		A_24_P931905	MYD88		AY090769	RPLP0	HYOU1
DIP2A		A_24_P932270	NDOR1		AY239294	RPS2	IFI35
EFNA5		A_32_P27558	NDUFS4		AY239294	RPS9	ITGA7
EIF2AK3		A_32_P57247	NGLY1		A_23_P206568	RUNDC2B	JPH2
EIF4B		BC031973	NOVA1		A_23_P393495	SAP130	KLHL21
EXOC5		BC038747	NPY6R		A_24_P195749	SCAND1	LMBR1L
FAM120C		BC070363	NRIP3		A_24_P54230	SP100	LOC440335
FBXL8		BCL2L12	NTRK3		A_24_P636834	SSSCA1	LOC51035
FOXQ1		BE064950	NUP98		A_24_P679997	STAT5A	LOC51255
GFM2		BF734670	NXF3		A_24_P753638	STC2	LRRC45
GPSM3		BI963219	OR7A17		A_24_P831005	T19827	LYSMD4
GRPEL2		BRD4	OR7E91P		A_32_P121234	TBC1D8	MAP7D2
IRS1		BX101288	OR8U1		A_32_P133402	THC2509970	MGC23985
KCND3		BX538250	OTOP2		A_32_P142407	THC2509970	MT1JP
KIAA0143		BX647075	PABPN1		A_32_P167723	THC2515611	NAP1L4
KLRC2		C11orf42	PCK2		A_32_P182246	THC2521188	NFKBIB
LHB		C12orf32	PDK2		A_32_P64894	THC2524477	NIPBL
LHX1		C14orf144	PHACS		BC001783	THC2532114	OTOP2
LMBR1L		C16orf70	PIK4CA		BC002470	THC2554100	PACSIN3
LOC339352		C19orf47	POLRMT		BC002811	THC2556753	PGD
LOC387895		C1orf88	PPM1D		BC007606	THC2559651	PIP5K1A
LOC645431		C2orf25	PPME1		BC008341	THC2563549	PITX2
LOC646161		C9orf16	PPP2R5C		BC011398	THC2563568	PLD2
LOC646643		C9orf7	PPY		BC013025	THC2564099	PLEC1
LOC650200		CA436847	PTDSS1		BC014023	THC2569209	PPP2CB
MAFA		CABP5	PUM2		BC014023	THC2572908	PRAM1
MAP3K7		CAMK1D	RBM18		BC020341	THC2579654	PTCH2
MATN1		CAPN10	REG1B		BCAS4	THC2582065	RILP
MIZF		CARS2	RGMA		BI869933	THC2587750	RNF31
MPDZ		CCDC49	RHOT2		BM504117	THC2587773	RPSAP10
NEK9		CCDC7	RPL35		BM975266	THC2591397	SASH1
NR4A2		CCND2	RUFY3		BQ233242	THC2597502	SEMA4C
NT5C		CCPG1	RUVBL2		BQ310837	THC2658813	SIRPB1
NUDT14		CCRL1	S80864		BU622073	THC2678411	SLC29A3
PDZD8		CD3EAP	SAP130		BU687083	THC2694215	SLC30A3
PEX11A		CDC42EP4	SEC22A		BX350880	THC2697162	SMEK1
PPIL6		CHODL	SERPINA7		BX360933	THC2734788	SOCS3
PRAME		CHRAC1	SHC1		BX413319	THC2755341	SUPT4H1
PRMT2		CIAPIN1	SLC25A17		C10orf130	THY1	SYMPK
RAB11A		COL14A1	SLC25A27		C9orf62	TMEM142A	TAAR2
RAD23B		COL5A3	SLC25A45		CA306742	TRABD	TBXAS1
RAMP2		CR2	SNTA1		CA414006	U01925	THC2612889
ROCK2		CRABP2	SNX12		CA431756	U22680	THC2722757
RORC		CRYGA	SOD1		CABP5	VHL	THC2765833
RSU1		CYB5D2	SPRYD3		CB114618	W05707	TLL2
SCRT2		CYB5R2	SRPK3		CDV3	W81715	TNFRSF21
SENP7		CYP2S1	SSSCA1		CORO6	WBSCR19	TNRC4
SETD7		DQ680071	ST14		CV575560	ZNF777	TRMT12
SH3BP2		DSC2	ST8SIA3		DB348311	tcag7.1017	UCKL1
SHARPIN		DYNC1H1	STAC2		DB356469		ZNF792
SLC27A1		E2F6	STARD9		DQ786272		ZSWIM6
THC2538856		ELL2	STAT5A		ENST00000269290		
THC2648849		ENST00000355625	STC1		ENST00000328474		
THC2650264		ENST00000360934	SYNGR1		ENST00000329385		
THC2659646		EPN3	TCEAL4		ENST00000330598		
THC2662468		FAM129C	TFAP2E		ENST00000361567		
TNXB		FARSB	TGFB1I1		ENST00000380231		
TSPAN31		FAS	THC2572376		EXOC3L2		
TUBA3D		FBF1	THC2617409		F7		
TUBGCP2		FBRS	THC2633920		FAIM3		
USHBP1		FLJ35700	THC2643762		FAM18B2		
X98562		FUT1	THC2646741		FAM39B		
YPEL1		FYN	THC2666580		FLJ11710		
ZC3H10		GPC4	THC2670523		FOXC2		
ZDHHC6		GPR114	THC2672701		GAST		

50 versus 60 years old		
Down	Up	Up
ACAT2	AA334114	SOX7
BAALC	AA631847	ST6GALNAC2
BC040420	AA714537	T19827
BI771091	ADAMTS13	THC2509970
CEP164	AF086335	THC2517184
CRAT	AF086436	THC2550620
DUSP3	AF116620	THC2556753
FAM131B	AF116719	THC2568627
FAM82C	AI267511	THC2687042
GLT25D1	AI754733	THC2697162
IFI35	AI925475	THC2770735
IL2RG	AK023472	TM7SF2
LOC51255	AK057071	TMEM37
LYSMD4	AK094323	TUB
N75427	AK098360	U01925
NCAPH	AK127378	ZBTB45
NUDT13	AK127904	
POLR2J2	AL522622	
PP8961	AL540920	
PTPN5	AL567699	
RABEP2	APC2	
RKHD1	ATP6V1B1	
SLC34A3	ATP6V1C2	
SLC8A1	AW858928	
SMEK1	AY239294	
THC2645975	A_23_P108534	
THC2778545	A_23_P11902	
TJP3	A_23_P141785	
TMEM35	A_24_P229438	
UBC	A_24_P315885	
UCHL1	A_24_P392661	
	A_24_P831005	
	A_24_P84268	
	A_32_P127454	
	A_32_P138933	
	A_32_P142407	
	A_32_P142664	
	A_32_P167577	
	A_32_P182246	
	A_32_P227496	
	A_32_P8971	
	BC001783	
	BC007809	
	BC008341	
	BC011398	
	BC070091	
	BCAS4	
	BI035281	
	BI869933	
	BM975266	
	BQ310837	
	BQ339228	
	BX362821	
	C10orf130	
	CA420643	
	CA441361	
	CB528527	
	CCDC50	
	CF528315	
	COX19	
	CXCL3	
	ENST00000302096	
	ENST00000320054	
	ENST00000328474	
	ENST00000329385	
	ENST00000331096	
	ENST00000361567	
	ENST00000381924	
	EPS8L2	
	FAM18B2	
	FGFRL1	
	FLJ11710	
	FRMD4A	
	GALNT3	
	GAST	
	GPR89A	
	HDAC7A	
	KRT18	
	LFNG	
	LOC387895	
	LOC402665	
	LOC643454	
	LOC728044	
	LOC728347	
	MESDC1	
	NAG8	
	NCAN	
	ND1	
	NM_001018022	
	NM_001018022	
	ODC1	
	PDZD7	
	PNKP	
	PSMD11	
	RPS2	
	S100A4	
	SEPHS2	
	SHC2	

60 versus 70 years old		
Down	Up	Up
AANAT	AA004800	PRNT
ABCC8	AA195394	RARRES3
AK094323	ACTL7A	RFC3
ANKK1	AF086511	RND1
APC2	AF130065	RREB1
AQP2	AK022109	RTF1
ASB16	AK023038	RUNX2
ATP6V1C2	AK026155	SCN3A
AY927536	AK027150	SCYL2
A_24_P110101	AK090442	SERTAD2
A_24_P153363	AK092942	SIDT1
A_24_P494658	ARMC2	SLC13A1
A_24_P922120	ASB2	SLC17A1
A_32_P167577	A_23_P111766	SLC26A6
A_32_P230059	A_24_P281285	SLC30A4
A_32_P8971	A_24_P290214	SMC1A
BC002570	A_24_P464963	SNCA
BC015588	A_24_P698759	SOCS4
BC063381	A_24_P880176	SRPK3
BC070091	A_32_P149461	ST3GAL6
BC104421	A_32_P40348	SYT14
BF089603	A_32_P47778	TAP2
BF436529	A_32_P52948	TCFL5
BM054818	A_32_P63734	TESSP2
BQ374929	BC013792	TFDP1
C1orf144	BC056907	TG
CSN1S2A	BE835490	THC2488952
ENST00000302096	BQ017638	THC2548775
ENST00000318930	BU733098	THC2612796
ENST00000329385	BX105574	THC2618720
FAM19A4	C1orf82	THC2655510
GPR150	C1orf88	THC2664350
HES4	C6orf166	THC2666580
HRASLS2	C8orf31	THC2679340
IRS1	CA436847	THC2694630
LHX1	CA437634	THC2697642
MAFA	CABP5	THC2698970
MSRA	CBX1	THC2721928
NEU1	CCNB1IP1	THC2778545
NFKBIB	CD226	TNRC6A
PAK4	CD518214	TRIM45
PFKFB3	CENPJ	TRPM3
PRR5	CES2	UBR1
PRSS8	CHML	UBXD2
REEP6	CIAPIN1	UNC50
SASH1	CYP1B1	WBSCR16
SCARF2	DNAJC10	WIF1
SCRT2	DOCK10	ZNF235
SDK1	DQ680071	ZNF253
STK11	DYNLT3	ZNF595
THC2539554	ELF1	ZNF616
THC2657348	ENST00000311061	ZRANB1
THC2719609	ENST00000366822	
THC2722749	ERGIC1	
TK1	FAM108A1	
TMEM158	FAM129C	
ZBTB45	FAM57B	
ZC3H10	FANCD2	
ZFPM1	FARP1	
ZNF2	FAS	
ZNF467	FLJ22167	
	FSTL1	
	FUBP3	
	FYN	
	GRB7	
	GTF2F1	
	H2AFY2	
	HLA-DMA	
	HOXC6	
	HSD17B7P2	
	HTATIP2	
	IFNA2	
	KCNH1	
	KCNN3	
	KRT5	
	LOC130728	
	LOC199882	
	LOC646808	
	LRRC34	
	MFSD2	
	MGC13053	
	MSL2L1	
	MYADM	
	MYBL1	
	NDOR1	
	NDUFV3	
	NP186050	
	NUP210L	
	PANX3	
	PCDHB4	
	PCNA	
	PER2	
	PGM1	
	PHF12	
	PIP5K1A	
	PLB1	
	POMGNT1	
	PREPL	

70 versus 80 years old	
Down	Up
ADAMTS13	ACD
ADAMTS7	ADAM33
AF289566	AF343666
AI825645	ALDOC
APOL1	A_32_P192586
A_24_P471099	BAIAP2
A_24_P862251	CD248
A_24_P941540	CDC25B
A_32_P138933	CLEC10A
BC080624	CTLA4
CASP8	DEPDC2
CLPTM1L	DYRK1B
CREBL1	ENST00000215202
CRHR1	FXYD6
DLX3	HR
ENST00000318930	LOC147650
EPS8L2	MASP2
FRMD4A	MGC4655
GAST	NT5DC1
KIAA0913	PIPOX
LBH	PRIMA1
LOC284889	RNF26
LOC339352	RNF31
LOC644042	SIRT6
LOC651746	SORBS3
LOC728449	SPTBN2
LOC728894	THAP8
LOC90113	
THC2760960	
TUB	

Table S11. Modulated genes demonstrating a continuous tendency to increase or decrease with epidermal aging.

HGNC Approved Symbol[1]	HGNC Approved Name[1]
Continuous increase	
SPRR2G	small proline-rich protein 2G
Continuous decrease	
CEBPA	CCAAT/enhancer binding protein (C/EBP), alpha
EMILIN1	elastin microfibril interfacer 1
FBXO17	F-box protein 17
FOXE1	forkhead box E1 (thyroid transcription factor 2)
IQSEC2	IQ motif and Sec7 domain 2
LCE1A	late cornified envelope 1A
OGFR	opioid growth factor receptor
OR2H1	olfactory receptor, family 2, subfamily H, member 1
PRB4	proline-rich protein BstNI subfamily 4
MEX3D	mex-3 RNA binding family member D
SOX8	SRY (sex determining region Y)-box 8

1. Information from HGNC (HUGO Gene Nomenclature Committee; www.genenames.org).

3.2. Capítulo II (Artigo experimental II)

Title: Plucked hair shafts-based transcriptome of human epidermal aging

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Keywords: hair, epidermis, skin, aging, transcriptome

Running title: Plucked hair shafts-based epidermal aging

Abstract

Hair follicle (HF) is a unique system constituted of epithelial and mesenchymal compartments with the ability to cyclically regenerate during lifetime. Easy to be manipulated it represents an excellent model to study biological mechanisms, including aging. Follicular epidermis (the epidermal component of HF) is a tubular structure derivate from tissue invagination, continuous with the interfollicular epidermis (IFE). Despite constituting the same tissue, FE and IFE represent distinct biological niches with functional and morphological particularities, such as the presence of different stem-cell populations and expression of different types of keratins. As any other living tissue, epidermis suffers the effect of aging in all its extension, with cumulative deterioration and impaired homeostasis over the lifetime. Despite its critical role in the homeostasis maintenance, little is known about the aging of the human epidermis. In this work, we performed transcriptomic analyses of plucked hair shafts from a panel of 54 volunteer women of different ages to investigate the *in vivo* mechanisms of skin aging. These analyses revealed 3,039 probe sets (2,024 recognized HGNC mapped probe sets representing 1,945 distinct human genes), with 1,597 up-regulated and 1,442 down-regulated (fold change value of 1.5, p-value cut-off of 0.05). Hierarchical clustering showed a clear distinction between young and old groups with only three individuals of each group being not well classified. By comparing to the DAVID database, 33 gene ontology (GO) terms were associated with down-regulated gene expression, and 55 were associated with up-regulated gene expression. KEGG database comparisons identified thirty pathways with significant modulation (p-values cut-off: 0.01) Approximately 50% of these pathways are associated with human diseases and organismal systems, not necessarily related to skin. Interestingly, several significant pathways were related to signaling processes, such as the MAPK, chemokine, insulin, mTOR, Wnt, Notch and calcium signaling pathways. The results of this work were compared with those form our previous analysis of epidermal aging using tape stripping. The overall result of the comparison is quite surprising since both studies identified different biological processes and cellular

pathways. A total of 514 identified DEGs were common to the two studies, indicating a certain degree of similarity but with considerable differences between the materials. In summary, our results it indicate that IE and FE must be analyzed and interpreted as distinct epidermal niches, not just in relation to morphological localization, but also regarding molecular control.

Introduction

Hair follicle (HF) is a complex and unique system with the ability to cyclically regenerate during lifetime, representing an excellent, easily manipulated and widely available model to the study of many biological mechanisms, including aging (Rompolas *et al.*, 2012; Keyes *et al.*, 2013). Most research is focused on the comprehension of HF cycling control because of the great clinical interest associated to hair loss or unwanted hair growth (Krause and Foitzik, 2006). Furthermore, special attention has been done to hair graying with age, mainly due to its aesthetical impact and the interest of cosmetic industry (Tobin, 2009; Trüeb, 2005). However, potential application of HF in the studies of aging might not be restricted to the analysis of hair specific modifications. As a cutaneous appendage, HF is constituted of epithelial and mesenchymal compartments, undergoing changes throughout life that could reflect or complement aspects of overall skin aging (Keyes *et al.*, 2013).

Follicular epidermis (FE) – the epidermal component of HF – is a tubular structure derivate from tissue invagination, continuous with the interfollicular epidermis (IFE). Despite constituting the same tissue, FE and IFE represent distinct biological niches with functional and morphological particularities, such as the presence of different stem-cell populations and the expression of different types of keratin (Jiang *et al.*, 2010; Mascré *et al.*, 2012; Schweizer *et al.*, 2007). IFE is responsible for skin barrier function against dehydration and external damage, composed of an inner basal layer of proliferative cells and suprabasal layers of differentiating progeny; while FE is responsible for hair fibers formation, with concentric layers of cells originated by proliferation activity at the base of HF (Blanpain and Fuchs, 2009). In case of damage to skin, HF stem cells can totally regenerate IFE, indicating the maintenance of a general epidermal programming (Ito *et al.*, 2005; Solanas and Benitah, 2013).

As any other living tissue, epidermis suffers the effect of aging in all its extension, with cumulative deterioration and impaired homeostasis over a lifetime (Kirkwood, 2005). Despite its critical role in the homeostasis maintenance, little is

known about the aging of the human epidermis. We have previously performed a study focused on transcriptomic analysis using a non-invasive technique to access IFE aging (Lorencini *et al.*, unpublished results). The use of global techniques of analysis has been growing massively in the last years and the term skinomics has emerged as a tendency in the field of dermatology (Blumenberg, 2005). Since the skin represents a complex organ, some groups have been working with isolated skin layers or cells to achieve comprehensive results without traces of confounding material (Jansen and Schalkwijk, 2003; Mitsui *et al.*, 2012).

The plucked hair shaft has been used in medical research over the last 60 years (Schembri *et al.*, 2013), and gene expression studies have been done on such experimental model for many different purposes, such as the analysis of atopic dermatitis, stem cell behavior and hair cycle evaluation (Kim *et al.*, 2006; Ohyama *et al.*, 2006, Yoshikawa *et al.*, 2013). Moreover, plucked hair represents an *in vivo* alternative that can be sampled easily without a major discomfort to the individual participating in the research with minimal (if not absent) harm potential (Schembri *et al.*, 2013). Gho *et al.* (2004) demonstrated that typical break of mechanical plucking is located conically surrounding the dermal papilla, which remains unaffected inside the skin. Most of the HF epithelial structures remain attached to the plucked hair and only the epidermal constituents are involved in ~90% of the cases (Bassukas and Horstein, 1989). Thus, the use of plucked hair shafts suggests a powerful tool with unprecedented application (except from hair graying analysis, of course) to the study of FE aging.

This study aimed to elucidate *in vivo* mechanisms of skin aging by applying the non-invasive plucked hair shafts collection from the eyebrows and a global analysis of transcriptome with DNA microarrays. It represents an innovative and relevant approach in the molecular evaluation of human epidermal aging, contributing to the expansion of dermatology knowledge in the era of skinomics.

Material and methods

Volunteers and samples

The Research Ethics Committee institutional review board from Universidade Positivo, Curitiba, Brazil, approved this study, and written informed consent was obtained before enrolling volunteers for participation in this study, which was performed in compliance with the Declaration of Helsinki Principles. Plucked hair shafts were obtained from the eyebrows of women of different ages and skin phototype II or III according to the Fitzpatrick scale. Twenty HFs were collected from the left and right sides of each volunteer. Samples from 54 healthy women were used for microarray analysis (Table S1), and an independent panel of 22 healthy women was used for real-time qPCR validation (Table S3).

RNA extraction and processing

RNA extraction was performed using the RNeasy Mini Kit (Qiagen, Hilden, Germany). Hair follicles were agitated in Tissuelyser LT (Qiagen) for 5 minutes at 50 Hz with lysis buffer and two 7-mm magnetic beads (Qiagen), followed by the subsequent steps for total RNA extraction. Purified RNAs were quantified with a 2000c NanoDrop spectrometer (Thermo Scientific, Wilmington, NC, USA), and the quality was checked using a 2100 Bioanalyzer (Agilent Technologies, Santa Clara, CA, USA) and a Agilent RNA 6000 Pico Kit (Agilent Technologies). Because of the low total RNA yields, the samples were amplified with the Arcturus RiboAmp PLUS HS Kit (Applied Biosystems) and SuperScript III Reverse Transcriptase (Applied Biosystems). All procedures were performed according to manufacturers' instructions.

RNA labeling, hybridization and microarray scanning

Amplified RNAs were processed using the Turbo Arcturus Labelling Kit (Applied Biosystems), and samples were labeled with Cy5. Universal Human Reference RNA (Agilent Technologies) from a unique batch was labeled with Cy3 for use in the data normalization of different arrays (Novoradovskaya *et al.*, 2004).

The use of exogenous RNA from the Agilent RNA Spike-in Kit (Agilent Technologies) was also used for the further calibration of the microarray measurements (Yang, 2006). After fragmentation with the Gene Expression Hybridization Kit (Agilent Technologies), 1:1 ratio mixtures of Cy5-labeled RNA from each volunteer and Cy3-labeled Universal Human Reference RNA (Agilent Technologies) were co-hybridized to two-color Agilent Whole Human Genome Oligo 44K microarrays (Agilent Technologies) to evaluate ~44,000 probe sets, which target 19,596 genes. Scanning and image analysis were performed using the Agilent DNA Microarray Scanner (Agilent Technologies). All procedures were performed according to manufacturers' instructions.

cDNA synthesis and real-time qPCR

To validate the gene expression patterns in the RNA samples, cDNA was obtained using a ReverAid First Strand cDNA Synthesis Kit (Thermo Scientific). cDNA from three or four volunteers in the same age group was pooled in equal quantities, resulting in three samples for analysis for each group (young and old), and real-time qPCR was performed in duplicate for each sample using the ViiA 7 Real Time PCR System (Applied Biosystems) with the TaqMan Fast Advanced Master Mix (Applied Biosystems) and TaqMan Gene Expression Assays (Applied Biosystems) for the following target genes: aquaporin 9 (AQP9, Hs01035888_m1); caveolin 1 (CAV1, Hs00971716_m1); CCAAT/enhancer binding protein, alpha (CEBPA, Hs00269972_s1); collagen, type XXVII, alpha 1 (COL27A1, collagen, type XXVII, alpha 1); D site of albumin promoter (albumin D-box) binding protein (DBP, Hs00609747_m1); fibroblast growth factor receptor 1 (FGFR1, Hs00915142_m1); forkhead box Q1 (FOXQ1, Hs00536425_s1); heme oxygenase (decycling) 2 (HMOX, Hs01558390_m1); interleukin 10 receptor, alpha (IL10RA, Hs00155485_m1); and procollagen-lysine, 2-oxoglutarate 5-dioxygenase 3 (PLOD3, Hs01126617_m1). Beta actin (ACTB, Hs99999903_m1) and glyceraldehyde-3-phosphate dehydrogenase (GAPDH, Hs03929097_g1) were

used as endogenous controls. All procedures were performed according to manufacturers' instructions.

Data analysis

Microarray raw data were extracted using the Agilent Feature Extraction v8.1 software (Agilent Technologies, Santa Clara, CA, USA). Data visualization and analysis were performed using the GeneSpring v12.5 software (Agilent Technologies). Data normalization was performed within and across the arrays using per gene, per chip normalization, according to Agilent's recommendation. To detect the differentially expressed genes (DEGs) between experimental conditions, unpaired t-test was performed with a p-value cut-off of 0.05, considering the minimal fold change (FC) of 1.5. Hierarchical clustering was performed using the Euclidean distance metric and Average rule. For real-time qPCR experiments, the FC was calculated using the ddCt technique (Livak and Schmittgen, 2001). The DAVID database was used to conduct functional enrichment analysis (Huang *et al.*, 2009a and 2009b). The human genome was used as a reference, and regulated GO terms were ranked according to their p-values (or called EASE score, a modified Fisher's exact test) with a cut-off of 0.01; Benjamini correction was also considered for ranking but not elimination (www.david.abcc.ncifcrf.gov). The KEGG database was used for the analysis of modulated pathways (Kanehisa and Goto, 2000; Kanehisa *et al.*, 2014), considering the human genome as a reference and an adjusted p-value cut-off of 0.01 (www.genome.jp/kegg).

Results

Panel of volunteers and sample considerations

We recruited a panel of volunteers comprising 54 women who were distributed into two groups of age i.e., 30 ± 8 years old (30 volunteers) and 64 ± 13 years old (24 volunteers) (Table S1). Using non-invasive eyebrow plucked hair

shafts collection, our analysis focused on FE. Most of the epidermal material of the HF remains attached to the plucked hair and only the epidermal constituents are involved in ~90% of the cases, with no contaminant dermal material (Bassukas and Horstein, 1989).

Microarray analysis and technical validation using real-time qPCR

By adopting a minimal fold change (FC) value of 1.5 and a p-value cut-off of 0.05, statistically significant differences were observed for 3,039 probe sets (2,024 recognized HGNC mapped probe sets representing 1,945 distinct human genes), with 1,597 up-regulated and 1,442 down-regulated (Table S2). Technical validation of the microarray results was performed using real-time qPCR in an independent young versus old panel including 12 volunteers who were 25 ± 3 years old and 10 volunteers who were 54 ± 2 years old (Table S3). Similar results were found for the expression of 10 randomly selected genes (up-, down- or non-regulated) (Figure 1).

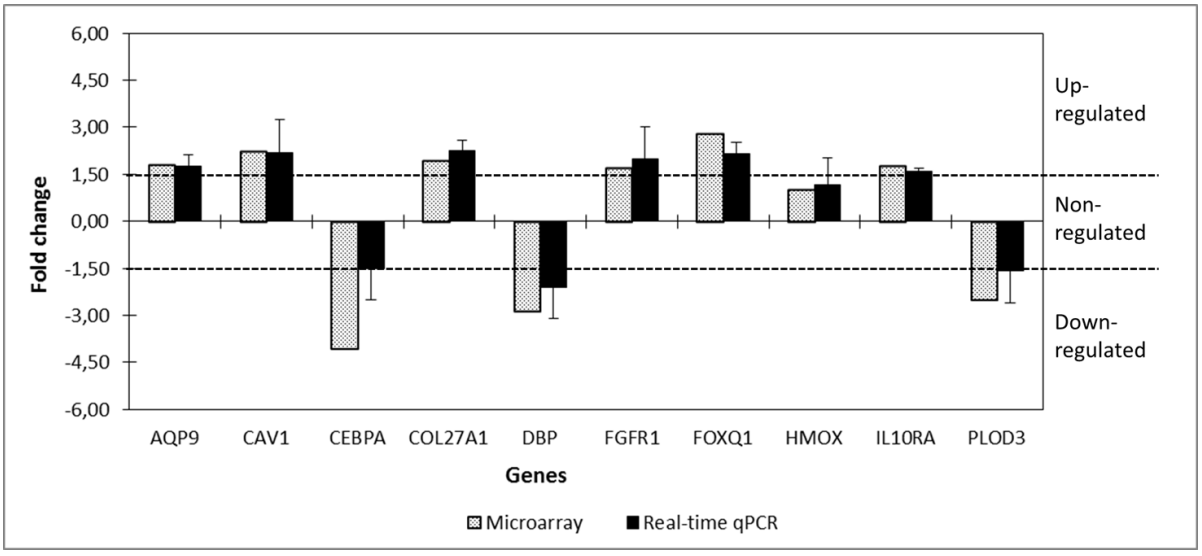

Figure 1. Real-time qPCR validation of microarray results. These qPCR results represent the median (± SD) of triplicate analyses using an independent secondary panel of volunteers (12 young, 10 old). GAPDH and ACTB were used as endogenous controls. A complete list of regulated genes can be found in Table S2.

A hierarchical clustering analysis was performed with the independent and consistently detected data of all volunteers, filtered according to a p-value cut-off of 0.05. A clear distinction between pre-defined groups of young and old volunteers was observed with only three individuals of each group that were not well classified (Figure 2).

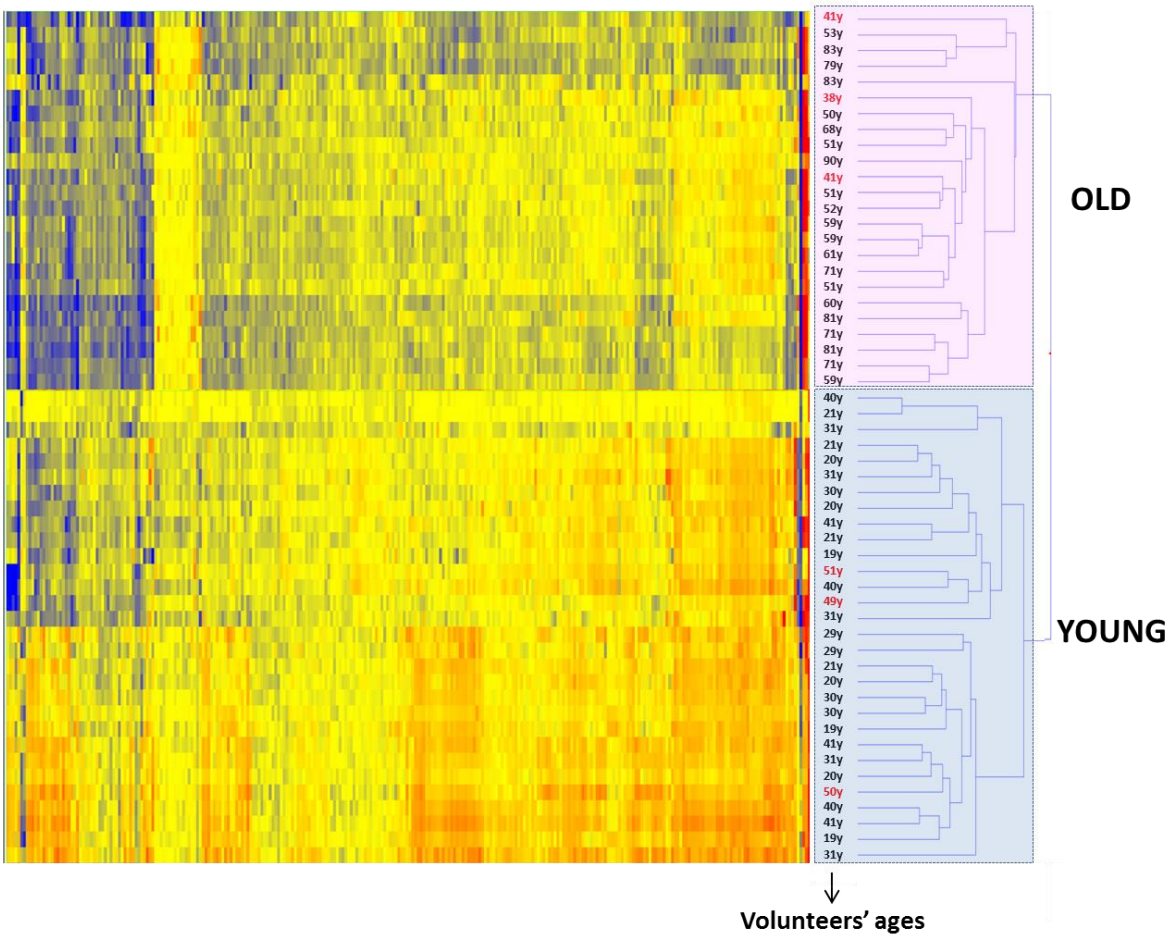

Figure 2. Hierarchical clustering analysis of the complete panel of independent volunteers. Spontaneous hierarchical clustering evidenced that young and old groups defined were quite homogeneous. The ages in red, at the right side, indicate few volunteers that were not classified as expected *a priori*.

Separate lists of the up- and down-regulated genes (Table S2) were analyzed in the DAVID database to identify significantly up- and down-modulated biological processes, respectively, ranked according to p-value (cut-off 0.01) (Table 1). 33 gene ontology (GO) terms were associated with down-regulated gene

expression, and 55 were associated with up-regulated gene expression. However, it is important to note that, among the up-regulated GO, many have the description “negative regulation of”, which can reverse our interpretation of that result.

Table 1. Gene ontology (GO) terms associated with sun-exposed epidermal aging.

GO term	GO code	Number of DEGs[1]	p-value
Up-regulated biological processes			
Cellular process	GO:0009987	672	0.00000004
Cellular metabolic process	GO:0044237	454	0.0000002
Primary metabolic process	GO:0044238	470	0.0000003
Cellular macromolecule metabolic process	GO:0044260	368	0.0000006
Cellular biosynthetic process	GO:0044249	255	0.000003
Gene expression	GO:0010467	227	0.000003
Cellular macromolecule biosynthetic process	GO:0034645	215	0.000003
Biosynthetic process	GO:0009058	261	0.000004
Metabolic process	GO:0008152	504	0.000004
Macromolecule biosynthetic process	GO:0009059	215	0.000007
Macromolecule metabolic process	GO:0043170	387	0.000020
Regulation of metabolic process	GO:0019222	260	0.000028
Cellular nitrogen compound metabolic process	GO:0034641	261	0.000055
Regulation of macromolecule metabolic process	GO:0060255	235	0.000069
Nucleobase, nucleoside, nucleotide and nucleic acid metabolic process	GO:0006139	244	0.000075
Regulation of cellular biosynthetic process	GO:0031326	215	0.000078
Regulation of biosynthetic process	GO:0009889	216	0.000086
Regulation of primary metabolic process	GO:0080090	236	0.000094
Regulation of cellular metabolic process	GO:0031323	246	0.000119
Transcription	GO:0006350	160	0.000125
Regulation of gene expression	GO:0010468	206	0.000236
Nitrogen compound metabolic process	GO:0006807	262	0.000320
Negative regulation of cellular metabolic process	GO:0031324	65	0.000352
Negative regulation of macromolecule metabolic process	GO:0010605	66	0.000353
Negative regulation of nitrogen compound metabolic process	GO:0051172	50	0.000451
Negative regulation of cellular biosynthetic process	GO:0031327	53	0.000471
Negative regulation of metabolic process	GO:0009892	68	0.000649
Regulation of macromolecule biosynthetic process	GO:0010556	201	0.000682
Negative regulation of biosynthetic process	GO:0009890	53	0.000755
Regulation of nitrogen compound metabolic process	GO:0051171	201	0.000805
Interspecies interaction between organisms	GO:0044419	31	0.000941
Negative regulation of nucleobase, nucleoside, nucleotide and nucleic acid metabolic process	GO:0045934	48	0.001067
Negative regulation of transcription	GO:0016481	44	0.001153
Negative regulation of gene expression	GO:0010629	47	0.001369
Negative regulation of macromolecule biosynthetic process	GO:0010558	50	0.001420
Organelle organization	GO:0006996	103	0.001674
Negative regulation of RNA metabolic process	GO:0051253	36	0.001914
Translational elongation	GO:0006414	15	0.001919

Regulation of nucleobase, nucleoside, nucleotide and nucleic acid metabolic process	GO:0019219	196	0.002133
Cellular component organization	GO:0016043	176	0.002368
Posttranscriptional regulation of gene expression	GO:0010608	24	0.002477
Regulation of transcription	GO:0045449	182	0.002597
Cellular protein metabolic process	GO:0044267	166	0.003214
Response to organic substance	GO:0010033	60	0.004023
Negative regulation of cellular process	GO:0048523	121	0.004672
Negative regulation of transcription, DNA-dependent	GO:0045892	34	0.004781
Regulation of transcription from RNA polymerase II promoter	GO:0006357	60	0.004856
Down-regulated biological processes			
Signal transduction	GO:0007165	173	0.0006
Developmental process	GO:0032502	189	0.0006
Cell development	GO:0048468	51	0.0007
System development	GO:0048731	144	0.0011
Multicellular organismal development	GO:0007275	172	0.0013
Anatomical structure development	GO:0048856	154	0.0013
Regulation of biological quality	GO:0065008	97	0.0013
Multicellular organismal process	GO:0032501	243	0.0019
Regulation of multicellular organismal process	GO:0051239	66	0.0020
Neurogenesis	GO:0022008	46	0.0024
Response to cold	GO:0009409	6	0.0028
Cell motion	GO:0006928	38	0.0030
Homeostatic process	GO:0042592	54	0.0037
Organ morphogenesis	GO:0009887	43	0.0037
Cell morphogenesis involved in differentiation	GO:0000904	23	0.0038
Positive regulation of molecular function	GO:0044093	44	0.0044
Response to external stimulus	GO:0009605	63	0.0044
Hormone metabolic process	GO:0042445	13	0.0052
Generation of neurons	GO:0048699	42	0.0053
Cell differentiation	GO:0030154	102	0.0057
Nervous system development	GO:0007399	72	0.0058
Cell adhesion	GO:0007155	50	0.0060
Biological adhesion	GO:0022610	50	0.0061
Regulation of hormone levels	GO:0010817	16	0.0066
Response to temperature stimulus	GO:0009266	11	0.0067
Cellular homeostasis	GO:0019725	36	0.0068
Cell communication	GO:0007154	55	0.0073
Protein kinase cascade	GO:0007243	30	0.0074
Regulation of oligodendrocyte differentiation	GO:0048713	4	0.0076
Neuron development	GO:0048666	28	0.0078
Positive regulation of cellular process	GO:0048522	112	0.0084
Anatomical structure morphogenesis	GO:0009653	77	0.0086
Cellular developmental process	GO:0048869	104	0.0099
Signal transduction	GO:0007165	173	0.0006
Developmental process	GO:0032502	189	0.0006
Cell development	GO:0048468	51	0.0007
System development	GO:0048731	144	0.0011
Multicellular organismal development	GO:0007275	172	0.0013
Anatomical structure development	GO:0048856	154	0.0013
Regulation of biological quality	GO:0065008	97	0.0013

Multicellular organismal process	GO:0032501	243	0.0019
Regulation of multicellular organismal process	GO:0051239	66	0.0020
Neurogenesis	GO:0022008	46	0.0024
Response to cold	GO:0009409	6	0.0028
Cell motion	GO:0006928	38	0.0030
Homeostatic process	GO:0042592	54	0.0037
Organ morphogenesis	GO:0009887	43	0.0037
Cell morphogenesis involved in differentiation	GO:0000904	23	0.0038
Positive regulation of molecular function	GO:0044093	44	0.0044
Response to external stimulus	GO:0009605	63	0.0044
Hormone metabolic process	GO:0042445	13	0.0052
Generation of neurons	GO:0048699	42	0.0053
Cell differentiation	GO:0030154	102	0.0057
Nervous system development	GO:0007399	72	0.0058
Cell adhesion	GO:0007155	50	0.0060
Biological adhesion	GO:0022610	50	0.0061
Regulation of hormone levels	GO:0010817	16	0.0066
Response to temperature stimulus	GO:0009266	11	0.0067
Cellular homeostasis	GO:0019725	36	0.0068
Cell communication	GO:0007154	55	0.0073
Protein kinase cascade	GO:0007243	30	0.0074
Regulation of oligodendrocyte differentiation	GO:0048713	4	0.0076
Neuron development	GO:0048666	28	0.0078

1. DEGs, differentially expressed genes.

To identify the modulated pathways, the complete list of modulated genes was analyzed using the KEGG database (Table S2). Thirty pathways showed significant modulation and were ranked according to their p-values (cut-off: 0.01) (Table S4). In addition to statistical significance, biological interpretation is essential for meaningful pathway analysis. Of the identified pathways, ~50% were associated with human diseases and organismal systems not necessarily related to skin. Interestingly, several significant pathways were related to signaling processes, such as the MAPK, chemokine, insulin, mTOR, Wnt, Notch and calcium signaling pathways.

The results of this work were compared with those form our previous analysis of epidermal aging using tape stripping (Lorencini *et al.*, unpublished results). A total of 514 identified DEGs were common to the two studies (Figure 3), indicating a certain degree of similarity but with considerable differences between the materials.

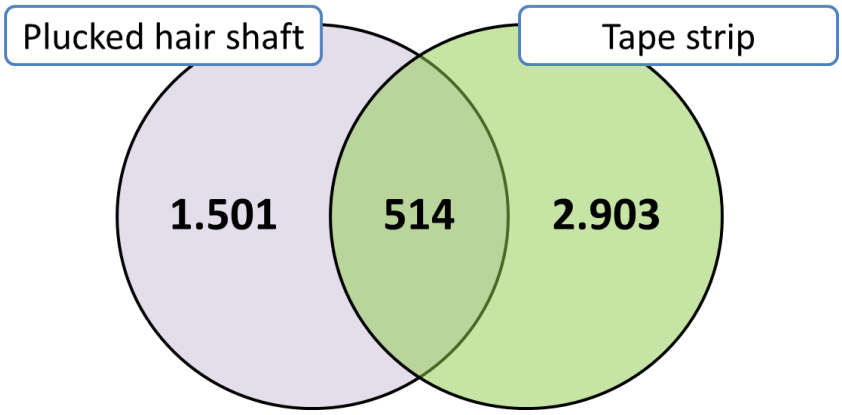

Figure 3. Comparison of gene expression modulation with aging in tape strip and plucked hair shaft. Numbers inside the circles represent the amount of differentially expressed genes (DEGs) observed in the young versus old comparison in the correspondent biological material.

Discussion

In this work, the analysis of aging was established by comparing adult women from two groups of age, representing the most common approach used by other groups in this field. Since menopause characterizes a typical age-associated systemic change with great impact on skin (Raine-Fenning *et al.*; 2003), it was adopted for the definition of young and old groups. Furthermore, spontaneous hierarchical clustering evidenced that pre- and post-menopause groups defined *a priori* were quite homogeneous, reinforcing the biological significance of our experimental approach. The epidermal material from plucked hair shaft demonstrated a better performance for the correct segregation of young versus old material in comparison to the use of tape strip (data not shown). These findings substantiate our choice and refuse any arbitrary decision, before continuing with global data analysis.

The analysis of regulated GO terms in HF showed interesting results, but difficult to correlate with clinical or morphological aspects of epidermal aging. In fact, it was observed a prevalence of broad spectrum terms, such as cellular, metabolic or biosynthetic processes, and gene expression or transcription. In the up-regulated list, the same processes appear more than once and sometimes are preceded by the expression “negative regulation of”. It suggests that even the up-

regulation associated with aging, which would be erroneous related to the interpretation of higher cellular metabolic activity, is linked to an inhibitory effect on those biological processes. Regarding the down-regulated GO terms, the processes of signal transduction and development were the most significant ones. Moreover, modulation of several signaling pathways was the most remarkable characteristic of aging in our results with HF, including several key genes such as an extensive representation of zinc finger proteins and associated elements (~70 related DEGs).

Accordingly to a recent work by Tevy *et al.* (2013), for unknown reasons, there is a decline in circadian rhythms with age, concomitant with declines in the overall metabolic tissue homeostasis. The timing of stem cells proliferation and differentiation in the epidermis of the HF occurs in a controlled manner through circadian rhythm. In a mice model presenting disturbed circadian rhythm, the epidermis is prematurely aged and predisposed to tumorigenesis (Janich *et al.*, 2011). So, considering all the findings of deregulated signaling transduction, our results might provide a link between disturbed circadian rhythm and the impaired regulation of stem cells behavior in the epidermal HF with age. Several other mechanistic and corroborative analyses could be further performed to understand which factor is causing or being caused by a wide impairment in cellular epidermal signaling.

The comparison of the HF results with that derived from tape indicates that, despite some similarities in gene expression, the two biological materials display very distinct profiles in the processes affected by aging. While tape analysis showed several processes associated to epidermal differentiation and keratinocytes regulation, results from HF indicated absolutely broader pathways, which is much more coherent to a tissue enriched in heterogeneous undifferentiated cells (Solanas *et al.*, 2013). Clearly, our results indicate that IE and FE must be analyzed and interpreted as distinct epidermal niches, not just in relation to morphological localization, but also regarding molecular control.

In conclusion, the use of plucked hair shaft represents a useful tool for the study of skin aging and, in particular, for the evaluation of age-related changes in

the FE. We have used eyebrow HF in our study, which can be a good alternative to study age-related changes in the face and could be a good tool for analyzing the effects of anti-aging products that are applied on the face.

Conflict of interests

Each author certifies that all affiliations with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the article are completely disclosed.

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Supplemental material

Table S1. Characterization of the main volunteer panel for microarray analyses.

Volunteer Number	Age (Years Old)	Skin Phototype [1]	Skin Type [2]	Ethnic Group [3]
1	19	II	Normal	Italian/Portuguese
2	19	II	Combination	Italian/Polish
3	19	II	Combination	Asian/Indigenous/Italian
4	20	II	Oily	Italian
5	20	III	Oily	German/Indigenous
6	20	II	Oily	Italian/Polish
7	20	II	Oily	Portuguese
8	21	III	Oily	Italian/Portuguese
9	21	III	Oily	German/Italian
10	21	III	Oily	African/Spanish
11	21	III	Oily	African/Portuguese
12	29	I	Combination	German/Indigenous
13	29	II	Combination	Portuguese
14	30	III	Dry	Asian
15	30	II	Combination	Indigenour/Spanish
16	30	III	Oily	Indigenous
17	31	III	Not declared	African/Portuguese
18	31	III	Oily	Italian
19	31	II	Oily	Ukrainian
20	31	III	Combination	Libanese/Portuguese
21	31	II	Oily	Italian/Spanish
22	38	III	Oily	African/Portuguese
23	40	II	Combination	Italian
24	40	III	Dry	Not declared
25	40	III	Combination	Not declared
26	41	II	Normal	Spanish
27	41	II	Combination	German/Indigenous
28	41	II	Combination	German/Indigenous
29	41	III	Combination	Indigenous/Portuguese
30	41	III	Combination	Italian
31	49	III	Oily	Japanese
32	50	II	Dry	Polish
33	50	III	Combination	German
34	51	II	Combination	German/Russian
35	51	III	Dry	Portuguese
36	51	II	Normal	Italian
37	51	II	Oily	Portuguese
38	52	III	Combination	Indigenous/Spanish
39	53	III	Combination	Jewish
40	59	II	Normal	Indigenous/Spanish
41	59	II	Dry	Italian/Polish
42	59	II	Oily	Asian
43	60	II	Dry	Italian
44	61	II	Dry	Spanish
45	68	II	Normal	Portuguese
46	71	II	Normal	German
47	71	II	Dry	Danish/Portuguese
48	71	II	Combination	Not declared
49	78	II	Dry	Polish
50	79	II	Combination	Japanese
51	81	II	Not declared	Polish
52	83	III	Dry	Portuguese
53	83	II	Dry	Portuguese
54	90	II	Dry	German/Polish

1. Classification according to Fitzpatrick phototyping scale

2. Personal declaration of predominant skin type in the body according to sebum production

3. Personal declaration of ethnic groups

Table S2. Probe sets modulated in the epidermis of young versus old volunteers with a minimal fold change of 1.5 and a p-value cut-off of 0.05 (only one long list).

HGNC Approved Symbol[1]	HGNC Approved Name[1]	FC	Reg.
37469	argonaute RISC catalytic component 2	2,09	up
AAAS	achalasia, adrenocortical insufficiency, alacrimia	1,53	down
AARS	alanyl-tRNA synthetase	1,53	up
ABCB10	ATP-binding cassette, sub-family B (MDR/TAP), member 10	1,62	up
ABCC6	ATP-binding cassette, sub-family C (CFTR/MRP), member 6	1,91	up
ABCC8	ATP-binding cassette, sub-family C (CFTR/MRP), member 8	1,81	down
ABCD1	ATP-binding cassette, sub-family D (ALD), member 1	1,64	up
ABCE1	ATP-binding cassette, sub-family E (OABP), member 1	2,09	up
ABHD1	abhydrolase domain containing 1	1,55	up
ABHD10	abhydrolase domain containing 10	1,86	up
ABHD11	abhydrolase domain containing 11	1,67	up
ABHD16B	abhydrolase domain containing 16B	2,14	down
ABI3	ABI family, member 3	1,78	down
ABL1	c-abl oncogene 1, non-receptor tyrosine kinase	1,62	down
ABTB1	ankyrin repeat and BTB (POZ) domain containing 1	1,53	down
ACAD10	acyl-CoA dehydrogenase family, member 10	1,93	down
ACAN	aggrecan	1,50	up
ACAT2	acetyl-CoA acetyltransferase 2	1,62	up
ACBD3	acyl-CoA binding domain containing 3	1,81	up
ACBD4	acyl-CoA binding domain containing 4	1,56	down
ACOT13	acyl-CoA thioesterase 13	1,88	up
ACP2	acid phosphatase 2, lysosomal	1,64	down
ACPT	acid phosphatase, testicular	1,89	down
ACSM3	acyl-CoA synthetase medium-chain family member 3	1,81	up
ACSM5	acyl-CoA synthetase medium-chain family member 5	6,14	down
ACSS1	acyl-CoA synthetase short-chain family member 1	1,67	down
ACTN4	actinin, alpha 4	1,78	down
ACTR1B	ARP1 actin-related protein 1 homolog B, centractin beta (yeast)	1,94	down
ACTR3	ARP3 actin-related protein 3 homolog (yeast)	1,73	up
ACVR2B	activin A receptor, type IIB	1,83	down
ACVRL1	activin A receptor type II-like 1	1,54	down
ADAD1	adenosine deaminase domain containing 1 (testis-specific)	1,52	down
ADAM17	ADAM metallopeptidase domain 17	1,86	up
ADAM21	ADAM metallopeptidase domain 21	1,55	down
ADAMTS4	ADAM metallopeptidase with thrombospondin type 1 motif, 4	2,08	down
ADAMTSL1	ADAMTS-like 1	1,71	up
ADAMTSL2	ADAMTS-like 2	1,53	down
ADCY3	adenylate cyclase 3	1,84	up
ADD3	adducin 3 (gamma)	1,67	down
ADI1	acireductone dioxygenase 1	1,81	up
ADM	adrenomedullin	1,51	down
ADORA3	adenosine A3 receptor	2,05	down
ADORA3	adenosine A3 receptor	1,75	down
ADPGK	ADP-dependent glucokinase	1,57	up
ADRA2A	adrenoceptor alpha 2A	2,46	down
ADRA2B	adrenoceptor alpha 2B	2,08	down
ADRBK2	adrenergic, beta, receptor kinase 2	1,52	down
AES	amino-terminal enhancer of split	2,21	up
AFG3L1P	AFG3-like AAA ATPase 1, pseudogene	2,16	up
AGPAT3	1-acylglycerol-3-phosphate O-acyltransferase 3	1,52	up
AGPAT4	1-acylglycerol-3-phosphate O-acyltransferase 4	1,87	down
AGR2	anterior gradient 2	2,65	up
AHCTF1	AT hook containing transcription factor 1	1,72	up
AHNAK	AHNAK nucleoprotein	2,21	up
AK1	adenylate kinase 1	2,05	up
AKAP17A	A kinase (PRKA) anchor protein 17A	1,69	down
AKIP1	A kinase (PRKA) interacting protein 1	1,69	up
ALDH4A1	aldehyde dehydrogenase 4 family, member A1	3,08	down
ALKBH5	alkB, alkylation repair homolog 5 (E. coli)	1,79	down
ALOX12B	arachidonate 12-lipoxygenase, 12R type	1,74	down
ALOX15	arachidonate 15-lipoxygenase	2,17	down
ALOX5AP	arachidonate 5-lipoxygenase-activating protein	2,28	down
ALPL	alkaline phosphatase, liver/bone/kidney	1,67	down
ALYREF	Aly/REF export factor	1,91	down
AMD1	adenosylmethionine decarboxylase 1	3,50	down
AMDHD1	amidohydrolase domain containing 1	1,85	up
AMER3	APC membrane recruitment protein 3	1,81	down
AMH	anti-Mullerian hormone	2,57	down
AMZ2	archaelysin family metallopeptidase 2	1,75	up
ANG	angiogenin, ribonuclease, RNase A family, 5	1,70	up
ANGEL2	angel homolog 2 (Drosophila)	1,55	up
ANK1	ankyrin 1, erythrocytic	1,76	down
ANKFY1	ankyrin repeat and FYVE domain containing 1	1,58	up
ANKHD1	ankyrin repeat and KH domain containing 1	1,59	up
ANKRA2	ankyrin repeat, family A (RFXANK-like), 2	2,45	up
ANKRD12	ankyrin repeat domain 12	2,28	up
ANKRD13B	ankyrin repeat domain 13B	1,52	down
ANKRD2	ankyrin repeat domain 2 (stretch responsive muscle)	1,52	down
ANXA2	annexin A2	8,70	up
ANXA2	annexin A2	3,02	up
ANXA2P1	annexin A2 pseudogene 1	2,04	up
ANXA6	annexin A6	2,34	up
ANXA8	annexin A8	1,67	up
AOX1	aldehyde oxidase 1	1,76	up
AP2A2	adaptor-related protein complex 2, alpha 2 subunit	1,66	up
APBA3	amyloid beta (A4) precursor protein-binding, family A, member 3	1,83	down
APH1B	APH1B gamma secretase subunit	1,76	up
APLP2	amyloid beta (A4) precursor-like protein 2	1,55	up
APOA1	apolipoprotein A-I	1,50	down
APOBEC3B	apolipoprotein B mRNA editing enzyme, catalytic polypeptide-like 3B	1,64	down
APOC1	apolipoprotein C-I	1,56	up
APOL3	apolipoprotein L, 3	2,11	down
APOPT1	apoptogenic 1, mitochondrial	1,96	up
APPBP2	amyloid beta precursor protein (cytoplasmic tail) binding protein 2	1,92	up
AQP2	aquaporin 2 (collecting duct)	1,73	down
AQP9	aquaporin 9	1,81	up
ARF1	ADP-ribosylation factor 1	2,06	up
ARHGAP27	Rho GTPase activating protein 27	1,96	down
ARHGEF1	Rho guanine nucleotide exchange factor (GEF) 1	2,30	down
ARHGEF17	Rho guanine nucleotide exchange factor (GEF) 17	1,52	down
ARHGEF25	Rho guanine nucleotide exchange factor (GEF) 25	1,68	down
ARHGEF3	Rho guanine nucleotide exchange factor (GEF) 3	1,73	up
ARHGEF38	Rho guanine nucleotide exchange factor (GEF) 38	2,42	down
ARHGEF5	Rho guanine nucleotide exchange factor (GEF) 5	1,51	up
ARID1A	AT rich interactive domain 1A (SWI-like)	1,88	up
ARID1B	AT rich interactive domain 1B (SWI1-like)	3,24	down
ARID5B	AT rich interactive domain 5B (MRF1-like)	1,58	up
ARL17B	ADP-ribosylation factor-like 17B	1,64	down
ARL3	ADP-ribosylation factor-like 3	2,28	up
ARL6IP1	ADP-ribosylation factor-like 6 interacting protein 1	1,79	up
ARRDC1	arrestin domain containing 1	1,52	up
ARRDC2	arrestin domain containing 2	1,70	up
ARSG	arylsulfatase G	1,50	up
ARVCF	armadillo repeat gene deleted in velocardiofacial syndrome	1,82	down
ARX	aristaless related homeobox	2,65	down
ASB13	ankyrin repeat and SOCS box containing 13	2,01	up
ASCL2	achaete-scute family bHLH transcription factor 2	1,71	up
ASPA	aspartoacylase	1,64	down
ASPHD2	aspartate beta-hydroxylase domain containing 2	1,97	down
ASRGL1	asparaginase like 1	1,52	down
ASTL	astacin-like metallo-endopeptidase (M12 family)	1,74	down
ASXL2	additional sex combs like 2 (Drosophila)	1,70	up
ATAD3A	ATPase family, AAA domain containing 3A	1,89	down
ATCAY	ataxia, cerebellar, Cayman type	4,80	down
ATG16L1	autophagy related 16-like 1 (S. cerevisiae)	1,85	up
ATG4A	autophagy related 4A, cysteine peptidase	3,06	down
ATG4D	autophagy related 4D, cysteine peptidase	1,98	down
ATG7	autophagy related 7	1,53	up
ATN1	atrophin 1	1,53	down
ATOH7	atonal homolog 7 (Drosophila)	2,53	down
ATOH8	atonal homolog 8 (Drosophila)	1,52	down
ATP1A4	ATPase, Na+/K+ transporting, alpha 4 polypeptide	1,82	up
ATP1B1	ATPase, Na+/K+ transporting, beta 1 polypeptide	2,43	up
ATP5E	ATP synthase, H+ transporting, mitochondrial F1 complex, epsilon subunit	1,77	up
ATP5J2	ATP synthase, H+ transporting, mitochondrial Fo complex, subunit F2	2,08	up
ATP6V1A	ATPase, H+ transporting, lysosomal 70kDa, V1 subunit A	1,67	up
ATP6V1C2	ATPase, H+ transporting, lysosomal 42kDa, V1 subunit C2	3,83	down
ATP6V1G2	ATPase, H+ transporting, lysosomal 13kDa, V1 subunit G2	1,77	up
ATP8B1	ATPase, aminophospholipid transporter, class I, type 8B, member 1	1,73	down
ATPAF1	ATP synthase mitochondrial F1 complex assembly factor 1	1,54	down
ATRNL1	attractin-like 1	1,82	down
ATXN7L3	ataxin 7-like 3	1,53	down
AXIN1	axin 1	1,69	down
AZIN1	antizyme inhibitor 1	1,57	up
B3GALNT1	beta-1,3-N-acetylgalactosaminyltransferase 1 (globoside blood group)	1,60	up
B3GAT2	beta-1,3-glucuronyltransferase 2 (glucuronosyltransferase S)	1,69	up
B4GALT1	UDP-Gal:betaGlcNAc beta 1,4- galactosyltransferase, polypeptide 1	1,83	up
BAALC	brain and acute leukemia, cytoplasmic	1,97	up
BAG3	BCL2-associated athanogene 3	1,57	up
BAI3	brain-specific angiogenesis inhibitor 3	1,61	up
BAP1	BRCA1 associated protein-1 (ubiquitin carboxy-terminal hydrolase)	1,60	up
BATF3	basic leucine zipper transcription factor, ATF-like 3	1,51	down
BAZ2A	bromodomain adjacent to zinc finger domain, 2A	1,63	down
BBC3	BCL2 binding component 3	2,41	up
BBS2	Bardet-Biedl syndrome 2	1,62	up
BBS4	Bardet-Biedl syndrome 4	1,52	down
BCAM	basal cell adhesion molecule (Lutheran blood group)	1,99	up
BCAN	brevican	1,88	down
BCAP29	B-cell receptor-associated protein 29	1,57	up
BCAS3	breast carcinoma amplified sequence 3	1,62	down
BCKDK	branched chain ketoacid dehydrogenase kinase	1,79	up
BCL7A	B-cell CLL/lymphoma 7A	1,57	down
BCL7C	B-cell CLL/lymphoma 7C	1,60	up
BCMO1	beta-carotene 15,15'-monooxygenase 1	1,66	up
BEGAIN	brain-enriched guanylate kinase-associated	1,87	up
BET1	Bet1 golgi vesicular membrane trafficking protein	1,50	down
BGN	biglycan	1,54	down
BHLHA15	basic helix-loop-helix family, member a15	1,52	down
BHLHE23	basic helix-loop-helix family, member e23	2,82	down
BIN1	bridging integrator 1	1,53	down

BIRC7	baculoviral IAP repeat containing 7	1,69	down
BLK	B lymphoid tyrosine kinase	1,73	down
BNIP3L	BCL2/adenovirus E1B 19kDa interacting protein 3-like	2,20	up
BOK	BCL2-related ovarian killer	1,86	down
BPTF	bromodomain PHD finger transcription factor	1,95	up
BRAT1	BRCA1-associated ATM activator 1	1,71	up
BRI3BP	BRI3 binding protein	1,58	down
BRI3BP	BRI3 binding protein	1,91	up
BRPF1	bromodomain and PHD finger containing, 1	1,55	up
BST2	bone marrow stromal cell antigen 2	1,51	down
BTBD16	BTB (POZ) domain containing 16	1,89	up
BTBD3	BTB (POZ) domain containing 3	2,41	down
BTBD7	BTB (POZ) domain containing 7	1,56	up
BTF3	basic transcription factor 3	1,98	up
BTG1	B-cell translocation gene 1, anti-proliferative	2,00	up
BTK	Bruton agammaglobulinemia tyrosine kinase	1,60	down
BTN2A2	butyrophilin, subfamily 2, member A2	1,65	down
BUB3	BUB3 mitotic checkpoint protein	1,56	up
BZW1	basic leucine zipper and W2 domains 1	1,55	up
BZW1	basic leucine zipper and W2 domains 1	1,52	up
C11orf86	chromosome 11 open reading frame 86	1,73	down
C15orf52	chromosome 15 open reading frame 52	1,54	up
C16orf92	chromosome 16 open reading frame 92	1,59	up
C19orf68	chromosome 19 open reading frame 68	2,05	down
C1GALT1	core 1 synthase, glycoprotein-N-acetylgalactosamine 3-beta-galactosyltransferase, 1	2,04	down
C1GALT1C1	C1GALT1-specific chaperone 1	1,82	down
C1QB	complement component 1, q subcomponent, B chain	1,58	down
C1QTNF1	C1q and tumor necrosis factor related protein 1	1,94	down
C2	complement component 2	2,05	up
C2CD4B	C2 calcium-dependent domain containing 4B	2,17	down
C2orf80	chromosome 2 open reading frame 80	1,72	down
C5AR1	complement component 5a receptor 1	1,60	up
C5AR2	complement component 5a receptor 2	1,66	down
C7orf62	chromosome 7 open reading frame 62	1,89	down
C8A	complement component 8, alpha polypeptide	1,66	up
CA6	carbonic anhydrase VI	2,24	up
CABIN1	calcineurin binding protein 1	1,66	up
CABP1	calcium binding protein 1	1,61	down
CACNA1B	calcium channel, voltage-dependent, N type, alpha 1B subunit	2,16	down
CACNA1F	calcium channel, voltage-dependent, L type, alpha 1F subunit	1,61	down
CACNG1	calcium channel, voltage-dependent, gamma subunit 1	1,61	down
CACNG7	calcium channel, voltage-dependent, gamma subunit 7	1,94	down
CACNG8	calcium channel, voltage-dependent, gamma subunit 8	2,45	down
CACYBP	calcyclin binding protein	1,82	up
CACYBP	calcyclin binding protein	1,57	up
CALD1	caldesmon 1	1,92	up
CALD1	caldesmon 1	1,86	up
CALML6	calmodulin-like 6	1,93	down
CALR3	calreticulin 3	1,88	up
CAMK2N1	calcium/calmodulin-dependent protein kinase II inhibitor 1	2,25	up
CAMSAP3	calmodulin regulated spectrin-associated protein family, member 3	1,70	up
CAND1	cullin-associated and neddylation-dissociated 1	1,75	down
CAND1	cullin-associated and neddylation-dissociated 1	1,57	down
CANX	calnexin	1,58	up
CAPS	calcyphosine	1,68	down
CARD10	caspase recruitment domain family, member 10	1,67	down
CARKD	carbohydrate kinase domain containing	2,76	down
CASC3	cancer susceptibility candidate 3	1,75	down
CASD1	CAS1 domain containing 1	1,92	down
CASKIN1	CASK interacting protein 1	1,97	up
CASP2	caspase 2, apoptosis-related cysteine peptidase	1,58	up
CASP5	caspase 5, apoptosis-related cysteine peptidase	1,78	up
CATSPERB	catsper channel auxiliary subunit beta	1,54	down
CATSPERG	catsper channel auxiliary subunit gamma	1,57	down
CAV1	caveolin 1, caveolae protein, 22kDa	2,23	up
CBFA2T2	core-binding factor, runt domain, alpha subunit 2; translocated to, 2	1,55	down
CBS	cystathionine-beta-synthase	1,83	up
CBWD2	COBW domain containing 2	1,97	up
CBX1	chromobox homolog 1	1,71	up
CCDC105	coiled-coil domain containing 105	1,93	down
CCDC109B	coiled-coil domain containing 109B	1,58	up
CCDC134	coiled-coil domain containing 134	1,64	up
CCDC144NL	coiled-coil domain containing 144 family, N-terminal like	2,04	up
CCDC151	coiled-coil domain containing 151	1,89	up
CCDC43	coiled-coil domain containing 43	1,55	up
CCDC57	coiled-coil domain containing 57	2,65	down
CCDC6	coiled-coil domain containing 6	1,75	up
CCDC74B	coiled-coil domain containing 74B	1,64	down
CCDC8	coiled-coil domain containing 8	1,78	down
CCDC90B	coiled-coil domain containing 90B	1,65	up
CCL13	chemokine (C-C motif) ligand 13	1,72	down
CCL15	chemokine (C-C motif) ligand 15	1,63	down
CCL19	chemokine (C-C motif) ligand 19	1,76	down
CCL20	chemokine (C-C motif) ligand 20	1,59	down
CCNB1	cyclin B1	1,50	up
CCND2	cyclin D2	1,97	up
CCND2	cyclin D2	1,75	up
CCND3	cyclin D3	2,38	down
CCNG1	cyclin G1	1,53	up
CCNT2	cyclin T2	1,52	up
CCR10	chemokine (C-C motif) receptor 10	1,56	down
CCR3	chemokine (C-C motif) receptor 3	1,90	down
CCSER2	coiled-coil serine-rich protein 2	1,68	up
CCT3	chaperonin containing TCP1, subunit 3 (gamma)	1,62	down
CCT6P1	chaperonin containing TCP1, subunit 6 (zeta) pseudogene 1	1,57	up
CD109	CD109 molecule	1,99	up
CD109	CD109 molecule	1,60	up
CD1A	CD1a molecule	1,63	down
CD1E	CD1e molecule	1,62	down
CD244	CD244 molecule, natural killer cell receptor 2B4	1,87	up
CD300E	CD300e molecule	2,02	down
CD300LB	CD300 molecule-like family member b	2,58	down
CD3E	CD3e molecule, epsilon (CD3-TCR complex)	1,59	down
CD96	CD96 molecule	1,63	down
CDC34	cell division cycle 34	2,20	down
CDC34	cell division cycle 34	1,66	up
CDC42EP1	CDC42 effector protein (Rho GTPase binding) 1	1,81	down
CDC42EP5	CDC42 effector protein (Rho GTPase binding) 5	1,92	up
CDH23	cadherin-related 23	1,53	down
CDH6	cadherin 6, type 2, K-cadherin (fetal kidney)	1,57	down
CDH7	cadherin 7, type 2	2,89	down
CDK9	cyclin-dependent kinase 9	1,58	up
CDKN2B	cyclin-dependent kinase inhibitor 2B (p15, inhibits CDK4)	1,90	down
CDX1	caudal type homeobox 1	1,54	down
CEACAM1	carcinoembryonic antigen-related cell adhesion molecule 1 (biliary glycoprotein)	2,00	up
CEACAM4	carcinoembryonic antigen-related cell adhesion molecule 4	1,51	down
CEBPA	CCAAT/enhancer binding protein (C/EBP), alpha	4,04	down
CELSR2	cadherin, EGF LAG seven-pass G-type receptor 2	1,81	up
CENPB	centromere protein B, 80kDa	1,51	down
CENPI	centromere protein I	1,80	down
CENPN	centromere protein N	1,51	down
CEP192	centrosomal protein 192kDa	1,54	up
CES2	carboxylesterase 2	1,56	down
CES2	carboxylesterase 2	2,26	up
CETN1	centrin, EF-hand protein, 1	1,52	down
CHAC2	ChaC, cation transport regulator homolog 2 (E. coli)	1,70	up
CHCHD1	coiled-coil-helix-coiled-coil-helix domain containing 1	1,83	up
CHCHD2	coiled-coil-helix-coiled-coil-helix domain containing 2	2,00	up
CHCHD2	coiled-coil-helix-coiled-coil-helix domain containing 2	1,84	up
CHD9	chromodomain helicase DNA binding protein 9	1,62	up
CHMP6	charged multivesicular body protein 6	2,74	down
CHRDL1	chordin-like 1	2,81	down
CHRNB1	cholinergic receptor, nicotinic, beta 1 (muscle)	1,62	up
CHST1	carbohydrate (keratan sulfate Gal-6) sulfotransferase 1	1,54	down
CHST10	carbohydrate sulfotransferase 10	1,63	down
CHST12	carbohydrate (chondroitin 4) sulfotransferase 12	2,27	up
CHST14	carbohydrate (N-acetylgalactosamine 4-0) sulfotransferase 14	1,97	down
CIDECP	cell death-inducing DFFA-like effector c pseudogene	1,74	up
CIRBP	cold inducible RNA binding protein	1,98	down
CKAP4	cytoskeleton-associated protein 4	2,04	up
CLCF1	cardiotrophin-like cytokine factor 1	2,01	down
CLCN3	chloride channel, voltage-sensitive 3	1,51	up
CLDN1	claudin 1	1,95	up
CLDN9	claudin 9	3,94	down
CLDN9	claudin 9	1,66	down
CLEC4A	C-type lectin domain family 4, member A	1,76	down
CLIC4	chloride intracellular channel 4	2,01	up
CLINT1	clathrin interactor 1	1,94	up
CLIP4	CAP-GLY domain containing linker protein family, member 4	1,57	up
CLPB	ClpB caseinolytic peptidase B homolog (E. coli)	1,53	up
CLPTM1L	CLPTM1-like	2,27	down
CLTCL1	clathrin, heavy chain-like 1	1,83	down
CMC1	C-x(9)-C motif containing 1	1,65	up
CMIP	c-Maf inducing protein	2,41	down
CMTM3	CKLF-like MARVEL transmembrane domain containing 3	1,97	up
CMTM5	CKLF-like MARVEL transmembrane domain containing 5	1,52	down
CNN2	calponin 2	1,89	up
CNOT10	CCR4-NOT transcription complex, subunit 10	1,53	up
CNOT4	CCR4-NOT transcription complex, subunit 4	1,53	down
CNOT6	CCR4-NOT transcription complex, subunit 6	2,03	up
CNOT6	CCR4-NOT transcription complex, subunit 6	1,52	up
CNOT6L	CCR4-NOT transcription complex, subunit 6-like	1,59	up
CNOT8	CCR4-NOT transcription complex, subunit 8	1,69	down
CNP	2',3'-cyclic nucleotide 3' phosphodiesterase	1,60	up
CNPY2	canopy FGF signaling regulator 2	1,53	up
CNPY4	canopy FGF signaling regulator 4	1,52	up
CNTN2	contactin 2 (axonal)	1,52	down
CNTNAP1	contactin associated protein 1	1,80	down
CNTNAP3	contactin associated protein-like 3	1,65	down
COA6	cytochrome c oxidase assembly factor 6 homolog (S. cerevisiae)	1,86	up
COBL	cordon-bleu WH2 repeat protein	1,70	up
COG3	component of oligomeric golgi complex 3	1,54	up
COL18A1	collagen, type XVIII, alpha 1	1,67	down
COL23A1	collagen, type XXIII, alpha 1	1,61	down
COL27A1	collagen, type XXVII, alpha 1	1,94	up
COL4A1	collagen, type IV, alpha 1	1,59	down
COL4A3BP	collagen, type IV, alpha 3 (Goodpasture antigen) binding protein	1,55	up
COL9A1	collagen, type IX, alpha 1	2,28	down
COLGALT1	collagen beta(1-O)galactosyltransferase 1	1,51	up
CORT	cortistatin	1,72	up
COX11	cytochrome c oxidase assembly homolog 11 (yeast)	1,54	up
COX18	COX18 cytochrome C oxidase assembly factor	1,90	down
COX19	cytochrome c oxidase assembly homolog 19 (S. cerevisiae)	1,66	down
COX20	COX20 cytochrome C oxidase assembly factor	1,63	up
COX5A	cytochrome c oxidase subunit Va	2,26	up
CPE	carboxypeptidase E	1,81	up
CRABP1	cellular retinoic acid binding protein 1	1,87	down
CRAMP1L	Crm, cramped-like (Drosophila)	1,99	up
CRB2	crumbs homolog 2 (Drosophila)	1,53	down
CRB3	crumbs homolog 3 (Drosophila)	1,55	down
CREB3L1	cAMP responsive element binding protein 3-like 1	3,63	down
CRHBP	corticotropin releasing hormone binding protein	1,50	down
CRHR1	corticotropin releasing hormone receptor 1	2,44	down
CRISP2	cysteine-rich secretory protein 2	1,94	up
CRMP1	collapsin response mediator protein 1	1,62	down
CROCC	ciliary rootlet coiled-coil, rootletin	1,91	down
CRTAP	cartilage associated protein	1,63	down
CRTC1	CREB regulated transcription coactivator 1	1,98	up
CRTC2	CREB regulated transcription coactivator 2	2,30	up
CRYAA	crystallin, alpha A	1,77	down

CRYBA2	crystallin, beta A2	2,33	down
CRYBG3	beta-gamma crystallin domain containing 3	1,68	up
CRYBG3	beta-gamma crystallin domain containing 3	1,51	up
CRYGS	crystallin, gamma S	1,61	up
CRYZ	crystallin, zeta (quinone reductase)	1,52	up
CSAD	cysteine sulfinic acid decarboxylase	1,54	down
CSF1	colony stimulating factor 1 (macrophage)	1,55	down
CSF3	colony stimulating factor 3 (granulocyte)	1,56	down
CSH2	chorionic somatomammotropin hormone 2	1,58	up
CSNK1A1	casein kinase 1, alpha 1	1,93	up
CSNK1D	casein kinase 1, delta	1,76	up
CST1	cystatin SN	2,31	up
CTAGE3P	CTAGE family, member 3, pseudogene	1,58	down
CTAGE4	CTAGE family, member 4	1,64	up
CTAGE4	CTAGE family, member 4	1,56	up
CTAGE4	CTAGE family, member 4	1,52	up
CTAGE7P	CTAGE family, member 7, pseudogene	1,54	down
CTBP1	C-terminal binding protein 1	1,65	down
CTBP1	C-terminal binding protein 1	2,08	up
CTBP2	C-terminal binding protein 2	1,65	down
CTNNA2	catenin (cadherin-associated protein), alpha 2	1,65	down
CTNNBIP1	catenin, beta interacting protein 1	2,79	up
CTNND1	catenin (cadherin-associated protein), delta 1	1,56	up
CTNND2	catenin (cadherin-associated protein), delta 2	2,15	up
CTRC	chymotrypsin C (caldecrin)	2,48	down
CTSB	cathepsin B	2,59	up
CTSC	cathepsin C	1,94	up
CTSE	cathepsin E	1,72	down
CTSE	cathepsin E	1,68	down
CTU1	cytosolic thiouridylase subunit 1	1,88	down
CXADR	gap junction protein, alpha 5, 40kDa	1,55	up
CXADR	gap junction protein, alpha 5, 40kDa	1,52	up
CXCL16	chemokine (C-X-C motif) ligand 16	1,52	up
CXCL2	chemokine (C-X-C motif) ligand 2	1,79	down
CXCR5	chemokine (C-X-C motif) receptor 5	1,93	up
CYB561	cytochrome b561	2,33	up
CYB5D2	cytochrome b5 domain containing 2	1,52	down
CYB5R3	cytochrome b5 reductase 3	2,50	up
CYBB	cytochrome b-245, beta polypeptide	1,67	up
CYCS	cytochrome c, somatic	2,11	up
CYHR1	cysteine/histidine-rich 1	1,54	up
CYP1B1	cytochrome P450, family 1, subfamily B, polypeptide 1	2,16	up
CYP2R1	cytochrome P450, family 2, subfamily R, polypeptide 1	1,70	up
CYP4F2	cytochrome P450, family 4, subfamily F, polypeptide 2	1,66	down
CYP4F2	cytochrome P450, family 4, subfamily F, polypeptide 2	1,59	up
CYP51A1	cytochrome P450, family 51, subfamily A, polypeptide 1	1,56	up
CYP51A1	cytochrome P450, family 51, subfamily A, polypeptide 1	1,55	up
CYP7B1	cytochrome P450, family 7, subfamily B, polypeptide 1	1,66	up
CYTH4	cytohesin 4	1,64	down
DAB2	Dab, mitogen-responsive phosphoprotein, homolog 2 (Drosophila)	1,71	up
DAP	death-associated protein	1,68	down
DBN1	drebrin 1	1,53	down
DBN1	drebrin 1	1,88	up
DBP	D site of albumin promoter (albumin D-box) binding protein	2,86	down
DCPS	decapping enzyme, scavenger	1,63	down
DCTD	dCMP deaminase	1,63	up
DDAH1	dimethylarginine dimethylaminohydrolase 1	1,92	up
DDI2	DNA-damage inducible 1 homolog 2 (S. cerevisiae)	1,54	down
DDO	D-aspartate oxidase	1,62	down
DDX5	DEAD (Asp-Glu-Ala-Asp) box helicase 5	1,84	up
DDX50	DEAD (Asp-Glu-Ala-Asp) box polypeptide 50	1,58	down
DEF8	differentially expressed in FDCP 8 homolog (mouse)	1,56	up
DEFB103A	defensin, beta 103A	1,55	up
DEK	DEK oncogene	1,82	up
DENND1C	DENN/MADD domain containing 1C	1,87	up
DENND2A	DENN/MADD domain containing 2A	1,71	up
DERL1	derlin 1	1,78	up
DESI2	desumoylating isopeptidase 2	1,54	down
DEXI	Dexi homolog (mouse)	2,21	up
DFFA	DNA fragmentation factor, 45kDa, alpha polypeptide	1,74	up
DFNB31	deafness, autosomal recessive 31	2,08	down
DGKQ	diacylglycerol kinase, theta 110kDa	1,77	down
DHDDS	dehydrodolichyl diphosphate synthase	1,51	up
DHRS13	dehydrogenase/reductase (SDR family) member 13	1,80	up
DHRS2	dehydrogenase/reductase (SDR family) member 2	2,00	down
DHX30	DEAH (Asp-Glu-Ala-His) box helicase 30	1,67	up
DHX34	DEAH (Asp-Glu-Ala-His) box polypeptide 34	1,81	down
DHX58	DEXH (Asp-Glu-X-His) box polypeptide 58	1,81	up
DIAPH2	diaphanous-related formin 2	1,56	up
DIMT1	DIM1 dimethyladenosine transferase 1 homolog (S. cerevisiae)	1,78	up
DIO2	deiodinase, iodothyronine, type II	1,52	down
DIP2A	DIP2 disco-interacting protein 2 homolog A (Drosophila)	1,64	down
DLGAP4	discs, large (Drosophila) homolog-associated protein 4	1,74	down
DMBX1	diencephalon/mesencephalon homeobox 1	1,58	down
DNAH1	dynein, axonemal, heavy chain 1	1,94	down
DNAH11	dynein, axonemal, heavy chain 11	1,77	up
DNAH14	dynein, axonemal, heavy chain 14	1,65	down
DNAH2	dynein, axonemal, heavy chain 2	2,11	down
DNAH8	dynein, axonemal, heavy chain 8	1,86	down
DNAJB1	DnaJ (Hsp40) homolog, subfamily B, member 1	1,55	up
DNAJB11	DnaJ (Hsp40) homolog, subfamily B, member 11	1,94	up
DNAJC27	DnaJ (Hsp40) homolog, subfamily C, member 27	1,67	up
DNAJC8	DnaJ (Hsp40) homolog, subfamily C, member 8	1,51	up
DNASE1	deoxyribonuclease I	1,92	down
DNM1P35	DNM1 pseudogene 35	2,18	up
DOCK3	dedicator of cytokinesis 3	3,04	down
DOCK6	dedicator of cytokinesis 6	1,56	down
DPP6	dipeptidyl-peptidase 6	2,05	down
DR1	down-regulator of transcription 1, TBP-binding (negative cofactor 2)	1,60	up
DRD3	dopamine receptor D3	2,64	down
DRD4	dopamine receptor D4	2,36	up
DRG1	developmentally regulated GTP binding protein 1	1,79	up
DSC2	desmocollin 2	1,88	up
DSCR4	Down syndrome critical region gene 4	1,52	down
DSCR4	Down syndrome critical region gene 4	1,66	up
DSG1	desmoglein 1	2,47	up
DSTN	destrin (actin depolymerizing factor)	2,60	up
DUS1L	dihydrouridine synthase 1-like (S. cerevisiae)	1,60	down
DUSP15	dual specificity phosphatase 15	2,41	down
DUSP18	dual specificity phosphatase 18	1,78	up
DUSP26	dual specificity phosphatase 26 (putative)	1,65	down
DUSP8	dual specificity phosphatase 8	1,63	up
DUX4	double homeobox 4	2,81	up
DVL3	dishevelled segment polarity protein 3	2,05	down
DYNC1LI2	dynein, cytoplasmic 1, light intermediate chain 2	1,78	up
EBF2	early B-cell factor 2	1,66	up
EDARADD	EDAR-associated death domain	1,92	up
EEF1A1	eukaryotic translation elongation factor 1 alpha 1	1,71	up
EFCAB4A	EF-hand calcium binding domain 4A	1,51	up
EFHD2	EF-hand domain family, member D2	1,52	up
EFNB3	ephrin-B3	1,56	up
EGFL7	EGF-like-domain, multiple 7	1,65	down
EGLN1	egl-9 family hypoxia-inducible factor 1	1,55	up
EHMT2	euchromatic histone-lysine N-methyltransferase 2	2,45	down
EID1	EP300 interacting inhibitor of differentiation 1	2,46	up
EIF3F	eukaryotic translation initiation factor 3, subunit F	1,72	up
EIF4A1	eukaryotic translation initiation factor 4A1	1,69	up
EIF4B	eukaryotic translation initiation factor 4B	2,32	up
ELOVL4	ELOVL fatty acid elongase 4	2,61	up
ELOVL6	ELOVL fatty acid elongase 6	2,01	up
ELP4	elongator acetyltransferase complex subunit 4	2,13	up
ELSPBP1	epididymal sperm binding protein 1	3,24	down
EMILIN1	elastin microfibril interfacer 1	1,77	down
ENC1	ectodermal-neural cortex 1 (with BTB domain)	1,54	down
ENDOV	endonuclease V	1,53	down
ENO1	enolase 1, (alpha)	2,32	up
ENPP4	ectonucleotide pyrophosphatase/phosphodiesterase 4 (putative)	1,60	up
ENTHD2	ENTH domain containing 2	1,99	up
ENTPD2	ectonucleoside triphosphate diphosphohydrolase 2	1,71	down
EPAS1	endothelial PAS domain protein 1	1,67	up
EPB41L4B	erythrocyte membrane protein band 4.1 like 4B	1,59	up
EPDR1	ependymin related 1	1,60	down
EPHA2	EPH receptor A2	1,57	down
EPHA4	EPH receptor A4	1,79	up
EPOR	erythropoietin receptor	1,51	up
EPS8	epidermal growth factor receptor pathway substrate 8	1,96	up
ERBB3	v-erb-b2 avian erythroblastic leukemia viral oncogene homolog 3	1,88	up
ERCC2	excision repair cross-complementing rodent repair deficiency, complementation group 2	2,07	down
ERCC6L2	excision repair cross-complementing rodent repair deficiency, complementation group 6-like 2	1,50	up
ERG	v-ets avian erythroblastosis virus E26 oncogene homolog	1,57	down
ERN1	endoplasmic reticulum to nucleus signaling 1	2,65	down
ERN1	endoplasmic reticulum to nucleus signaling 1	1,74	up
ESCO1	establishment of sister chromatid cohesion N-acetyltransferase 1	1,84	up
ESRRA	estrogen-related receptor alpha	1,60	up
ESRRB	estrogen-related receptor beta	1,83	down
ESYT2	extended synaptotagmin-like protein 2	1,57	up
ETF1	eukaryotic translation termination factor 1	2,21	up
EVL	Enah/Vasp-like	2,10	up
EXD2	exonuclease 3'-5' domain containing 2	1,79	down
EXD2	exonuclease 3'-5' domain containing 2	1,61	up
EXOC3L2	exocyst complex component 3-like 2	2,12	up
EXOC7	exocyst complex component 7	1,78	up
EXOSC7	exosome component 7	1,50	down
EXTL3	exostosin-like glycosyltransferase 3	1,61	down
EZR	ezrin	2,55	up
FABP3	fatty acid binding protein 3, muscle and heart (mammary-derived growth inhibitor)	2,10	down
FABP4	fatty acid binding protein 4, adipocyte	2,29	up
FABP5	fatty acid binding protein 5 (psoriasis-associated)	3,16	up
FADS2	fatty acid desaturase 2	1,60	up
FADS3	fatty acid desaturase 3	1,58	down
FAIM3	Fas apoptotic inhibitory molecule 3	1,79	down
FAM101B	family with sequence similarity 101, member B	1,77	up
FAM107A	family with sequence similarity 107, member A	1,78	up
FAM110B	family with sequence similarity 110, member B	1,57	down
FAM126A	family with sequence similarity 126, member A	1,93	down
FAM129B	family with sequence similarity 129, member B	2,29	up
FAM129C	family with sequence similarity 129, member C	2,17	down
FAM133B	family with sequence similarity 133, member B	1,58	up
FAM134A	family with sequence similarity 134, member A	1,50	down
FAM160B1	family with sequence similarity 160, member B1	1,96	up
FAM160B2	family with sequence similarity 160, member B2	1,58	up
FAM167B	family with sequence similarity 167, member B	1,74	down
FAM187B	family with sequence similarity 187, member B	1,53	down
FAM20B	family with sequence similarity 20, member B	1,75	up
FAM210B	family with sequence similarity 210, member B	1,61	up
FAM21C	family with sequence similarity 21, member C	1,90	up
FAM53B	family with sequence similarity 53, member B	2,19	down
FAM65A	family with sequence similarity 65, member A	2,49	down
FAM83B	family with sequence similarity 83, member B	1,50	up
FAM83E	family with sequence similarity 83, member E	1,82	down
FAM83H	family with sequence similarity 83, member H	1,81	down
FAM84A	family with sequence similarity 84, member A	1,65	up
FAM86C1	family with sequence similarity 86, member C1	1,52	up
FAM90A9P	family with sequence similarity 90, member A9, pseudogene	1,60	down
FARP1	FERM, RhoGEF (ARHGEF) and pleckstrin domain protein 1 (chondrocyte-derived)	2,17	up
FARP1	FERM, RhoGEF (ARHGEF) and pleckstrin domain protein 1 (chondrocyte-derived)	1,84	up
FAT2	FAT atypical cadherin 2	1,79	up
FBRSL1	fibrosin-like 1	1,88	down
FBXL13	F-box and leucine-rich repeat protein 13	1,83	up
FBXL17	F-box and leucine-rich repeat protein 17	1,80	down

FBXL7	F-box and leucine-rich repeat protein 7	1,77	up
FBXO11	F-box protein 11	1,84	up
FBXO34	F-box protein 34	1,69	up
FBXO9	F-box protein 9	2,01	up
FCN1	ficolin (collagen/fibrinogen domain containing) 1	1,51	down
FCRL2	Fc receptor-like 2	2,11	down
FER1L6-AS1	FER1L6 antisense RNA 1	1,94	up
FES	feline sarcoma oncogene	1,55	down
FEZ2	fasciculation and elongation protein zeta 2 (zygin II)	1,97	down
FFAR1	free fatty acid receptor 1	1,63	down
FGD6	FYVE, RhoGEF and PH domain containing 6	1,70	up
FGF1	fibroblast growth factor 1(acidic)	2,26	up
FGF5	fibroblast growth factor 5	1,51	down
FGFR1	fibroblast growth factor receptor 1	1,72	up
FGFRL1	fibroblast growth factor receptor-like 1	1,94	down
FHL1	four and a half LIM domains 1	1,50	up
FHOD1	formin homology 2 domain containing 1	1,59	down
FIBCD1	fibrinogen C domain containing 1	2,01	down
FKBP1A	FK506 binding protein 1A, 12kDa	1,61	down
FKBP1A	FK506 binding protein 1A, 12kDa	1,79	up
FKBP9	FK506 binding protein 9, 63 kDa	2,42	up
FLG	filaggrin	2,45	up
FLRT2	fibronectin leucine rich transmembrane protein 2	1,57	up
FNDC3A	fibronectin type III domain containing 3A	1,55	up
FNDC5	fibronectin type III domain containing 5	1,67	down
FNTB	farnesyltransferase, CAAX box, beta	1,50	up
FOS	FBJ murine osteosarcoma viral oncogene homolog	1,65	down
FOSB	FBJ murine osteosarcoma viral oncogene homolog B	1,68	down
FOXA2	forkhead box A2	1,59	up
FOXA3	forkhead box A3	2,12	down
FOXG1	forkhead box G1	1,84	down
FOXH1	forkhead box H1	3,17	down
FOXJ1	forkhead box J1	1,62	down
FOXN2	forkhead box N2	2,26	up
FOXN3	forkhead box N3	2,00	up
FOXP1	forkhead box P1	2,08	up
FOXP4	forkhead box P4	1,79	up
FOXQ1	forkhead box Q1	2,81	up
FPGS	folylpolyglutamate synthase	1,72	down
FPR1	formyl peptide receptor 1	3,57	down
FRAT2	frequently rearranged in advanced T-cell lymphomas 2	2,41	up
FRMD4A	FERM domain containing 4A	2,18	down
FRMD8P1	FERM domain containing 8 pseudogene 1	2,63	down
FRY	furry homolog (Drosophila)	1,52	up
FRYL	FRY-like	1,99	up
FSCN2	fascin homolog 2, actin-bundling protein, retinal (Strongylocentrotus purpuratus)	2,21	down
FTSJ1	FtsJ RNA methyltransferase homolog 1(E. coli)	1,67	down
FTSJ1	FtsJ RNA methyltransferase homolog 1(E. coli)	1,54	down
FUBP3	far upstream element (FUSE) binding protein 3	1,59	up
FUZ	fuzzy planar cell polarity protein	1,58	down
FXN	frataxin	1,67	down
FZR1	fizzy/cell division cycle 20 related 1(Drosophila)	2,21	down
G6PC3	glucose 6 phosphatase, catalytic, 3	1,56	up
GAA	glucosidase, alpha; acid	1,90	up
GABARAPL1	GABA(A) receptor-associated protein like 1	1,83	down
GABRB2	gamma-aminobutyric acid (GABA) A receptor, beta 2	1,57	up
GABRP	gamma-aminobutyric acid (GABA) A receptor, pi	1,86	up
GABRQ	gamma-aminobutyric acid (GABA) A receptor, theta	1,57	down
GALK2	galactokinase 2	2,00	down
GALNT6	UDP-N-acetyl-alpha-D-galactosamine:polypeptide N-acetylgalactosaminyltransferase 6 (GalNAc-T6)	1,52	up
GAN	gigaxonin	2,18	up
GAREM	GRB2 associated, regulator of MAPK1	1,55	up
GAS6	growth arrest-specific 6	1,62	down
GATA2	GATA binding protein 2	1,54	down
GATA3	GATA binding protein 3	1,84	up
GATS	GATS, stromal antigen 3 opposite strand	1,66	up
GCK	glucokinase (hexokinase 4)	1,71	down
GCSAML	germinal center-associated, signaling and motility-like	1,63	down
GCSH	glycine cleavage system protein H (aminomethyl carrier)	1,93	up
GDF5OS	growth differentiation factor 5 opposite strand	1,97	down
GDNF	glial cell derived neurotrophic factor	1,91	up
GDNF	glial cell derived neurotrophic factor	1,70	up
GEMIN6	gem (nuclear organelle) associated protein 6	1,51	up
GFOD1	glucose-fructose oxidoreductase domain containing 1	2,34	up
GGA1	golgi-associated, gamma adaptin ear containing, ARF binding protein 1	1,71	down
GGNBP2	gametogenetin binding protein 2	1,51	up
GGT1	gamma-glutamyltransferase 1	1,99	down
GGT3P	gamma-glutamyltransferase 3 pseudogene	1,50	up
GGTLC2	gamma-glutamyltransferase light chain 2	1,89	up
GHDC	GH3 domain containing	1,71	down
GIGYF1	GRB10 interacting GYF protein 1	1,81	up
GIGYF2	GRB10 interacting GYF protein 2	1,66	up
GIPC1	GIPC PDZ domain containing family, member 1	1,58	down
GIT2	G protein-coupled receptor kinase interacting ArfGAP 2	1,60	down
GJB7	gap junction protein, beta 7, 25kDa	2,22	down
GJC1	gap junction protein, gamma 1, 45kDa	2,45	down
GJC2	gap junction protein, gamma 2, 47kDa	1,79	down
GK2	glycerol kinase 2	1,52	down
GK5	glycerol kinase 5 (putative)	1,60	down
GLB1L3	galactosidase, beta 1-like 3	1,82	down
GLDC	glycine dehydrogenase (decarboxylating)	1,62	down
GLI3	GLI family zinc finger 3	1,62	up
GLIPR1L1	GLI pathogenesis-related 1 like 1	1,50	down
GLIS3	GLIS family zinc finger 3	1,50	up
GLRX	glutaredoxin (thioltransferase)	3,65	up
GLS	glutaminase	2,27	down
GLTSCR1	glioma tumor suppressor candidate region gene 1	1,97	down
GM2A	GM2 ganglioside activator	1,65	up
GMCL1P1	germ cell-less, spermatogenesis associated 1 pseudogene 1	1,51	down
GMPPB	GDP-mannose pyrophosphorylase B	2,01	down
GMPPB	GDP-mannose pyrophosphorylase B	1,62	up
GNAI2	guanine nucleotide binding protein (G protein), alpha inhibiting activity polypeptide 2	1,68	up
GNAL	guanine nucleotide binding protein (G protein), alpha activating activity polypeptide, olfactory type	1,56	up
GNAQ	guanine nucleotide binding protein (G protein), q polypeptide	1,65	up
GNG12	guanine nucleotide binding protein (G protein), gamma 12	1,71	up
GNG13	guanine nucleotide binding protein (G protein), gamma 13	2,24	down
GNG7	guanine nucleotide binding protein (G protein), gamma 7	1,61	up
GNGT1	guanine nucleotide binding protein (G protein), gamma transducing activity polypeptide 1	1,57	down
GNL2	guanine nucleotide binding protein-like 2 (nucleolar)	1,63	up
GNRH2	gonadotropin-releasing hormone 2	3,00	down
GNRH2	gonadotropin-releasing hormone 2	1,75	down
GOLPH3L	golgi phosphoprotein 3-like	1,56	up
GON4L	gon-4-like (C. elegans)	1,59	up
GOT1	glutamic-oxaloacetic transaminase 1, soluble	2,17	up
GOT1	glutamic-oxaloacetic transaminase 1, soluble	1,55	up
GP6	glycoprotein VI (platelet)	1,97	down
GPAA1	glycosylphosphatidylinositol anchor attachment 1	1,79	down
GPR113	G protein-coupled receptor 113	1,64	up
GPR115	G protein-coupled receptor 115	2,39	up
GPR135	G protein-coupled receptor 135	1,60	down
GPR135	G protein-coupled receptor 135	1,72	up
GPR15	G protein-coupled receptor 15	1,67	up
GPR162	G protein-coupled receptor 162	1,68	down
GPR171	G protein-coupled receptor 171	1,95	up
GPR174	G protein-coupled receptor 174	1,72	down
GPR27	G protein-coupled receptor 27	1,66	down
GPR3	G protein-coupled receptor 3	1,58	up
GPR6	G protein-coupled receptor 6	1,54	down
GPR62	G protein-coupled receptor 62	1,59	up
GPR78	G protein-coupled receptor 78	1,81	down
GPR87	G protein-coupled receptor 87	1,59	up
GPX4	glutathione peroxidase 4	1,79	up
GRAP	GRB2-related adaptor protein	1,90	down
GRID2	glutamate receptor, ionotropic, delta 2	2,87	down
GRIN2D	glutamate receptor, ionotropic, N-methyl D-aspartate 2D	2,38	up
GRK1	G protein-coupled receptor kinase 1	1,61	down
GRM4	glutamate receptor, metabotropic 4	1,89	down
GRN	granulin	2,46	down
GSN	gelsolin	1,77	down
GSTT1	glutathione S-transferase theta 1	1,61	down
GTF2A1	general transcription factor IIA, 1, 19/37kDa	1,64	up
GTF2F1	general transcription factor IIF, polypeptide 1, 74kDa	2,31	up
GTF2H5	general transcription factor IIH, polypeptide 5	2,04	up
GTF2I	general transcription factor IIi	1,59	up
GTF3C2	general transcription factor IIIC, polypeptide 2, beta 110kDa	1,66	down
GTF3C4	general transcription factor IIIC, polypeptide 4, 90kDa	1,89	up
GTPBP6	GTP binding protein 6 (putative)	1,69	up
GYG2	glycogenin 2	1,57	down
GYPC	glycophorin C (Gerbich blood group)	1,75	up
GYPE	glycophorin E (MNS blood group)	2,19	down
GZMH	granzyme H (cathepsin G-like 2, protein h-CCPX)	1,59	down
GZMM	granzyme M (lymphocyte met-ase 1)	1,64	down
HAAO	3-hydroxyanthranilate 3,4-dioxygenase	1,56	down
HAPLN4	hyaluronan and proteoglycan link protein 4	1,77	down
HAUS6	HAUS augmin-like complex, subunit 6	1,62	up
HAUS7	HAUS augmin-like complex, subunit 7	1,63	up
HBZ	hemoglobin, zeta	1,92	down
HCFC1	host cell factor C1(VP16-accessory protein)	2,82	down
HCG18	HLA complex group 18 (non-protein coding)	1,79	up
HCN2	hyperpolarization activated cyclic nucleotide-gated potassium channel 2	2,30	up
HCP5	HLA complex P5 (non-protein coding)	2,06	down
HDLBP	high density lipoprotein binding protein	1,78	down
HECW2	HECT, C2 and WW domain containing E3 ubiquitin protein ligase 2	1,51	down
HELZ2	helicase with zinc finger 2, transcriptional coactivator	1,59	down
HES4	hes family bHLH transcription factor 4	2,59	down
HFE	hemochromatosis	1,96	down
HGD	homogentisate 1,2-dioxygenase	1,64	up
HGS	hepatocyte growth factor-regulated tyrosine kinase substrate	2,51	down
HGS	hepatocyte growth factor-regulated tyrosine kinase substrate	1,75	down
HHLA3	HERV-H LTR-associating 3	1,51	down
HIF3A	hypoxia inducible factor 3, alpha subunit	2,13	down
HIP1	huntingtin interacting protein 1	1,73	down
HIRA	histone cell cycle regulator	1,65	up
HIST1H1D	histone cluster 1, H1d	2,41	up
HIST1H1E	histone cluster 1, H1e	2,55	up
HIST1H2BE	histone cluster 1, H2be	1,59	up
HIST1H2BO	histone cluster 1, H2bo	1,90	up
HIST1H3A	histone cluster 1, H3a	3,09	up
HIST1H3E	histone cluster 1, H3e	2,51	up
HIST1H3I	histone cluster 1, H3i	1,61	down
HIST1H4E	histone cluster 1, H4e	3,00	up
HIST2H2AC	histone cluster 2, H2ac	2,51	up
HIST4H4	histone cluster 4, H4	1,74	down
HIVEP2	human immunodeficiency virus type I enhancer binding protein 2	1,68	down
HIVEP3	human immunodeficiency virus type I enhancer binding protein 3	1,57	up
HK2	hexokinase 2	2,12	up
HLA-DQB1	major histocompatibility complex, class II, DQ beta 1	2,04	down
HLA-DQB2	major histocompatibility complex, class II, DQ beta 2	2,05	down
HLA-DRB3	major histocompatibility complex, class II, DR beta 3	1,94	down
HLA-DRB3	major histocompatibility complex, class II, DR beta 3	1,59	down
HLA-G	major histocompatibility complex, class I, G	1,59	down
HLA-G	major histocompatibility complex, class I, G	1,58	down
HMBOX1	homeobox containing 1	2,30	up
HMGB1	high mobility group box 1	1,96	up
HMGN1	high mobility group nucleosome binding domain 1	2,06	up
HMGN4	high mobility group nucleosomal binding domain 4	1,55	up
HMOX2	heme oxygenase (decycling) 2	1,93	down
HNRNPK	heterogeneous nuclear ribonucleoprotein K	1,89	up
HOXA1	homeobox A1	1,62	down
HOXA3	homeobox A3	2,67	up

HOXA4	homeobox A4	1,95	down
HOXB9	homeobox B9	1,69	down
HOXC9	homeobox C9	1,86	down
HPN	hepsin	2,32	down
HRCT1	histidine rich carboxyl terminus 1	1,61	down
HRH3	histamine receptor H3	1,87	up
HS1BP3	HCLS1 binding protein 3	1,73	down
HS6ST2	heparan sulfate 6-O-sulfotransferase 2	1,80	up
HSD11B2	hydroxysteroid (11-beta) dehydrogenase 2	1,92	down
HSD17B14	hydroxysteroid (17-beta) dehydrogenase 14	2,14	down
HSDL1	hydroxysteroid dehydrogenase like 1	1,70	down
HSF1	heat shock transcription factor 1	2,82	up
HSP90AA1	heat shock protein 90kDa alpha (cytosolic), class A member 1	1,61	up
HSP90AB1	heat shock protein 90kDa alpha (cytosolic), class B member 1	1,81	up
HSPA12B	heat shock 70kD protein 12B	2,41	down
HSPA5	heat shock 70kDa protein 5 (glucose-regulated protein, 78kDa)	1,76	up
HSPA6	heat shock 70kDa protein 6 (HSP70B')	1,68	down
HSPA8	heat shock 70kDa protein 8	1,89	up
HSPA9	heat shock 70kDa protein 9 (mortalin)	1,55	up
HSPB2	heat shock 27kDa protein 2	2,04	down
HSPB9	heat shock protein, alpha-crystallin-related, B9	1,87	up
HTR1E	5-hydroxytryptamine (serotonin) receptor 1E, G protein-coupled	1,54	down
HTR3E	5-hydroxytryptamine (serotonin) receptor 3E, ionotropic	1,89	up
HUWE1	HECT, UBA and WWE domain containing 1, E3 ubiquitin protein ligase	1,51	up
IBA57	IBA57, iron-sulfur cluster assembly homolog (S. cerevisiae)	2,14	down
IBTK	inhibitor of Bruton agammaglobulinemia tyrosine kinase	1,68	up
ICAM5	intercellular adhesion molecule 5, telencephalin	1,86	up
IDE	insulin-degrading enzyme	1,84	up
IDH3A	isocitrate dehydrogenase 3 (NAD+) alpha	1,70	down
IDH3B	isocitrate dehydrogenase 3 (NAD+) beta	2,19	down
IDI2	isopentenyl-diphosphate delta isomerase 2	1,59	up
IDI2-AS1	IDI2 antisense RNA 1	1,78	down
IDO1	indoleamine 2,3-dioxygenase 1	1,60	up
IDS	iduronate 2-sulfatase	1,87	up
IER5L	immediate early response 5-like	1,60	down
IFI27	interferon, alpha-inducible protein 27	2,11	up
IFI30	interferon, gamma-inducible protein 30	2,44	up
IFT172	intraflagellar transport 172 homolog (Chlamydomonas)	1,98	up
IGF1	insulin-like growth factor 1 (somatomedin C)	2,02	down
IGF2BP1	insulin-like growth factor 2 mRNA binding protein 1	1,51	down
IGF2BP2	insulin-like growth factor 2 mRNA binding protein 2	1,73	down
IGFALS	insulin-like growth factor binding protein, acid labile subunit	1,69	down
IGFBP7	insulin-like growth factor binding protein 7	1,82	up
IGFLR1	IGF-like family receptor 1	2,23	down
IGHA1	immunoglobulin heavy constant alpha 1	1,52	down
IGKC	immunoglobulin kappa constant	1,79	down
IGLL1	immunoglobulin lambda-like polypeptide 1	1,65	down
IL10RA	interleukin 10 receptor, alpha	1,76	down
IL16	interleukin 16	1,63	up
IL17A	interleukin 17A	1,60	down
IL1R2	interleukin 1 receptor, type II	1,52	down
IL1R2	interleukin 1 receptor, type II	1,88	up
IL2RA	interleukin 2 receptor, alpha	1,61	down
ILF3	interleukin enhancer binding factor 3, 90kDa	2,00	up
IMPA1	inositol(myo)-1(or 4)-monophosphatase 1	1,60	down
IMPA2	inositol(myo)-1(or 4)-monophosphatase 2	2,23	up
INO80	INO80 complex subunit	1,58	up
INPP5D	inositol polyphosphate-5-phosphatase, 145kDa	1,52	down
INPP5E	inositol polyphosphate-5-phosphatase, 72 kDa	1,73	up
INTS12	integrator complex subunit 12	1,68	up
INTS4L1	integrator complex subunit 4-like 1	1,74	up
IQCD	IQ motif containing D	1,65	up
IQCH	IQ motif containing H	1,63	down
IQSEC3	IQ motif and Sec7 domain 3	1,52	down
IRF1	interferon regulatory factor 1	1,74	down
IRF2BP2	interferon regulatory factor 2 binding protein 2	1,65	up
IRF7	interferon regulatory factor 7	1,80	down
IRS2	insulin receptor substrate 2	1,63	up
IRX3	iroquois homeobox 3	2,47	down
IRX4	iroquois homeobox 4	2,08	up
ISYNA1	inositol-3-phosphate synthase 1	1,58	down
ITFG1	integrin alpha FG-GAP repeat containing 1	1,96	up
ITGA3	integrin, alpha 3 (antigen CD49C, alpha 3 subunit of VLA-3 receptor)	1,54	down
ITGAM	integrin, alpha M (complement component 3 receptor 3 subunit)	1,64	down
ITGB5	integrin, beta 5	2,26	up
ITM2B	integral membrane protein 2B	1,83	up
ITPK1	inositol-tetrakisphosphate 1-kinase	1,50	down
ITPK1	inositol-tetrakisphosphate 1-kinase	1,61	up
ITPKB	inositol-trisphosphate 3-kinase B	2,35	up
ITPR3	inositol 1,4,5-trisphosphate receptor, type 3	1,81	up
ITPRIP	inositol 1,4,5-trisphosphate receptor interacting protein	2,23	up
ITSN2	intersectin 2	1,63	up
JADE2	jade family PHD finger 2	1,99	down
JAK3	Janus kinase 3	1,80	down
JARID2	jumonji, AT rich interactive domain 2	2,13	up
JDP2	Jun dimerization protein 2	1,63	up
KALRN	kalirin, RhoGEF kinase	1,88	up
KANK1	KN motif and ankyrin repeat domains 1	2,34	up
KCNC4	potassium voltage-gated channel, Shaw-related subfamily, member 4	2,11	up
KCND2	potassium voltage-gated channel, Shal-related subfamily, member 2	1,54	down
KCNG1	potassium voltage-gated channel, subfamily G, member 1	1,68	down
KCNH2	potassium voltage-gated channel, subfamily H (eag-related), member 2	2,99	down
KCNH6	potassium voltage-gated channel, subfamily H (eag-related), member 6	2,56	down
KCNJ5	potassium inwardly-rectifying channel, subfamily J, member 5	1,80	up
KCNK3	potassium channel, subfamily K, member 3	3,74	down
KCNN2	potassium intermediate/small conductance calcium-activated channel, subfamily N, member 2	1,89	up
KCNQ4	potassium voltage-gated channel, KQT-like subfamily, member 4	2,40	down
KCTD12	potassium channel tetramerization domain containing 12	1,52	down
KCTD17	potassium channel tetramerization domain containing 17	1,96	down
KIAA0101	KIAA0101	1,82	down
KIAA0101	KIAA0101	1,56	up
KIAA0513	KIAA0513	1,62	up
KIAA0556	KIAA0556	1,51	down
KIAA0753	KIAA0753	1,53	up
KIAA1614	KIAA1614	1,58	up
KIAA1875	KIAA1875	1,69	down
KIAA1919	KIAA1919	2,31	up
KIF12	kinesin family member 12	1,52	down
KIF13B	kinesin family member 13B	2,13	up
KIF17	kinesin family member 17	1,85	down
KIF1C	kinesin family member 1C	1,98	up
KIF21A	kinesin family member 21A	2,15	up
KIRREL2	kin of IRRE like 2 (Drosophila)	2,27	down
KLF1	Kruppel-like factor 1 (erythroid)	2,69	down
KLF16	Kruppel-like factor 16	1,94	up
KLF9	Kruppel-like factor 9	1,67	up
KLHDC7B	kelch domain containing 7B	2,01	down
KLHL15	kelch-like family member 15	1,57	down
KLHL18	kelch-like family member 18	1,71	up
KLHL23	kelch-like family member 23	1,79	down
KLHL8	kelch-like family member 8	1,54	up
KLK10	kallikrein-related peptidase 10	1,81	down
KLK11	kallikrein-related peptidase 11	1,88	up
KLK12	kallikrein-related peptidase 12	1,96	up
KLK15	kallikrein-related peptidase 15	1,66	down
KLK2	kallikrein-related peptidase 2	1,60	down
KLK7	kallikrein-related peptidase 7	2,56	up
KLKB1	kallikrein B, plasma (Fletcher factor) 1	1,72	down
KMT2A	lysine (K)-specific methyltransferase 2A	1,64	up
KMT2C	lysine (K)-specific methyltransferase 2C	1,53	up
KMT2D	lysine (K)-specific methyltransferase 2D	1,61	down
KMT2E	lysine (K)-specific methyltransferase 2E	2,00	up
KREMEN2	kringle containing transmembrane protein 2	1,78	down
KRR1	KRR1, small subunit (SSU) processome component, homolog (yeast)	1,53	up
KRT16	keratin 16	2,78	up
KRT18P12	keratin 18 pseudogene 12	2,46	down
KRT24	keratin 24	1,50	down
KRT6C	keratin 6C	2,50	up
KRT8P10	keratin 8 pseudogene 10	2,13	up
KSR1	kinase suppressor of ras 1	1,86	down
KYNU	kynureninase	1,64	up
L1CAM	L1 cell adhesion molecule	1,90	down
L3MBTL4	l(3)mbt-like 4 (Drosophila)	1,50	down
LAMA1	laminin, alpha 1	1,56	down
LAMA2	laminin, alpha 2	1,63	down
LAMA3	laminin, alpha 3	2,34	up
LAMA5	laminin, alpha 5	2,81	down
LAMB1	laminin, beta 1	1,66	up
LAMC3	laminin, gamma 3	1,61	down
LAMP2	lysosomal-associated membrane protein 2	1,81	up
LARP1B	La ribonucleoprotein domain family, member 1B	1,68	up
LARP4	La ribonucleoprotein domain family, member 4	2,00	up
LATS2	large tumor suppressor kinase 2	1,83	up
LBH	limb bud and heart development	3,42	down
LBX1	ladybird homeobox 1	2,62	up
LCN6	lipocalin 6	1,78	down
LDLR	low density lipoprotein receptor	1,63	up
LENG1	leukocyte receptor cluster (LRC) member 1	1,75	down
LEPREL1	leprecan-like 1	1,73	up
LETMD1	LETM1 domain containing 1	1,84	up
LFNG	LFNG O-fucosylpeptide 3-beta-N-acetylglucosaminyltransferase	3,80	down
LGALS9	lectin, galactoside-binding, soluble, 9	2,74	down
LGALSL	lectin, galactoside-binding-like	2,03	up
LHB	luteinizing hormone beta polypeptide	1,69	down
LHFPL1	lipoma HMGIC fusion partner-like 1	1,61	down
LIG1	ligase I, DNA, ATP-dependent	1,71	up
LILRA3	leukocyte immunoglobulin-like receptor, subfamily A (without TM domain), member 3	1,63	down
LILRA4	leukocyte immunoglobulin-like receptor, subfamily A (with TM domain), member 4	1,91	down
LILRA5	leukocyte immunoglobulin-like receptor, subfamily A (with TM domain), member 5	1,76	down
LIME1	Lck interacting transmembrane adaptor 1	2,53	down
LIN7C	lin-7 homolog C (C. elegans)	1,53	down
LINC00094	long intergenic non-protein coding RNA 94	2,15	up
LINC00176	long intergenic non-protein coding RNA 176	1,75	down
LINC00313	long intergenic non-protein coding RNA 313	1,91	down
LINC00482	long intergenic non-protein coding RNA 482	1,57	down
LINC00652	long intergenic non-protein coding RNA 652	1,66	up
LINC00905	long intergenic non-protein coding RNA 905	1,55	down
LINC01101	long intergenic non-protein coding RNA 1101	1,68	down
LINC01106	long intergenic non-protein coding RNA 1106	2,34	down
LIPH	lipase, member H	1,53	up
LMBRD2	LMBR1 domain containing 2	1,56	up
LMF2	lipase maturation factor 2	1,65	down
LMX1B	LIM homeobox transcription factor 1, beta	1,54	down
LOXL3	lysyl oxidase-like 3	1,79	down
LPHN3	latrophilin 3	1,56	up
LRFN1	leucine rich repeat and fibronectin type III domain containing 1	1,95	up
LRFN3	leucine rich repeat and fibronectin type III domain containing 3	1,65	down
LRIT1	leucine-rich repeat, immunoglobulin-like and transmembrane domains 1	1,95	down
LRP10	low density lipoprotein receptor-related protein 10	1,74	down
LRP6	low density lipoprotein receptor-related protein 6	1,66	down
LRPAP1	low density lipoprotein receptor-related protein associated protein 1	1,52	down
LRRC1	leucine rich repeat containing 1	1,56	up
LRRC4C	leucine rich repeat containing 4C	1,52	down
LRRC61	leucine rich repeat containing 61	2,02	down
LRRC73	leucine rich repeat containing 73	1,54	down
LRRN4	leucine rich repeat neuronal 4	1,57	down
LRSAM1	leucine rich repeat and sterile alpha motif containing 1	1,74	down
LRTOMT	leucine rich transmembrane and O-methyltransferase domain containing	1,66	up
LSM12	LSM12 homolog (S. cerevisiae)	1,89	up
LSP1	lymphocyte-specific protein 1	1,93	down

LTB4R2	leukotriene B4 receptor 2	3,33	down
LTBP2	latent transforming growth factor beta binding protein 2	1,87	down
LTBP4	latent transforming growth factor beta binding protein 4	1,58	down
LTC4S	leukotriene C4 synthase	1,87	down
LTK	leukocyte receptor tyrosine kinase	1,95	down
LUZP1	leucine zipper protein 1	1,98	down
LY6H	lymphocyte antigen 6 complex, locus H	2,20	down
LY6K	lymphocyte antigen 6 complex, locus K	1,58	down
LYRM2	LYR motif containing 2	1,71	up
LYZ	lysozyme	1,68	down
LZIC	leucine zipper and CTNNBIP1 domain containing	1,72	up
MADD	MAP-kinase activating death domain	1,88	down
MAFG	v-maf avian musculoaponeurotic fibrosarcoma oncogene homolog G	2,01	down
MAGEA11	melanoma antigen family A, 11	1,50	down
MAGEH1	melanoma antigen family H, 1	2,02	up
MAGIX	MAGI family member, X-linked	1,59	up
MAGOHB	mago-nashi homolog B (Drosophila)	2,00	up
MALAT1	metastasis associated lung adenocarcinoma transcript 1 (non-protein coding)	2,71	up
MAMDC4	MAM domain containing 4	2,54	down
MAN2A2	mannosidase, alpha, class 2A, member 2	1,52	down
MAP2K7	mitogen-activated protein kinase kinase 7	1,99	down
MAP3K11	mitogen-activated protein kinase kinase kinase 11	1,88	down
MAP3K6	mitogen-activated protein kinase kinase kinase 6	1,92	up
MAP4K1	mitogen-activated protein kinase kinase kinase kinase 1	1,59	up
MAPK15	mitogen-activated protein kinase 15	1,90	up
MAPK8IP1	mitogen-activated protein kinase 8 interacting protein 1	1,72	up
MAPK8IP3	mitogen-activated protein kinase 8 interacting protein 3	1,99	down
MAPRE2	microtubule-associated protein, RP/EB family, member 2	1,50	up
MARCKS	myristoylated alanine-rich protein kinase C substrate	2,53	up
MARCO	macrophage receptor with collagenous structure	1,64	down
MARK2	MAP/microtubule affinity-regulating kinase 2	2,03	up
MARK3	MAP/microtubule affinity-regulating kinase 3	1,71	up
MARS	methionyl-tRNA synthetase	1,96	up
MAT1A	methionine adenosyltransferase I, alpha	3,73	down
MAT2B	methionine adenosyltransferase II, beta	1,73	up
MATR3	matrin 3	1,79	up
MAU2	MAU2 sister chromatid cohesion factor	2,24	up
MAX	MYC associated factor X	1,75	up
MAZ	MYC-associated zinc finger protein (purine-binding transcription factor)	1,52	down
MB	myoglobin	1,82	down
MBL1P	mannose-binding lectin (protein A) 1, pseudogene	1,79	down
MBOAT2	membrane bound O-acyltransferase domain containing 2	1,79	up
MBTPS1	membrane-bound transcription factor peptidase, site 1	1,55	down
MBTPS1	membrane-bound transcription factor peptidase, site 1	1,68	up
MCFD2	multiple coagulation factor deficiency 2	1,53	up
MCM2	minichromosome maintenance complex component 2	1,63	down
MECR	mitochondrial trans-2-enoyl-CoA reductase	1,59	down
MED13L	mediator complex subunit 13-like	3,49	up
MEF2B	myocyte enhancer factor 2B	1,86	down
MEF2C	myocyte enhancer factor 2C	1,52	down
MEIS3	Meis homeobox 3	2,13	down
MESDC2	mesoderm development candidate 2	1,51	down
MESP1	mesoderm posterior 1 homolog (mouse)	1,80	up
METAP2	methionyl aminopeptidase 2	1,54	up
METRN	meteorin, glial cell differentiation regulator	1,53	down
METTL1	methyltransferase like 1	1,89	down
METTL13	methyltransferase like 13	1,80	up
METTL15	methyltransferase like 15	2,32	up
METTL18	methyltransferase like 18	1,56	down
METTL9	methyltransferase like 9	1,54	up
MFGE8	milk fat globule-EGF factor 8 protein	1,51	down
MFN1	mitofusin 1	2,67	up
MFN1	mitofusin 1	1,95	up
MFSD12	major facilitator superfamily domain containing 12	2,19	down
MFSD9	major facilitator superfamily domain containing 9	1,95	down
MICALL2	MICAL-like 2	2,09	up
MIR22HG	MIR22 host gene (non-protein coding)	2,77	down
MKL1	megakaryoblastic leukemia (translocation) 1	1,52	down
MKRN1	makorin ring finger protein 1	2,10	down
MLLT1	myeloid/lymphoid or mixed-lineage leukemia (trithorax homolog, Drosophila); translocated to, 1	1,85	up
MLLT10	myeloid/lymphoid or mixed-lineage leukemia (trithorax homolog, Drosophila); translocated to, 10	1,63	down
MLXIPL	MLX interacting protein-like	2,92	down
MMP27	matrix metallopeptidase 27	1,54	down
MMS19	MMS19 nucleotide excision repair homolog (S. cerevisiae)	1,86	up
MOB1A	MOB kinase activator 1A	1,53	up
MON1A	MON1 secretory trafficking family member A	1,50	down
MORC1	MORC family CW-type zinc finger 1	1,62	up
MORC2	MORC family CW-type zinc finger 2	1,57	up
MPRIP	myosin phosphatase Rho interacting protein	1,62	up
MPZL1	myelin protein zero-like 1	1,76	up
MPZL2	myelin protein zero-like 2	2,05	up
MRFAP1	Morf4 family associated protein 1	1,66	up
MRGPRX2	MAS-related GPR, member X2	1,58	down
MRPL35	mitochondrial ribosomal protein L35	1,53	up
MRPL43	mitochondrial ribosomal protein L43	1,78	down
MRPL9	mitochondrial ribosomal protein L9	2,22	up
MRPS15	mitochondrial ribosomal protein S15	1,65	up
MRPS6	mitochondrial ribosomal protein S6	1,80	up
MSANTD2	Myb/SANT-like DNA-binding domain containing 2	1,52	down
MSLN	mesothelin	1,67	down
MSMB	microseminoprotein, beta-	1,52	up
MT1M	metallothionein 1M	2,04	up
MTERFD2	MTERF domain containing 2	1,76	up
MTHFD1	methylenetetrahydrofolate dehydrogenase (NADP+ dependent) 1, methenyltetrahydrofolate cyclohydrolase, formyltetrahydrofolate synthetase	1,63	up
MTHFD1L	methylenetetrahydrofolate dehydrogenase (NADP+ dependent) 1-like	1,71	down
MTMR1	myotubularin related protein 1	1,55	up
MTMR11	myotubularin related protein 11	1,66	up
MT-ND1	mitochondrially encoded NADH dehydrogenase 1	1,69	up
MT-ND2	mitochondrially encoded NADH dehydrogenase 2	1,88	up
MTPN	myotrophin	1,53	up
MTRF1L	mitochondrial translational release factor 1-like	1,57	down
MUC17	mucin 17, cell surface associated	1,57	up
MUC3A	mucin 3A, cell surface associated	2,73	down
MUC5B	mucin 5B, oligomeric mucus/gel-forming	2,36	down
MUSK	muscle, skeletal, receptor tyrosine kinase	1,63	down
MUTYH	mutY homolog	1,53	down
MVP	major vault protein	1,95	down
MXD1	MAX dimerization protein 1	1,61	up
MXRA5	matrix-remodelling associated 5	1,91	up
MYBL1	v-myb avian myeloblastosis viral oncogene homolog-like 1	1,66	down
MYBPH	myosin binding protein H	1,67	down
MYD88	myeloid differentiation primary response 88	1,67	down
MYF5	myogenic factor 5	1,57	down
MYH15	myosin, heavy chain 15	1,59	down
MYL3	myosin, light chain 3, alkali; ventricular, skeletal, slow	1,70	up
MYL9	myosin, light chain 9, regulatory	1,63	up
MYLK	myosin light chain kinase	1,69	up
MYO1A	myosin IA	1,51	down
MYO1C	myosin IC	1,88	up
MYO6	myosin VI	1,99	up
MYOF	myoferlin	1,62	up
NAA38	N(alpha)-acetyltransferase 38, NatC auxiliary subunit	1,71	up
NAA38	N(alpha)-acetyltransferase 38, NatC auxiliary subunit	1,62	up
NADSYN1	NAD synthetase 1	1,89	up
NAGPA	N-acetylglucosamine-1-phosphodiester alpha-N-acetylglucosaminidase	1,55	down
NAGS	N-acetylglutamate synthase	2,00	up
NANOS3	nanos homolog 3 (Drosophila)	1,89	up
NAP1L3	nucleosome assembly protein 1-like 3	1,66	down
NAPRT1	nicotinate phosphoribosyltransferase domain containing 1	3,64	down
NAPRT1	nicotinate phosphoribosyltransferase domain containing 1	1,51	down
NAPSA	napsin A aspartic peptidase	2,46	down
NBL1	neuroblastoma 1, DAN family BMP antagonist	1,82	down
NBPF14	neuroblastoma breakpoint family, member 14	2,49	up
NBPF15	neuroblastoma breakpoint family, member 15	1,53	up
NBPF3	neuroblastoma breakpoint family, member 3	3,52	up
NCKIPSD	NCK interacting protein with SH3 domain	1,51	down
NCL	nucleolin	1,72	up
NCOR1	nuclear receptor corepressor 1	1,79	up
NDC1	NDC1 transmembrane nucleoporin	1,63	up
NDEL1	nudE neurodevelopment protein 1-like 1	1,77	up
NDRG2	NDRG family member 2	1,58	up
NDST1	N-deacetylase/N-sulfotransferase (heparan glucosaminyl) 1	1,83	down
NDST2	N-deacetylase/N-sulfotransferase (heparan glucosaminyl) 2	2,29	down
NDUFA3	NADH dehydrogenase (ubiquinone) 1 alpha subcomplex, 3, 9kDa	1,94	down
NDUFA6	NADH dehydrogenase (ubiquinone) 1 alpha subcomplex, 6, 14kDa	1,64	up
NDUFAF2	NADH dehydrogenase (ubiquinone) complex I, assembly factor 2	1,58	up
NDUFAF7	NADH dehydrogenase (ubiquinone) complex I, assembly factor 7	1,67	up
NDUFB7	NADH dehydrogenase (ubiquinone) 1 beta subcomplex, 7, 18kDa	1,62	down
NDUFB9	NADH dehydrogenase (ubiquinone) 1 beta subcomplex, 9, 22kDa	2,42	up
NEAT1	nuclear paraspeckle assembly transcript 1 (non-protein coding)	2,09	up
NEB	nebulin	1,56	down
NEFM	neurofilament, medium polypeptide	1,66	up
NEK9	NIMA-related kinase 9	1,61	up
NES	nestin	1,85	up
NEU4	sialidase 4	1,68	down
NF1	neurofibromin 1	1,68	down
NFIB	nuclear factor I/B	1,69	up
NFKBIB	nuclear factor of kappa light polypeptide gene enhancer in B-cells inhibitor, beta	1,72	down
NFYC	nuclear transcription factor Y, gamma	1,61	up
NHLH2	nescient helix loop helix 2	1,53	down
NIPAL2	NIPA-like domain containing 2	1,90	up
NIPBL	Nipped-B homolog (Drosophila)	2,78	down
NIPBL	Nipped-B homolog (Drosophila)	1,57	up
NIT1	nitrilase 1	3,52	down
NKAPP1	NFKB activating protein pseudogene 1	2,34	down
NLGN2	neuroligin 2	2,48	down
NLRP12	NLR family, pyrin domain containing 12	1,64	down
NLRP2	NLR family, pyrin domain containing 2	1,55	down
NMB	neuromedin B	1,97	up
NMT1	N-myristoyltransferase 1	1,79	up
NMUR2	neuromedin U receptor 2	1,58	up
NOL6	nucleolar protein 6 (RNA-associated)	1,59	down
NOLC1	nucleolar and coiled-body phosphoprotein 1	1,57	up
NOLC1	nucleolar and coiled-body phosphoprotein 1	1,56	up
NOP2	NOP2 nucleolar protein	1,79	up
NOTCH2NL	notch 2 N-terminal like	1,85	up
NOTCH3	notch 3	1,85	down
NOTCH4	notch 4	1,75	down
NOTCH4	notch 4	2,02	up
NOV	nephroblastoma overexpressed	1,52	up
NOXA1	NADPH oxidase activator 1	2,04	down
NOXO1	NADPH oxidase organizer 1	2,62	down
NPAS3	neuronal PAS domain protein 3	2,18	down
NPCDR1	nasopharyngeal carcinoma, down-regulated 1	1,61	up
NPDC1	neural proliferation, differentiation and control, 1	1,60	down
NPFFR2	neuropeptide FF receptor 2	1,82	up
NPHP3	nephronophthisis 3 (adolescent)	2,22	up
NPHS2	nephrosis 2, idiopathic, steroid-resistant (podocin)	1,93	up
NPTN	neuroplastin	1,76	up
NPW	neuropeptide W	2,31	down
NR1D1	nuclear receptor subfamily 1, group D, member 1	1,78	up
NR1H2	nuclear receptor subfamily 1, group H, member 2	4,46	down
NR2C2	nuclear receptor subfamily 2, group C, member 2	1,65	up
NR2C2AP	nuclear receptor 2C2-associated protein	2,89	up
NR4A2	nuclear receptor subfamily 4, group A, member 2	1,77	down
NRAP	nebulin-related anchoring protein	1,54	down
NRIP3	nuclear receptor interacting protein 3	1,57	up
NRL	neural retina leucine zipper	1,75	down
NRSN2	neurensin 2	1,88	down
NRTN	neurturin	1,59	down

MTRF1L	mitochondrial translational release factor 1-like	1,57	down
MUC17	mucin 17, cell surface associated	1,57	up
MUC3A	mucin 3A, cell surface associated	2,73	down
MUC5B	mucin 5B, oligomeric mucus/gel-forming	2,36	down
MUSK	muscle, skeletal, receptor tyrosine kinase	1,63	down
MUTYH	mutY homolog	1,53	down
MVP	major vault protein	1,95	down
MXD1	MAX dimerization protein 1	1,61	up
MXRA5	matrix-remodelling associated 5	1,91	up
MYBL1	v-myb avian myeloblastosis viral oncogene homolog-like 1	1,66	down
MYBPH	myosin binding protein H	1,67	down
MYD88	myeloid differentiation primary response 88	1,67	down
MYF5	myogenic factor 5	1,57	down
MYH15	myosin, heavy chain 15	1,59	down
MYL3	myosin, light chain 3, alkali; ventricular, skeletal, slow	1,70	up
MYL9	myosin, light chain 9, regulatory	1,63	up
MYLK	myosin light chain kinase	1,69	up
MYO1A	myosin IA	1,51	down
MYO1C	myosin IC	1,88	up
MYO6	myosin VI	1,99	up
MYOF	myoferlin	1,62	up
NAA38	N(alpha)-acetyltransferase 38, NatC auxiliary subunit	1,71	up
NAA38	N(alpha)-acetyltransferase 38, NatC auxiliary subunit	1,62	up
NADSYN1	NAD synthetase 1	1,89	up
NAGPA	N-acetylglucosamine-1-phosphodiester alpha-N-acetylglucosaminidase	1,55	down
NAGS	N-acetylglutamate synthase	2,00	up
NANOS3	nanos homolog 3 (Drosophila)	1,89	up
NAP1L3	nucleosome assembly protein 1-like 3	1,66	down
NAPRT1	nicotinate phosphoribosyltransferase domain containing 1	3,64	down
NAPRT1	nicotinate phosphoribosyltransferase domain containing 1	1,51	down
NAPSA	napsin A aspartic peptidase	2,46	down
NBL1	neuroblastoma 1, DAN family BMP antagonist	1,82	down
NBPF14	neuroblastoma breakpoint family, member 14	2,49	up
NBPF15	neuroblastoma breakpoint family, member 15	1,53	up
NBPF3	neuroblastoma breakpoint family, member 3	3,52	up
NCKIPSD	NCK interacting protein with SH3 domain	1,51	down
NCL	nucleolin	1,72	up
NCOR1	nuclear receptor corepressor 1	1,79	up
NDC1	NDC1 transmembrane nucleoporin	1,63	up
NDEL1	nudE neurodevelopment protein 1-like 1	1,77	up
NDRG2	NDRG family member 2	1,58	up
NDST1	N-deacetylase/N-sulfotransferase (heparan glucosaminyl) 1	1,83	down
NDST2	N-deacetylase/N-sulfotransferase (heparan glucosaminyl) 2	2,29	down
NDUFA3	NADH dehydrogenase (ubiquinone) 1 alpha subcomplex, 3, 9kDa	1,94	down
NDUFA6	NADH dehydrogenase (ubiquinone) 1 alpha subcomplex, 6, 14kDa	1,64	up
NDUFAF2	NADH dehydrogenase (ubiquinone) complex I, assembly factor 2	1,58	up
NDUFAF7	NADH dehydrogenase (ubiquinone) complex I, assembly factor 7	1,67	up
NDUFB7	NADH dehydrogenase (ubiquinone) 1 beta subcomplex, 7, 18kDa	1,62	down
NDUFB9	NADH dehydrogenase (ubiquinone) 1 beta subcomplex, 9, 22kDa	2,42	up
NEAT1	nuclear paraspeckle assembly transcript 1 (non-protein coding)	2,09	up
NEB	nebulin	1,56	down
NEFM	neurofilament, medium polypeptide	1,66	up
NEK9	NIMA-related kinase 9	1,61	up
NES	nestin	1,85	up
NEU4	sialidase 4	1,68	down
NF1	neurofibromin 1	1,68	down
NFIB	nuclear factor I/B	1,69	up
NFKBIB	nuclear factor of kappa light polypeptide gene enhancer in B-cells inhibitor, beta	1,72	down
NFYC	nuclear transcription factor Y, gamma	1,61	up
NHLH2	nescient helix loop helix 2	1,53	down
NIPAL2	NIPA-like domain containing 2	1,90	up
NIPBL	Nipped-B homolog (Drosophila)	2,78	down
NIPBL	Nipped-B homolog (Drosophila)	1,57	up
NIT1	nitrilase 1	3,52	down
NKAPP1	NFKB activating protein pseudogene 1	2,34	down
NLGN2	neuroligin 2	2,48	down
NLRP12	NLR family, pyrin domain containing 12	1,64	down
NLRP2	NLR family, pyrin domain containing 2	1,55	down
NMB	neuromedin B	1,97	up
NMT1	N-myristoyltransferase 1	1,79	up
NMUR2	neuromedin U receptor 2	1,58	up
NOL6	nucleolar protein 6 (RNA-associated)	1,59	down
NOLC1	nucleolar and coiled-body phosphoprotein 1	1,57	up
NOLC1	nucleolar and coiled-body phosphoprotein 1	1,56	up
NOP2	NOP2 nucleolar protein	1,79	up
NOTCH2NL	notch 2 N-terminal like	1,85	up
NOTCH3	notch 3	1,85	down
NOTCH4	notch 4	1,75	down
NOTCH4	notch 4	2,02	up
NOV	nephroblastoma overexpressed	1,52	up
NOXA1	NADPH oxidase activator 1	2,04	down
NOXO1	NADPH oxidase organizer 1	2,62	down
NPAS3	neuronal PAS domain protein 3	2,18	down
NPCDR1	nasopharyngeal carcinoma, down-regulated 1	1,61	up
NPDC1	neural proliferation, differentiation and control, 1	1,60	down
NPFFR2	neuropeptide FF receptor 2	1,82	up
NPHP3	nephronophthisis 3 (adolescent)	2,22	up
NPHS2	nephrosis 2, idiopathic, steroid-resistant (podocin)	1,93	up
NPTN	neuroplastin	1,76	up
NPW	neuropeptide W	2,31	down
NR1D1	nuclear receptor subfamily 1, group D, member 1	1,78	up
NR1H2	nuclear receptor subfamily 1, group H, member 2	4,46	down
NR2C2	nuclear receptor subfamily 2, group C, member 2	1,65	up
NR2C2AP	nuclear receptor 2C2-associated protein	2,89	up
NR4A2	nuclear receptor subfamily 4, group A, member 2	1,77	down
NRAP	nebulin-related anchoring protein	1,54	down
NRIP3	nuclear receptor interacting protein 3	1,57	up
NRL	neural retina leucine zipper	1,75	down
NRSN2	neurensin 2	1,88	down
NRTN	neurturin	1,59	down
NSA2	NSA2 ribosome biogenesis homolog (S. cerevisiae)	1,66	up
NSUN5P2	NOP2/Sun domain family, member 5 pseudogene 2	1,81	up
NT5DC3	5'-nucleotidase domain containing 3	1,54	down
NTN3	netrin 3	3,21	down
NUAK1	NUAK family, SNF1-like kinase, 1	1,91	up
NUCKS1	nuclear casein kinase and cyclin-dependent kinase substrate 1	2,04	up
NUDC	nudC nuclear distribution protein	1,70	down
NUDT4	nudix (nucleoside diphosphate linked moiety X)-type motif 4	1,57	up
NUMBL	numb homolog (Drosophila)-like	1,95	up
NUP205	nucleoporin 205kDa	1,72	up
OBFC1	oligonucleotide/oligosaccharide-binding fold containing 1	2,03	up
OBP2A	odorant binding protein 2A	1,56	down
OCLM	oculomedin	1,76	down
OFCC1	orofacial cleft 1 candidate 1	1,58	down
OGFOD2	2-oxoglutarate and iron-dependent oxygenase domain containing 2	1,76	down
OGG1	8-oxoguanine DNA glycosylase	1,56	up
OLFM1	olfactomedin 1	2,73	down
OPN1LW	opsin 1 (cone pigments), long-wave-sensitive	2,01	down
OPN1MW	opsin 1 (cone pigments), medium-wave-sensitive	2,62	down
OPTC	opticin	1,50	up
OR1DG8	olfactory receptor, family 10, subfamily G, member 8	1,83	down
OR1DH1	olfactory receptor, family 10, subfamily H, member 1	1,50	down
OR1DH2	olfactory receptor, family 10, subfamily H, member 2	2,25	down
OR1DP1	olfactory receptor, family 10, subfamily P, member 1	1,74	up
OR1DT2	olfactory receptor, family 10, subfamily T, member 2	2,08	up
OR1D2	olfactory receptor, family 1, subfamily D, member 2	1,54	up
OR2V2	olfactory receptor, family 2, subfamily V, member 2	1,79	down
OR4D5	olfactory receptor, family 4, subfamily D, member 5	1,60	down
OR5P2	olfactory receptor, family 5, subfamily P, member 2	1,51	down
OR7A5	olfactory receptor, family 7, subfamily A, member 5	1,56	down
OR7E13P	olfactory receptor, family 7, subfamily E, member 13 pseudogene	1,63	up
OR7E24	olfactory receptor, family 7, subfamily E, member 24	2,27	up
OR7G3	olfactory receptor, family 7, subfamily G, member 3	2,26	down
ORAI1	ORAI calcium release-activated calcium modulator 1	2,06	up
OS9	osteosarcoma amplified 9, endoplasmic reticulum lectin	2,07	up
OSBPL1A	oxysterol binding protein-like 1A	1,93	up
OXA1L	oxidase (cytochrome c) assembly 1-like	1,59	up
P2RX4	purinergic receptor P2X, ligand-gated ion channel, 4	1,58	down
P2RX5	purinergic receptor P2X, ligand-gated ion channel, 5	1,55	down
P2RY10	purinergic receptor P2Y, G-protein coupled, 10	1,53	down
P2RY4	pyrimidinergic receptor P2Y, G-protein coupled, 4	2,34	down
PA2G4	proliferation-associated 2G4, 38kDa	2,58	up
PABPC3	poly(A) binding protein, cytoplasmic 3	1,87	up
PABPN1	poly(A) binding protein, nuclear 1	2,25	up
PADI4	peptidyl arginine deiminase, type IV	1,63	up
PAEP	progestagen-associated endometrial protein	1,51	up
PAFAH2	platelet-activating factor acetylhydrolase 2, 40kDa	1,53	down
PAIP2	poly(A) binding protein interacting protein 2	1,74	up
PAK2	p21 protein (Cdc42/Rac)-activated kinase 2	1,87	up
PAK3	p21 protein (Cdc42/Rac)-activated kinase 3	1,99	down
PAK4	p21 protein (Cdc42/Rac)-activated kinase 4	3,46	down
PAK7	p21 protein (Cdc42/Rac)-activated kinase 7	1,54	down
PANK3	pantothenate kinase 3	1,62	up
PANX2	pannexin 2	2,05	down
PAPOLA	poly(A) polymerase alpha	2,19	up
PAPPA	pregnancy-associated plasma protein A, pappalysin 1	1,60	up
PAPSS1	3'-phosphoadenosine 5'-phosphosulfate synthase 1	1,59	up
PARP10	poly (ADP-ribose) polymerase family, member 10	2,82	down
PARP10	poly (ADP-ribose) polymerase family, member 10	1,90	up
PASK	PAS domain containing serine/threonine kinase	1,56	up
PATZ1	POZ (BTB) and AT hook containing zinc finger 1	1,63	down
PAX4	paired box 4	1,80	up
PBX2	pre-B-cell leukemia homeobox 2	1,55	up
PCAT4	prostate cancer associated transcript 4 (non-protein coding)	1,52	down
PCDH15	protocadherin-related 15	1,59	down
PCDHA1	protocadherin alpha 1	1,50	down
PCDHA5	protocadherin alpha 5	1,69	down
PCDHB7	protocadherin beta 7	1,64	up
PCDHB9	protocadherin beta 9	1,59	up
PCDHGC4	protocadherin gamma subfamily C, 4	1,57	down
PCGF1	polycomb group ring finger 1	1,56	up
PCGF2	polycomb group ring finger 2	1,82	down
PCSK1N	proprotein convertase subtilisin/kexin type 1 inhibitor	2,21	down
PCSK4	proprotein convertase subtilisin/kexin type 4	2,49	down
PCSK5	proprotein convertase subtilisin/kexin type 5	1,54	up
PCSK7	proprotein convertase subtilisin/kexin type 7	1,69	up
PDE2A	phosphodiesterase 2A, cGMP-stimulated	1,52	down
PDE6B	phosphodiesterase 6B, cGMP-specific, rod, beta	1,57	down
PDIA2	protein disulfide isomerase family A, member 2	1,58	down
PDIA3	protein disulfide isomerase family A, member 3	2,22	up
PDIA3	protein disulfide isomerase family A, member 3	1,85	up
PDK4	pyruvate dehydrogenase kinase, isozyme 4	1,66	down
PDLIM5	PDZ and LIM domain 5	1,73	up
PDS5B	PDS5, regulator of cohesion maintenance, homolog B (S. cerevisiae)	2,11	up
PDZD2	PDZ domain containing 2	1,65	up
PDZD7	PDZ domain containing 7	1,89	up
PDZD8	PDZ domain containing 8	1,60	up
PEAK1	pseudopodium-enriched atypical kinase 1	1,67	up
PELI3	pellino E3 ubiquitin protein ligase family member 3	1,66	down
PEPD	peptidase D	2,24	up
PER2	period circadian clock 2	1,55	up
PEX10	peroxisomal biogenesis factor 10	1,90	down
PEX11A	peroxisomal biogenesis factor 11 alpha	1,56	down
PEX19	peroxisomal biogenesis factor 19	1,61	up
PEX2	peroxisomal biogenesis factor 2	1,52	up
PEX5	peroxisomal biogenesis factor 5	1,77	down
PFKFB1	6-phosphofructo-2-kinase/fructose-2,6-biphosphatase 1	1,69	down
PFKL	phosphofructokinase, liver	2,51	down
PFN1P2	profilin 1 pseudogene 2	1,58	up
PGC	progastricsin (pepsinogen C)	1,51	down

PGD	phosphogluconate dehydrogenase	2,49	up
PGM5	phosphoglucomutase 5	2,61	down
PGRMC2	progesterone receptor membrane component 2	2,68	up
PHACTR3	phosphatase and actin regulator 3	1,54	down
PHF2	PHD finger protein 2	1,61	up
PHF20	PHD finger protein 20	1,51	down
PHIP	pleckstrin homology domain interacting protein	1,62	up
PHKA2	phosphorylase kinase, alpha 2 (liver)	1,61	up
PHKB	phosphorylase kinase, beta	1,65	up
PHLDA1	pleckstrin homology-like domain, family A, member 1	1,71	down
PIAS2	protein inhibitor of activated STAT, 2	1,54	up
PID1	phosphotyrosine interaction domain containing 1	1,51	up
PIGG	phosphatidylinositol glycan anchor biosynthesis, class G	1,58	up
PIGG	phosphatidylinositol glycan anchor biosynthesis, class G	1,54	up
PIGT	phosphatidylinositol glycan anchor biosynthesis, class T	1,85	up
PIGY	phosphatidylinositol glycan anchor biosynthesis, class Y	1,66	up
PIK3CD	phosphatidylinositol-4,5-bisphosphate 3-kinase, catalytic subunit delta	1,65	down
PIK3IP1	phosphoinositide-3-kinase interacting protein 1	1,53	down
PIK3IP1	phosphoinositide-3-kinase interacting protein 1	1,55	up
PIN1P1	peptidylprolyl cis/trans isomerase, NIMA-interacting 1 pseudogene 1	1,94	down
PIN1P1	peptidylprolyl cis/trans isomerase, NIMA-interacting 1 pseudogene 1	1,80	up
PIP5K1A	phosphatidylinositol-4-phosphate 5-kinase, type I, alpha	1,51	up
PITPNC1	phosphatidylinositol transfer protein, cytoplasmic 1	1,62	down
PKD1L2	polycystic kidney disease 1-like 2	1,61	down
PKD2L1	polycystic kidney disease 2-like 1	1,61	down
PKD2L2	polycystic kidney disease 2-like 2	1,61	up
PKP2	plakophilin 2	1,70	up
PLA2G16	phospholipase A2, group XVI	1,74	down
PLA2G2F	phospholipase A2, group IIF	1,56	down
PLAC1	placenta-specific 1	1,87	up
PLCB2	phospholipase C, beta 2	1,61	up
PLD1	phospholipase D1, phosphatidylcholine-specific	1,99	up
PLEKHA6	pleckstrin homology domain containing, family A member 6	2,51	down
PLEKHF1	pleckstrin homology domain containing, family F (with FYVE domain) member 1	1,87	down
PLEKHG4B	pleckstrin homology domain containing, family G (with RhoGef domain) member 4B	1,66	down
PLEKHM1P	pleckstrin homology domain containing, family M (with RUN domain) member 1 pseudogene	2,54	down
PLIN3	perilipin 3	1,75	up
PLIN4	perilipin 4	1,53	down
PLK2	polo-like kinase 2	2,00	up
PLOD3	procollagen-lysine, 2-oxoglutarate 5-dioxygenase 3	2,50	down
PLXDC2	plexin domain containing 2	1,85	up
PLXNA4	plexin A4	1,64	up
PLXND1	plexin D1	1,74	down
PM20D1	peptidase M20 domain containing 1	1,51	down
PMEPA1	prostate transmembrane protein, androgen induced 1	1,86	down
PMFBP1	polyamine modulated factor 1 binding protein 1	1,69	up
PMP2	peripheral myelin protein 2	2,05	down
PMP22	peripheral myelin protein 22	2,29	up
PNKD	paroxysmal nonkinesigenic dyskinesia	1,59	up
PNMA3	paraneoplastic Ma antigen 3	1,60	down
PNMA6A	paraneoplastic Ma antigen family member 6A	1,71	down
PNMAL1	paraneoplastic Ma antigen family-like 1	2,08	down
PNPLA8	patatin-like phospholipase domain containing 8	1,68	up
POC1A	POC1 centriolar protein A	1,68	down
POLA1	polymerase (DNA directed), alpha 1, catalytic subunit	1,51	up
POLD2	polymerase (DNA directed), delta 2, accessory subunit	1,55	down
POLE2	polymerase (DNA directed), epsilon 2, accessory subunit	2,30	down
POLE3	polymerase (DNA directed), epsilon 3, accessory subunit	2,34	up
POLL	polymerase (DNA directed), lambda	1,68	down
POLQ	polymerase (DNA directed), theta	1,70	down
POLR1C	polymerase (RNA) I polypeptide C, 30kDa	1,54	up
POLR2B	polymerase (RNA) II (DNA directed) polypeptide B, 140kDa	1,81	up
PON3	paraoxonase 3	2,10	up
POU5F1	POU class 5 homeobox 1	1,51	up
PPAN	peter pan homolog (Drosophila)	1,68	down
PPCS	phosphopantothenoylcysteine synthetase	1,56	up
PPFIA1	protein tyrosine phosphatase, receptor type, f polypeptide (PTPRF), interacting protein (liprin), alpha 1	1,57	down
PPFIA4	protein tyrosine phosphatase, receptor type, f polypeptide (PTPRF), interacting protein (liprin), alpha 4	1,66	down
PPIA	peptidylprolyl isomerase A (cyclophilin A)	1,59	up
PPIAL4A	peptidylprolyl isomerase A (cyclophilin A)-like 4A	2,05	up
PPIAL4A	peptidylprolyl isomerase A (cyclophilin A)-like 4A	1,96	up
PPIAL4A	peptidylprolyl isomerase A (cyclophilin A)-like 4A	1,90	up
PPIAL4A	peptidylprolyl isomerase A (cyclophilin A)-like 4A	1,82	up
PPOX	protoporphyrinogen oxidase	1,97	down
PPP3R35	protein phosphatase 1, regulatory subunit 35	1,73	up
PPP1R3C	protein phosphatase 1, regulatory subunit 3C	1,95	up
PPP1R3D	protein phosphatase 1, regulatory subunit 3D	1,80	up
PPP2CA	protein phosphatase 2, catalytic subunit, alpha isozyme	1,55	up
PPP2CB	protein phosphatase 2, catalytic subunit, beta isozyme	1,81	up
PPP2R2D	protein phosphatase 2, regulatory subunit B, delta	1,61	up
PPP2R5D	protein phosphatase 2, regulatory subunit B', delta	1,53	down
PPP4R4	protein phosphatase 4, regulatory subunit 4	1,62	down
PPP6R2	protein phosphatase 6, regulatory subunit 2	1,54	down
PPP6R3	protein phosphatase 6, regulatory subunit 3	1,57	down
PPRC1	peroxisome proliferator-activated receptor gamma, coactivator-related 1	1,91	up
PRAF2	PRA1 domain family, member 2	1,60	down
PRAM1	PML-RARA regulated adaptor molecule 1	1,60	down
PRCD	progressive rod-cone degeneration	1,72	up
PRDM11	PR domain containing 11	1,51	up
PRDM8	PR domain containing 8	1,70	up
PRICKLE4	prickle homolog 4 (Drosophila)	1,65	down
PRKAA2	protein kinase, AMP-activated, alpha 2 catalytic subunit	1,52	down
PRKAG2	protein kinase, AMP-activated, gamma 2 non-catalytic subunit	1,95	up
PRKD3	protein kinase D3	1,60	up
PRKRA	protein kinase, interferon-inducible double stranded RNA dependent activator	1,54	up
PRLHR	prolactin releasing hormone receptor	2,30	down
PRMT7	protein arginine methyltransferase 7	1,87	up
PROM1	prominin 1	1,54	down
PROP1	PROP paired-like homeobox 1	4,39	down
PRR5	proline rich 5 (renal)	1,70	up
PRR7	proline rich 7 (synaptic)	1,87	up
PRRC1	proline-rich coiled-coil 1	1,64	up
PRRG1	proline rich Gla (G-carboxyglutamic acid) 1	1,56	up
PRRG2	proline rich Gla (G-carboxyglutamic acid) 2	2,24	down
PRSS42	protease, serine, 42	1,63	up
PRSS53	protease, serine, 53	1,60	up
PSD3	pleckstrin and Sec7 domain containing 3	1,56	up
PSMC2	proteasome (prosome, macropain) 26S subunit, ATPase, 2	1,87	up
PSMC5	proteasome (prosome, macropain) 26S subunit, ATPase, 5	1,51	up
PSMG2	proteasome (prosome, macropain) assembly chaperone 2	1,88	up
PSTPIP1	proline-serine-threonine phosphatase interacting protein 1	3,00	down
PTAR1	protein prenyltransferase alpha subunit repeat containing 1	1,85	up
PTBP3	polypyrimidine tract binding protein 3	2,92	up
PTCH2	patched 2	1,98	down
PTCRA	pre T-cell antigen receptor alpha	1,73	down
PTDSS2	phosphatidylserine synthase 2	1,73	up
PTEN	phosphatase and tensin homolog	1,79	up
PTGDR	prostaglandin D2 receptor (DP)	2,01	up
PTGER4	prostaglandin E receptor 4 (subtype EP4)	1,53	up
PTGES3	prostaglandin E synthase 3 (cytosolic)	1,52	up
PTMA	prothymosin, alpha	1,94	up
PTMA	prothymosin, alpha	1,67	up
PTN	pleiotrophin	2,19	up
PTPDC1	protein tyrosine phosphatase domain containing 1	1,60	down
PTPLAD2	protein tyrosine phosphatase-like A domain containing 2	1,55	down
PTPN11	protein tyrosine phosphatase, non-receptor type 11	1,59	up
PTPN2	protein tyrosine phosphatase, non-receptor type 2	1,69	up
PTPN5	protein tyrosine phosphatase, non-receptor type 5 (striatum-enriched)	1,52	down
PTPRH	protein tyrosine phosphatase, receptor type, H	1,58	down
PUM2	pumilio RNA-binding family member 2	1,84	up
PVALB	parvalbumin	1,99	down
PVRL2	poliovirus receptor-related 2 (herpesvirus entry mediator B)	1,88	up
PYCRL	pyrroline-5-carboxylate reductase-like	1,68	up
PYDC1	PYD (pyrin domain) containing 1	1,51	up
PYGB	phosphorylase, glycogen; brain	1,98	down
PYGO1	pygopus family PHD finger 1	1,58	up
QPRT	quinolinate phosphoribosyltransferase	2,03	up
QSOX2	quiescin Q6 sulfhydryl oxidase 2	1,63	down
R3HDM2	R3H domain containing 2	1,97	up
RAB22A	RAB22A, member RAS oncogene family	2,12	up
RAB2A	RAB2A, member RAS oncogene family	1,60	up
RAB36	RAB36, member RAS oncogene family	1,62	down
RAB3D	RAB3D, member RAS oncogene family	1,75	up
RAB42	RAB42, member RAS oncogene family	1,75	down
RAB43	RAB43, member RAS oncogene family	1,58	down
RAB4B	RAB4B, member RAS oncogene family	1,50	down
RAB7B	RAB7B, member RAS oncogene family	1,79	up
RABGAP1	RAB GTPase activating protein 1	1,52	up
RABGEF1	RAB guanine nucleotide exchange factor (GEF) 1	1,55	up
RABIF	RAB interacting factor	1,80	up
RABL6	RAB, member RAS oncogene family-like 6	2,49	down
RAD23B	RAD23 homolog B (S. cerevisiae)	1,53	up
RAD51C	RAD51 paralog C	1,58	up
RAI1	retinoic acid induced 1	1,53	up
RANBP2	RAN binding protein 2	1,58	up
RANBP3	RAN binding protein 3	1,69	up
RAPGEF1	Rap guanine nucleotide exchange factor (GEF) 1	1,73	up
RARRES2	retinoic acid receptor responder (tazarotene induced) 2	1,54	up
RASGEF1A	RasGEF domain family, member 1A	1,55	up
RASGEF1C	RasGEF domain family, member 1C	1,87	down
RASGRP2	RAS guanyl releasing protein 2 (calcium and DAG-regulated)	1,61	down
RASGRP4	RAS guanyl releasing protein 4	1,62	up
RAX2	retina and anterior neural fold homeobox 2	2,09	up
RBBP4	retinoblastoma binding protein 4	3,09	up
RBM15B	RNA binding motif protein 15B	1,74	up
RBM17	RNA binding motif protein 17	2,20	up
RBM17	RNA binding motif protein 17	1,57	up
RBM28	RNA binding motif protein 28	1,76	down
RBM39	RNA binding motif protein 39	1,62	up
RBM41	RNA binding motif protein 41	1,80	up
RBMX2	RNA binding motif protein, X-linked 2	1,57	down
RCOR2	REST corepressor 2	2,27	up
RFESD	Rieske (Fe-S) domain containing	1,52	down
RFX2	regulatory factor X, 2 (influences HLA class II expression)	2,25	up
RFX7	regulatory factor X, 7	1,57	up
RGAG4	retrotransposon gag domain containing 4	1,80	down
RGCC	regulator of cell cycle	1,53	up
RGS19	regulator of G-protein signaling 19	2,02	down
RHBDD2	rhomboid domain containing 2	2,24	up
RHBDL3	rhomboid, veinlet-like 3 (Drosophila)	2,07	up
RHOA	ras homolog family member A	1,93	up
RHOD	ras homolog family member D	1,58	up
RHOT2	ras homolog family member T2	1,77	down
RHPN1	rhophilin, Rho GTPase binding protein 1	1,65	down
RHPN2	rhophilin, Rho GTPase binding protein 2	1,51	up
RLTPR	RGD motif, leucine rich repeats, tropomodulin domain and proline-rich containing	1,97	down
RNF112	ring finger protein 112	1,98	down
RNF113A	ring finger protein 113A	2,03	up
RNF114	ring finger protein 114	1,70	up
RNF151	ring finger protein 151	3,33	down
RNF152	ring finger protein 152	1,66	up
RNF216	ring finger protein 216	1,51	up
RNF39	ring finger protein 39	2,59	up
RNH1	ribonuclease/angiogenin inhibitor 1	2,15	down
ROR2	receptor tyrosine kinase-like orphan receptor 2	1,74	down
RPAP1	RNA polymerase II associated protein 1	1,71	up
RPIA	ribose 5-phosphate isomerase A	1,61	up
RPL10	ribosomal protein L10	2,01	down
RPL12	ribosomal protein L12	2,29	up
RPL17	ribosomal protein L17	2,00	up

RPL18	ribosomal protein L18	2,43	up
RPL21	ribosomal protein L21	2,46	up
RPL21	ribosomal protein L21	2,01	up
RPL21	ribosomal protein L21	1,83	up
RPL21	ribosomal protein L21	1,58	up
RPL22	ribosomal protein L22	1,55	up
RPL23	ribosomal protein L23	3,03	up
RPL29	ribosomal protein L29	2,07	up
RPL38	ribosomal protein L38	4,08	up
RPL7A	ribosomal protein L7a	2,32	up
RPL9	ribosomal protein L9	1,72	up
RPN2	ribophorin II	1,61	up
RPP14	ribonuclease P/MRP 14kDa subunit	1,56	up
RPP25	ribonuclease P/MRP 25kDa subunit	2,11	down
RPP38	ribonuclease P/MRP 38kDa subunit	1,98	up
RPS10	ribosomal protein S10	2,88	up
RPS13	ribosomal protein S13	4,78	up
RPS26	ribosomal protein S26	2,64	up
RPS2P45	ribosomal protein S2 pseudogene 45	1,72	down
RPS6	ribosomal protein S6	7,71	up
RPS6KA1	ribosomal protein S6 kinase, 90kDa, polypeptide 1	1,57	up
RPS6KA3	ribosomal protein S6 kinase, 90kDa, polypeptide 3	1,81	up
RTDR1	rhabdoid tumor deletion region gene 1	1,53	up
RTEL1	regulator of telomere elongation helicase 1	2,02	down
RWDD2A	RWD domain containing 2A	1,54	down
RXFP4	relaxin/insulin-like family peptide receptor 4	1,76	up
RXRA	retinoid X receptor, alpha	1,66	down
RYBP	RING1and YY1binding protein	1,94	up
S1PR3	sphingosine-1-phosphate receptor 3	1,61	down
SAMD1	sterile alpha motif domain containing 1	1,61	up
SAMD4A	sterile alpha motif domain containing 4A	1,52	down
SAP30L	SAP30-like	1,98	up
SAR1B	SAR1homolog B (S. cerevisiae)	1,93	up
SASS6	spindle assembly 6 homolog (C. elegans)	1,80	down
SATB1	SATB homeobox 1	1,85	up
SC5D	sterol-C5-desaturase	1,93	up
SCAF11	SR-related CTD-associated factor 11	2,04	up
SCAND2P	SCAN domain containing 2 pseudogene	1,63	down
SCD5	stearoyl-CoA desaturase 5	2,00	down
SCG3	secretogranin III	1,53	down
SCMH1	sex comb on midleg homolog 1(Drosophila)	1,66	up
SCN3A	sodium channel, voltage-gated, type III, alpha subunit	1,50	up
SCN3B	sodium channel, voltage-gated, type III, beta subunit	1,84	down
SCN4B	sodium channel, voltage-gated, type IV, beta subunit	1,69	up
SCNN1G	sodium channel, non-voltage-gated 1, gamma subunit	1,80	down
SCRT1	scratch family zinc finger 1	4,49	down
SCTR	secretin receptor	2,05	down
SCYL2	SCY1-like 2 (S. cerevisiae)	2,63	up
SDC3	syndecan 3	1,52	down
SDC4	syndecan 4	1,57	down
SDHAF2	succinate dehydrogenase complex assembly factor 2	2,07	up
SDHD	succinate dehydrogenase complex, subunit D, integral membrane protein	2,02	up
SDK1	sidekick cell adhesion molecule 1	2,52	down
SEC14L1	SEC14-like 1(S. cerevisiae)	1,82	up
SEL1L	sel-1suppressor of lin-12-like (C. elegans)	1,61	up
SEMA4C	sema domain, immunoglobulin domain (Ig), transmembrane domain (TM) and short cytoplasmic domain, (semaphorin) 4C	1,54	up
SEMA6C	sema domain, transmembrane domain (TM), and cytoplasmic domain, (semaphorin) 6C	1,56	down
SEPT12	septin 12	1,97	up
SEPT5	septin 5	1,53	down
SEPT7	septin 7	2,10	up
SEPT7	septin 7	1,87	up
SERF2	small EDRK-rich factor 2	4,39	up
SERINC3	serine incorporator 3	1,64	up
SERPINB13	serpin peptidase inhibitor, clade B (ovalbumin), member 13	1,53	up
SERPINB2	serpin peptidase inhibitor, clade B (ovalbumin), member 2	2,27	up
SERTAD2	SERTA domain containing 2	1,51	up
SESN2	sestrin 2	1,65	down
SETD4	SET domain containing 4	1,75	up
SETD8	SET domain containing (lysine methyltransferase) 8	1,57	up
SETD9	SET domain containing 9	1,53	up
SF3A1	splicing factor 3a, subunit 1, 120kDa	2,00	up
SF3B1	splicing factor 3b, subunit 1, 155kDa	2,36	up
SFI1	Sfi1homolog, spindle assembly associated (yeast)	1,67	up
SFT2D3	SFT2 domain containing 3	1,90	down
SFTPA1	surfactant protein A1	1,56	down
SH2D3A	SH2 domain containing 3A	1,58	down
SH2D3C	SH2 domain containing 3C	1,70	down
SH3BP5	SH3-domain binding protein 5 (BTK-associated)	2,08	up
SH3RF2	SH3 domain containing ring finger 2	1,71	up
SHB	Src homology 2 domain containing adaptor protein B	1,84	up
SHH	sonic hedgehog	2,23	down
SHMT1	serine hydroxymethyltransferase 1(soluble)	1,61	down
SHPK	sedoheptulokinase	2,06	up
SIGIRR	single immunoglobulin and toll-interleukin 1receptor (TIR) domain	1,56	down
SIGLEC5	sialic acid binding Ig-like lectin 5	2,09	down
SIL1	SIL1nucleotide exchange factor	1,94	down
SIM1	single-minded family bHLH transcription factor 1	1,77	down
SIX2	SIX homeobox 2	1,85	down
SLC12A2	solute carrier family 12 (sodium/potassium/chloride transporter), member 2	1,53	up
SLC12A7	solute carrier family 12 (potassium/chloride transporter), member 7	1,51	up
SLC15A3	solute carrier family 15 (oligopeptide transporter), member 3	2,17	up
SLC16A1	solute carrier family 16 (monocarboxylate transporter), member 1	1,77	up
SLC16A8	solute carrier family 16 (monocarboxylate transporter), member 8	2,84	down
SLC17A6	solute carrier family 17 (vesicular glutamate transporter), member 6	1,51	down
SLC1A7	solute carrier family 1(glutamate transporter), member 7	1,91	down
SLC22A10	solute carrier family 22, member 10	2,00	down
SLC22A14	solute carrier family 22, member 14	1,61	down
SLC23A3	solute carrier family 23, member 3	1,53	down
SLC25A26	solute carrier family 25 (S-adenosylmethionine carrier), member 26	1,80	up
SLC25A32	solute carrier family 25 (mitochondrial folate carrier), member 32	1,81	up
SLC25A36	solute carrier family 25 (pyrimidine nucleotide carrier), member 36	1,67	up
SLC25A47	solute carrier family 25, member 47	1,82	down
SLC25A52	solute carrier family 25, member 52	1,91	down
SLC2A4	solute carrier family 2 (facilitated glucose transporter), member 4	1,67	down
SLC2A4RG	SLC2A4 regulator	1,92	down
SLC2A8	solute carrier family 2 (facilitated glucose transporter), member 8	1,56	up
SLC30A1	solute carrier family 30 (zinc transporter), member 1	1,67	up
SLC30A8	solute carrier family 30 (zinc transporter), member 8	1,96	up
SLC31A1	solute carrier family 31(copper transporter), member 1	1,61	up
SLC35E3	solute carrier family 35, member E3	1,67	up
SLC35E4	solute carrier family 35, member E4	2,23	up
SLC35F2	solute carrier family 35, member F2	1,58	up
SLC36A3	solute carrier family 36, member 3	1,52	up
SLC36A4	solute carrier family 36 (proton/amino acid symporter), member 4	1,58	up
SLC38A2	solute carrier family 38, member 2	1,92	up
SLC38A5	solute carrier family 38, member 5	1,82	down
SLC38A7	solute carrier family 38, member 7	1,87	down
SLC39A5	solute carrier family 39 (zinc transporter), member 5	1,67	down
SLC45A4	solute carrier family 45, member 4	1,67	down
SLC48A1	solute carrier family 48 (heme transporter), member 1	2,12	down
SLC48A1	solute carrier family 48 (heme transporter), member 1	1,99	up
SLC4A11	solute carrier family 4, sodium borate transporter, member 11	2,99	down
SLC4A5	solute carrier family 4 (sodium bicarbonate cotransporter), member 5	1,63	up
SLC5A1	solute carrier family 5 (sodium/glucose cotransporter), member 1	1,85	up
SLC5A10	solute carrier family 5 (sodium/sugar cotransporter), member 10	1,69	up
SLC6A14	solute carrier family 6 (amino acid transporter), member 14	1,55	up
SLC6A19	solute carrier family 6 (neutral amino acid transporter), member 19	2,88	down
SLC6A6	solute carrier family 6 (neurotransmitter transporter), member 6	1,98	up
SLC8A2	solute carrier family 8 (sodium/calcium exchanger), member 2	1,57	down
SLCO4C1	solute carrier organic anion transporter family, member 4C1	1,57	down
SLFNL1	schlafen-like 1	1,69	down
SLIRP	SRA stem-loop interacting RNA binding protein	1,83	up
SMAD7	SMAD family member 7	1,71	down
SMAP1	small ArfGAP 1	1,54	up
SMARCA4	SWI/SNF related, matrix associated, actin dependent regulator of chromatin, subfamily a, member 4	1,84	up
SMARCC1	SWI/SNF related, matrix associated, actin dependent regulator of chromatin, subfamily c, member 1	2,15	up
SMARCD1	SWI/SNF related, matrix associated, actin dependent regulator of chromatin, subfamily d, member 1	1,87	up
SMARCD2	SWI/SNF related, matrix associated, actin dependent regulator of chromatin, subfamily d, member 2	1,81	up
SMARCE1	SWI/SNF related, matrix associated, actin dependent regulator of chromatin, subfamily e, member 1	2,26	up
SMG1	SMG1 phosphatidylinositol 3-kinase-related kinase	2,37	up
SMOC1	SPARC related modular calcium binding 1	1,87	up
SMOC2	SPARC related modular calcium binding 2	1,88	up
SMPDL3B	sphingomyelin phosphodiesterase, acid-like 3B	2,00	up
SMURF1	SMAD specific E3 ubiquitin protein ligase 1	1,54	up
SNAI1	snail family zinc finger 1	2,12	down
SNAP25	synaptosomal-associated protein, 25kDa	1,62	up
SNAP29	synaptosomal-associated protein, 29kDa	1,98	up
SNCG	synuclein, gamma (breast cancer-specific protein 1)	1,68	down
SND1-IT1	SND1 intronic transcript 1 (non-protein coding)	2,23	down
SND1-IT1	SND1 intronic transcript 1 (non-protein coding)	2,02	down
SNURF	SNRPN upstream reading frame	1,57	down
SNX13	sorting nexin 13	1,51	up
SNX19	sorting nexin 19	1,59	up
SNX3	sorting nexin 3	1,52	up
SOCS7	suppressor of cytokine signaling 7	1,76	down
SOGA1	suppressor of glucose, autophagy associated 1	1,54	down
SORBS1	sorbin and SH3 domain containing 1	1,68	up
SORBS2	sorbin and SH3 domain containing 2	1,70	up
SOWAHD	sosondowah ankyrin repeat domain family member D	2,27	down
SOX12	SRY (sex determining region Y)-box 12	2,11	down
SOX17	SRY (sex determining region Y)-box 17	1,65	down
SOX21	SRY (sex determining region Y)-box 21	1,87	down
SOX3	SRY (sex determining region Y)-box 3	2,53	up
SP5	Sp5 transcription factor	2,02	down
SPAG9	sperm associated antigen 9	1,51	up
SPANXB2	SPANX family, member B2	1,58	up
SPATA2	spermatogenesis associated 2	1,51	up
SPATA25	spermatogenesis associated 25	2,06	down
SPATA32	spermatogenesis associated 32	1,68	up
SPATC1L	spermatogenesis and centriole associated 1-like	1,95	down
SPHAR	S-phase response (cyclin related)	1,79	up
SPN	sialophorin	1,64	up
SPRN	shadow of prion protein homolog (zebrafish)	1,64	down
SPRR2B	small proline-rich protein 2B	2,66	down
SPTB	spectrin, beta, erythrocytic	1,74	down
SPTLC3	serine palmitoyltransferase, long chain base subunit 3	1,60	up
SQLE	squalene epoxidase	1,58	up
SRF	serum response factor (c-fos serum response element-binding transcription factor)	1,85	down
SRI	sorcin	1,50	up
SRP14P1	signal recognition particle 14kDa (homologous Alu RNA binding protein) pseudogene 1	1,64	up
SRP72	signal recognition particle 72kDa	1,58	up
SRP9	signal recognition particle 9kDa	1,57	up
SRPK1	SRSF protein kinase 1	1,86	up
SRRM1	serine/arginine repetitive matrix 1	1,58	up
SRRM2	serine/arginine repetitive matrix 2	1,80	down
SRRT	serrate RNA effector molecule homolog (Arabidopsis)	1,87	up
SRSF11	serine/arginine-rich splicing factor 11	1,88	up
SRSF2	serine/arginine-rich splicing factor 2	1,54	down
SRSF8	serine/arginine-rich splicing factor 8	1,58	up
SSB	Sjogren syndrome antigen B (autoantigen La)	1,95	up
SSBP2	single-stranded DNA binding protein 2	2,28	up
SSNA1	Sjogren syndrome nuclear autoantigen 1	1,99	up
ST13	suppression of tumorigenicity 13 (colon carcinoma) (Hsp70 interacting protein)	1,57	up
ST6GALNAC2	ST6 (alpha-N-acetyl-neuraminyl-2,3-beta-galactosyl-1,3)-N-acetylgalactosaminide alpha-2,6-sialyltransferase 2	2,03	up
ST6GALNAC3	ST6 (alpha-N-acetyl-neuraminyl-2,3-beta-galactosyl-1,3)-N-acetylgalactosaminide alpha-2,6-sialyltransferase 3	1,88	down
STAG2	stromal antigen 2	1,53	up
STEAP3	STEAP family member 3, metalloreductase	1,62	up
STK25	serine/threonine kinase 25	1,60	down
STK39	serine threonine kinase 39	1,55	up
STMN3	stathmin-like 3	1,71	down

STMN3	stathmin-like 3	1,56	down
STOM	stomatin	1,87	up
STOML2	stomatin (EPB72)-like 2	1,76	up
STOX2	storkhead box 2	2,73	up
STRBP	spermatid perinuclear RNA binding protein	1,80	up
STRC	stereocilin	1,52	up
STX12	syntaxin 12	1,64	up
STX1A	syntaxin 1A (brain)	1,64	up
STX6	syntaxin 6	1,72	up
SUB1	SUB1 homolog (S. cerevisiae)	1,95	up
SULT1B1	sulfotransferase family, cytosolic, 1B, member 1	1,66	down
SULT4A1	sulfotransferase family 4A, member 1	1,64	up
SUPT4H1	suppressor of Ty 4 homolog 1 (S. cerevisiae)	2,66	up
SUZ12	SUZ12 polycomb repressive complex 2 subunit	1,98	up
SWSAP1	SWIM-type zinc finger 7 associated protein 1	1,77	down
SYAP1	synapse associated protein 1	1,52	up
SYK	spleen tyrosine kinase	1,79	up
SYNC	syncoilin, intermediate filament protein	1,64	up
SYNCRIP	synaptotagmin binding, cytoplasmic RNA interacting protein	1,95	up
SYNCRIP	synaptotagmin binding, cytoplasmic RNA interacting protein	1,72	up
SYNGR3	synaptogyrin 3	1,95	down
SYNPO2L	synaptopodin 2-like	1,57	down
SYT12	synaptotagmin XII	1,50	down
SYT6	synaptotagmin VI	1,85	down
SYT8	synaptotagmin VIII	1,62	up
SZT2	seizure threshold 2 homolog (mouse)	1,54	up
TACR1	tachykinin receptor 1	1,85	down
TAF1C	TATA box binding protein (TBP)-associated factor, RNA polymerase I, C, 110kDa	1,54	up
TAF1L	TAF1 RNA polymerase II, TATA box binding protein (TBP)-associated factor, 210kDa-like	2,50	down
TAF2	TAF2 RNA polymerase II, TATA box binding protein (TBP)-associated factor, 150kDa	1,52	up
TAF9	TAF9 RNA polymerase II, TATA box binding protein (TBP)-associated factor, 32kDa	1,65	up
TAF9	TAF9 RNA polymerase II, TATA box binding protein (TBP)-associated factor, 32kDa	1,52	up
TANGO2	transport and golgi organization 2 homolog (Drosophila)	1,66	down
TAOK2	TAO kinase 2	2,70	down
TAS2R4	taste receptor, type 2, member 4	3,33	down
TATDN1	TatD DNase domain containing 1	1,57	down
TBC1D20	TBC1 domain family, member 20	2,13	up
TBC1D2B	TBC1 domain family, member 2B	1,88	down
TBCD	tubulin folding cofactor D	1,65	down
TBKBP1	TBK1 binding protein 1	2,44	down
TBL1XR1	transducin (beta)-like 1X-linked receptor 1	2,19	up
TBL3	transducin (beta)-like 3	1,67	down
TBPL1	TBP-like 1	1,58	up
TBX21	T-box 21	1,55	down
TBX3	T-box 3	1,69	up
TCEA3	transcription elongation factor A (SII), 3	1,77	up
TCEAL1	transcription elongation factor A (SII)-like 1	1,74	up
TCEAL5	transcription elongation factor A (SII)-like 5	1,62	up
TCEAL6	transcription elongation factor A (SII)-like 6	1,94	up
TCEAL8	transcription elongation factor A (SII)-like 8	2,11	up
TCEB3B	transcription elongation factor B polypeptide 3B (elongin A2)	1,60	down
TCF12	transcription factor 12	1,67	up
TCL1A	T-cell leukemia/lymphoma 1A	2,71	down
TCL6	T-cell leukemia/lymphoma 6 (non-protein coding)	1,56	down
TCP11L2	t-complex 11, testis-specific-like 2	1,51	up
TCTE3	t-complex-associated-testis-expressed 3	1,54	up
TCTN2	tectonic family member 2	2,03	down
TDP1	tyrosyl-DNA phosphodiesterase 1	1,85	up
TEAD4	TEA domain family member 4	1,68	up
TENC1	tensin like C1 domain containing phosphatase (tensin 2)	1,59	down
TENM1	teneurin transmembrane protein 1	1,63	up
TEPP	testis, prostate and placenta expressed	1,50	down
TERT	telomerase reverse transcriptase	1,58	down
TET2	tet methylcytosine dioxygenase 2	1,61	up
TEX261	testis expressed 261	1,80	down
TEX261	testis expressed 261	1,80	up
TEX37	testis expressed 37	1,64	up
TFAP2B	transcription factor AP-2 beta (activating enhancer binding protein 2 beta)	2,76	up
TFCP2L1	transcription factor CP2-like 1	1,55	up
TFF2	trefoil factor 2	1,77	up
TFG	TRK-fused gene	2,18	up
TFIP11	tuftelin interacting protein 11	2,20	down
TFPI	tissue factor pathway inhibitor (lipoprotein-associated coagulation inhibitor)	2,75	down
TFPT	TCF3 (E2A) fusion partner (in childhood Leukemia)	1,60	down
TGFBRAP1	transforming growth factor, beta receptor associated protein 1	1,63	up
TGS1	trimethylguanosine synthase 1	1,55	down
THAP3	THAP domain containing, apoptosis associated protein 3	1,57	down
THBS2	thrombospondin 2	1,80	up
THEG	theg spermatid protein	1,89	down
THRAP3	thyroid hormone receptor associated protein 3	1,51	up
THRSP	thyroid hormone responsive	1,68	up
TIGD7	tigger transposable element derived 7	1,75	down
TIMM10	translocase of inner mitochondrial membrane 10 homolog (yeast)	1,53	up
TIMM8A	translocase of inner mitochondrial membrane 8 homolog A (yeast)	1,67	up
TIMP3	TIMP metallopeptidase inhibitor 3	2,67	up
TJP1	tight junction protein 1	1,89	up
TJP2	tight junction protein 2	1,73	down
TLL2	tolloid-like 2	1,87	up
TM4SF5	transmembrane 4 L six family member 5	1,92	down
TM9SF3	transmembrane 9 superfamily member 3	1,71	up
TMBIM1	transmembrane BAX inhibitor motif containing 1	1,87	up
TMBIM4	transmembrane BAX inhibitor motif containing 4	1,57	up
TMCO1	transmembrane and coiled-coil domains 1	1,75	up
TMCO1	transmembrane and coiled-coil domains 1	1,52	up
TMED10P1	transmembrane emp24-like trafficking protein 10 (yeast) pseudogene 1	1,58	up
TMED2	transmembrane emp24 domain trafficking protein 2	1,53	up
TMED4	transmembrane emp24 protein transport domain containing 4	1,69	up
TMEM109	transmembrane protein 109	1,61	down
TMEM121	transmembrane protein 121	1,51	down
TMEM125	transmembrane protein 125	2,28	down
TMEM150A	transmembrane protein 150A	4,31	down
TMEM151A	transmembrane protein 151A	2,48	down
TMEM158	transmembrane protein 158 (gene/pseudogene)	1,80	up
TMEM169	transmembrane protein 169	1,54	down
TMEM200C	transmembrane protein 200C	3,08	down
TMEM209	transmembrane protein 209	1,55	up
TMEM214	transmembrane protein 214	1,87	up
TMEM223	transmembrane protein 223	1,64	up
TMEM237	transmembrane protein 237	1,78	up
TMEM259	transmembrane protein 259	1,92	down
TMEM33	transmembrane protein 33	1,74	up
TMEM35	transmembrane protein 35	1,72	down
TMEM52	transmembrane protein 52	1,75	down
TMEM55A	transmembrane protein 55A	1,84	up
TMEM70	transmembrane protein 70	1,72	up
TMEM86B	transmembrane protein 86B	2,52	down
TMEM92	transmembrane protein 92	1,77	down
TMEM97	transmembrane protein 97	1,61	up
TMPRSS6	transmembrane protease, serine 6	1,87	down
TMSB4X	thymosin beta 4, X-linked	2,31	up
TMTC3	transmembrane and tetratricopeptide repeat containing 3	1,88	up
TMUB1	transmembrane and ubiquitin-like domain containing 1	1,60	down
TMX2	thioredoxin-related transmembrane protein 2	1,96	down
TMX4	thioredoxin-related transmembrane protein 4	1,53	up
TNFAIP8	tumor necrosis factor, alpha-induced protein 8	1,90	up
TNFAIP8L3	tumor necrosis factor, alpha-induced protein 8-like 3	1,53	down
TNFRSF18	tumor necrosis factor receptor superfamily, member 18	1,93	down
TNFRSF21	tumor necrosis factor receptor superfamily, member 21	2,15	up
TNFRSF6B	tumor necrosis factor receptor superfamily, member 6b, decoy	1,69	down
TNFSF14	tumor necrosis factor (ligand) superfamily, member 14	1,57	down
TNIP2	TNFAIP3 interacting protein 2	1,69	down
TNK2	tyrosine kinase, non-receptor, 2	1,89	down
TNKS	tankyrase, TRF1-interacting ankyrin-related ADP-ribose polymerase	1,87	up
TNNI2	troponin I type 2 (skeletal, fast)	2,01	down
TNNT1	troponin T type 1 (skeletal, slow)	1,59	down
TNPO1	transportin 1	2,09	up
TNPO2	transportin 2	1,79	up
TNRC18	trinucleotide repeat containing 18	4,28	down
TNRC18	trinucleotide repeat containing 18	2,38	down
TNS1	tensin 1	1,58	down
TNXB	tenascin XB	2,50	down
TOB1	transducer of ERBB2, 1	2,34	up
TONSL	tonsoku-like, DNA repair protein	1,68	down
TOR3A	torsin family 3, member A	1,50	up
TP53I11	tumor protein p53 inducible protein 11	1,67	down
TP53I13	tumor protein p53 inducible protein 13	1,50	down
TP53INP2	tumor protein p53 inducible nuclear protein 2	2,04	up
TP53TG1	TP53 target 1 (non-protein coding)	1,51	up
TPCN1	two pore segment channel 1	1,81	up
TPCN2	two pore segment channel 2	1,74	down
TPM1	tropomyosin 1 (alpha)	1,55	up
TPM1	tropomyosin 1 (alpha)	1,51	up
TPM3	tropomyosin 3	2,41	up
TPM4	tropomyosin 4	1,75	up
TPR	translocated promoter region, nuclear basket protein	1,60	up
TPRX1	tetra-peptide repeat homeobox 1	1,64	down
TRA	T cell receptor alpha locus	1,58	down
TRAF2	TNF receptor-associated factor 2	1,87	down
TRAF3IP1	TNF receptor-associated factor 3 interacting protein 1	1,53	up
TRAIP	TRAF interacting protein	1,85	down
TRAK1	trafficking protein, kinesin binding 1	2,13	up
TRAPPC8	trafficking protein particle complex 8	1,66	up
TREML1	triggering receptor expressed on myeloid cells-like 1	1,89	down
TRH	thyrotropin-releasing hormone	2,29	down
TRIL	TLR4 interactor with leucine-rich repeats	1,50	down
TRIM11	tripartite motif containing 11	1,92	up
TRIM13	tripartite motif containing 13	1,65	up
TRIM33	tripartite motif containing 33	1,74	up
TRIM35	tripartite motif containing 35	2,06	up
TRIM45	tripartite motif containing 45	1,79	up
TRIM56	tripartite motif containing 56	1,73	down
TRIM62	tripartite motif containing 62	1,73	up
TRIM7	tripartite motif containing 7	2,63	down
TRIM72	tripartite motif containing 72	2,64	down
TRIM72	tripartite motif containing 72	1,52	down
TRIM74	tripartite motif containing 74	1,73	down
TRMT1	tRNA methyltransferase 1 homolog (S. cerevisiae)	1,77	down
TRMT2B	tRNA methyltransferase 2 homolog B (S. cerevisiae)	1,68	up
TRMT5	tRNA methyltransferase 5	1,82	up
TRMT6	tRNA methyltransferase 6 homolog (S. cerevisiae)	1,69	up
TRMU	tRNA 5-methylaminomethyl-2-thiouridylate methyltransferase	1,70	down
TRPC2	transient receptor potential cation channel, subfamily C, member 2, pseudogene	1,80	down
TRPM2	transient receptor potential cation channel, subfamily M, member 2	1,54	down
TRPM5	transient receptor potential cation channel, subfamily M, member 5	1,51	down
TRPV1	transient receptor potential cation channel, subfamily V, member 1	1,78	up
TRPV2	transient receptor potential cation channel, subfamily V, member 2	1,58	down
TSC1	tuberous sclerosis 1	1,68	down
TSEN2	TSEN2 tRNA splicing endonuclease subunit	1,51	up
TSG101	tumor susceptibility 101	2,17	up
TSHZ1	teashirt zinc finger homeobox 1	1,50	up
TSPAN32	tetraspanin 32	1,60	down
TSPAN33	tetraspanin 33	1,92	down
TSPYL2	TSPY-like 2	1,80	down
TSPYL4	TSPY-like 4	1,73	up
TSSC1	tumor suppressing subtransferable candidate 1	1,57	down
TSSK1B	testis-specific serine kinase 1B	1,69	up
TTC28	tetratricopeptide repeat domain 28	1,66	down
TTC3	tetratricopeptide repeat domain 3	1,95	up
TTC33	tetratricopeptide repeat domain 33	1,51	down
TTC39A	tetratricopeptide repeat domain 39A	2,63	down

TTI1	TELO2 interacting protein 1	1,51	down
TTLL5	tubulin tyrosine ligase-like family, member 5	2,31	down
TTTY14	testis-specific transcript, Y-linked 14 (non-protein coding)	1,82	down
TUB	tubby bipartite transcription factor	1,88	down
TUBA3D	tubulin, alpha 3d	2,63	down
TUBB	tubulin, beta class I	2,60	up
TUBB3	tubulin, beta 3 class III	1,56	up
TUBB4B	tubulin, beta 4B class IVb	1,69	up
TUBGCP2	tubulin, gamma complex associated protein 2	1,75	up
TUBGCP5	tubulin, gamma complex associated protein 5	1,51	down
TUSC1	tumor suppressor candidate 1	1,53	up
TUT1	terminal uridylyl transferase 1, U6 snRNA-specific	2,01	down
TXNDC2	thioredoxin domain containing 2 (spermatozoa)	2,33	down
TXNL4A	thioredoxin-like 4A	1,68	up
U2SURP	U2 snRNP-associated SURP domain containing	2,65	up
UBA2	ubiquitin-like modifier activating enzyme 2	1,55	up
UBD	ubiquitin D	2,04	down
UBE2D4	ubiquitin-conjugating enzyme E2D 4 (putative)	2,32	up
UBE2L3	ubiquitin-conjugating enzyme E2L 3	1,70	up
UBE2N	ubiquitin-conjugating enzyme E2N	1,99	up
UBE4B	ubiquitination factor E4B	1,75	up
UBQLN1	ubiquilin 1	2,37	up
UBXN6	UBX domain protein 6	1,80	up
UGGT2	UDP-glucose glycoprotein glucosyltransferase 2	1,87	up
UHRF1BP1	UHRF1 binding protein 1	1,59	up
ULBP3	UL16 binding protein 3	1,60	down
ULK2	unc-51 like autophagy activating kinase 2	2,13	down
UMOD	uromodulin	1,83	up
UNC13B	unc-13 homolog B (C. elegans)	1,57	down
UNC5A	unc-5 homolog A (C. elegans)	1,58	down
UNC5B	unc-5 homolog B (C. elegans)	2,31	up
UNC93B1	unc-93 homolog B1 (C. elegans)	3,40	down
UNG	uracil-DNA glycosylase	1,82	down
UNKL	unkempt family zinc finger-like	1,99	up
UPB1	ureidopropionase, beta	2,43	down
UPF1	UPF1 regulator of nonsense transcripts homolog (yeast)	1,71	up
UPK1A	uroplakin 1A	2,01	down
URM1	ubiquitin related modifier 1	2,22	down
USHBP1	Usher syndrome 1C binding protein 1	1,99	down
USP14	ubiquitin specific peptidase 14 (tRNA-guanine transglycosylase)	1,70	up
USP31	ubiquitin specific peptidase 31	1,85	up
USP35	ubiquitin specific peptidase 35	1,90	up
USP54	ubiquitin specific peptidase 54	2,30	up
UTF1	undifferentiated embryonic cell transcription factor 1	2,51	down
UTS2R	urotensin 2 receptor	1,76	down
VASH1	vasohibin 1	1,76	down
VEGFA	vascular endothelial growth factor A	1,58	up
VGLL4	vestigial like 4 (Drosophila)	1,84	up
VHL	von Hippel-Lindau tumor suppressor, E3 ubiquitin protein ligase	2,84	up
VIL1	villin 1	1,61	down
VIPR2	vasoactive intestinal peptide receptor 2	1,64	up
VPS11	vacuolar protein sorting 11 homolog (S. cerevisiae)	1,70	up
VPS16	vacuolar protein sorting 16 homolog (S. cerevisiae)	2,01	up
VPS9D1	VPS9 domain containing 1	1,53	down
VRTN	vertebrae development associated	1,52	down
WDR1	WD repeat domain 1	1,89	up
WDR1	WD repeat domain 1	1,79	up
WDR24	WD repeat domain 24	2,34	down
WDR26	WD repeat domain 26	1,50	up
WDR48	WD repeat domain 48	1,89	up
WDR63	WD repeat domain 63	1,52	down
WDR70	WD repeat domain 70	1,55	up
WDR76	WD repeat domain 76	1,53	down
WDR82	WD repeat domain 82	1,52	up
WDR89	WD repeat domain 89	1,57	up
WDR90	WD repeat domain 90	2,05	down
WFDC10B	WAP four-disulfide core domain 10B	1,57	up
WFDC2	WAP four-disulfide core domain 2	1,62	down
WHSC1	Wolf-Hirschhorn syndrome candidate 1	1,52	down
WNT7A	wingless-type MMTV integration site family, member 7A	1,63	down
WRB	tryptophan rich basic protein	1,55	down
WWP1	WW domain containing E3 ubiquitin protein ligase 1	1,63	up
XIST	X inactive specific transcript (non-protein coding)	2,22	up
XKR8	XK, Kell blood group complex subunit-related family, member 8	1,88	up
XRCC5	X-ray repair complementing defective repair in Chinese hamster cells 5 (double-strand-break rejoining)	1,62	up
YAP1	Yes-associated protein 1	1,81	up
YARS	tyrosyl-tRNA synthetase	2,14	down
YBEY	ybeY metallopeptidase (putative)	1,60	up
YBX1	Y box binding protein 1	2,21	up
YBX3	Y box binding protein 3	1,95	up
YIPF5	Yip1 domain family, member 5	1,99	down
YPEL1	yippee-like 1 (Drosophila)	1,96	up
YWHAE	tyrosine 3-monooxygenase/tryptophan 5-monooxygenase activation protein, epsilon	1,78	up
YWHAZ	tyrosine 3-monooxygenase/tryptophan 5-monooxygenase activation protein, zeta	2,11	up
YWHAZ	tyrosine 3-monooxygenase/tryptophan 5-monooxygenase activation protein, zeta	1,93	up
YWHAZ	tyrosine 3-monooxygenase/tryptophan 5-monooxygenase activation protein, zeta	1,90	up
YWHAZ	tyrosine 3-monooxygenase/tryptophan 5-monooxygenase activation protein, zeta	1,70	up
ZAN	zonadhesin (gene/pseudogene)	3,79	down
ZBTB10	zinc finger and BTB domain containing 10	1,68	down
ZC3H12A	zinc finger CCCH-type containing 12A	1,83	up
ZCCHC17	zinc finger, CCHC domain containing 17	1,94	up
ZDHHC21	zinc finger, DHHC-type containing 21	1,52	up
ZDHHC23	zinc finger, DHHC-type containing 23	1,72	down
ZDHHC4	zinc finger, DHHC-type containing 4	1,87	up
ZFAND5	zinc finger, AN1-type domain 5	2,14	up
ZFHX2	zinc finger homeobox 2	1,55	down
ZFP62	ZFP62 zinc finger protein	2,02	up
ZFYVE26	zinc finger, FYVE domain containing 26	1,82	up
ZKSCAN1	zinc finger with KRAB and SCAN domains 1	2,36	up
ZKSCAN1	zinc finger with KRAB and SCAN domains 1	1,59	up
ZMIZ2	zinc finger, MIZ-type containing 2	1,67	up
ZMYM3	zinc finger, MYM-type 3	1,54	down
ZNF148	zinc finger protein 148	2,02	up
ZNF154	zinc finger protein 154	2,06	up
ZNF226	zinc finger protein 226	1,73	up
ZNF253	zinc finger protein 253	1,61	up
ZNF254	zinc finger protein 254	3,34	up
ZNF292	zinc finger protein 292	1,51	up
ZNF300	zinc finger protein 300	1,55	down
ZNF333	zinc finger protein 333	1,63	up
ZNF346	zinc finger protein 346	1,57	up
ZNF365	zinc finger protein 365	1,53	up
ZNF394	zinc finger protein 394	1,56	up
ZNF423	zinc finger protein 423	1,51	up
ZNF430	zinc finger protein 430	2,58	up
ZNF440	zinc finger protein 440	1,77	up
ZNF446	zinc finger protein 446	2,13	down
ZNF449	zinc finger protein 449	1,74	down
ZNF467	zinc finger protein 467	1,92	down
ZNF467	zinc finger protein 467	1,91	down
ZNF467	zinc finger protein 467	1,73	up
ZNF488	zinc finger protein 488	1,73	down
ZNF493	zinc finger protein 493	1,75	up
ZNF532	zinc finger protein 532	1,69	up
ZNF559	zinc finger protein 559	1,53	down
ZNF572	zinc finger protein 572	1,51	down
ZNF575	zinc finger protein 575	1,58	down
ZNF581	zinc finger protein 581	2,00	up
ZNF587	zinc finger protein 587	1,68	up
ZNF587	zinc finger protein 587	1,61	up
ZNF600	zinc finger protein 600	1,92	up
ZNF626	zinc finger protein 626	1,94	up
ZNF641	zinc finger protein 641	1,75	down
ZNF644	zinc finger protein 644	1,69	up
ZNF66	zinc finger protein 66	2,81	up
ZNF675	zinc finger protein 675	1,80	up
ZNF681	zinc finger protein 681	2,18	up
ZNF682	zinc finger protein 682	1,86	down
ZNF683	zinc finger protein 683	1,57	up
ZNF697	zinc finger protein 697	2,37	down
ZNF708	zinc finger protein 708	2,35	up
ZNF708	zinc finger protein 708	1,51	up
ZNF713	zinc finger protein 713	1,97	up
ZNF714	zinc finger protein 714	1,71	up
ZNF738	zinc finger protein 738	1,62	up
ZNF746	zinc finger protein 746	2,02	up
ZNF761	zinc finger protein 761	1,64	up
ZNF767	zinc finger family member 767	1,51	up
ZNF789	zinc finger protein 789	1,55	down
ZNF792	zinc finger protein 792	1,60	up
ZNF92	zinc finger protein 92	2,20	up
ZSCAN10	zinc finger and SCAN domain containing 10	2,13	down
ZXDC	ZXD family zinc finger C	1,65	up
ZYG11B	zyg-11 family member B, cell cycle regulator	1,57	down

1. Information from HGNC (HUGO Gene Nomenclature Committee; www.genenames.org).
2. Type of regulation.

Table S3. Characterization of the secondary volunteer panel for real-time qPCR validation.

Volunteer Number	Age (Years Old)	Skin Phototype [1]	Skin Type [2]	Ethnic Group [3]
1	20	II	Normal	Polish
2	21	II	Normal	Polish
3	22	III	Not declared	Not declared
4	23	III	Not declared	Not declared
5	24	II	Not declared	Not declared
6	25	III	Not declared	Not declared
7	25	II	Not declared	Not declared
8	25	III	Combination	African/German
9	27	II	Not declared	Not declared
10	29	II	Not declared	Not declared
11	29	III	Normal	Italian/Libanese/Spanish
12	30	II	Normal	Italian
13	50	II	Not declared	Not declared
14	51	II	Not declared	Not declared
15	52	II	Normal	Polish
16	52	III	Oily	African
17	53	III	Oily	Italian
18	54	III	Normal	African
19	54	III	Normal	Spanish
20	55	III	Not declared	Not declared
21	56	II	Dry	Polish
22	58	II	Normal	Italian

1 Classification according to Fitzpatrick phototyping scale

2. Personal declaration of predominant skin type in the body according to sebum production

3. Personal declaration of ethnic groups

Table S4. KEGG pathways modulated in sun-exposed epidermal aging considering p-value cut-off 0.01.

KEGG pathway name	KEGG code	Number of DEGs [1]
Systemic lupus erythematosus	hsa05322	72
Neuroactive ligand-receptor interaction	hsa04080	37
MAPK signaling pathway	hsa04010	33
Focal adhesion	hsa04510	27
Small cell lung cancer	hsa05222	16
Ribosome	hsa03010	15
Endocytosis	hsa04144	23
Base excision repair	hsa03410	9
ECM-receptor interaction	hsa04512	14
Axon guidance	hsa04360	18
Chemokine signaling pathway	hsa04062	23
Hypertrophic cardiomyopathy (HCM)	hsa05410	14
Insulin signaling pathway	hsa04910	18
mTOR signaling pathway	hsa04150	10
Wnt signaling pathway	hsa04310	19
Phosphatidylinositol signaling system	hsa04070	12
Notch signaling pathway	hsa04330	9
RNA degradation	hsa03018	10
Antigen processing and presentation	hsa04612	13
Dilated cardiomyopathy	hsa05414	13
Pathogenic Escherichia coli infection	hsa05130	10
Renal cell carcinoma	hsa05211	11
Protein export	hsa03060	6
Regulation of actin cytoskeleton	hsa04810	22
Arrhythmogenic right ventricular cardiomyopathy (ARVC)	hsa05412	11
Inositol phosphate metabolism	hsa00562	9
Basal transcription factors	hsa03022	7
Cytokine-cytokine receptor interaction	hsa04060	25
Calcium signaling pathway	hsa04020	19

1. DEGs, differentially expressed genes.

Table S5. Epidermal age-modulated genes in plucked hair shaft shared with previous study using tape strip.

HGNC Approved Symbol [1]	HGNC Approved Name [1]
ABCC6	ATP-binding cassette, sub-family C (CFTR/MRP), member 6
ABCE1	ATP-binding cassette, sub-family E (OABP), member 1
ABHD1	abhydrolase domain containing 1
ACBD4	acyl-CoA binding domain containing 4
ACTR1B	ARP1 actin-related protein 1 homolog B, centractin beta (yeast)
ADD3	adducin 3 (gamma)
ADRBK2	adrenergic, beta, receptor kinase 2
AES	amino-terminal enhancer of split
AFG3L1P	AFG3-like AAA ATPase 1, pseudogene
AGPAT4	1-acylglycerol-3-phosphate O-acyltransferase 4
ALOX5AP	arachidonate 5-lipoxygenase-activating protein
AMDHD1	amidohydrolase domain containing 1
ANKFY1	ankyrin repeat and FYVE domain containing 1
ANXA8	annexin A8
AP2A2	adaptor-related protein complex 2, alpha 2 subunit
APH1B	APH1B gamma secretase subunit
APLP2	amyloid beta (A4) precursor-like protein 2
APPBP2	amyloid beta precursor protein (cytoplasmic tail) binding protein 2
AQP2	aquaporin 2 (collecting duct)
ARF1	ADP-ribosylation factor 1
ARHGEF25	Rho guanine nucleotide exchange factor (GEF) 25
ARHGEF3	Rho guanine nucleotide exchange factor (GEF) 3
ARID5B	ATrich interactive domain 5B (MRF1-like)
ARL3	ADP-ribosylation factor-like 3
ARL6IP1	ADP-ribosylation factor-like 6 interacting protein 1
ARRDC1	arrestin domain containing 1
ATCAY	ataxia, cerebellar, Cayman type
ATG16L1	autophagy related 16-like 1 (S. cerevisiae)
ATOH7	atonal homolog 7 (Drosophila)
ATP1A4	ATPase, Na+/K+ transporting, alpha 4 polypeptide
ATP6V1A	ATPase, H+ transporting, lysosomal 70kDa, V1 subunit A
BCAM	basal cell adhesion molecule (Lutheran blood group)
BCAT2	branched chain amino-acid transaminase 2, mitochondrial
BCAN	brevican
BCKDK	branched chain ketoacid dehydrogenase kinase
BCL7A	B-cell CLL/lymphoma 7A
BHLHE23	basic helix-loop-helix family, member e23
BHLHE23	basic helix-loop-helix family, member e23
BNIP3L	BCL2/adenovirus E1B 19kDa interacting protein 3-like
BPTF	bromodomain PHD finger transcription factor
BRAT1	BRCA1-associated ATM activator 1
BTF3	basic transcription factor 3
BTN3A3	butyrophilin, subfamily 3, member A3
BTG1	B-cell translocation gene 1, anti-proliferative
C2	complement component 2
C5AR1	complement component 5a receptor 1
CABIN1	calcineurin binding protein 1
CACNA1B	calcium channel, voltage-dependent, N type, alpha 1B subunit
CACNG7	calcium channel, voltage-dependent, gamma subunit 7
CASD1	CAS1 domain containing 1
CASP5	caspase 5, apoptosis-related cysteine peptidase
CAV1	caveolin 1, caveolae protein, 22kDa
CBS	cystathionine-beta-synthase
CCDC134	coiled-coil domain containing 134
CCDC144NL	coiled-coil domain containing 144 family, N-terminal like
CCDC90B	coiled-coil domain containing 90B
CCND2	cyclin D2
CCND3	cyclin D3
CD109	CD109 molecule
CD1E	CD1e molecule
CD244	CD244 molecule, natural killer cell receptor 2B4
CDC42EP1	CDC42 effector protein (Rho GTPase binding) 1
CEACAM1	carcinoembryonic antigen-related cell adhesion molecule 1 (biliary glycoprotein)
CEACAM4	carcinoembryonic antigen-related cell adhesion molecule 4
CEBPA	CCAAT/enhancer binding protein (C/EBP), alpha
CHAC2	ChaC, cation transport regulator homolog 2 (E. coli)
CHRDL1	chordin-like 1
CIDECP	cell death-inducing DFFA-like effector c pseudogene
CIRBP	cold inducible RNA binding protein
CLCF1	cardiotrophin-like cytokine factor 1
CLINT1	clathrin interactor 1
CLPTM1L	CLPTM1-like
CMIP	c-Maf inducing protein
CNOT4	CCR4-NOT transcription complex, subunit 4
CNOT6	CCR4-NOT transcription complex, subunit 6
COL18A1	collagen, type XVIII, alpha 1
CORT	cortistatin
CRABP1	cellular retinoic acid binding protein 1
CRHR1	corticotropin releasing hormone receptor 1
CRTC1	CREB regulated transcription coactivator 1
CRTC2	CREB regulated transcription coactivator 2
CSAD	cysteine sulfinic acid decarboxylase
CTNND2	catenin (cadherin-associated protein), delta 2
CTSB	cathepsin B
CYB5R3	cytochrome b5 reductase 3
CYHR1	cysteine/histidine-rich 1
CYP4F2	cytochrome P450, family 4, subfamily F, polypeptide 2
DAB2	Dab, mitogen-responsive phosphoprotein, homolog 2 (Drosophila)
DBN1	drebrin 1
DBP	D site of albumin promoter (albumin D-box) binding protein
GC	group-specific component (vitamin D binding protein)
HSD17B4	hydroxysteroid (17-beta) dehydrogenase 4
DENND1C	DENN/MADD domain containing 1C
DESI2	desumoylating isopeptidase 2
DFFA	DNA fragmentation factor, 45kDa, alpha polypeptide
DHX34	DEAH (Asp-Glu-Ala-His) box polypeptide 34
DMBX1	diencephalon/mesencephalon homeobox 1
DNAH11	dynein, axonemal, heavy chain 11
DNAH2	dynein, axonemal, heavy chain 2
DNAJB11	DnaJ (Hsp40) homolog, subfamily B, member 11
DNM1P35	DNM1 pseudogene 35
DOCK3	dedicator of cytokinesis 3
DRD4	dopamine receptor D4
DSC2	desmocollin 2
DSC3	desmocollin 3
DUX4	double homeobox 4
DVL3	dishevelled segment polarity protein 3
EFHD2	EF-hand domain family, member D2
ELOVL6	ELOVL fatty acid elongase 6
EMILIN1	elastin microfibril interfacer 1
ENC1	ectodermal-neural cortex 1 (with BTB domain)
ENPP4	ectonucleotide pyrophosphatase/phosphodiesterase 4 (putative)
EPAS1	endothelial PAS domain protein 1
EPB41L4B	erythrocyte membrane protein band 4.1 like 4B
EPHA4	EPH receptor A4
ERCC6L2	excision repair cross-complementing rodent repair deficiency, complementation group 6-like 2
ERG	v-ets avian erythroblastosis virus E26 oncogene homolog
ERN1	endoplasmic reticulum to nucleus signaling 1
EXOC3L2	exocyst complex component 3-like 2
FABP3	fatty acid binding protein 3, muscle and heart (mammary-derived growth inhibitor)
FADS2	fatty acid desaturase 2
FAIM3	Fas apoptotic inhibitory molecule 3
FAM101B	family with sequence similarity 101, member B
FAM129B	family with sequence similarity 129, member B
FAM129C	family with sequence similarity 129, member C
FAM21C	family with sequence similarity 21, member C
FAT2	FAT atypical cadherin 2
FBXL17	F-box and leucine-rich repeat protein 17
FBXL7	F-box and leucine-rich repeat protein 7
FBXO9	F-box protein 9
FCN1	ficolin (collagen/fibrinogen domain containing) 1
FER1L6-AS1	FER1L6 antisense RNA 1
FGD6	FYVE, RhoGEF and PH domain containing 6
FGF5	fibroblast growth factor 5
FKBP1A	FK506 binding protein 1A, 12kDa
FOXG1	forkhead box G1
FOXJ1	forkhead box J1
FOXN3	forkhead box N3
FOXP1	forkhead box P1
FOXQ1	forkhead box Q1
FRMD4A	FERM domain containing 4A
FUBP3	far upstream element (FUSE) binding protein 3
FXN	frataxin
FZR1	fizzy/cell division cycle 20 related 1 (Drosophila)
GALNT6	UDP-N-acetyl-alpha-D-galactosamine:polypeptide N-acetylgalactosaminyltransferase 6 (GalNAc-T6)
GDNF	glial cell derived neurotrophic factor
GFOD1	glucose-fructose oxidoreductase domain containing 1
GGT1	gamma-glutamyltransferase 1
GGT3P	gamma-glutamyltransferase 3 pseudogene
GGTLC2	gamma-glutamyltransferase light chain 2
GIT2	G protein-coupled receptor kinase interacting ArfGAP 2
GJC2	gap junction protein, gamma 2, 47kDa
GLDC	glycine dehydrogenase (decarboxylating)
GLIS3	GLIS family zinc finger 3
GLRX	glutaredoxin (thioltransferase)
GM2A	GM2 ganglioside activator
GNG13	guanine nucleotide binding protein (G protein), gamma 13
GPR115	G protein-coupled receptor 115
GPR62	G protein-coupled receptor 62
GRIN2D	glutamate receptor, ionotropic, N-methyl D-aspartate 2D
GTF3C4	general transcription factor IIIC, polypeptide 4, 90kDa
GYPC	glycophorin C (Gerbich blood group)
HAPLN4	hyaluronan and proteoglycan link protein 4
HCP5	HLA complex P5 (non-protein coding)
CYCSP5	cytochrome c, somatic pseudogene 5
HGD	homogentisate 1,2-dioxygenase
HGS	hepatocyte growth factor-regulated tyrosine kinase substrate
HIF3A	hypoxia inducible factor 3, alpha subunit
HIP1	huntingtin interacting protein 1
HIST1H2BE	histone cluster 1, H2be

HIST1H4E	histone cluster 1, H4e
HIVEP3	human immunodeficiency virus type I enhancer binding protein 3
HLA-DQB1	major histocompatibility complex, class II, DQ beta 1
HMGN1	high mobility group nucleosome binding domain 1
HRH3	histamine receptor H3
HS1BP3	HCLS1 binding protein 3
HSD17B14	hydroxysteroid (17-beta) dehydrogenase 14
IDI2	isopentenyl-diphosphate delta isomerase 2
IFI27	interferon, alpha-inducible protein 27
IFI30	interferon, gamma-inducible protein 30
IGHA1	immunoglobulin heavy constant alpha 1
IL10RA	interleukin 10 receptor, alpha
IL17A	interleukin 17A
IMPA1	inositol(myo)-1(or 4)-monophosphatase 1
IMPA2	inositol(myo)-1(or 4)-monophosphatase 2
IRX4	iroquois homeobox 4
KALRN	kalirin, RhoGEF kinase
KCNG1	potassium voltage-gated channel, subfamily G, member 1
KCNH2	potassium voltage-gated channel, subfamily H (eag-related), member 2
KIAA0513	KIAA0513
KIAA0753	KIAA0753
KIAA1614	KIAA1614
KIAA1875	KIAA1875
KIAA1919	KIAA1919
KIF1C	kinesin family member 1C
KLHL15	kelch-like family member 15
KLHL18	kelch-like family member 18
KLK10	kallikrein-related peptidase 10
KLK15	kallikrein-related peptidase 15
KLK2	kallikrein-related peptidase 2
KLK7	kallikrein-related peptidase 7
KLK6	kallikrein-related peptidase 6
KMT2C	lysine (K)-specific methyltransferase 2C
KSR1	kinase suppressor of ras 1
L1CAM	L1 cell adhesion molecule
LAMA1	laminin, alpha 1
LARP1B	La ribonucleoprotein domain family, member 1B
LATS2	large tumor suppressor kinase 2
LBH	limb bud and heart development
C6orf1	chromosome 6 open reading frame 1
LFNG	LFNG O-fucosylpeptide 3-beta-N-acetylglucosaminyltransferase
LINC00094	long intergenic non-protein coding RNA 94
LRP10	low density lipoprotein receptor-related protein 10
LRTOMT	leucine rich transmembrane and O-methyltransferase domain containing
LY6H	lymphocyte antigen 6 complex, locus H
LY6K	lymphocyte antigen 6 complex, locus K
MAGOHB	mago-nashi homolog B (Drosophila)
MALAT1	metastasis associated lung adenocarcinoma transcript 1 (non-protein coding)
MAN2A2	mannosidase, alpha, class 2A, member 2
MAPK15	mitogen-activated protein kinase 15
MAPK8IP1	mitogen-activated protein kinase 8 interacting protein 1
MARCKS	myristoylated alanine-rich protein kinase C substrate
MAU2	MAU2 sister chromatid cohesion factor
MCFD2	multiple coagulation factor deficiency 2
MED13L	mediator complex subunit 13-like
MEF2B	myocyte enhancer factor 2B
METTL15	methyltransferase like 15
MFN1	mitofusin 1
MFSD12	major facilitator superfamily domain containing 12
MIR22HG	MIR22 host gene (non-protein coding)
MLXIPL	MLX interacting protein-like
MOB1A	MOB kinase activator 1A
MPRIP	myosin phosphatase Rho interacting protein
MRPL35	mitochondrial ribosomal protein L35
MSANTD2	Myb/SANT-like DNA-binding domain containing 2
MSMB	microseminoprotein, beta-
MTPN	myotrophin
MTRF1L	mitochondrial translational release factor 1-like
MUC5B	mucin 5B, oligomeric mucus/gel-forming
MXRA5	matrix-remodelling associated 5
MYBL1	v-myb avian myeloblastosis viral oncogene homolog-like 1
MYD88	myeloid differentiation primary response 88
MYL3	myosin, light chain 3, alkali; ventricular, skeletal, slow
MYO1C	myosin IC
MYO1E	myosin IE
MYO6	myosin VI
NADSYN1	NAD synthetase 1
NAGS	N-acetylglutamate synthase
NCKIPSD	NCK interacting protein with SH3 domain
NCL	nucleolin
NDC1	NDC1 transmembrane nucleoporin
NDRG2	NDRG family member 2
NDST1	N-deacetylase/N-sulfotransferase (heparan glucosaminyl) 1
NDST2	N-deacetylase/N-sulfotransferase (heparan glucosaminyl) 2
NDUFA3	NADH dehydrogenase (ubiquinone) 1alpha subcomplex, 3, 9kDa
NDUFAF7	NADH dehydrogenase (ubiquinone) complex I, assembly factor 7
NDUFB7	NADH dehydrogenase (ubiquinone) 1beta subcomplex, 7, 18kDa
NEK9	NIMA-related kinase 9
NES	nestin
NFIB	nuclear factor I/B
NMT1	N-myristoyltransferase 1
NMUR2	neuromedin U receptor 2
NOL6	nucleolar protein 6 (RNA-associated)
NOTCH4	notch 4
NOV	nephroblastoma overexpressed
RPL10	ribosomal protein L10
PLXNA1	plexin A1
NPAS3	neuronal PAS domain protein 3
NPFFR2	neuropeptide FF receptor 2
NPHP3	nephronophthisis 3 (adolescent)
NPHS2	nephrosis 2, idiopathic, steroid-resistant (podocin)
NPTN	neuroplastin
NRAP	nebulin-related anchoring protein
NOL6	nucleolar protein 6 (RNA-associated)
NRSN2	neurensin 2
NUCKS1	nuclear casein kinase and cyclin-dependent kinase substrate 1
OGFOD2	2-oxoglutarate and iron-dependent oxygenase domain containing 2
OGG1	8-oxoguanine DNA glycosylase
OLFM1	olfactomedin 1
OPTC	opticin
OR10H2	olfactory receptor, family 10, subfamily H, member 2
OR10P1	olfactory receptor, family 10, subfamily P, member 1
OR1D2	olfactory receptor, family 1, subfamily D, member 2
OR7E13P	olfactory receptor, family 7, subfamily E, member 13 pseudogene
OR7E24	olfactory receptor, family 7, subfamily E, member 24
OSBPL1A	oxysterol binding protein-like 1A
PADI4	peptidyl arginine deiminase, type IV
PARP10	poly (ADP-ribose) polymerase family, member 10
PBX2	pre-B-cell leukemia homeobox 2
PBX2P1	pre-B-cell leukemia homeobox 2 pseudogene 1
PCDHA1	protocadherin alpha 1
PCDHB9	protocadherin beta 9
PCDHGC4	protocadherin gamma subfamily C, 4
PCGF1	polycomb group ring finger 1
PCSK1N	proprotein convertase subtilisin/kexin type 1 inhibitor
PDE6B	phosphodiesterase 6B, cGMP-specific, rod, beta
PDIA3	protein disulfide isomerase family A, member 3
PEAK1	pseudopodium-enriched atypical kinase 1
PER2	period circadian clock 2
PEX10	peroxisomal biogenesis factor 10
PEX2	peroxisomal biogenesis factor 2
PFKFB1	6-phosphofructo-2-kinase/fructose-2,6-biphosphatase 1
PFKL	phosphofructokinase, liver
PGRMC2	progesterone receptor membrane component 2
PID1	phosphotyrosine interaction domain containing 1
PIGG	phosphatidylinositol glycan anchor biosynthesis, class G
PIGT	phosphatidylinositol glycan anchor biosynthesis, class T
PIGY	phosphatidylinositol glycan anchor biosynthesis, class Y
PKD2L2	polycystic kidney disease 2-like 2
PLAC1	placenta-specific 1
PLD1	phospholipase D1, phosphatidylcholine-specific
PCLD	polycystic liver disease
PLEKHF1	pleckstrin homology domain containing, family F (with FYVE domain) member 1
PNMA3	paraneoplastic Ma antigen 3
PNPLA8	patatin-like phospholipase domain containing 8
POC1A	POC1 centriolar protein A
PON3	paraoxonase 3
POU5F1	POU class 5 homeobox 1
PPFIA1	protein tyrosine phosphatase, receptor type, f polypeptide (PTPRF), interacting protein (liprin), alpha 1
PPIA	peptidylprolyl isomerase A (cyclophilin A)
PPP1R3C	protein phosphatase 1, regulatory subunit 3C
PPP2CB	protein phosphatase 2, catalytic subunit, beta isozyme
PPP6R3	protein phosphatase 6, regulatory subunit 3
PRAF2	PRA1 domain family, member 2
PRDM11	PR domain containing 11
PRKAG2	protein kinase, AMP-activated, gamma 2 non-catalytic subunit
PRLHR	prolactin releasing hormone receptor
PROP1	PROP paired-like homeobox 1
PRR5	proline rich 5 (renal)
PRR7	proline rich 7 (synaptic)
PRSS42	protease, serine, 42
PRSS53	protease, serine, 53
PTBP3	polypyrimidine tract binding protein 3
PUM2	pumilio RNA-binding family member 2
PYGO1	pygopus family PHD finger 1
QPRT	quinolinate phosphoribosyltransferase
QSOX2	quiescin Q6 sulfhydryl oxidase 2
RAB22A	RAB22A, member RAS oncogene family
RAB43	RAB43, member RAS oncogene family
RABIF	RAB interacting factor
RABL6	RAB, member RAS oncogene family-like 6
RAD23B	RAD23 homolog B (S. cerevisiae)
RAPGEF1	Rap guanine nucleotide exchange factor (GEF) 1
RASGEF1A	RasGEF domain family, member 1A
RASGRP2	RAS guanyl releasing protein 2 (calcium and DAG-regulated)
RASGRP4	RAS guanyl releasing protein 4
RBM15B	RNA binding motif protein 15B
RFX2	regulatory factor X, 2 (influences HLA class II expression)
RHBDL3	rhomboid, veinlet-like 3 (Drosophila)
RHOA	ras homolog family member A
RHOA	ras homolog family member A
RHPN1	rhophilin, Rho GTPase binding protein 1
RHPN2	rhophilin, Rho GTPase binding protein 2
RNH1	ribonuclease/angiogenin inhibitor 1
RNASEH1P1	ribonuclease H1 pseudogene 1
RPL22	ribosomal protein L22
RPL23	ribosomal protein L23
RPL17	ribosomal protein L17
RPL29	ribosomal protein L29
RPL7A	ribosomal protein L7a
RPP25	ribonuclease P/MRP 25kDa subunit
RPS13	ribosomal protein S13
RPS26	ribosomal protein S26
RPS6	ribosomal protein S6
RPS6KA1	ribosomal protein S6 kinase, 90kDa, polypeptide 1
RXFP4	relaxin/insulin-like family peptide receptor 4
SAMD4A	sterile alpha motif domain containing 4A
SC5D	sterol-C5-desaturase
SCAND2P	SCAN domain containing 2 pseudogene
SCN3A	sodium channel, voltage-gated, type III, alpha subunit

SDHAF2	succinate dehydrogenase complex assembly factor 2
SDHD	succinate dehydrogenase complex, subunit D, integral membrane protein
SEMA4C	sema domain, immunoglobulin domain (Ig), transmembrane domain (TM) and short cytoplasmic domain, (semaphorin) 4C
SEPT12	septin 12
SERF2	small EDRK-rich factor 2
SERTAD2	SERTA domain containing 2
SETD4	SET domain containing 4
SETD8	SET domain containing (lysine methyltransferase) 8
SETD9	SET domain containing 9
SH3BP5	SH3-domain binding protein 5 (BTK-associated)
SHB	Src homology 2 domain containing adaptor protein B
SHPK	sedoheptulokinase
SLC16A1	solute carrier family 16 (monocarboxylate transporter), member 1
SLC23A3	solute carrier family 23, member 3
SLC25A52	solute carrier family 25, member 52
SLC2A8	solute carrier family 2 (facilitated glucose transporter), member 8
SLC31A1	solute carrier family 31(copper transporter), member 1
SLC35E3	solute carrier family 35, member E3
SLC5A1	solute carrier family 5 (sodium/glucose cotransporter), member 1
SLC6A6	solute carrier family 6 (neurotransmitter transporter), member 6
SMARCC1	SWI/SNF related, matrix associated, actin dependent regulator of chromatin, subfamily c, member 1
SMARCD1	SWI/SNF related, matrix associated, actin dependent regulator of chromatin, subfamily d, member 1
SMARCD2	SWI/SNF related, matrix associated, actin dependent regulator of chromatin, subfamily d, member 2
SMG1	SMG1phosphatidylinositol 3-kinase-related kinase
SMPDL3B	sphingomyelin phosphodiesterase, acid-like 3B
SND1-IT1	SND1intronic transcript 1(non-protein coding)
SNX13	sorting nexin 13
SOGA1	suppressor of glucose, autophagy associated 1
SORBS1	sorbin and SH3 domain containing 1
SOX12	SRY(sex determining region Y)-box 12
SOX17	SRY(sex determining region Y)-box 17
SOX3	SRY(sex determining region Y)-box 3
SP5	Sp5 transcription factor
SPAG9	sperm associated antigen 9
SPATA32	spermatogenesis associated 32
SPRR2B	small proline-rich protein 2B
SPTLC3	serine palmitoyltransferase, long chain base subunit 3
SRSF11	serine/arginine-rich splicing factor 11
SSB	Sjogren syndrome antigen B (autoantigen La)
SSBP2	single-stranded DNA binding protein 2
STEAP3	STEAP family member 3, metalloreductase
STOM	stomatin
STOML2	stomatin (EPB72)-like 2
STX12	syntaxin 12
SULT4A1	sulfotransferase family 4A, member 1
SYNC	syncoilin, intermediate filament protein
SZT2	seizure threshold 2 homolog (mouse)
TACR1	tachykinin receptor 1
TBC1D20	TBC1domain family, member 20
TCEA3	transcription elongation factor A (SII), 3
TCL6	T-cell leukemia/lymphoma 6 (non-protein coding)
TCTE3	t-complex-associated-testis-expressed 3
TENC1	tensin like C1domain containing phosphatase (tensin 2)
TEX261	testisexpressed 261
TFPI	tissue factor pathway inhibitor (lipoprotein-associated coagulation inhibitor)
THRAP3	thyroid hormone receptor associated protein 3
TIMM8A	translocase of inner mitochondrial membrane 8 homolog A (yeast)
TMCO1	transmembrane and coiled-coil domains 1
TMED2	transmembrane emp24 domain trafficking protein 2

1. Information from HGNC (HUGO Gene Nomenclature Committee; www.genenames.org).

TMEM169	transmembrane protein 169
TMEM209	transmembrane protein 209
TMEM214	transmembrane protein 214
TMEM237	transmembrane protein 237
TMEM55A	transmembrane protein 55A
TMEM97	transmembrane protein 97
TMPRSS6	transmembrane protease, serine 6
TNFRSF21	tumor necrosis factor receptor superfamily, member 21
TNRC18	trinucleotide repeat containing 18
TNS1	tensin 1
TNXB	tenascin XB
TP53I11	tumor protein p53 inducible protein 11
TPCN1	two pore segment channel 1
TPM1	tropomyosin 1(alpha)
TRAK1	trafficking protein, kinesin binding 1
TREML1	triggering receptor expressed on myeloid cells-like 1
TRIM33	tripartite motif containing 33
TRIM35	tripartite motif containing 35
TRIM62	tripartite motif containing 62
TRMT2B	tRNA methyltransferase 2 homolog B (S. cerevisiae)
TRMT6	tRNA methyltransferase 6 homolog (S. cerevisiae)
TRPV1	transient receptor potential cation channel, subfamily V, member 1
TRPV2	transient receptor potential cation channel, subfamily V, member 2
TSSK1B	testis-specific serine kinase 1B
TUBB4B	tubulin, beta 4B classIVb
U2SURP	U2 snRNP-associated SURP domain containing
UBA2	ubiquitin-like modifier activating enzyme 2
UHRF1BP1	UHRF1binding protein 1
UMOD	uromodulin
USP54	ubiquitin specific peptidase 54
UTF1	undifferentiated embryonic cell transcription factor 1
UTS2R	urotensin 2 receptor
VEGFA	vascular endothelial growth factor A
VIPR2	vasoactive intestinal peptide receptor 2
VPS11	vacuolar protein sorting 11homolog (S. cerevisiae)
WDR90	WD repeat domain 90
WHSC1	Wolf-Hirschhorn syndrome candidate 1
YBEY	ybeY metallopeptidase (putative)
YBX1	Ybox binding protein 1
YWHAE	tyrosine 3-monooxygenase/tryptophan 5-monooxygenase activation protein, epsilon
YWHAZ	tyrosine 3-monooxygenase/tryptophan 5-monooxygenase activation protein, zeta
ZDHHC21	zinc finger, DHHC-type containing 21
ZDHHC4	zinc finger, DHHC-type containing 4
ZFAND5	zinc finger, AN1-type domain 5
ZFHX2	zinc finger homeobox 2
ZFYVE26	zinc finger, FYVE domain containing 26
ZNF226	zinc finger protein 226
ZNF333	zinc finger protein 333
ZNF346	zinc finger protein 346
ZNF440	zinc finger protein 440
ZNF467	zinc finger protein 467
ZNF532	zinc finger protein 532
ZNF581	zinc finger protein 581
ZNF644	zinc finger protein 644
ZNF681	zinc finger protein 681
ZNF697	zinc finger protein 697
ZNF761	zinc finger protein 761
ZNF767	zinc finger family member 767
ZYG11B	zyg-11family member B, cell cycle regulator

1. Information from HGNC (HUGO Gene Nomenclature Committee; www.genenames.org).

3.3. Capítulo III (Artigo experimental III)

Title: Aged keratinocytes: is there an alteration in the *in vitro* proliferation and differentiation potential compared to neonatal keratinocytes?

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Keywords: keratinocytes, aging, reconstructed skin, keratinocyte stem cells, transit amplifying cells

Running title: Age versus neonatal keratinocytes

Abstract

One of the major unanswered questions regarding the morphological characteristics of the skin during the aging process is whether the thickness of its main layers is altered. Some studies propose that stem cells are responsible for maintaining the proliferative potential of the epidermis *in vivo,* while others argue that this potential is lost during the aging process. In this study, we compare keratinocytes from neonatal and 26-, 36- and 48-year-old groups to evaluate their proliferative and differentiation potential, both in monolayer cultures and in skin reconstituted *in vitro*. Cells isolated from neonatal donors show higher expression levels of Ki67 and keratins 10 and 14. Furthermore, the number of neonatal cells in the G2/M phase of the cell cycle was strikingly higher. To determine the number of stem cells present in this population, we used the β1 and α6 integrins as molecular markers. Interestingly, we did not observe any differences among these cells in culture. In the reconstituted skin model, the cells isolated at different ages were able to undergo epidermal proliferation and differentiation in a similar manner. The expression of Ki67 and of keratins 10 and 14 were also higher in skin reconstituted with cells isolated from neonatal donors. In conclusion, cultured neonatal cells have a higher proliferative capacity and differentiation potential relative to adult cells isolated at different donor ages, as revealed by the markers tested. The monolayer and reconstituted skin models generated from cultured cells represent important alternative methods to investigate the process of skin aging.

Introduction

All cells and organs of the body age gradually, and the skin can be used as a marker of this inevitable process. Skin is the largest organ of the human body and is a self-renewable tissue that is responsible for numerous physiological functions such as thermoregulation, protection against pathogens and ultraviolet radiation, tactile sensations, secretions, and excretion of toxins (Geusau *et al.*, 2001; Yamaguchi *et al.*, 2006; Kirschner *et al.*, 2013; Polak *et al.*, 2013). Moreover, it is the first organ that shows the health and well-being of the individual and reflects numerous aesthetic parameters.

The skin consists of two compartments: the epidermis and the dermis (Gangatirkar *et al.*, 2007). The epidermis is a stratified tissue that is histologically composed of four layers: the basal layer, containing epidermal stem cells (SC) and a population of transient amplifying cells (TA); the spinous layer, containing differentiating cells; the granular layer, containing cells that have already differentiated; and the stratum corneum, which is populated by dead cells (Rizvi and Wong, 2005; Gangatirkar *et al.*, 2007).

Aged skin is thinner and has a lower healing potential compared with youthful skin. Nevertheless, it is still able to heal and regenerate its epithelium, showing that it retains, at least partially, cell renewal potential (Webb and Kaur, 2006; Racila and Bickenbach, 2009; Winter and Bickenbach; 2009). Numerous studies in the literature have addressed whether the characteristics of skin cells are related to the anatomical morphology of the skin. One of the major points discussed in these studies is the thickness of the epidermal layer. Many studies describe a flattening at the epidermal-dermal junction and a decrease in the thickness of these layers in aged skin (Fenske and Lober 1986; Fenske and Conard, 1988). However, some authors still argue against these points, showing that there is no consensus on this topic. Different studies have reported large variations in the epidermal and dermal thickness during the aging process. However, it is important to note that these studies have compared different parameters, such as the anatomical sites and phenotypic features of the

individuals examined (Ya-Xian *et al.*, 1999; Nozdrin *et al.*, 2011; Baroni *et al.*, 2012; Crisan *et al.*, 2012; Waaijer *et al.*, 2012; Tsugita *et al.*, 2013; Shlivko *et al.*, 2013).

One explanation for the decreased epidermal thickness is related to the decreased proliferative potential of its main cell type, the keratinocyte, during the aging process. Grove and Kligman (1983) evaluated cell renewal in the human epidermis using a fluorescent marker. These authors reported that the dye disappeared from the stratum corneum at 20 days in young adults, while it persisted for up to 30 days in older adults. However, these authors note that the number of layers of horny cells did not change with increasing age. This finding was proposed to result from a decreased proliferation of epidermal cells. This study also reported that cells maintain a constant renewal rate in the early years of life that decreases over time, with a dramatic reduction after 50 years (Grove and Kligman, 1983). Subsequent studies have attempted to explain possible differences in the thickness of the epithelium *in vivo* by correlating the presence of SC with the proliferative capacity of keratinocytes *in vitro*. Stem cells derived from adult tissues in some regions of the body are defined as rare and relatively quiescent, with the capacity to constantly self-renew and regenerate tissues during homeostasis. Some authors claim that epidermal SC appears to resist aging. They do not show age-related changes in gene expression, cell number and telomere length, thus maintaining the capacity to respond to environmental changes. In addition, these cells do not show defects associated with increasing levels of reactive oxygen species encountered during the process of cellular aging (Li *et al.*, 2004; Racila and Bickenbach, 2009). However, other studies suggest that the transient amplifying cells also possess multipotency and an extensive capacity for tissue regeneration (Clayton *et al.*, 2007; Schlüter *et al.*, 2011). Another important issue to note is that some authors claim that it is more difficult to isolate and to maintain cultured keratinocytes from elderly donors compared with young or neonatal donors. Youn *et al.* (2004) reported that this can be explained by cellular senescence, chronological aging, or repeated sub-culture that induces the loss of SC in keratinocyte cultures and *in vitro* reconstituted epidermis models.

By comparing the literature, we have observed that the many different findings may correlate, and depend upon, the experimental model used in each study. Our study focuses on *in vitro* models, which are extensively used due to their ease of production, practicality and reproducibility. Therefore, we compare keratinocytes from neonatal and 26-, 36- and 48-year-old groups in this study to determine the differences in their proliferative capacity and differentiation potential, both in a monolayer model as well as in an *in vitro* reconstituted skin model. We also determined the number of stem cells (SC) and transient amplifying cells (TA) present in each of these populations. The data presented here confirm that the proliferation capacity and differentiation potential of neonatal and adult cells is significantly different for all conditions examined, while the cells isolated from adult donors do not show striking differences *in vitro.*

Materials and methods

Cell culture

The primary cells used in this work were obtained from Cascade Biologics (Portland, OR, USA). The keratinocytes used were isolated at different donor ages: neonatal and 26, 34, 36 and 48 years old (lots 979196, 950451, 952853, 1030541, 1249380 and 1139070, respectively). Fibroblasts were isolated from a 37-year-old donor (lot 759506). Fibroblasts were grown in Dulbecco's modified Eagle's medium (DMEM) (Gibco, Grand Island, NY, USA) supplemented with 10% fetal bovine serum (FBS, Gibco), 50 U/mL penicillin and 50 µg/mL streptomycin (Gibco). Keratinocytes were maintained in Epilife media (SKU # M-EPICF-500, Cascade Biologics) supplemented with Human Keratinocyte Growth Supplement (HKGS, SKU # S-001, Cascade Biologics). All cells were maintained at 37°C under 5% CO_2.

Fluorescence microscopy

Keratinocyte monolayer cultures derived from donors of different ages were plated in 96-well plates. After the incubation period, the cells were fixed with methanol (Sigma, St. Louis, MO, USA) for ten minutes followed by three washes with PBS (Sigma, diluted 10x). The primary antibody staining was performed overnight at 4°C. The antibodies used were Ki-67 (clone B56, BD Pharmingen, Biosciences, Bedford, MA, USA), keratin 10 MAb Ms (Abcam, ab9026; Cambridge, Cambridgeshire, England) and keratin 14 MAb Ms (Abcam, ab7800). The antibodies were diluted in PBS containing 2% BSA (Sigma, 9576). Following the primary antibody incubation, the cells were washed with PBS and incubated with the secondary antibodies, Alexa Fluor 488 goat anti-mouse (Molecular Probes, Eugene, OR, USA; A11029) or Alexa Fluor 488 goat anti-rabbit (Molecular Probes, A11034), diluted in PBS containing 1% BSA and 0.1% Tween 20 for one hour (Amersham Biosciences, Uppsala, Uppsala Country, Sweden,17-1316-01). The cells were washed with the same buffer, and then fixed with NucBlue cell stain (Molecular Probes, R37606) for nuclear staining. All images were acquired using an Image Xpress Micro microscope (Molecular Devices). The fluorescence intensity analyses were performed with the MetaXpress 4.0 software.

Cell cycle analysis

DAPI, which binds stoichiometrically to DNA, was used to quantitatively assess DNA content. Seventy thousand cells were centrifuged at 1000 rpm for 5 min at 4°C. The pelleted cells were fixed in ice-cold 70% ethanol for 30 minutes and washed twice in PBS. Cells were subsequently incubated for 1 h at room temperature with DAPI, and then evaluated by a FACS Aria I flow cytometer using the DIVA software (Becton Dickinson, San Diego, CA, USA). Ten thousand events were analyzed per experiment. The processed single cells were plotted on gated histograms to calculate the number of cells in the G1, S and G2/M phases.

Determination of stem cells in the cultures isolated from donors of different ages

To determine the percentage of KSC in the samples isolated from donors of different ages, 10^5 cells from each individual donor were used. Following trypsinization and washing with PBS, the cells were blocked with 500 µL of BSA Stain Buffer (BD, 554657) and double-stained with the following antibodies: CD29 (BD, 555443) and CD49f (BD, 551129). After 30 minutes of labeling at 4°C in the dark, the cells were centrifuged at 6300 rpm for 3 minutes, resuspended in PBS and kept at 4°C until analysis on a FACS Aria I flow cytometer (Becton Dickinson). Ten thousand events were acquired per experiment. The data were analyzed using the DIVA software.

In vitro skin reconstitution

The skin reconstitution model was adapted from Gangatirkar *et al.* (2007). Briefly, the dermal equivalent was prepared using $6x10^4$ fibroblasts embedded in a type I collagen matrix (BD). After polymerization of the dermal equivalent, $1.2x10^5$ keratinocytes isolated from donors of different ages (neonatal and 26, 34, 36 and 48 years old) purchased from Cascade Biologics or freshly isolated were plated above the dermal layer. After 24 hours, the equivalent was kept on an air-liquid interface while maintaining contact with the differentiation medium consisting of 15% of DME (Gibco, 12800-017), 5% Ham's F12 (Gibco, 114971), 2% Fetal Bovine Serum (Gibco, F0926), 0.5 µg/mL Transferrin (T-8158, Sigma), 5 µg/mL Insulin (I-9278, Sigma) and 10 ng/mL EGF (human epidermal growth factor, 53003-18, Gibco). After 10 days on the air-liquid interface, the reconstituted skin was fixed in 4% formaldehyde (Sigma, F8775).

Immunostaining

After deparaffinization and rehydration, antigen retrieval was performed in Tris- EDTA, pH 9.0 (S3307, Dako, Carpinteria, CA, USA), using a water bath

heated with steam and maintained at 97°C for 30 minutes. The slides were cooled to room temperature for 20 minutes and then washed with distilled water and TBST buffer (Tris-buffered saline with 0.01% Tween-20, 3306, Dako). The slides were blocked with 2% BSA for 2 hours at 37°C. Immunohistochemical analyses were performed with the following primary antibodies: Ki-67 (clone B56, BD Pharmingen, 556027), keratin 10 MAb Ms (Abcam, ab9026) and keratin 14 mAb Ms (Abcam, ab7800) ARK (Animal Research Kit, K3954, Dako). The primary antibody was omitted in the negative controls.

Statistical analyses

Cell cycle and fluorescence microscopy analyses are expressed as means ± SEM. The Graph Pad Prism 6 (version 6.00 for Windows Vista, Graph Pad Software, San Diego, CA, USA) software and a two way ANOVA test were used to perform statistical analyses. A one-way ANOVA with multiple comparison test (Tukey–Kramer Multiple Comparisons Test) was used for data analyses. We used correlation analysis to identify potentially causal associations between variables.

Results

Cell differentiation and proliferation in monolayer cultures

To assess the differences among keratinocytes isolated from donors of different ages, monolayer cultures of cells isolated from neonatal and from 26-, 36- and 46-year-old donors were stained with a nuclear marker of cell proliferation, Ki67, and markers of cell differentiation, keratin 10 and 14. As shown in Figure 1, the neonatal cells display both an increased number of Ki67-labeled nuclei and a more pronounced staining with this cell proliferation marker, indicating higher expression levels of Ki67 in the neonatal cells. A quantification of the fluorescence intensity of Ki67 staining revealed a significant difference between the neonatal and adult cells ($p<0.05$). Higher expression levels were also observed for the

differentiation markers keratin 10 ($p<0.01$) and keratin 14 ($p<0.05$) in neonatal keratinocytes compared with adult keratinocytes. However, no differences were observed among the keratinocytes isolated from the adults of different ages.

Cell cycle analyses

Because Ki67 expression analyses in monolayers revealed an increased expression of this proliferation marker in neonatal cells (Figure 1), we performed cell cycle analyses to determine whether there is indeed a difference in cell cycle phases among cells isolated from donors of different ages. The cell cycle analyses were performed by flow cytometry, using DAPI staining of the DNA content to differentiate between the cell cycle phases. Figure 2a shows the histograms obtained from these analyses. This figure shows the distribution of the number of cells in each cell cycle phase for the four ages analyzed. Figure 2b shows that the neonatal cultures exhibit a significant decrease in the number of cells in the G0/G1 phase ($p <0.01$) and a striking increase in the number of cells in the G2/M phase ($p <0.001$) compared with adult cells. The only difference detected among the adult cells was a reduction in the number of S phase cells from the 48-year-old donor ($p <0.05$); no significant differences were observed in the other phases analyzed.

Analysis of keratinocyte stem cells

To determine whether the differences in cell proliferation were related to changes in the number of KSC (keratinocyte stem cell) present in the neonatal and adult cell populations, we tested two typical markers of KSC: the β1 and α6 integrin. The KSC population should be double positive for the β1 (CD29) and α6 integrin (CD49f) markers. The KSCs are distinguished from the transient amplifying cells (TAs) by exhibiting a strong, bright signal for β1 integrin, whereas TA cells exhibit a dim signal. The α6 integrin signal is bright for both populations. Both cell types can be accordingly identified as $KSC^{\beta 1bri,\alpha 6\ bri}$ differentiating cells and $TA^{\beta 1dim,\alpha 6\ bri}$ differentiated keratinocytes (Kaur and Li, 2000).

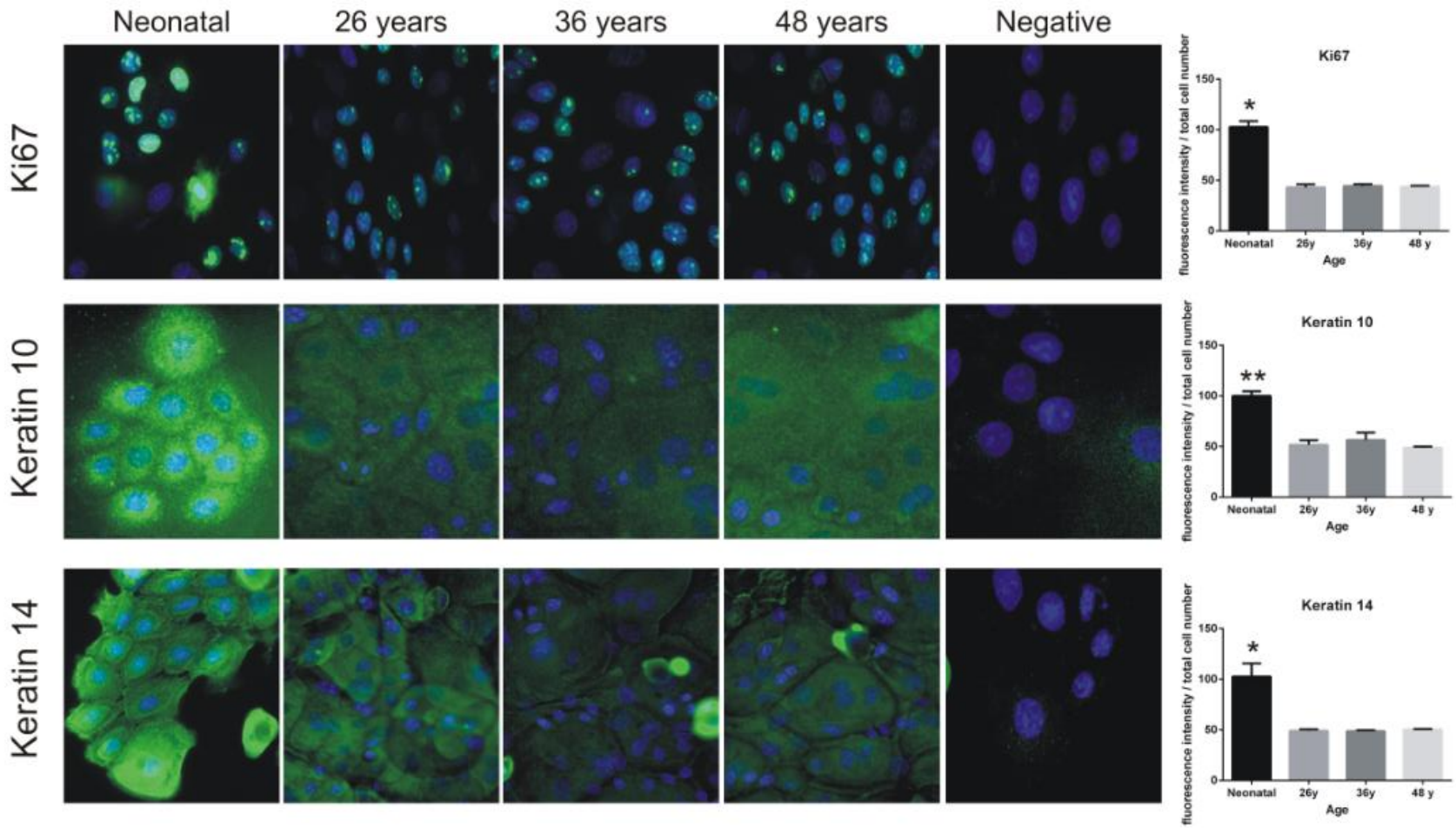

Figure 1. Fluorescence microscopy analysis of proliferation (Ki67) or differentiation (keratin 10 and 14) markers and their respective negative controls. Cells isolated from neonatal or 26-, 36- and 48-year-old adult donors were used in these analyses. The graphs on the right hand side show the ratio of fluorescence intensity per total cell number for the three marker proteins tested. A significantly higher number of neonatal cells ($p < 0.05$) demonstrate positive staining for the three markers tested compared with adult cells. Magnification 20x

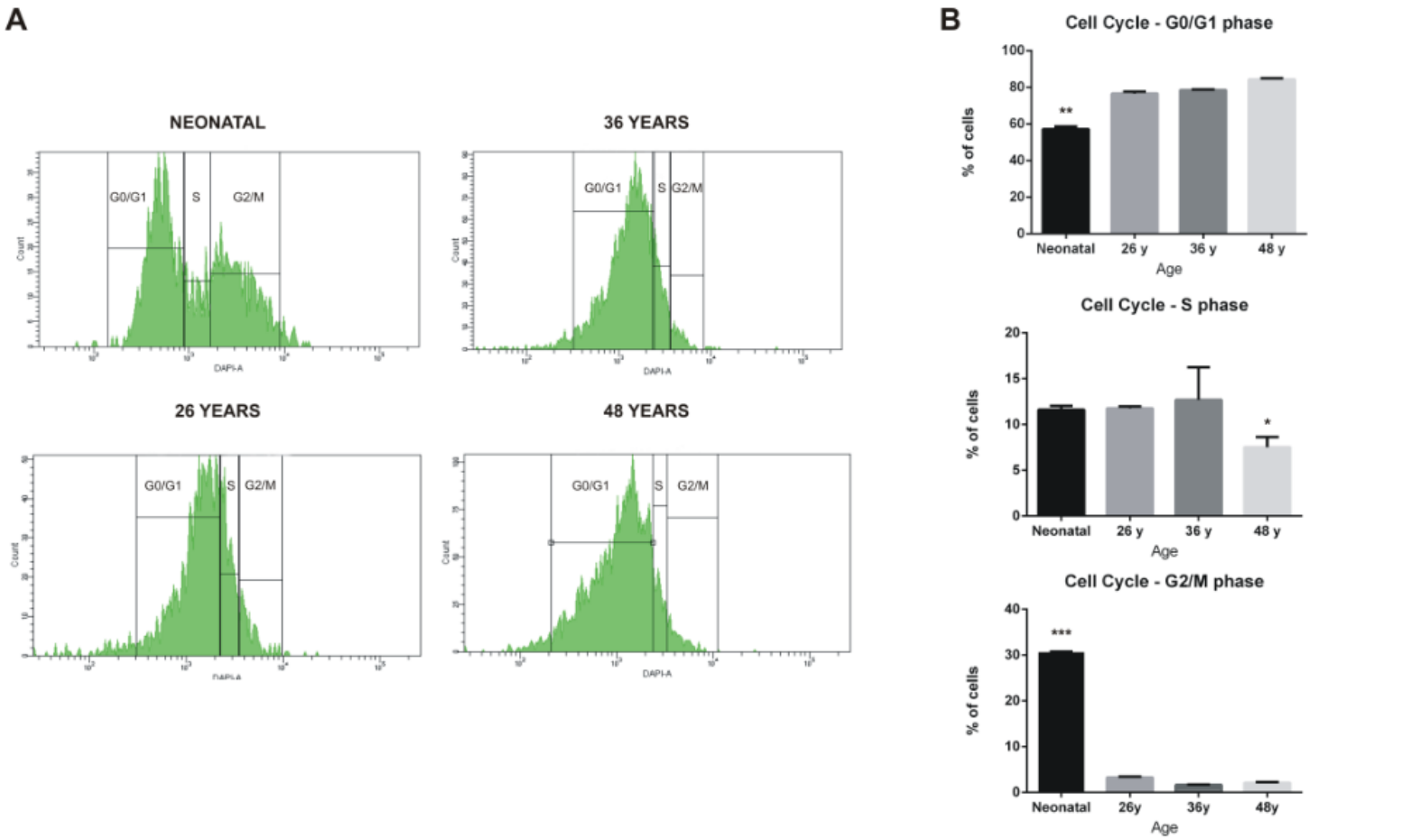

Figure 2. Cell cycle analyses of keratinocytes isolated from donors of different ages. (A) The histograms show the cell cycle distribution according to the DNA content for each age tested. G0/G1, S and G2/M indicate the cell cycle phases. (B) The graphs show the percentage of cells in each cell cycle phase for the four ages tested. Note that the neonatal cells have a smaller number of cells in the G0/G1 ($p < 0.01$) and a strikingly large number of cells in the G2/M proliferative phase ($p < 0.001$). On the other hand, the 48-year-old cells show a significant reduction in the number of S phase cells ($p < 0.05$).

As shown in Figure 3, it was not possible to detect KSCs in any of the cells analyzed because the populations were very homogenous and stained brightly for both the β1 and α6 integrins. No differences were observed among the adult cells isolated from donors of different ages (data not shown).

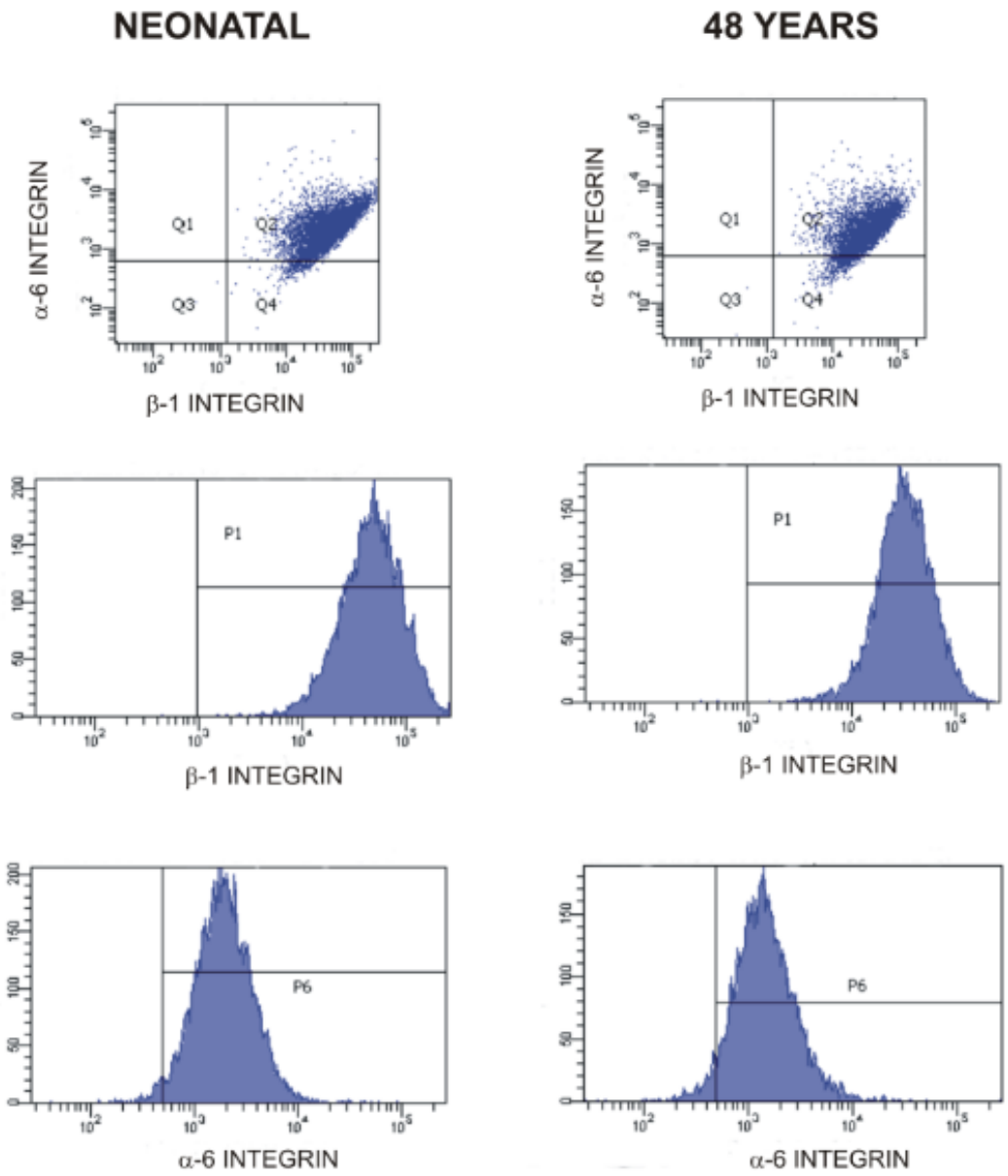

Figure 3. The dotplot and histograms show the β1 and α6 integrin staining in neonatal and 48 year-old donor cells. All cells are positive for both markers. Only one population detected shows that cells in culture form a homogenous population, as determined by the expression of the β1 and α6 integrin markers.

Skin reconstitution using cells from donors of different ages

To examine keratinocyte proliferation and differentiation in a model that mimics human skin, cells isolated from donors of different ages were used to reconstitute skin *in vitro*. As shown in Figure 4, all cells were able to differentiate and form a multi-layered epithelium containing the four main layers of the epidermis (basal, spinous, granular and stratum corneous; HandE staining). As in the monolayer model, more intense Ki67 labeling and an increased number of Ki67-labeled nuclei (indicated by arrows) were observed in the skin reconstituted with neonatal cells relative to skin reconstituted with aged cells. Higher expression levels of keratin 14, a marker for basal cells, were also present in the skin reconstituted with neonatal derived cells. A similar increase in the expression levels of keratin 10, a marker of differentiated cells was observed in the skin reconstituted with neonatal cells; however, it was less pronounced than the increased expression of Ki67 and keratin 14.

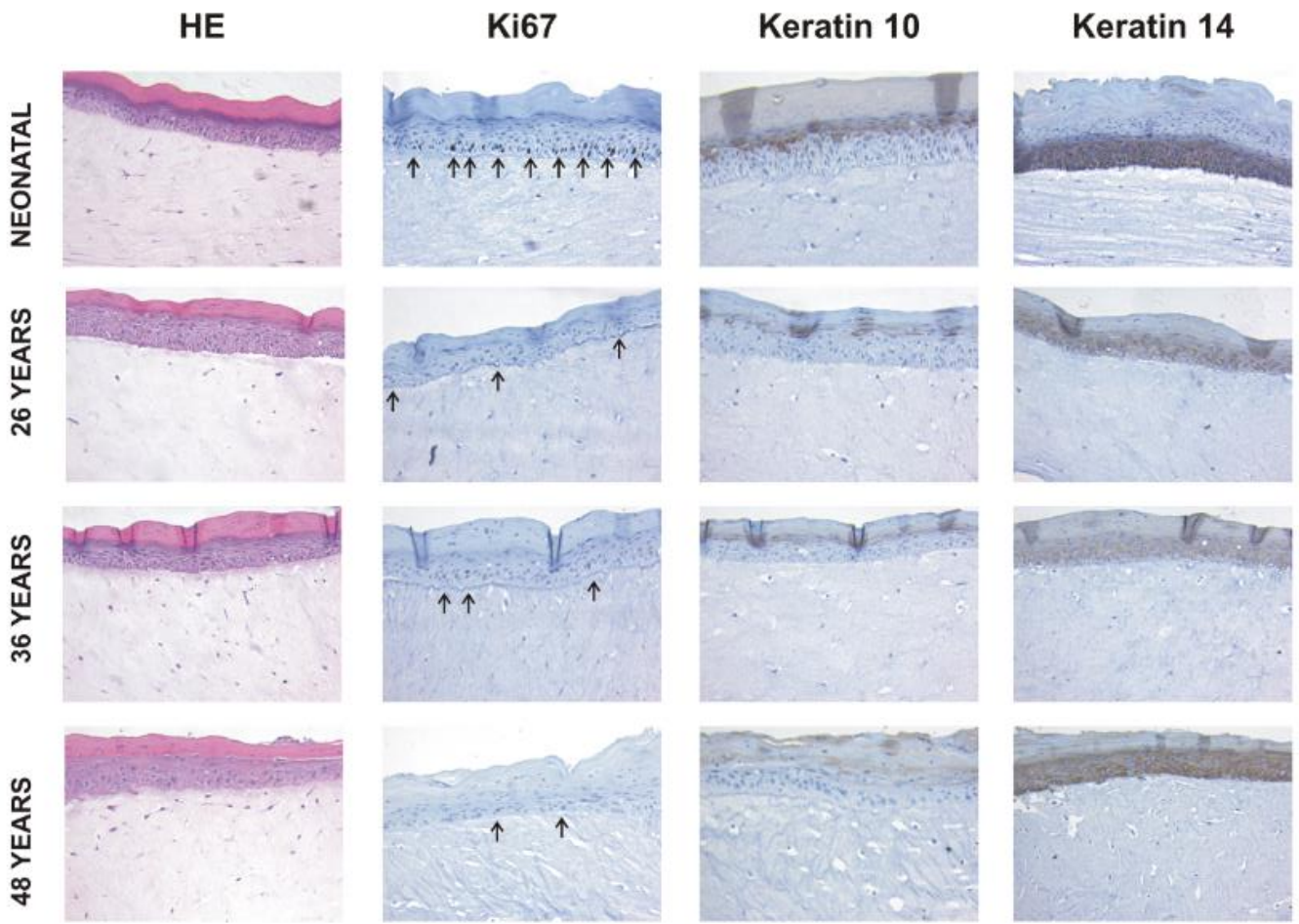

Figure 4. Analysis of skin reconstituted *in vitro*. Keratinocytes isolated from different age groups were used to show the proliferation and differentiation potential in a three-dimensional model. The H&E staining shows that all cells have a similar potential to form the main layers of the epidermis. However, neonatal cells show a stronger signal than adult cells for Ki67, keratin 10 and keratin 14 staining. The negative controls for immunostaining are shown. Magnification 20x.

Discussion

One of the most controversial issues in the literature describing the morphological characteristics of skin aging is the proliferation and differentiation of keratinocytes. Some authors claim that there is a decrease in the proliferative potential of these cells during aging, while others argue that there are no detectable differences in the thickness of the epidermis at different ages. Ya-Xian *et al.* (1999) determined the number of cell layers in the stratum corneum of normal skin at different anatomical locations in the body of 301 volunteers of various ages. These authors reported large variations in the number of cell layers that depended on two factors: body location and genetic variability. In contrast, Baroni *et al.* (2012) reported no significant age associated differences in the thickness of the epidermal and dermal layers in a study including 218 Caucasian women. However, in a study of 286 Dutch individuals from middle-aged offspring with siblings older than 90 years, and therefore, a genetic predisposition to longevity, and their partners without this favorable genetic condition, Waaijer *et al.* (2012) demonstrated that epidermal thickness is reduced during the aging process. Furthermore, there were no differences between the genetically privileged and non-privileged individuals. We presumed that the variations among the experimental models used in these studies might explain the different conclusions reached by the investigators. Thus, we compared keratinocytes cultures derived from donors of different ages in this study to evaluate the effects of culture conditions on keratinocyte proliferation and differentiation.

To understand how the experimental conditions affect the proliferative capacity and differentiation potential of keratinocytes, we tested different markers identifying these processes in monolayer and reconstituted skin cultures using cells isolated from donors of different ages (Figure 1). Ki67 is a nuclear antigen present in proliferating cells, but absent from cells in the S phase of the cell cycle (Gerdes *et al.*, 1983; Rahmanzadeh *et al.*, 2010). A previous study of scalps isolated during the autopsies of males between 7 months and 75 years of age (Nozdrin *et al.*, 2011), analyzed the expression of p53, Ki67 and involucrin and determined their

relationship to the proliferative layers of the epidermis. This report found that the epidermis was thinner in children with low p53 and Ki67 expression. This study also reported that the maximum proliferative activity was obtaining in skin isolated from 19- to 21-year-old individuals. Aging was associated with a reduction in the proliferation rate and, consequently, a thinning of the epidermis and an increase in the number of p53-positive cells. No changes were detected in the expression of involucrin. Contrary to the results described by Nozdrin *et al.* (2011), the neonatal cells cultured *in vitro* in this study exhibited higher expression levels of Ki67 compared with adult cells isolated from donors of different ages, both in the monolayer model (Figure 1) and in the *in vitro* reconstructed skin model (Figure 4).

Keratins are major structural proteins synthesized by keratinocytes (Prokshk *et al.*, 2008). Keratinization is the terminal differentiation process of epidermal keratinocytes from the basal layer to the stratum corneum, forming a three-dimensional network and a highly dynamic cytoskeleton that is essential for the mechanical stability of epithelial tissues (Arin, 2009; Ramot *et al.*, 2009). During this process, pairs of keratins are expressed in a highly specific manner for each dynamic stage of epithelial differentiation (Moll *et al.*, 2008; Arin, 2009). The keratin family consists of 54 functional genes that have different modes of expression in different skin layers and in different organs, representing physiological and pathological states of epithelial cells and epidermal cells (Ramot *et al.*, 2009). In the epidermis, the transition of keratinocytes from the proliferative basal layer to the spinous layer during the terminal differentiation process is characterized by changes in keratin expression. This involves a change in expression from the basal keratins (keratins 5, 14 and 15) to the suprabasal keratins (type II keratin 1 and subsequently type I keratin 10) (Moll *et al.*, 2008; Arin *et al.*, 2009).

The data presented here show that all cultured keratinocytes, regardless of age, are capable of passing through terminal differentiation as demonstrated by the stratification observed in the *in vitro* reconstituted skin model (Figure 4, HandE). However, neonatal keratinocytes exhibit higher expression levels of keratin 10 and 14, both in monolayer cultures (Figure 1) and in reconstituted skin (Figure 4), although keratin 10 does not seem to be expressed at the same levels as keratin

14. Together, these results reveal that a larger number of neonatal cells have proliferative potential compared with adult cells.

Numerous analyses of epithelial cell kinetics *in vivo* suggest that the sustained cell renewal of the epidermis can be attributed to long-lived SC because the life expectancy of the majority of proliferating epidermal cells (transient amplifying cells) is short, and a rapid loss of those cells occurs due to terminal differentiation within a period of weeks (Morris *et al.*, 1985; Bickenbach *et al.*, 1986, Li *et al.*, 2004). The growth capacity exhibited by the cultured epidermal cells is attributed to the activity of stem cells; once transplanted, cells maintain the ability to renew the epithelium over a longer period of time (Pellegrini *et al.* 1999; Li *et al.*, 2004).

Epidermal stem cells or keratinocyte stem cells (KSCs) are unique among somatic stem cells because, regardless of the age of the skin, the epidermis must be replaced continuously, requiring these cells to function correctly (Webb and Kaur, 2006; Racila and Bickenbach 2009). As their name indicates, KSCs are pre-keratinocyte. The cell division of KSCs gives rise to a new population of keratinocytes in culture (Papini *et al.*, 2003). Moreover, after isolation and selection, KSC cultures produce keratinocytes that will differentiate and give rise to the three populations of transiently amplified and differentiated keratinocytes.

Several enrichment protocols have been reported in the literature for the separation of the basal layer of KSC or progenitors (TA), including the use of β1 integrin (Jones *et al.*, 1995; Kaur and Li, 2000), integrin α6 and transferrin receptor CD71 (Li *et al.*, 1998; Tani *et al.*, 2000). Thus, we examined the KSC and TA populations present in keratinocyte cultures from donors of different ages (Figure 3). Interestingly, no differences were detected among the cells isolated from donors of different ages, as it was not possible to differentiate the $KSC^{\beta 1bri,\alpha 6\ bri}$ from the $TA^{\beta 1dim,\alpha 6\ bri}$ populations in cultured keratinocytes. One explanation for this result is that these are cultured, and not freshly isolated cells. Kaur *et al.* (2004) note the importance of working with freshly isolated cells rather than cultured cells to identify and isolate epidermal stem cells. They claim that the expression of the main markers present *in vivo* may be altered following *in vitro* culturing. In our lab,

we have observed that it is possible to separate the KSC population and to obtain thicker epithelia in skin reconstructed *in vitro* (data not shown) by using freshly isolated samples. In addition, the higher expression levels of the keratin 10 differentiation marker observed in the cultured cells could explain the lack of a KSC population (Webb *et al.*, 2004). Another possibility is that the isolation of adult keratinocytes and, therefore, separation of KSC, is more complex compared with neonatal keratinocytes. A study by Gragnani *et al.* (2008) examined primary keratinocytes isolated from the skin of 22 patients with ages ranging between 0 and 15 years and found that the highest number of single cells was obtained in the 0- to 3-year-old group, with approximately 4 x 10^6 cells. The number of single cells isolated falls to 10^6 in the oldest ages, and a direct inverse relationship was observed between age and the number of isolated cells: as age increased, the number of isolated cells decreased.

In conclusion, this work shows that *in vitro* models are promising tools for studying the epidermal aging process, although some issues, such as the reprogramming of gene expression and the selection of cell subpopulations, still need to be considered. Cultured neonatal cells have a higher proliferative capacity and differentiating potential compared with adult cells. The adult cells derived from donors of different ages did not exhibit differences in their proliferation capacity or differentiation potential in either the monolayer or reconstructed skin models, as determined by Ki67 or keratin 10 and 14 labeling, respectively. KSCs should be studied in freshly isolated cell preparations because reliable markers for KSC identification are still lacking, and the integrins used to enrich stem cell populations are upregulated when keratinocytes are cultured. Finally, this work shows that cultured cells can be used as an alternative method to understanding the differences in the proliferation and differentiation processes between neonatal and adult cells. Future studies are needed to verify whether there are the differences in adult cells freshly isolated from donors of different ages cultured *in vitro*.

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Competing interests statement

Each author certifies that all affiliations with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the article are completely disclosed.

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4. DISCUSSÃO GERAL

Com base na análise global da expressão de genes, o presente trabalho indica evidências para a regulação molecular associada ao processo de envelhecimento epidermal, mais especificamente de regiões continuamente expostas à radiação solar. O estudo experimental inicial, baseado na avaliação da epiderme obtida com fitas adesivas, evidenciou a regulação de processos biológicos de diferenciação e atividade dos queratinócitos. Processos como proliferação celular não foram enriquecidos, possivelmente porque as células da camada basal da epiderme não puderam ser coletadas devido a limitações da técnica empregada. Considerando amostras coletadas do dorso das mãos, este trabalho representou o primeiro estudo com foco na avaliação do transcriptoma epidermal humano de região exposta ao sol.

É importante notar que alguns estudos já avaliaram os efeitos do envelhecimento em pele humana completa, contendo epiderme e derme. Entretanto, a maioria tem provado dificuldades de interpretação frente à heterogeneidade das amostras biológicas, tanto em termos de varialibidade interindividual como também com relação à complexidade tecidual (Gromov *et al.*, 2003). Visando superar tal dificuldade, as análises de expressão gênica global em nosso trabalho foram conduzidas apenas com material de origem epidermal e com um tamanho amostral significativo, possibilitando um delineamento experimental reforçado e favorecendo o enriquecimento de listas de genes diferencialmente expressos. Além disso, buscando completar as informações já existentes na literatura científica, utilizamos um painel experimental de amplo espectro com relação às faixas etárias avaliadas, segmentado a cada década entre 20 e 80 anos.

Inicialmente, buscando estabelecer comparativos com a grande maioria dos estudos, realizamos uma análise prévia com os indivíduos organizados em dois grupos polarizados quanto ao envelhecimento: abaixo de 50 anos ou jovens e acima de 50 anos ou idosos. Dentre os processos biológicos que apresentaram regulação significativa com o avanço da idade, alguns complementam achados

prévios da literatura, como a indução de apoptose na epiderme fotoenvelhecida, marcada pela presença de queratinócitos apoptóticos (Leyden, 2001; Van Laethem *et al.*, 2005). Um estudo recente avaliou mudanças relacionadas à idade na composição do envelope córneo na pele humana (Rinnerthaler *et al.*, 2013). Corroborando com nossos achados, os autores observaram alterações significativas na expressão dos genes envolvidos nas etapas iniciais de montagem do estrato córneo. Por outro lado, nossos dados mostraram padrões distintos na expressão de genes como loricrina, sugerindo características específicas da regulação gênica epidermal em tecido exposto ao sol. Tal ocorrência poderia ajudar a explicar mudanças clínicas só observadas na pele fotoexposta, como o espessamento epidermal (Leyden, 2001; El-Domyati *et al.*, 2002), que não acomete regiões fotoprotegidas (Lock-Andersen *et al.*, 1997; Makrantonaki e Zouboulis, 2007). Ainda, também evidenciamos modulações em vias metabólicas relacionadas à sinalização de cálcio e sinalização do citoesqueleto de actina, podendo contribuir na elucidação de mecanismos moleculares envolvidos na perda do gradiente epidermal de cálcio (Denda *et al.*, 2003) ou em alterações morfológicas que acometem queratinócitos envelhecidos, que apresentam forma irregular, alargada e achatada (Soroka *et al.*, 2008). Dessa maneira, nossos resultados sugerem um mecanismo diferenciado do envelhecimento epidermal em regiões de pele fotoexposta, incluindo distúrbios na formação do estrato córneo, ainda sem descrição na literatura e com potencial desdobramento em estudos futuros.

Além dos resultados já destacados, utilizamos uma abordagem diferenciada para análise do envelhecimento em nosso modelo experimental. Com base na proposição de que o envelhecimento é um processo contínuo e cumulativo, também realizamos análises com voluntários agrupados em diferentes décadas de vida. Em cada década, utilizamos como critério de inclusão dos voluntários uma variação reduzida ao redor da idade média desejada, como nos grupos de 20 ± 1 ano ou 30 ± 1 ano, por exemplo, visando restringir possíveis componentes de variabilidade individual intragrupo. Por outro lado, a diferença entre as idades médias de cada grupo, de 10 anos, foi mantida constante. Tais definições foaram

adotadas no estudo visando facilitar a identificação de características comuns dentro de uma faixa etária específica e que pudessem apresentar variação entre as diferentes idades. Calculando a diferença entre o número de genes com aumento de expressão e aqueles com diminuição de expressão em cada década, observamos um perfil oscilatório ao longo das idades, remetendo à idéia de um equilíbrio dinâmico de regulação constante como o que ocorre em respostas compensatórias de restabelecimento homeostático. Ainda, uma análise adicional foi realizada para identificar genes que tendem a mudar sua expressão de forma contínua ao longo da vida.

No segundo trabalho experimental da tese, uma nova análise de expressão gênica global aplicando microarranjos de DNA foi utilizada para avaliar modulações transcricionais associadas ao envelhecimento da epiderme, desta vez coletada a partir de bulbos de folículos pilosos da região das sobrancelhas. A análise do envelhecimento foi determinada comparando mulheres adultas distribuídas em dois grupos de idade, com menos de 50 anos ou jovens e mais de 50 anos ou idosas, divididas de acordo com o critério biológico da ocorrência de menopausa ao redor dos 50 anos da mulher. Interessantemente, o agrupamento hierárquico espontâneo das amostras biológicas evidenciou uma repartição em dois grupos muito similares ao que se esperava obter com a proposição dos grupos pré e pós-menopausa, reforçando a significância da ocorrência da menopausa na mulher como agente desencadeante de uma mudança sistêmica com grande impacto sobre a pele (Raine-Fenning *et al.*, 2003).

Uma diferença importante que deve ser destacada ao compararmos nossos resultados obtidos a partir da epiderme derivada de fitas adesivas ou folículos pilosos: as camadas ou mesmo os tipos celulares coletados a partir de cada uma das técnicas são significativamente distintos. Enquanto o material proveniente de fitas adesivas deve ser enriquecido em queratinócitos em estágio final de diferenciação das camadas espinhosa ou granulosa (principalmente), o material dos folículos pilosos deve ser rico em células epidermais não diferenciadas ou em estágio inicial de diferenciação, representando nichos biológicos com particularidades funcionais e moleculares (Blanpain and Fuchs, 2009). Além disso,

o processo de diferenciação destas células presentes no folículo piloso é distinto da diferenciação epidermal prevista para regiões interfoliculares, provavelmente envolvendo a ocorrência de eventos moleculares independentes que culminam com a expressão de diferentes tipos de queratina, dentre outros (Schweizer *et al.*, 2007; Jiang *et al.*, 2010; Mascré *et al.*, 2012).

Diferentemente dos resultados obtidos com fitas adesivas, as análises do material epidermal proveniente de pelos de sobrancelhas revelou resultados difíceis de correlacionar com aspectos clínicos e morfológicos do envelhecimento epidérmico. De fato, observou-se uma prevalência de processos biológicos de largo espectro ou generalistas, tais como metabolismo celular, processos biossintéticos e regulação da expressão gênica ou transcrição. Além disso, a modulação de diversas vias de sinalização foi uma característica marcante do envelhecimento deste tipo de material biológico, incluindo genes representativos como proteínas do tipo *zinc finger* e elementos associados. De acordo com um recente trabalho de Tevy *et al.* (2013), por razões ainda desconhecidas, há um declínio no ritmo circadiano com a idade. A temporização da divisão e diferenciação de células proliferativas na epiderme do folículo piloso, por sua vez, depende de um controle associado ao ritmo circadiano, de forma que camundongos com ritmo circadiano perturbado apresentam envelhecimento epidermal prematuro e predisposição à tumorigênese (Janich *et al.*, 2011). Assim, estudos futuros poderiam ser conduzidos para estabelecer uma ligação entre a ocorrência de um ritmo circadiano perturbado com a regulação do comportamento de células proliferativas na epiderme do folículo piloso com a idade. Considerando nossos resultados, a desregulação da sinalização celular na epiderme folicular com o envelhecimento pode ser um dos caminhos decisivos para o melhor entendimento destes aspectos.

No terceiro trabalho experimental, buscamos estabelecer um comparativo entre características do envelhecimento epidermal *in vivo* e modelos que aplicam culturas *in vitro* de queratinócitos. Para isso, trabalhamos com células adquiridas comercialmente e isoladas de doadoras de diferentes faixas etárias, avaliando

características como potencial proliferativo, expressão de marcadores de diferenciação epidermal e capacidade de originar epiderme reconstituída *in vitro*.

A literatura científica não é homogênea quanto ao potencial proliferativo dos queratinócitos com o envelhecimento. Ya-Xian *et al.* (1999) determinou o número de camadas celulares no estrato córneo de 301 voluntários de várias idades, relatando variações que dependem da localização do corpo e fatores genéticos. Baroni *et al.* (2012) não relataram diferenças significativas na espessura das camadas epidérmicas com a idade em 218 mulheres caucasianas. Por sua vez, Waaijer *et al.* (2012) demonstraram que a espessura da epiderme é reduzida com o envelhecimento em 286 indivíduos de descendência holandesa.

Em nossos ensaios *in vitro*, as células de doadores de diferentes idades foram capazes de originar epidermes reconstituídas, indicando um potencial proliferativo e de diferenciação preservados com o avanço da idade. Entretanto, a expressão dos marcadores moleculares de proliferação e diferenciação foi significativamente maior nas células derivadas de neonatos, em comparação com as demais faixas etárias avaliadas que variavam de 20 a 50 anos, aproximadamente. Tal ocorrência foi observada para a expressão de Ki67, um antigénio nuclear marcador de proliferação, e queratinas, incluindo os tipos 10 e 14, tanto no modelo de cultivo em monocamada quanto na pele reconstituída. Como não foi possível detectar diferenças entre as faixas etárias adultas, ao contrário do que já foi observado *in vivo* para marcadores como o Ki67 (Nozdrin *et al.*, 2011), nossos resultados sugerem limitações do modelo *in vitro* para determinados estudos de envelhecimento cutâneo. Como foi possível diferenciar ao menos a expressão dos marcadores nas células de neonatos, acreditamos que os modelos *in vitro* consigam preservar e evidenciar mudanças moleculares que caracterizam o envelhecimento epidermal. Entretanto, mudanças mais tênues podem ser perdidas ao longo da manutenção das células *in vitro*, podendo ser este um ponto de atenção para tais modelos de estudo.

O tema de manutenção da atividade de células-tronco epidermais ao longo do envelhecimento é bastante discutido. Há trabalhos relatando ausência de alterações na atividade das células-tronco da epiderme, com mudanças no

controle das chamadas células amplificadoras transientes (Liang *et al.*, 2004; Stern e Bickenbach, 2007; Charruyer *et al.*, 2009). Buscando uma melhor compreensão desta questão, outro ensaio realizado em nosso trabalho com queratinócitos *in vitro* foi avaliar marcadores de superfície celular capazes de diferenciar populações de células-tronco ou células amplificadoras transientes. Curiosamente, não foram detectadas diferenças quanto à expressão destes marcadores entre as células de doadores de diferentes idades. Novamente, o uso de células cultivadas durante algum período, e não recém-isoladas, pode ter comprometido a detecção de diferenças associadas ao envelhecimento. Kaur *et al.* (2004) observaram que a expressão dos principais marcadores presentes *in vivo pode* ser alterada ao longo da manutenção de culturas *in vitro*. Em ensaios anteriores, observamos que é possível obter epidermes reconstituídas mais espessas ao utilizar células recém-isoladas. Além disso, o isolamento de células-tronco de adultos, e até mesmo queratinócitos, é mais complexo. Gragnani *et al.* (2008) observaram uma relação inversa entre o aumento da idade dos doadores e o número de células isoladas. De maneira geral, percebemos que os modelos *in vitro* podem representar ferramentas promissoras para estudo do envelhecimento epidemal, embora algumas questões, tais como a reprogramação da expressão gênica e a seleção de subpopulações celulares ainda precisam ser mais bem avaliadas.

5. CONCLUSÕES

De forma geral, os resultados encontrados neste trabalho reafirmam a epiderme como um componente ativo da pele, cujas funções biológicas são significativamente afetadas pelo envelhecimento.

Especificamente, pode-se concluir que:

- Alterações possivelmente associadas à desregulação homeostática acometem a epiderme ao longo do envelhecimento, sugerindo uma perda gradativa na capacidade do tecido epidermal de responder a elementos externos que desafiam o equilíbrio cutâneo.
- Apesar de diversas variações, alguns genes demonstraram tendência clara de aumento ou redução contínua ao longo do envelhecimento da epiderme. Dentre eles, foram identificados marcadores com envolvimento na função de barreira, como SPPR2G (*small proline-rich protein 2G*) e o componente de envelope córneo LCE1 (*late cornified envelope 1A*).
- A avaliação global de transcritos associados ao envelhecimento da epiderme humana em amostras de pele fotoexpostas permitiu a identificação de processos moleculares que podem auxiliar no entendimento de características clínicas ou morfológicas. A regulação do gene da actina beta (ACTB), por exemplo, pode estar relacionada à ocorrência de ceratose hiperproliferativa.
- Há diferenças significativas na interpretação do envelhecimento epidermal de acordo com a técnica empregada para amostragem. Em nosso caso, as coletas de fitas adesivas ou de pelos de sobrancelha apontaram para a regulação de processos ou vias biológicas distintas, evidenciando nichos biológicos com particularidades funcionais e moleculares nas regiões folicular ou interfolicular da epiderme.
- Maior capacidade de proliferação e diferenção foram observadas para queratinócitos *in vitro* isolados de doadores neonatos quando comparados a doadores adultos de entre 20 e 50 anos, aproximadamente.

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7. ANEXOS

7.1. Artigo de revisão I

Title: Overview of epidermal aging: refilling the old bath model with recent biological findings and functional mechanisms

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Keywords: epidermis, aging, skin, signaling, molecular biology

Running title: Overview of epidermal aging

Abstract

As the outer layer of the skin, epidermis plays multiple essential protective roles; the transitory nature of epidermal layers implies a continuous supply of new cells to maintain a multilayered tissue that undergoes permanent homeostasis throughout life. However, like any biological system, epidermis has an imperfect balance. Thus, epidermal homeostasis progressively deteriorates with aging, which is reflected in loss of the ability of the epidermis to give stability to its major molecules and cells, and consequently to preserve its own organizational and functional integrity. The bathtub elegantly illustrates the “modus operandi” of the epidermis, because the model is perfectly compatible with current biological findings: 1) tap flow has been enriched by the boom in epidermal stem cell research – fundamental for a comprehensive view of epidermal renewal dynamics; 2) bath volume has grown with the discovery of molecular pathways involved in epidermal stratification, differentiation, and cell signaling through a complex regulatory network; and finally 3) plug-hole has been refined with the discovery of details on important biochemical and physicochemical properties of the stratum corneum, as well as on its genesis and subsequent desquamation. Furthermore, age-related intrinsic and extrinsic components have considerable effects on epidermal machinery, leading to disturbances in skin physiology and possible impairments in the quality of life of elderly people. This work presents an overview of the structure and function of epidermis, by refilling the old bath model with the results of recent advances to provide an integrative perspective, and discusses the main epidermal changes that come with aging, suggesting new opportunities for future studies and/or possible dermatological therapies.

Introduction

Epidermis – the outer layer of the skin – represents a functional barrier in the control of substances that can be released from or absorbed into the body (Sotoodian and Maibach, 2012) and plays an important role in the prevention of water and nutrient loss, while performing multiple essential protective functions against environmental insults, such as toxins, pathogens, chemicals, pollution, mechanical stress and solar ultraviolet (UV) radiation (Simpson *et al.*, 2011; Ramos-e-Silva and Jacques, 2012). As the most exposed body part, epidermis is also an important indicator of skin health, which has significant psychosocial implications (Farage *et al.*, 2008c and 2010a). Skin imperfections have a negative influence on self-esteem and can cause considerable emotional distress. Outweighing the aesthetic importance, some diseases or disturbances specifically affecting epidermal organization, such as vitiligo or psoriasis, interfere considerably with the quality of life of the patients by causing anxiety, depression, and social withdrawal (Bilgiç *et al.*, 2011; Jobling and Naldi, 2006; Sotoodian and Maibach, 2012).

Although aging is a natural process, it is also a factor that significantly affects epidermal tissue. Over time, cumulative exposures to external aggressors wear down the machinery of the human body, leading to functional deterioration and changes in biological structures. Considering that the population is aging rapidly, the skin is a portal of knowledge on aging, and the body of knowledge is burgeoning on this subject, Farage *et al.* (2010b) organized a comprehensive textbook that covers details in respect to structure and function, cellular and molecular mechanisms, and the latest bioengineering instruments used to assess age-related changes in the skin. As for the epidermis, aging causes disturbances in its barrier function. Aged skin tends to have an overall drier, duller and tired aspect, and is more predisposed to wrinkling. A common clinical sign in the elderly is xerosis – i.e., abnormal dryness of skin (Durai *et al.*, 2008). It is usually a source of discomfort, either because of the unsightly aspect of increased skin flaking or

because of the annoying pruritus, of which excessive dryness is the most common cause in older adults (White-Chu and Reddy, 2011).

Specifically on the subject of aged epidermal permeability barrier, a review by Elias and Ghadially in 2002 focused on the basis of functional abnormalities. Since then, increasing numbers of scientific publications related to the subject have emerged. A search in the Pubmed literature base (www.pubmed.com) using the words “epidermis” and “aging” shows that the total number of citations from 1954 to 2002 was 556, a figure that had almost doubled, to 1176, by the end of 2012. More than looking at recent researches merely from a quantitative perspective, it is important to consider the qualitative approach taken in such works with respect to the technological advances and innovative areas that evolved over the last decade. Some of these developments appeared during the boom in stem cell research (including stem cells present in the skin and particularly in epidermis) (Castilho *et al.*, 2009; Fuchs, 2008); others gave rise to the emergence of new fields derived from cell and molecular biology (such as “omics” and high throughput analyses, development of reliable alternative methods based on 3D reconstructed models, description of new signaling pathways, and others) (Blumenberg, 2012; Boulter *et al.*, 2013; Brohem *et al.*, 2011; Castilho *et al.*, 2009).

This review summarizes recent biological findings and functional mechanisms related to epidermal aging from an integrative perspective, rethinking the bath model as an opportunity to discuss scientific works that have been published since one of the first propositions for the “modus operandi” of epidermis was put forward.

Epidermal structure and bath model

More than a physical structure, epidermis is a highly specialized epithelium that undergoes a continuous renewal process and is characterized by overlapped cells that form a stratified barrier on the surface of the body to protect it against external aggressions and maintain its required balance of fluids and ions. A variety of cell types are found in epidermis: keratinocytes (corresponding to 80-95% of the

epidermal cells), melanocytes (that produce melanin for skin pigmentation), Langerhans cells (antigen presenting cells for immunosurveillance), and Merkel cells (capable of synthesizing catecholamines and thought to act as tactile receptors). Four main cell strata are distinguished according to the level of keratinocyte maturation: basal layer (BL; cells with a high proliferative capacity), spinous layer (SL; desmosome-enriched, thorny-looking cells), granular layer (GL; cells abundant in lipid and protein granules), and stratum corneum (SC; dead, enucleated and flattened cells, also called corneocytes, interspersed with intercellular lipids). BL is the inner layer and its proliferative cells are responsible for constant epidermal replenishment. They migrate toward the skin surface, crossing both SL and GL, until their complete differentiation in SC. The process occurs every four weeks throughout the lifetime. In some anatomic regions where skin is especially thick, such as the soles and palms, it is possible to differentiate a fifth layer between SC and GL: the stratum lucidum, designed to help the body handle friction (Brohem *et al.*, 2011; Fuchs and Raghavan, 2002; Simpson *et al.*, 2011).

"Epidermal engine" was the term defined by Marks (1986) in his paper on epidermal complexity and dynamics. The "epidermal bath model" was used as a practical analogy in which the size of the cell population was likened to the bath volume, and the rates of inflow from the tap and outflow from the plughole were taken to resemble epidermopoiesis and desquamation, respectively (Figure 1). Dynamic balance presupposes a perfect reposition system, by which the proliferation of cells is activated inside the epidermis as other cells are lost outside it. The basis of this system is similar to that of homeostasis, defined by O'Neill (1997) as the ability of a living organism to control its internal conditions in spite of fluctuations in the external environment. In terms of energy balance, however, living organisms are not perfect systems, and constant exposure to external insults, associated with a preprogrammed resistance of internal genetic-based components, leads to a continuous systemic degeneration.

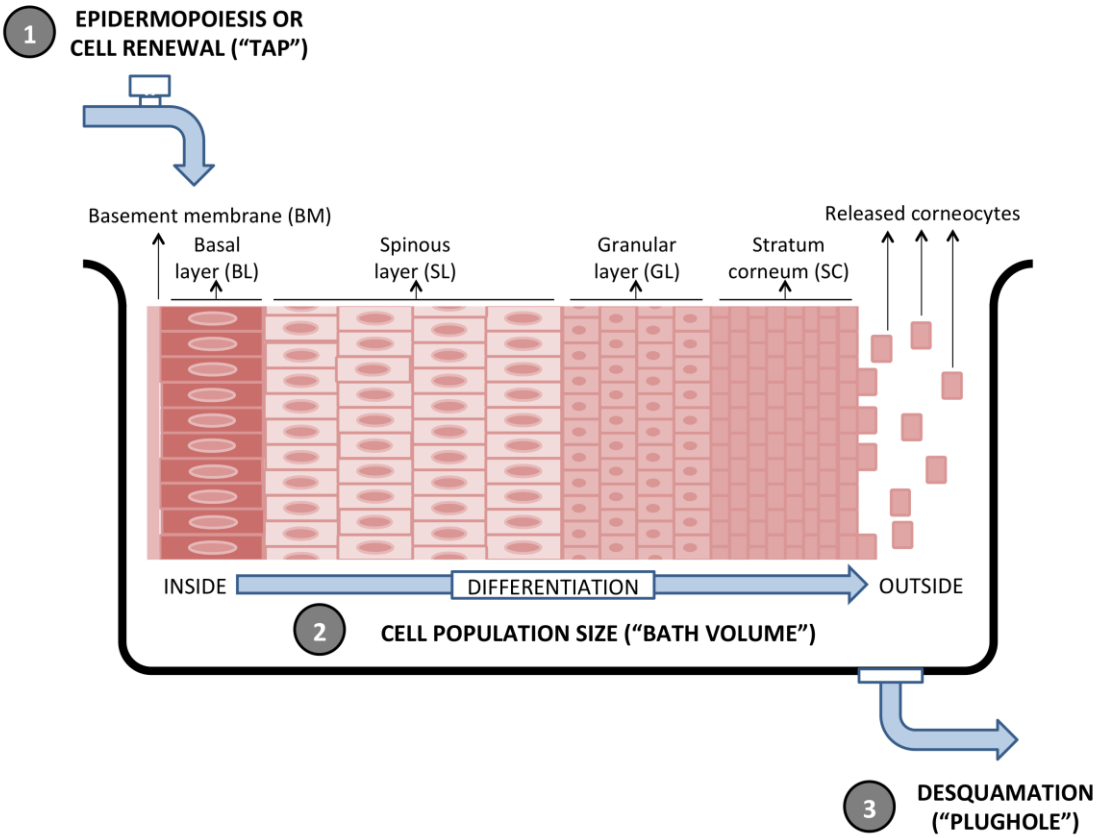

Figure 1. Epidermal bath model, originally proposed by Marks (1986). The model consists of three main components: (1) tap, which represents epidermopoiesis or cell renewal that results from constant proliferation in the layer connected to basement membrane (BM); (2) bath volume, which corresponds to the size of epidermal cell population; and (3) plughole, which stands for the desquamation process of continuous corneocyte release due to physical stressors. Keratinocyte flow is indicated by blue arrows, including the direction of their differentiation process, which drives them from the inside to the outside toward the body surface and through different epidermal layers, in the following sequence: basal layer (BL), spinous layer (SL), granular layer (GL) and stratum corneum (SC).

Aging and loss of homeostasis capacity

Aging – a key concept in explaining homeostasis failures during life – is a highly complex biological process involving cumulative changes that affect the ability of the organism to respond adaptively to stress (Gilhar *et al.*, 2004; Kirkwood, 2005). Impact of aging can be perceived in different parts of the organism, where it promotes loss of function and affects the self-adaptive capacity

of the system to maintain optimal internal conditions. Progressive deterioration of the ability of cells and tissues to preserve the stability in some of their biological molecules, such as nucleic acids or proteins, that comes with age also contributes to the functional loss (Garinis *et al.*, 2008; Koga *et al.*, 2011). Overall system failure in controlling homeostasis results from the sum of interdependent occurrences. Since the human body is an integrated system, disturbances in the original function of specific components are expected to reflect on others in a domino effect. Aging leads to physiological and metabolic failures in systems of temperature control, intra- and extracellular ion level regulation (especially for sodium and potassium), and water and hormone balance (Copinschi and Caufriez, 2013; O'Neill, 1997). All these changes may impact the skin.

Elderly seem more susceptible to hypo- or hyperthermia when exposed to thermal stress, which can cause cell death or DNA damage (Anderson *et al.*, 1996; Roti Roti, 2008). Keratinocyte response to hyperthermia shows intriguing results, such as the development of heat tolerance and UVB resistance (Kane and Maytin, 1995; Maytin, 1992; Maytin *et al.*, 1993 and 1994), or apoptosis induction and micronuclei formation (Hintzsche *et al.*, 2012; Wang *et al.*, 2009). However different the experimental designs, the activation of cellular anti-stress systems is a common feature, sometimes marked by the expression of heat shock proteins (HSP). Independently of protective or damaging responses, any deviation in physiological patterns leads the cells to turn on warning signals mediated by consistent epidermal mechanisms of tissue recovery. Still, according to Maytin (1992), changes in the expression of many stress-inducible genes often occur under conditions ultimately lethal to the cells, calling into question their adaptive significance.

Regarding hormonal imbalance with aging, postmenopausal women usually have reduced levels of estrogens; this accelerates the decline in the appearance of the skin by affecting several of its functions, such as hair growth and the pigmentation, vascularity, elasticity, and water-holding capacity of the skin (Shu and Maibach, 2011; Verdier-Sévrain *et al.*, 2006; Zouboulis *et al.*, 2007). In addition, skin collagen content decreases at a rate of 2% per year (Brincat *et al.*,

1987; Shah and Maibach, 2001). In men, aging-induced reductions in androgen levels correlate to decreased skin thickness and body hair (Wespes and Schulman, 2002; Zouboulis *et al.*, 2007). Such findings substantiate the fact that age-related systemic homeostasis failures cause significant structural changes in the skin and diminish its capability to regenerate its original, or younger, organization.

Homeostasis presupposes the need of an organism to sense and respond to environmental changes by setting in motion mechanisms to restore its previous state of balance (O'Neill, 1997). Skin plays a fundamental role in the interaction with the external environment: it acts as a selective barrier and a major sensory organ of the body. Consequently, aged skin might have a cumulative impact on the entire aged organism, since its diminished internal capacity to adjust to environmental changes is further reduced by a compromised protective barrier that may fail to capture outside signals (Benedetto, 1998; Dufour and Candas, 2007; Farage *et al.*, 2008b; Farage *et al.*, 2009) (Figure 2). Epidermis, in particular, is the first line of contact with the surroundings, which increases the significance of a better understanding of the impacts of aging on this element of the skin (De Luca and Valacchi, 2010). Denda's group, a specialized team working on epidermal issues, hypothesizes that an information-processing function may exist in the epidermis, particularly because of its ectoderm-derived origin – the same as the nervous system – and also because of the expression of neurotransmitter receptors in different cells (Boulais and Misery, 2008; Denda and Tsutsumi, 2011). Basically, Merkel cells form an enigmatic skin cell population, found at the epidermal/dermal border, synaptic-connected with sensory terminals. Merkel cells are proposed to be mechanotransducers related to light touch responses. However, exactly how Merkel cells transduce mechanical signals remains unknown (Maricich *et al.*, 2009; Reed-Geaghan and Maricich, 2011). A recent review suggested that the acid-sensing ion channels (ASICs), expressed in Merkel cell-neurite complexes, might be a possible component that would help to elucidate mechanotransduction pathways in the skin (Chen and Wong, 2013).

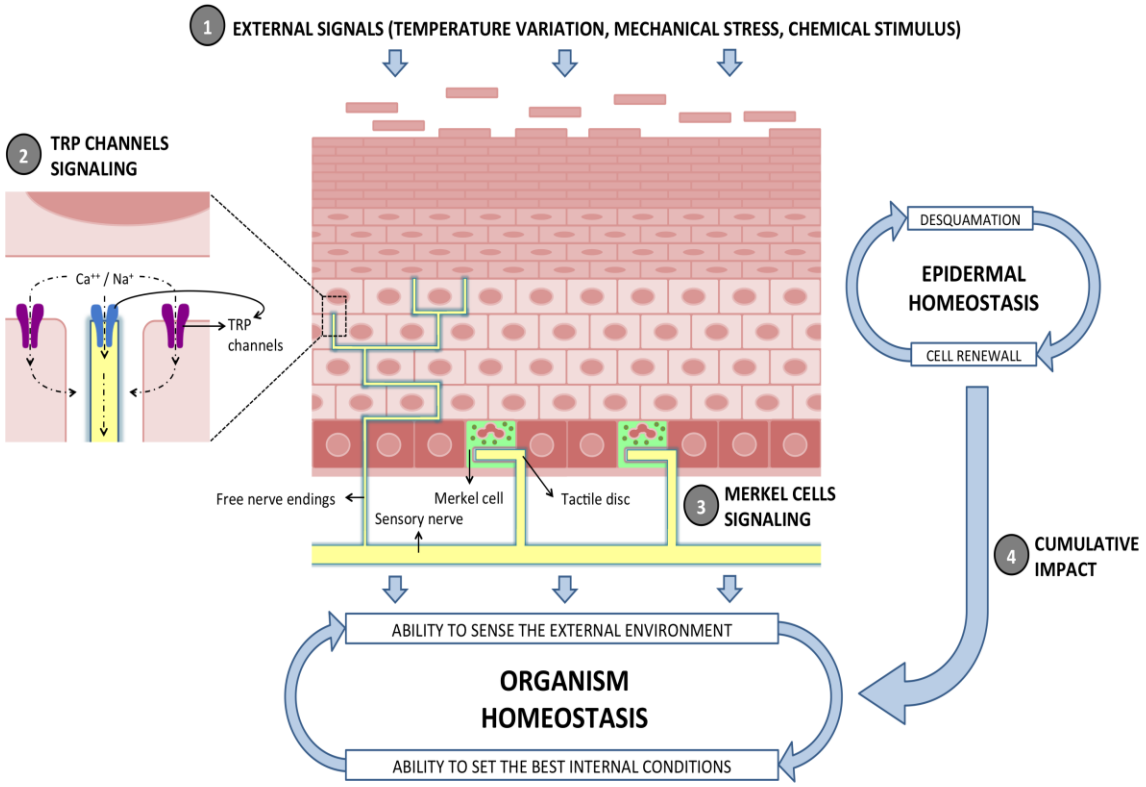

Figure 2. Epidermal mechanisms for capturing of external signals and regulation of homeostasis. (1) An important component of the ability of the organism to sense external environment, it allows different signals to be detected by epidermis, including temperature variations, mechanical stress and chemical stimuli. (2) Transient receptor potential channels (TRP) are ionic channels located in the membrane of free nerve endings and keratinocytes, and constitute an epidermal sensitive mechanism. Primarily related but not restricted to thermal oscillations, various environmental factors are sensed by TRP receptors, and their signals are transferred to peripheral sensory nerve fibers. (3) Merkel receptors are described as part of the cutaneous sensory system, composed of Merkel cells (containing numerous neuropeptides inside dense core neurosecretory granules) and sensory afferents (with structures known as tactile discs), which are connected to periphery nerve fibers. Exact way by which Merkel cells work is still object of debate, but some authors consider them as excitable neurone-like cells that may respond to various stimuli, and recent findings proved their essential contribution to light touch responses. (4) In view of the crucial role of epidermis as a sensory tissue, epidermal homeostasis has direct implications in the overall homeostasis of the organism. Aging affects the epidermal balance between cell renewal and desquamation, much as it affects several internal organs, which experience loss of functional properties. Thus, reduced ability of aged epidermis to deploy best internal defenses against environmental aggressors may be further compounded by its diminished ability to sense external signals. This extends the cumulative impact of epidermal aging to homeostasis of the whole organism.

In addition to terminal sensory nerves and Merkel cells, keratinocytes have also been recently described as sensitive cells. Recent studies have been specifically targeted to determine the sensitive properties of keratinocytes, and the superfamily of transient receptor potential channels (TRPs) has emerged (Denda and Tsutsumi, 2011). TRPs are non-selective cation channels expressed throughout the body and regulated by stimuli; they are subdivided into seven families: TRPA (ankyrin), TRPC (canonical), TRPM (melastatin), TRPML (mucolipin), TRPN (no mechanoreceptor potential C), TRPP (polycystin), and TRPV (vanilloid) (Fernandes *et al.*, 2012; Steinhoff and Bíró, 2009). Since TRPV1 was identified in epidermal keratinocytes, the involvement of TRP in epidermal tissue has significantly changed (Denda *et al.*, 2001b). After TRPV1, TRPV3 was found to mediate a cell autonomous response in keratinocytes upon exposure to heat (Peier *et al.* 2002). Subsequently, other channels have been shown to play a temperature regulatory role in keratinocytes, such as TRPV-4 (sensitive to heat) and TRPA1 (sensitive to cold) (Atoyan *et al.*, 2009; Denda *et al.*, 2007; Fernandes *et al.*, 2012; Lee and Caterina, 2005). Temperature-sensitive ion channels affect other functions and skin processes as well, including cellular differentiation and proliferation, water flow control, reinforcement of cell junctions and mechanosensory properties (Akazawa *et al.*, 2013; Bíró and Kovács, 2009; Denda and Tsutsumi, 2011; O'Neil and Heller, 2005; Steinhoff and Bíró, 2009;).

How skin undergoes aging and epidermal organization impact

Aging is a complex and multifactorial phenomenon, composed of intrinsic and extrinsic factors, defined respectively by individual genetic constitution and external insults. In humans, aging is said to be directly influenced by lifestyle and, according to Farage *et al.* (2007 and 2008a), the intrinsic rate of skin aging in any individual can also be dramatically influenced by personal, socioeconomic and environmental factors. Nevertheless, as the lifetime of an individual unfolds, a particular set of genetically programmed events drive the changes that take place in all tissues and lead to the aging of the whole organism (Makrantonaki *et al.*,

2012; Zouboulis and Makrantonaki, 2011). Aging skin undergoes progressive degenerative changes; constant exposure of the skin to environmental aggressors contributes to accelerating or intensifying the process (Farage *et al.*, 2009). According to the micro-inflammatory model, UV radiation skin exposure promotes migration of macrophages and production of free radicals affecting resident cells, such as fibroblasts or keratinocytes. Neo-synthesis of adhesion molecules is stimulated in endothelial cells by recruiting new inflammatory cells, thus closing the cycle of self-maintained micro-inflammation, which results in the disruption of skin tissue and the ensuing loss of volume and elasticity (Giacomoni and Rein, 2004). From the clinical viewpoint, skin aging is characterized by wrinkling, flabbiness, increased fragility, blister formation, impaired wound healing, dryness, pigmentation changes, and increased risk of cancer (Farage *et al.*, 2007, 2008b and 2009). Deeper wrinkles and a leathery appearance result from extensive sunlight exposure (Scharffetter-Kochanek *et al.*, 2000). Clinical signs reflect internal and structural changes extensively reviewed by Waller and Maibach (2005 and 2006), including diminished blood flow, reduced thickness of different skin layers, disorganized collagen and elastic fiber patterns, reduced activity of enzymes involved in post-translational modification processes, protein aggregate formation, changes in deposition of glycosaminoglycans (GAGs) which then tend to interact less with water molecules, and changes in the lipid content of the skin.

Even with the numerous dermal aging studies based mainly on the supportive function and fiber-enriched structure of the dermis, the epidermis has recently been receiving more attention. Although epidermal machinery becomes less efficient with age, the balance between cell production and cell loss may change over the entire lifetime (Gilhar *et al.*, 2004). Several studies suggest that, much more than just undergoing minor functional abnormalities, the epidermal structure in fact suffers multiple impacts from intrinsic and extrinsic aging (Table 1). Many other mechanisms have been identified since the 1980’s to complement the epidermal bath model, and many studies explain the more significant changes that affect the aging epidermis. Discovery of new molecules and the identification of new biological functions make it important to rethink and complement the three

main steps of the epidermal bath model in light of recent advances in cell and molecular biology.

Table 1. Structural changes in epidermis with aging.

Affected characteristic	Observed effect of aging	Skin condition*	Reference
Epidermal surface	Increase in number of pores	PP	Rawlings, 2006
	Deterioration of fine reticular patterning in the SC surface	PP/PE	Shekar *et al.*, 2005
	Deteriorated surface appearance and weakening in the adhesion of keratinocytes to SC, especially in photoaging	PP/PE	Chu and Kollias, 2011
	Change in the rhomboidal epidermal furrow pattern to a linear appearance	PE	Longo *et al.*, 2013
Epidermal thickness	Decrease in thickness of viable cellular epidermis, without changes in SC	PP	Lock-Andersen *et al.*, 1997
	Thinning epidermis by 10-50% between 30 and 80 years	PP	Makrantonaki and Zouboulis, 2007
	SL atrophy	PP	Zouboulis and Makrantonaki, 2011
	Constant mean epidermal thickness from 6-84 years in sun-exposed and protected skin, showing thicker epidermis in facial in comparison with abdominal skin	PP/PE	El-Domyati *et al.*, 2002
	Decrease in epidermal thickness and in the amount of viable cell layers from 17 to 81 years	PP/PE	Levakov *et al.*, 2012
	Thickening of the SC with faulty degradation of desmosomes, dehydration and microfissures	PE	Leyden, 2001
	Reduced epidermal thickness by 30% in individuals older than 65 years, despite a slight increase in middle-aged subjects	PE	Longo *et al.*, 2013

Epidermal shrinkage	Decrease in epidermal shrinkage by 22% in superficial layers and 6% in the lower epidermis	PP	Moragas *et al.*, 1993
Dermo-epidermal junction organization	Flattening of the dermo-epidermal junction, with 36.3% decrease in the rete peg-related roughness index, mainly between 40 and 60 years	PP	Moragas *et al.*, 1993
	Flattening of dermal-epidermal junction from 17 to 81 years	PP/PE	Levakov *et al.*, 2012
	Reduced collagen type VII containing anchoring fibrils, while collagen IV might be also degraded	PE	Scharffetter-Kochanek *et al.*, 2000
Cellular morphology and distribution	Expanded intercellular space throughout epidermis	PP	Minematsu *et al.*, 2011
	Increased heterogeneity in basal cell size, decreased mitotic activity, increased duration of cell cycle and migration time of keratinocytes, slow replacement of lipids in the SC, decrease and heterogeneity of melanocytes, decrease of Langerhans cells	PP	Zouboulis and Makrantonaki, 2011
	Increase in the amount of keratohyalin granules from 17 to 81 years	PP/PE	Levakov *et al.*, 2012
	Appearance of "sunburn" cells (keratinocyte apoptotic cells), DNA damage to basal keratinocytes, increased numbers of melanocytes and melanocytic hyperplasia, and Langerhans cell depletion	PE	Leyden, 2001
	Impaired adhesion, proliferation and differentiation of keratinocytes	PE	Makrantonaki and Zouboulis, 2007
	Presence of irregularly shaped keratinocytes, irregular honeycomb pattern and areas with unevenly distributed pigmentation	PE	Longo *et al.*, 2013

*PP: photo-protected; PE: photo-exposed.

Opening the tap flow: cell renewal dynamics in BL

The first step illustrated in the epidermal bath model (Figure 1) refers to tap flow, focused on the cell renewal dynamics that occurs in the BL. A massive

amount of recent studies related to epidermal stem cells accounts for the elucidation of epidermopoietic regulation. The BL contains a heterogeneous proliferative cell population and also cells committed to terminal differentiation (Fuchs, 2008). Basically, tissue renewal depends on epidermal stem cells with a high-proliferation capacity and a low terminal-differentiation probability. Characteristically, such stem cells express relatively higher levels of γ-catenin and β1 integrins and lower levels of E-cadherin and β-catenin than other basal keratinocytes (Molès and Watt, 1997). Proliferative populations also express keratin 5 (K5) and K14, as well as p63, an important molecule working as a gatekeeper of proliferation in epithelial stem cells (Fuchs, 2008; Senoo *et al.*, 2007). In addition, many studies recognize that the stem cells engender transit-amplifying cells designed to undergo terminal differentiation after a few rounds of division, about five times before reducing its adhesiveness to the underlying BM and delaminating (Fuchs, 2008). Although there are heterogeneous concepts about the exact function of proliferating cells in the BL, as well as about the epidermal proliferative unit organization, a consensus has, nevertheless, been reached about BM as a niche for epidermal progenitors, and displacement is likely to play a significant role in cell fate (Ray and Lechler, 2011). In BL, a fine regulation occurs to maintain the renewal cycle of the epidermis, with two main classes of cell division – symmetric and asymmetric – and different possibilities of spindle orientation (Figure 3).

Occurrence of asymmetrical divisions provides a different view of how a basal stem cell and a committed cell might arise. In the first of the studies on this subject, epidermal stem cells were shown to shift from a lateral to a more perpendicular spindle orientation to undergo asymmetrical divisions, which account for 70% of total basal cell mitoses, while 30% of the cell mitoses remained symmetric (Lechler and Fuchs, 2005). Clayton *et al.* (2007) demonstrated that most asymmetrical divisions in epidermis leave both daughter cells adhering to BM, with the committed cells inheriting a stronger Notch signal as a key transcriptional determinant of the spinous cell fate. An additional consideration is that distinct patterns of cell division and proliferation can operate in different life

stages. During early stages of embryonic skin development, most cell divisions are symmetric and parallel to BM, which ensures the growth of the surface with the epithelium as a single layer. During epidermal stratification, the majority of cell divisions become asymmetric, such that the mitotic spindle aligns perpendicularly to the BM in order to allow the quick development of suprabasal cells, which differentiate terminally and form stratified layers. In adult skin, predominant plane of asymmetric divisions is parallel to the BM, such that one daughter cell remains a stem cell, while the other is committed to terminal differentiation and probably undergoes delamination to reach the suprabasal layers (Blanpain and Fuchs, 2009).

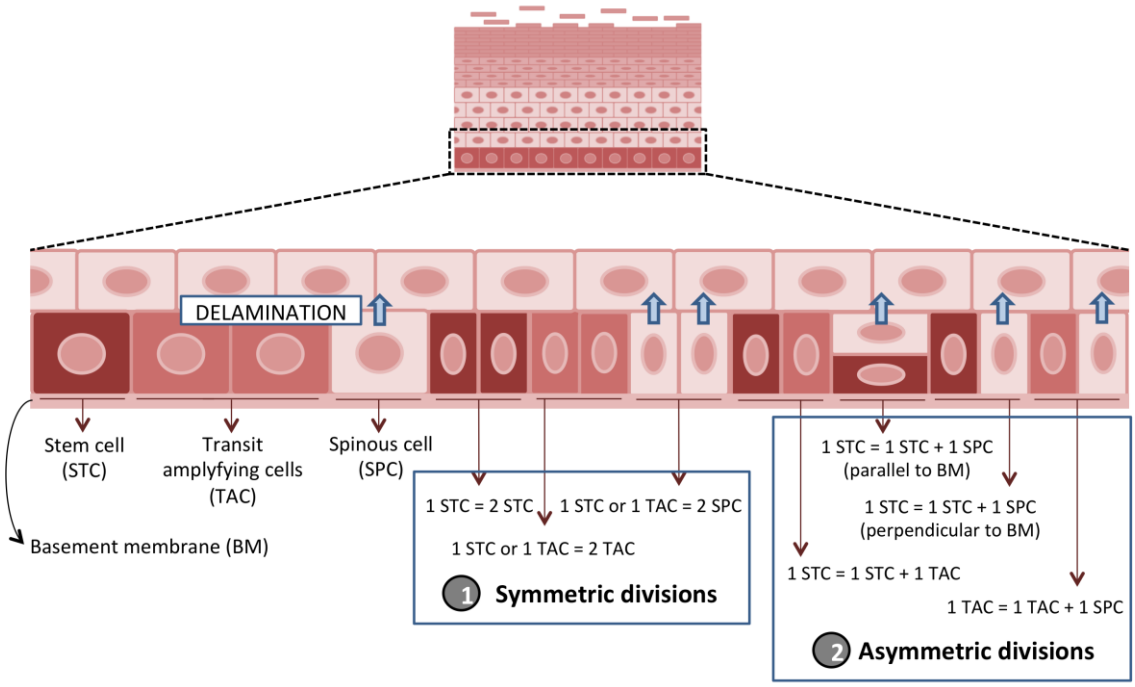

Figure 3. Epidermal cell renewal. Epidermopoiesis depends on proliferative cells present in the basal layer (BL). Stem cells (STC) generate transit amplifying cells (TAC), which have been postulated to divide four to five times, and/or spinous cells (SPC) committed to terminal differentiation. There are two main classifications for cell divisions: (1) symmetric, when both daughters adopt the same fate, or (2) asymmetric, when there is unequal segregation of a cell fate determinant, or when one of the daughters strays from the STC niche, resulting in daughters with distinct fates. The cell division plane can be parallel or perpendicular to the basement membrane

(BM). When spinous cells committed to terminal differentiation are originated in contact with the BM, a reduction of the adhesiveness to the substratum is needed for delamination (blue arrows), which allows cell migration and differentiation.

Specific markers have been identified as important controllers for the orientation of the division in basal cells; examples of such markers are the differential segregation of integrins, growth factor receptors, and the more recently described apical positioning of Par complex associated with the mInsc/LGN/NuMA complex for the anchorage of dynein and microtubules (Blanpain and Fuchs, 2009; Ray and Lechler, 2011). Recent studies on the maintenance of proper balance between stem cell quiescence and proliferation over the lifetime of the organism uncovered new regulatory networks for the control of the proliferation and terminal differentiation of epidermal stem cells, such as the regulation of Yap (Yes-associated protein) – a transcriptional effector of Hippo growth pathway – by the adherens junction component α-catenin (Flores and Halder, 2011; Schlegelmilch *et al.*, 2011; Zhang *et al.*, 2011).

Regarding the effect of aging under the conditions imposed by the dynamics of cell renewal in BL, thinning of the epidermis and its diminished self-healing capacity were at first associated with decreasing numbers of, or functional changes in, epidermal stem cells (Winter and Bickenbach, 2009). But this topic remains under discussion in the scientific community. Giangreco *et al.* (2010) observed, especially in subjects over 60 years, a significant reduction in rete ridge height and basal cell density, as well as a lower expression of two markers of human interfollicular epidermal stem cells: melanoma chondroitin sulfate proteoglycan (MCSP) and β1 integrins. There is a decline in the regenerative potential of tissue with age, which could be ascribed to intrinsic aging of stem cells and/or of the microenvironment of the tissue lodging the stem cells (Rando, 2006). Using a murine model, Liang and coworkers (2004) demonstrated that aged and young stem cells show similar plasticity response when placed in the developmental environment of a blastocyst, as well as similar gene and protein expression profiles. Stern and Bickenbach (2007) did not find significant differences in the epidermal stem cell number per unit area of the epidermis of footpads of young

and old adult mice. Moreover, they found similar characteristics in cell cultures from each of the two groups, including the same lengths for the telomeres and similar results for gene expressions related to cell cycling, apoptosis, stress response, and stem cell dynamics (no differences in the 422 tested genes, when comparing freshly isolated young and old epidermal stem cells). These results led the authors to conclude that epidermal stem cells are resistant to cellular aging. Both studies conducted by Liang *et al.* (2004) and Stern and Bickenbach (2007), suggest that the ability of stem cells to respond to environmental influences might not diminish with age. In support of this hypothesis, Giangreco and coworkers (2008) showed that epidermal stem cells are retained by the organism throughout its lifetime despite significant age-associated changes in dermal thickness, epidermal proliferation, and peripheral immune cell abundance, suggesting that local environmental or dermal factors, rather than stem-cell-intrinsic factors, influence skin aging. How stem cells preserve this capacity throughout lifetime remains unclear, but it may be due to an intrinsic set of stem cell genes, which are to be determined. In a study with stem cells from the bulge of skin hair follicles of young and aged human skin, the results found by Rittié *et al.* (2009) were similar to those observed in mice: aging did not alter the expression or location of hair follicle stem cell markers, and there were no significant differences in hair follicle density or bulge cell numbers between young and aged human scalp skin. Regarding the mechanisms of stem cell retention in the skin, the authors noted that hedgehog (Hh) signaling is activated in human bulge cells *in vivo* and down-regulated in differentiated hair follicule keratinocytes, both in young and aged skin. Some controversial results notwithstanding, increased telomerase expression and activity in epidermal basal cells may represent another possible mechanism for preserving the stem cell potential (Buckingham and Klingelhutz, 2011).

Even so, if the number and functionality of epidermal stem cells are not affected by aging, the question remains: what causes the structural changes observed in the elderly epidermis. Transit amplifying cells seem to play a key part in the answer. Even the authors, who did not detect differences in stem cells of the young and old, were able to identify some particularities in the characteristics of

transit amplifying cells (Giangreco *et al.*, 2008; Liang *et al.*, 2004; Stern and Bickenbach, 2007). Charruyer *et al.* (2009) demonstrated that transit amplifying cell frequency and cell cycle kinetics are altered in the aged epidermis. They used *in vivo* transplantation of green fluorescent protein-labeled epidermal cells to evaluate the formation of replicating units (RUs) from stem cells (long-term RUs, survived more than 9 weeks) or transit amplifying cells (short-term RUs, lost before 9 weeks). No differences were observed in the number of long-term RUs when comparing young and old keratinocytes, which indicated that the number of stem cells is relatively constant in aged and young epidermis. However, fewer short-term RUs were found after transplantation of young cells in comparison with transplantation of old cells, which seemed contradictory. The answer for this intriguing question was provided by a complementary discovery: the increased cell cycle duration in the aged cells. In their comments on the study, Winter and Bickenbach (2009) compared the findings described by Charruyer *et al.* (2009) to a crowded freeway: when the vehicles travel at lower speeds, overall result is more vehicles on the road at any given time, which could be an analogy to more transit amplifying cells in the aged epidermis. Increased number of transit amplifying cells in the aged epidermis might be a means of compensating their decreasing activity with age. Although the number of long-term RUs containing stem cells is similar in young and in aged epidermis, aging skin heals more slowly or is thinner because of a reduction in the efficiency of regeneration from transit amplifying cells.

When evaluating the effect of photoaging in epidermal proliferative populations, Kwon *et al.* (2008) found less keratinocyte stem cells and more transit amplifying cells in photoaged than in chronologically aged skin. In keratinocyte cultures, replicative senescence is a gradual process that occurs only when all stem cells have completed their clonal evolution and give rise to terminal transit amplifying cells, named paraclones. Cordisco and coworkers (2010) observed that human keratinocyte replicative senescence is associated with a progressive increase in the expression of $p16^{INK4a}$, whose expression is also detectable in primary keratinocytes from elderly subjects; $p16^{INK4a}$ is in particular constantly present in individuals of more than 70 years of age. Remarkably, first-passage

keratinocyte cultures show a strong positive correlation between stem cell depletion and early $p16^{INK4a}$ expression, indicating the presence of senescent cells in the epidermis from old donors. Presence of higher paraclone percentages and $p16^{INK4a}$ levels in keratinocyte cultures from old photoexposed skin, as compared with non-photoexposed skin, indicated that chronic UV exposure contributes to keratinocyte senescence. Moreover, the authors assigned the downregulation of Bmi-1, a $p16^{INK4a}$ repressor, a key role in the enforcement of primary human keratinocyte aging.

Although many studies corroborate the importance of transit amplifying cells, some authors understand that these cells might not be required for epidermal homeostasis; they favor, instead, a single proliferative progenitor cell population to sustain epithelial renewal (Clayton *et al.*, 2007). To clarify this issue and prove existence of transit amplifying cells, Mascré *et al.* (2012) conducted an elegant study based on the application of two Cre recombinase-oestrogen receptor (Cre-ER) transgenic mice that target interfollicular epidermis progenitors: Cre-ER under the control of the K14 promoter (K14-Cre-ER) and Cre-ER under the control of the involucrin promoter (Inv-Cre-ER); both allowing lineage tracing experiments by analyses of tamoxifen-induced fluorescence. Inv-Cre-ER targets committed progenitors (or transit amplifying cells) while K14-Cre-ER targets long-lived stem cells. Pattern of growth of individual clones targeted by the Inv-Cre-ER indicated that, following the divisions of committed progenitors (about 1 division per week), 80% resulted in asymmetric fate (leading to one dividing and one differentiated cell) with the remainder leading to symmetric duplication or differentiation with approximately equal probability. Dynamics of the clones targeted by K14-Cre-ER followed a quite different pattern, with an initial abrupt expansion followed by deceleration over the first few weeks, which indicates that, after division, stem cells re-enter a quiescent phase whereas their progeny go on to proliferate and differentiate. With a slower division rate (4 to 6 divisions per year), 80 ± 10% of stem cell divisions result in asymmetric fate (one stem cell and one committed progenitor cell), whereas the remaining divisions are equally balanced between stem cell duplication and symmetrical differentiation into two committed progenitor

cells (Figure 3). Mascré *et al.* (2012) also performed a molecular characterization of the cells, proving the existence, as much as the hierarchical organization and proliferation dynamics, of two distinct types of progenitors involved in epidermal homeostasis and repair.

Even without characterizing different progenitor cell lines, Doles and coworker (2012) showed changes in hair follicle stem cells during skin aging; such changes included increased cell numbers, decreased cell function, and an inability of cells to tolerate stress. This study shows that aging epidermis plays a part in the disruption of cytokine and stem cell homeostasis; this is characterized by an imbalance in the epidermal Jak-Stat signaling, which could easily be adjusted to fit the micro-inflammatory model (Giacomoni and Rein, 2004). Decline in epidermal functionality was interpreted as a mechanism for suppression of tumors that might occur with age. Castilho *et al.* (2009) used a murine transgenic model to evaluate the consequences of persistently expressing Wnt1 on epidermal stem cells. Rapid growth of the hair follicles caused epithelial cell senescence, disappearance of the epidermal stem cell compartment by the persistent activation of mTOR, and progressive hair loss. While the exhaustion of stem cells may act as a protective mechanism, helping to maintain the genetic integrity of the stem cell population and suppressing tumor formation, persistent activation of mTOR may contribute to cell senescence and, consequently, accelerate aging. Absence of the vitamin D receptor also leads to a reduction in the number of keratinocyte stem cells and impair their function, both *in vivo* and *in vitro*, disturbing the cyclic regeneration of the hair follicle (Luderer and Demay, 2010). Some authors believe that the aging-induced delay in epidermal turnover is related to a decrease in the energy metabolism of epidermal basal cells, suggesting that adenosine 5’-monophosphate (AMP) may accelerate the epidermal turnover delayed by aging (Furukawa *et al.*, 2008). Janich *et al.* (2011) described a circadian molecular clock in a murine model that creates epidermal stem cell heterogeneity, with coexisting populations of cells at opposite phases of the clock, like dormancy and activation. Core clock protein aryl hydrocarbon receptor nuclear translocator-like (Arntl or Bmal1) modulates the expression of stem cell regulatory genes in an oscillatory manner, to create

populations that are either predisposed or less prone to activation. Janich *et al.* (2011) also found that stem cell arrhythmia can lead to premature epidermal aging.

Most studies on the source of epidermal renewal focus the cellular properties of keratinocytes in BL, but other cells types and the supportive structure of BM also seem affected. Proliferative cells must be maintained in a specific microenvironment to preserve renewal potential. Therefore, age-associated effects of the structural organization of this niche may impact the maintenance of proliferative cells over life. Relatively high incidence of anti-BM antibodies observed in serum samples from elderly subjects exemplifies this and, in fact, highlights occurrence of a specific immune defect in elderly individuals; this probably contributes to the reduction of the rete ridge height of aged epidermis, which, in turn, could lead to a decreasing exchange of nutrients between the epidermis and dermis (Hachisuka *et al.*, 1996). BM of sun-exposed skin becomes damaged and multilayered, and partly disrupted in comparison with the BM of sun-protected skin; BM fragmentation includes the participation of matrix metalloproteinases (MMPs) and plasmin (Amano, 2009).

As for the different proliferative cells types in epidermal BL, Steingrímsson *et al.* (2005) reviewed the subject of melanocyte stem cells and their impact on hair graying, and discussed importance of paired box 3 (Pax3) transcription factor and of microphthalmia-associated transcription factor (Mitf) as key molecules that help to regulate the balance between maintenance and differentiation of melanocyte stem cells. Pax3 works simultaneously to initiate a melanogenic cascade while acting downstream to prevent terminal differentiation. Pax3 activates Mitf expression and at the same time prevents Mitf from activating downstream genes, by competing for enhancer occupancy. Thus, Mitf accumulates until the Pax3-mediated repression is relieved by external stimuli, when the cellular dormant state is broken and differentiation occurs rapidly (Lang *et al.*, 2005). Using the Mitf presence as a typical marker of proliferative melanocytes, Nishimura *et al.* (2005) evaluated the presence of these cells in aging human hair follicles and identified Bcl-2 as a critical molecule for the preservation of melanocyte stem cells – specifically for their entry into dormancy. While melanocyte stem cells were

abundant in follicles from young (20-30 year-old) subjects, which represented 2 to 3% of the total basal keratinocytes in the bulge area, the numbers of melanocyte stem cells were lower in middle-age (40-60 year-old) individuals and absent in most hair follicles of old (70-90 year-old) subjects. Briefly, there is a loss of melanocyte stem cells with age, which temporally precedes loss of differentiated melanocytes in hair matrix.

Describing bath volume: differentiation and signaling mechanisms

Bath Volume represents the second step of the epidermal bath model that is here refilled in detail (Figure 1). Several molecular pathways are involved in regulation of processes creating the stratified epidermal structure. The multilayer organization contains cells with different profiles, which go through a course of continuous differentiation that is governed by a complex network of signaling mechanisms. As such, epidermal bath volume represents a complex and integrated biological system to be explored especially in regard to dynamic changes related to aging (Figure 4).

Calcium is a good example of ions involved in the control of epidermal structure and functionality. Calcium is differentially distributed among cell layers, as an essential element for keratinocyte differentiation, and for maintaining skin barrier homeostasis (Elias *et al.*, 2002). The distribution of calcium in the epidermis varies with age (Denda *et al.* 2003). In young and healthy skin, there is a calcium gradient characterized by low concentration levels in inner layers, such as BL and SL, and by an increasing availability of extra and intracellular calcium, which is reached at its highest levels of concentration in GL. In skin samples of older individuals, however, calcium is distributed equally among all epidermal layers, without forming the gradients observed in young skin (Denda *et al.* 2003). Although direct evidence for this difference in calcium distribution is lacking, it is probably related to structural changes and clinical disorders that affect aged epidermis.

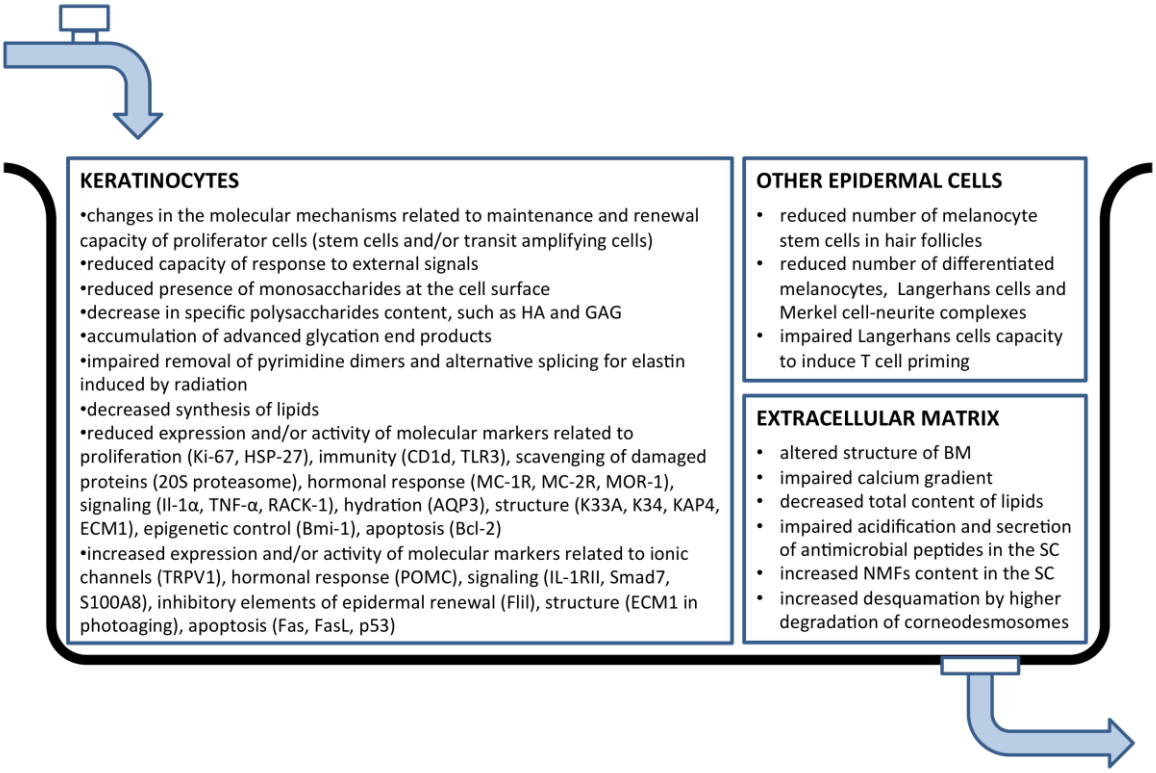

Figure 4. Refilling bath volume with the major cell and molecular changes involved in epidermal aging. Several mechanisms and pathways describe the effects of aging on epidermis. The vast majority of literature focuses on keratinocyte-related changes, but investigations of other epidermal cells and of the epidermal extracellular matrix organization have also yielded interesting findings. AQP3 (aquaporin 3), Bcl-2 (apoptosis protein B-cell lymphoma 2), BM (basement membrane), Bmi-1 (polycomb ring finger oncogene BMi-1), CD1d (cluster of differentiation 1d), ECM1 (extracellular matrix protein 1), Fas (cluster of differentiation 95), FasL (cluster of differentiation 95 ligand), Flil (flightless 1), GAG (glycosaminoglycan), HA (hyaluronic acid), HSP-27 (heat shock protein 27), Il-1α (interleukin 1α), IL-1RII (interleukin 1 receptor type II), K33 (keratin 33), K34 (keratin 34), KAP4 (keratin-associated proteins group 4), Ki-67 (nuclear protein Ki-67), MC-1R (melanocortin receptor 1), MC-2R (melanocortin receptor 2), MOR-1 (μ-opiate receptor 1), NMFs (natural moisturizing factors), p53 (protein 53), POMC (pro-opiomelanocortin), RACK-1 (receptor for activated C kinase 1), Smad7 (intracellular protein mothers against decapentaplegic homolog 7), S100A8 (S100 calcium binding protein 8), SC (stratum corneum), TLR3 (toll-like receptor 3), TNF-α (tumor necrosis factor α), TRPV1 (transient receptor potential cation channel subfamily V member 1).

Using a mouse model, Denda *et al.* (2001a) showed that the skin surface potential is affected by the ion flow between the outside and the inside of

keratinocytes. When calcium or magnesium ions move toward the bottom of the epidermis, skin surface potential becomes negative. Whether potential itself has a role in the epidermal function requires investigation, but it has already been reported to induce keratinocyte migration, accelerate wound healing, and influence skin metabolism or homeostasis (Denda *et al.*, 2001a; Nuccitelli, 2003; Sheridan *et al.*, 1996; Weiss *et al.*, 1990). Thus, an inadequate calcium distribution in aged epidermis may contribute to damage the regeneration capacity of the skin – a typical clinical sign in elderly. Another consequence of the altered calcium gradation in epidermis of older subjects is an increase in exocytosis of lamellar bodies (Menon *et al.*, 1994). Lamellar body secretion and lipid structure is abnormal in the epidermis of patients with Netherton syndrome, a skin disorder characterized by chronic inflammation and universal pruritus (Fartasch *et al.*, 2009). Pruritus is common in older adults and possibly associated with changes in the nerve fibers of aged skin. TRPV1, an ion channel permeable to calcium expressed in keratinocytes and free epidermal nerve endings, has recently been reported to be increasingly expressed under conditions of intrinsic aging and photoaging (Lee *et al.*, 2009a; Lee *et al.*, 2012). While increased TRPV1 expression in nerve fibers in aged skin suggests an important role of this ion channel in the pathophysiology of itchy skin in elderly subjects, it also points to a possible cause for the age-disrupted epidermal calcium gradient. Until now, the few publications in this field do not provide a robust model for ion dynamics at the cellular level of aged epidermis; an overall dysfunction in pumps, ion channels or ionotropic receptors, however, might be a reliable candidate to explain altered dispersion of calcium and consequent morphologic and functional abnormalities seen in older individuals (Denda *et al.*, 2003). Since monosaccharides are capable of regulating calcium pump function, it is possible that abnormal distribution of calcium in aged epidermis may be related to the reduced presence of monosaccharides at the surface of epidermal cells (Georgiou *et al.*, 2005; González Flecha *et al.*, 1999; Tengholm *et al.*, 2001). A study analyzing the influence of age on the carbohydrate residue composition of keratinocyte plasma membranes in human sun-protected skin detected no changes in the concentration

and distribution of β-D-galactose, D-galactose-β-(1,3 N-acetylo-D-galactosamine), β-(1,4-D-N-acetylo-βD-glucosamine) and α-D-N-acetylo-D-galactosamine at the cell surface with age, while the expression of α-D-mannose, α-D-glucose and α-L-fucose at the cell surface reveals marked reductions in the groups of people over 50 years of age (Georgiou *et al.*, 2005).

Other findings point to molecules or mechanisms related to increased difficulty of the epidermis to sense external signs, protect the interior of the body and/or eliminate damage caused by aggressors, when comparing samples from individuals of different age groups. Overall, the effect of increasing age on keratinocyte response both to exogenous and endogenous mitogens is striking and marked by a significant decrease in mitogenic responsiveness and colony-forming potential (Gilchrest and Yaar, 1992). Ki-67 is a nuclear protein that is associated with, and may be necessary for, cellular proliferation. Staining of Ki-67, an indication of proliferation index in young epidermis, was approximately twice as strong in younger than in older epidermis (Gilhar *et al.*, 2004). HSP-27 decreases in the epidermis with age, which might impair keratinocyte differentiation (Jonak *et al.*, 2006; Jonak *et al.*, 2011). A gradually decreasing level of CD1d protein production in human epidermis with age was also reported, suggesting a lowering of the immune response. CD1d belongs to a family of antigen-presenting molecules that are structurally related to the classic major histocompatibility complex (MHC) class I proteins; in normal human skin, CD1d protein production is confined to keratinocytes immediately beneath the lipid-rich stratum corneum (Adly *et al.*, 2006). The 20S proteasome shows an age-related decline in activity that is associated with changes in its subunits, suggesting impairment of the epidermal proteolytic system, which should be responsible for the removal of abnormal and oxidatively damaged proteins (Bulteau *et al.*, 2000).

A key element of innate protection is the recognition of pathogen-associated molecular patterns (PAMPs) by Toll-like receptors (TLRs) expressed by several cell types, including skin keratinocytes. TLR3, specifically related to antiviral defense, exhibited enormous differences in the magnitude of expression and function, including enhanced secretion of cytokines (such as CXCL8/IL8,

CXCL10/IP-10 and TNF-α) in epidermal keratinocytes, before and after birth, when compared with adults, suggesting the existence of age-specific responses (Iram *et al.*, 2012). In assessing the ability of keratinocytes to respond to hormonal stimulation according to the aging status, Pain *et al.* (2010) studied pro-opiomelanocortin (POMC) and related receptors, such as melanocortin receptors 2 and 1 (MC-2R and MC-1R) and μ-opiate receptor 1 (MOR-1) for adrenocorticotrophic hormone (ACTH), α-melanocyte stimulating hormone (α-MSH), and β-endorphin, respectively. Gene and protein expression of MC-1R, MC-2R and MOR-1 dramatically decreased with age, whereas POMC increased five-fold. Results were more significant around 50 years of age, which could include menopausal women, suggesting a significant contribution of menopause to changes in epidermal physiology with aging. Ye *et al.* (2002) addressed the hypothesis that cytokine dysregulation may cause permeability barrier abnormality in aged epidermis, mainly as a result of altered expression of interleukin 1 (IL-1) family of cytokines and receptors, which could help to explain decreasing mitogenesis and lipid synthesis with epidermal aging. Gene and protein expression of aquaporin 3 (AQP3), involved in the transport of water and glycerol to hydrate the skin, decreases with increasing age in human epidermis and isolated keratinocytes; this decrease is probably involved in the development of xerosis (Li *et al.*, 2010). In a study with knockout mice, Rezvani *et al.* (2011) identified a significant role of the hypoxia-inducible factor 1a (HIF-1a) in epidermal homeostasis, because the downregulation of HIF-1a lead to decreased expression of α6 integrin and β1 integrin, diminished keratinocyte- colony-forming efficiency, and arrested cell cycle progression, which, acting together, could contribute to epidermal aging and pronounced failure in epidermal reconstruction.

Aging in hair follicles is associated with a decline of structural proteins such as certain keratins and keratin-associated proteins (KAP). While the expression of K31, K32, K36, K85 and K86 is unaffected by aging, K33A, K34 and the group of KAP4 genes produce a statistically significant decline in gene activity above 50 years of age (Giesen *et al.*, 2011). Aging additionally leads to a diminished epidermal content in specific polysaccharides, such as hyaluronic acid (HA) and

GAGs usually attached to extracellular matrix proteins to form proteoglycans (PG). Oh *et al.* (2011) described the age-promoted reduction in epidermal HA and heparan sulphate content, determined as an isolated GAG or composing different PGs such as perlecan and syndecan-1. According to Stern and Maibach (2008), although dermal HA is responsible for most skin HA, epidermal cells are also able to synthesize HA, mainly located in the upper SL and GL, where most of it is extracellular; BL also has HA, but it is predominantly intracellular. Proportion of total GAG synthesis devoted to HA is greater in the epidermis than in the dermis and, in senile skin, HA is still present in the dermis, whereas the HA of the epidermis seems to disappear with unknown reasons (Meyer and Stern, 1994; Stern and Maibach, 2008). An increase in the content of keratan sulphate beginning at age 50 and a decrease in chondroitin 6-sulphate after age 60 were observed in human epidermis (Willen *et al.*, 1991). These changes may indicate declining skin physiologies, including epidermal proliferation, cell adhesion, migration and various cellular signalings (Bourguignon *et al.*, 2006; Lundqvist *et al.*, 2001; Parish, 2006; Tkachenko *et al.*, 2005).

Epigenetics is also part of the age-affected mechanisms in epidermis. Proteins of the Polycomb group (PcG) are epigenetic suppressors that act by modifying histones to change the structure of chromatin and modulate gene expression and cell behavior. These proteins are found in a wide variety of cells in the progenitor, BL and suprabasal layers of the epidermis, where they regulate the keratinocyte cell-cycle progression, apoptosis, senescence, and differentiation (Eckert *et al.*, 2011). PcG protein expression, such as Bmi-1, declines in aging epidermis, which shows that a loss of PcG protein expression is associated with keratinocyte senescence both *in vivo* and in cell culture models (Cordisco *et al.*, 2010; Eckert *et al.*, 2011). The presence of the β6 integrin subunit in epidermis helps to explain the significant delay that occurs in the wound healing of elderly people (AlDahlawi *et al.*, 2006). In addition to the decreasing numbers of structural molecules, inhibitory elements of epidermal renewal are up-regulated with age; one such element is the actin-remodeling protein Flightless I (FliI), an important mediator of wound repair by inhibiting cell proliferation and motility (Adams *et al.*,

2008). Skin immunosenescence refers to a functional immune impairment with age. In the epidermis, it is associated with decreased expression of the receptor for activated C kinase (RACK-1), defective protein kinase C (PKC) translocation, and reduced tumor necrosis factor (TNF-α) (Corsini *et al.*, 2009). Formation of advanced glycation end products (AGEs) is the result of a chemical reaction between reducing sugars and amino acids of proteins, and is related to skin aging. AGE accumulation has been extensively studied in dermal proteins, but the presence of N^{ε}-(Carboxymethyl) lysine was recently described in the human epidermis as affecting specifically K10 (Kawabata *et al.*, 2011).

Impact of UV light on human skin is a particular source of epidermal dysfunction throughout life. Yamada *et al.* (2006) found that the removal of pyrimidine dimers induced by UVB occurs more slowly in the epidermis of older individuals. Time for complete removal of dimers was 4 days in the 22- to 26-year-old group, while 14 days were needed in the 70- to 78-year-old group. DNA damage induced by generation of free radicals can be yet another pathway involved in skin photoaging. In photoaged skin, a significant depletion of antioxidant enzyme expression, including copper-zinc superoxide dismutase and catalase, was observed inside the SC and in viable epidermis (Sander *et al.*, 2002). Transforming growth factor-beta (TGF-β) signaling in the epidermis – important for cell growth and collagen regulation – is also affected by UV-induced photoaging. Upon activation, TGF-β receptors (TβR) propagate a signal downstream to intracellular proteins termed Smads. Han *et al.* (2005) demonstrated that the UV-induced down-regulation of TβRII and the concerted over-expression of Smad7 in aged and photoaged epidermis may trigger the inhibition of the TGF-β-induced phosphorylation of Smad2, suggesting an active role of the epidermal compartment in the induction of age-related dermal collagen damage. S100 calcium-binding proteins are highly conserved, low-molecular-weight, acidic proteins with important regulatory functions in calcium buffering, regulation of kinases and phosphatases, cell proliferation, differentiation, energy metabolism, cytoskeletal-membrane interactions, embryogenesis, cell migration, and inflammation (Donato, 2001). Lee *et al.* (2009b) studied changes in S100A8

expression in UV-irradiated and aged human skin *in vivo*, finding increased mRNA and protein in the sun-protected epidermis of elderly people in comparison with youth. Additionally, in the same elderly individuals, sun-exposed skin expressed more S100A8 than sun-protected areas, evincing the intrinsic involvement of S100A8 in both the aging and the photoaging processes of the epidermis.

Another example of a molecular mechanism affected in the epidermis by UV-induced aging is the regulation of alternative splicing, as in the case of the primary transcript of elastin. Elastin transcript containing exon 26A was found upregulated in keratinocytes of photoaged forearm skin compared with intrinsically aged buttock skin in the same elderly individuals, which can affect normal elastic fiber formation and contribute to the development of solar elastosis (Chen *et al.*, 2009). Several publications point to UV-induced photoaging as an exacerbation of the signs of intrinsic aging. However, mainly at the molecular level, the result of cumulative UV exposure sometimes differs from the effect of intrinsic aging. Expression of extracellular matrix protein 1 (ECM1) in BL and upper epidermal cell layers in aged skin, for example, is significantly lower than in young skin. In contrast, and similarly to solar elastosis in the dermis, photoaging shows an increased epidermal expression of ECM1. More than impairing the regular dynamics of keratinocyte proliferation and/or differentiation, ECM1 has a key interaction with BM perlecan, and an affected ECM1 expression may impact the dermal-epidermal junction physiology (Sander *et al.*, 2006).

Terminal differentiation of keratinocytes is marked by cell death that typically occurs in GL to originate corneocytes in the composition of the SC. There is controversy as to whether the terminal differentiation of keratinocytes is a variant of apoptosis. Both processes share activation of endonucleases and degradation of DNA. However, apoptosis differs from terminal differentiation in other respects. When comparing sun-protected skin of two groups of people with a mean age of 70 years and 23 years respectively, epidermal thinning with age was associated with a decrease in the proliferative capacity and an increase in the rate of apoptosis of keratinocytes below GL, along with a higher expression of Fas (CD95) and Fas ligand (FasL). In contrast, keratinocytes showing DNA strand breaks, which occur

at the GL as part of normal keratinocyte differentiation, do not appear related to Fas (Gilhar *et al.*, 2004).

Since cellular senescence and apoptosis occur together in aging tissues, it is important to understand their mutual relationships in aging. Wang *et al.* (2004) found increased senescence-associated β-galactosidase activity in aging keratinocyte cultures as well as in epidermal *in vivo* aging. In parallel, they observed increased levels of Fas and different components of the Fas-mediated pathway of apoptosis (such as Fas-L, FAAD adaptor and caspase-8 – all contributors to the death-inducing signaling complex, or "DISC"), higher levels of p53 (a tumor suppressor protein that can promote either apoptosis or transient growth arrest and cellular senescence), and lower levels of Bcl-2 (a mitochondrial component and crucial inhibitor of the intrinsic pathway of apoptosis) under the same conditions, both *in vitro* and *in vivo*. Moreover, when the Fas receptor was activated by antibody binding, or when the culture medium was exhausted (a possible cause of death signal induction), apoptotic cells appeared in larger numbers in senescent keratinocytes, showing that the Fas-dependent apoptotic machinery was indeed potentiated in keratinocytes at senescence. Considering the existence of distinct apoptotic pathways and of results that vary with the different experimental models, Wang *et al.* (2004) concluded that it was reasonable to assume that in senescent keratinocytes, the Fas-mediated pathway can be readily activated, while the p53-dependent pathway is kept in a stand-by state.

In addition to the changes affecting keratinocytes with aging, there are modifications associated with distinct epidermal cell types, such as a reduction in number of melanocytes, and a decline in the amount of Langerhans cells (which may impair the immune protection against radiation). There are also changes in the structural organization of Merkel cells (Bergman *et al.*, 2000; Ortonne, 1990; Wulf *et al.*, 2004). With aging, melanocytes become unevenly distributed in epidermis, which affects the interaction between keratinocytes and melanocytes (Ortonne, 1990). The number of functional melanocytes in nonexposed human skin decreases with age, at a rate of 8-20% each decade. However, in UV-irradiated skin there are approximately twice as many melanocytes as in unexposed areas,

but there is still a comparable decrease in melanocytes with age (Costin and Hearing, 2007). Secretion of melanocyte-stimulating cytokines was impaired in old donors (Okazaki *et al.*, 2005). mRNA expression and activity of nicotinamide adenine dinucleotide (NADH) dehydrogenase decreases in late passage cultures of keratinocytes, suggesting reduction in enzyme production with epidermal aging (Nakama *et al.*, 2012). Furthermore, inhibition of NADH dehydrogenase induces production of reactive oxygen species (ROS) in mammalian tissue (Paradies *et al.*, 2004). As positive feedback, increased levels of ROS induce the production of IL-1α and endothelin 1 (EDN1), upregulation of tyrosinase expression, and acceleration of skin melanogenesis (Hughes *et al.*, 1996; Karg *et al.*, 1993; Nakama *et al.*, 2012). Consequently, age-related decrease in NADH dehydrogenase might be directly involved in the regulation of keratinocyte-melanocyte signaling, and lead to increased skin pigmentation. Mouse models also indicate age-dependent reduction in Langerhans cell frequency without affecting their survival and proliferation in epidermis, suggesting either a deficiency in bone marrow-derived Langerhans cell progenitors, or a less responsive profile to signals known to be required for the recruitment of these progenitors into skin. Functionally, the capacity of aged Langerhans cells to induce T cell priming is impaired. Moreover, expression of microRNAs (miRNAs) in aged epidermal Langerhans cells shows an altered profile in comparison with that of a young epidermis, a condition that is especially noteworthy in miRNAs related to the downregulation of TGF-β signaling pathway, which affects the development of Langerhans cells (Xu *et al.*, 2012). TNF-α-induced migration of Langerhans cells appears reduced in elderly (Bhushan *et al.*, 2002). However, another study concluded that phenotype and function of monocyte-derived Langerhans cells are not altered by aging, and that changes in the epidermal environment are likely to be more important (Ogden *et al.*, 2011). Notwithstanding a few differing opinions, in the photoaging of human skin, the numbers of Langerhans cells are inversely proportional to photodamage severity: cells are reduced by up to 50% in UV-exposed skin areas in comparison with UV-protected skin areas (Grewe, 2001). Regarding the effect of aging on the epidermal sensorial system, a decrease in the

target neurotrophin (NT) expression has been demonstrated, particularly in NT3 and NT4, which results in a site-specific loss of sensory terminals with a reduction in the number of Merkel cell-neurite complexes (Bergman *et al.*, 2000).

Unstopping the plughole: biological and physicochemical properties and SC desquamation

The third step of the bath model, desquamation (Figure 1), emphasizes SC structure and organization. Basically, SC is composed of two compartments: intact, lipid-depleted and protein-enriched corneocytes, which represent the “bricks” embedded in a continuous, lipid-enriched (mainly ceramides, cholesterol and free fatty acids) extracellular matrix that is organized into functional membrane bilayers representing the ‘‘mortar’’ (Michaels *et al.*, 1975). The construction of competent epidermal lipid bilayers takes place according to the following sequence: lipid synthesis, secretion of lamellar body lipids at the GL-SC interface, and extracellular processing of secreted polar lipid precursors into a hydrophobic mixture that forms functionally competent lamellar membranes (Choi *et al.*, 2007). In fact, corneocytes in the SC are dead cells, but this does not make it an inert layer. On the contrary: SC is metabolically active and interactive with the underlying nucleated cell layers of the epidermis (Elias and Ghadially, 2002). Changes that the SC suffers with aging have a great impact on the epidermal permeability barrier, damaging the basic composition of the “brick and mortar” model (Figure 5).

Xerosis is an uncomfortable manifestation of aged skin, which may result from a decrease in lipid synthesis (Akimoto *et al.*, 1993). Schmuth *et al.* (2005) showed differences in production of fatty acid transport proteins between embryonic and adult epidermal tissues, indicating that a dynamic regulation of these constituents is active throughout the development stages of an individual. Ghadially *et al.* (1995) found a reduction in the delivery of secreted lipids to the SC, resulting in less extracellular lamellar bilayers. There is an overall reduction in aged SC lipids that totals about one third less lipid weight percentage than in young SC, suggesting that aged epidermis possibly has a more porous extracellular matrix

than the young one (Elias and Ghadially, 2002). In addition, several molecular pathways involved in SC lipid metabolism are down-regulated at the level of gene expression in the aging skin and probably contribute to the decreased capacity of aged skin to maintain and repair the epidermal barrier (Jarrold *et al.*, 2009). Decreased levels of IL-1α with chronologic aging must be associated with a decreased production of epidermal lipids (Ye *et al.*, 1999). According to Ghadially *et al.* (1996), cholesterol seems the most age-affected class of lipids in the SC, which shows a reduced deposition of cholesterol molecules and a decreased activity of its rate-limiting enzyme, 3-hydroxy-3-methylglutaryl-coenzyme A reductase. Several studies show that different classes of SC lipids are differently affected by aging.

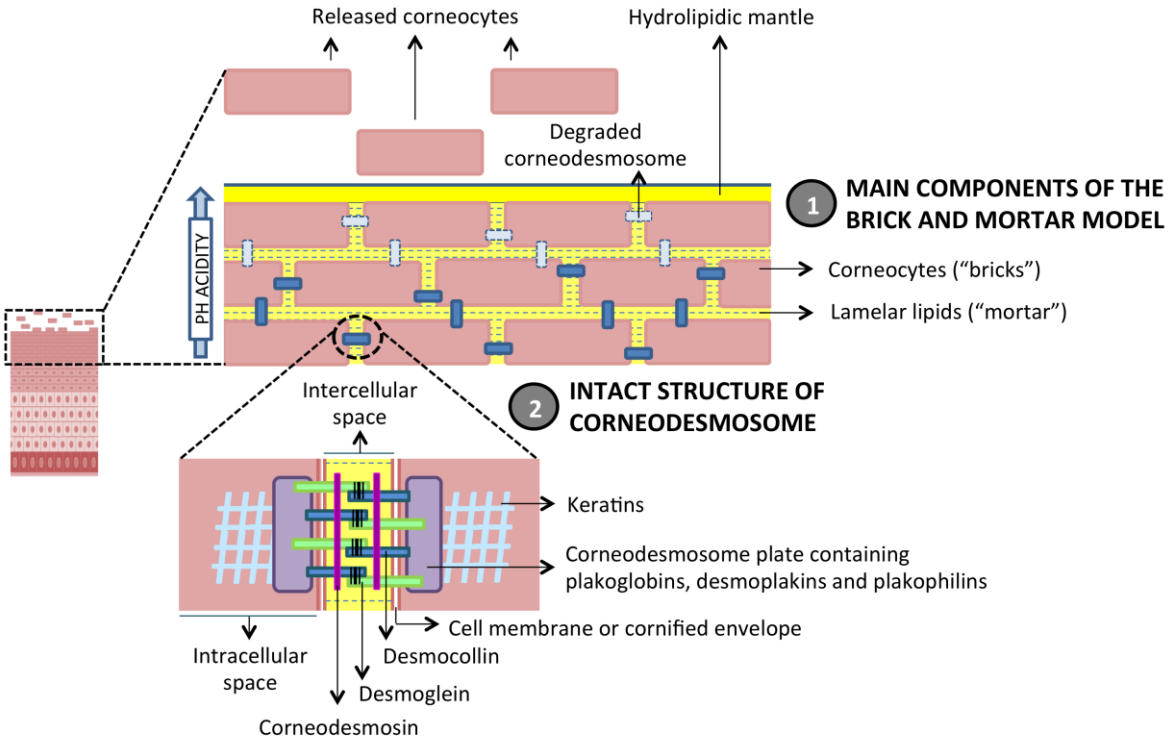

Figure 5. Stratum corneum (SC) organization. (1) “Brick and mortar model” proposed by Michaels *et al.* (1975) highlights the main components of SC structure: the “bricks” are lipid-depleted and protein-enriched dead corneocytes embedded in the “mortar”, which is composed of a continuous, lipid-enriched (mostly by ceramides, cholesterol and free fatty acids) extracellular matrix organized into functional membrane bilayers. Extracellular pH is neutral up to the transition between granular layer (GL) and SC. Then it turns more acidic and reaches approximately 4.5 up to the skin surface,

where there is a hydrolipidic or acid mantle composed of a mixture of sebum, sweat, corneocyte debris and constituents of natural moisturizing factors. (2) Corneodesmosomes – structures derived from desmosomes – are responsible for securing the cohesion of intercorneocytes, and are present at the cell edges on the skin surface. Corneodesmosomes are incorporated into the cell membrane or cornified envelope and are composed of several cytoplasmic (plakoglobins, desmoplakins and plakophilins), transmembrane (desmogleins and desmocollins) and extracellular proteins (corneodesmosin). Corneodesmosin bonds to desmosomes to form corneodesmosomes. During corneocyte maturation, corneodesmosomes are progressively degraded by several serine, cysteine and aspartic enzymes, including kallikrein-related peptidases and cathepsins. This facilitates the desquamation process which is characterized by the release of corneocytes from the skin surface by friction forces.

Epidermal ceramides are obtained by hydrolysis of sphingomyelin or else by means of a synthesis from sphingosin and fatty acids, and are degraded by ceramidase. Sphingomyelinase activity declines with age: 80-year-old individuals have 25% of the activity found in 20-year-olds (Yamamura and Tezuka, 1990). Denda *et al.* (1993) demonstrated age- and sex-dependent change in SC sphingolipids, by evaluating ceramides 1-6. No differences were found in men, while women showed significant modifications: from prepubertal age to adulthood, ceramides 1 and 2 increased while ceramides 3 and 6 decreased; after reaching maturity, ceramide 2 decreased and ceramide 3 increased with age. These results suggest a significant influence of female hormones on SC sphingolipid composition. De Paepe *et al.* (2004) found sex-related differences at the level of total ceramide concentration: there were higher ceramide concentrations in men as compared with age-matched females. Effect of aging was significant only for a decrease in cholesterol sulfate and cholesterol concentrations in the abdominal skin. However, evaluations of the total amounts of lipids showed no changes due to sex or aging, which calls into question the high intervariability of the studies of lipids in the human SC, because of the different origins of the skin samples and variety of extraction methods currently in use. Jensen *et al.* (2005) used a mice model to identify the age-related reduction in acid sphingomyelinase (A-SMase) and ceramide synthase activities, but the changes were observed only in the inner layers of epidermis, not the SC.

Regarding SC free fatty acid composition, Kim *et al.* (2010a; 2010b) studied the effect of aging in photoprotected and photoexposed areas of the skin. Levels of palmitic acid, stearic acid, linoleic acid and 11,14,17-eicosatrienoic acid (ETA) decreased in aged skin by 15%, 31%, 7%, and 56%, respectively, in comparison with levels of the same acids in young skin. In contrast, palmitoleic acid and oleic acid levels increased in aged skin by 67% and 22%, respectively. Levels of palmitic acid and stearic acid in photoaged forearm epidermis decreased by 11% and 23%, respectively, compared with levels of these acids in the buttock skin of the same elderly individuals. Conversely, amounts of linoleic acid and ETA in photoaged forearm epidermis increased by 19% and 69%, respectively. The authors emphasized the results for ETA, an omega-3 polyunsaturated acid, which increased significantly in photoaged human epidermis *in vivo*, but decreased significantly in intrinsically aged epidermis. They also demonstrated that ETA inhibited MMP-1 expression after UV-irradiation, which may suggest the existence of a photoprotective effect for human skin. In general, Kim *et al.* (2010a; 2010b) concluded that the amounts of free fatty acids and triglycerides decreased significantly in the epidermis of photoaged human SC. Moreover, the expression of genes related to lipid synthesis, including acetyl-CoA carboxylase (ACC), fatty acid synthase (FAS), stearoyl-CoA desaturase (SCD), sterol regulatory element binding proteins (SREBPs), and peroxisome proliferation-activated receptors (PPARγ) decreased markedly with photoaging.

Although several studies focus on differences in the composition of lipids and on the regulatory mechanisms related to lipid synthesis, secretion and processing of lipids are crucial steps in construction of an efficient epidermal barrier. Secretion is regulated by changes in extracellular calcium and potassium concentrations (Mauro *et al.*, 1998a and b; Menon *et al.*, 1985). Association of calcium with lamellar body disc membranes and contents suggests that it may contribute to lamellar body secretion as well as to the formation of intercorneocyte membrane bilayers (Menon *et al.*, 1985). In addition, selective obliteration of the epidermal calcium gradient by means of sonophoresis enhanced lamellar body secretion (Menon *et al.*, 1994). As previously mentioned, aging hinders the

formation of calcium gradients in epidermis (Denda *et al.* 2003). It can therefore be said that age-induced changes in the distribution of calcium in the epidermis may have an impact on the SC formation in elderly individuals. While lipid secretion is strongly influenced by ions, lipid processing is controlled by the pH of the extracellular spaces and requires two acidity-dependent lipid hydrolases: β-glucocerebrosidase (BCG) and A-SMase (Hachem *et al.*, 2005). SC normally has a low pH value, which favors the enzymatic activity necessary for its formation. However, changes in pH values may cause modifications in the enzymatic dynamics of the SC; again, aging is a relevant factor in the control of the pH on the skin surface. Choi *et al.* (2007) demonstrated that SC acidification is already weakened in moderately aged human and murine skin, showing that pH value rises progressively in aged humans beginning at about age 50. Prolonged SC neutralization causes profound abnormalities in SC function, due to the activity of pH-induced high serine proteases, which, in turn, degrade lipid processing enzymes, such as BCG and aSM'ase (Hachem *et al.*, 2005). Investigating the molecular regulation of pH changes in the SC, Choi *et al.* (2007) found a diminished Na^+/H^+ antiporter (NHE1) expression that lead to increased pH values in the SC and, consequently, to defective processing of lipids and delayed maturation of lamellar membranes.

Nevertheless, divergences should be noted in results regarding continuous pH increase with aging. Luebberding *et al.* (2013) evaluated 150 women aged 18 to 80 years and found decreased surface pH associated with a continuous decline in sebum production with age. Interestingly, pH decrease was not observed in moderately aged, 50-60 year-old women, who showed slightly increased pH values. In a large Chinese panel consisting of 713 subjects, skin surface forehead pH of males and females over the age of 70 was higher than in younger groups (Man *et al.*, 2009). These differences could, of course, be attributed to different experimental designs and applied techniques, but they are in agreement with the finding of impaired acidification in moderately aged epidermis. According to Choi *et al.* (2007), advanced aging is likely to reveal a combination of abnormalities in the synthesis and processing of lipids; however, at least in moderately aged epidermis,

barrier dysfunction due to an impaired acidification of the SC leads, not to an abnormal synthesis, but to a diminished processing of lipids.

Antimicrobial protection depends on the maintenance of an acid pH in the SC to create an ecological milieu that is simultaneously hostile to microbial pathogens and favorable to the growth of the normal flora. Rodriguez-Martin *et al.* (2011) evaluated antimicrobial peptides in a mouse model for aging and found reduced levels of cathelicidin antimicrobial peptide (CAMP) and increased levels of β-defensin 3 (BD3) and of the neuroendocrine peptide catestatin (Cst). Whether further abnormalities in antimicrobial defense mechanisms occur in moderately aged and/or more-advanced aged and/or photoaged epidermis is not known. However, taken together, these findings suggest that antimicrobial protective function of SC might become impaired relatively early in older people. Mixture of sebum and small amounts of lipids, produced by keratinizing epidermal cells (mainly corneocytes), forms the skin surface lipids (SSL) that mantle human epidermis, and thus constitutes a protection of the body against exogenous oxidative insults (Passi *et al.*, 2002). Total SSL vary according to sex and age: they are higher in males than in females, peak at maturity and diminish with age because of a reduction in the activity of sebaceous glands (Cotterill *et al.*, 1972). Different fatty acids of triglycerides seem to follow the activity of the sebaceous glands: they are higher at maturity than in childhood and advancing age; while squalene, vitamin E and Coenzyme Q_{10} increase from childhood to maturity to decrease again significantly in old age (Passi *et al.*, 2002). These results suggest important changes at the top of SC with aging, which may be indicators of lowered protection against exogenous oxidative insults, particularly from harmful UV rays. Mixture of SSL, from sebum and corneocyte debris, with water, and from sweat and substances derived from protein degradation such as NMFs, compose the hydrolipidic or acid mantle (Shetage *et al.*, 2013).

Regarding protein component of SC as part of its “bricks”, Takahashi and Tezuka (2004) observed reduction in protein level of filaggrin in older epidermis, while the mRNA level was not affected by age, and formation of natural moisturizing factors (NMF) derived from enzymatic degradation of filaggrin

increased in elderly individuals. Consequently, the reduction in the protein level of filaggrin might be caused not only by changes affecting gene expression, but also by intensified proteolytic activity, which may degrade epidermal filaggrin before it can form large molecules (Takahashi and Tezuka, 2004). It is also essential to look at the organization of corneodesmosomes – the modified desmosomes that are present in corneocytes to keep them attached to each other. Corneodesmossomes are major determinants of SC cohesiveness; they are lodged in the edges of the cells on the surface of the skin, incorporated in the cell membrane or cornified envelope, and composed of several cytoplasmic (plakoglobins, desmoplakins and plakophilins), transmembrane (desmogleins and desmocollins) and extracellular proteins (corneodesmosins) (Chapman *et al.*, 1991; Ishida-Yamamoto *et al.*, 2011; Rawlings, 2003). During corneocyte maturation, corneodesmosin is progressively proteolyzed (Ishida-Yamamoto *et al.*, 2011). Both exogenous and endogenous proteases are involved in the cleavage of the corneodesmosome junctions. Among endogenous proteases, there are several serine, cysteine and aspartic enzymes, including kallikrein-related peptidases (KLK) and cathepsins, both produced by keratinocytes (Ishida-Yamamoto *et al.*, 2011; Rawlings, 2003). The pH-induced high serine protease activity caused by impaired acidification of the SC with aging also degrades corneodesmosome proteins, such as desmoglein 1 (Hachem *et al.*, 2005). This complements the finding that corneocyte detachment becomes more prevalent with age, and helps to explain the prevalence of xerosis and pruritus in the elderly (Chu and Kollias, 2011; White-Chu and Reddy, 2011).

Usually, changes that are seen in chronologically aged skin are further aggravated (by about 20%) in human skin areas with superimposed photoaging (Elias and Ghadially, 2002; Reenstra *et al.*, 1996). Shekar *et al.* (2005) applied microtopography to show that deterioration of fine reticular patterning of the SC, also referred to as skin pattern on the Beagley-Gibson scale, occurs over time. In an elegant study, they estimated the extent to which changes are due to genetic or environmental influences by analyzing nuclear twin families. Variation in skin pattern was due to genetic influences in the proportion of 86% at age 12, 75% at age 14, 72% at age 16, and 62% in an adult sample aged between 32 and 86

years. While the genetic influence decreased with aging, environmental factors appeared to have a growing and cumulative impact throughout the lifetime. Analyses of the adult group showed that extrinsic components were related to a more extensive deterioration in the skin pattern but, surprisingly, caused very little variation in the adult skin pattern (less than 2%), which was explained by the inability to tan and prolonged outdoor work. The results corroborated previous data, and also concluded that the variation in stratum corneum patterning was indicative of intrinsic skin aging rather than photoaging (Seddon *et al.*, 1992). Subsequently, Shekar *et al.* (2006) conducted the first genome-wide linkage scan study of epidermal reticular patterning with adolescent twins and siblings, and found a suggestive linkage at chromosomal markers such as 12p13.31 and 4q23. Identified regions in chromosomes probably correspond to genetic factors associated with the structure or regulation of the epidermis, like MMP and protease inhibitor α-2-macroglobulin, as well as the subunit 1 of NF-κB involved in regulating keratinocyte differentiation and proliferation.

Concluding remarks and future perspectives

Increasing number of studies related to the epidermis is a clear indication of its importance as a dynamic structure in the control of skin and organism homeostasis. Recent cell biology studies provide consistent evidence to propose a working model for renewal of the epidermis, based mainly on the emerging researches on epidermal proliferative cells, which allow discussing the new significant findings about epidermal development and aging. An innovative in silico study was developed to model long-term colony dynamics in the epidermis, as a complement to experimental studies (Li *et al.*, 2013). Different models were challenged using the in silico approach, and hypothesis of populational asymmetry with stem cells (Mascré *et al.*, 2012) provided the best mechanism for sustained tissue regeneration and homeostasis.

Cell signaling studies also indicate great opportunities to discover the major pathways related to the physiology and aging of the epidermis. This has been

significantly accelerated with the application of new “omics” techniques based on global analyses and associated with the birth of bioinformatics technologies. The term “skinomics”, for example, was applied to define the transcriptional profiling in dermatology and skin biology (Blumenberg, 2012). A number of studies have been conducted to understand global mRNA or protein expression of human epidermis, which harbors a wealth of information about the genes involved in skin function and genetic skin disorders (Jansen and Schalkwijk, 2003). An extensive study using DNA microarrays quantified and described considerable differences in the transcriptional profiling of epidermal keratinocytes, by comparing the gene expression in skin, cultured keratinocytes, and reconstituted epidermis (Gazel *et al.*, 2003). An Investigation of the transcriptome of accelerated and replicatively senescent keratinocytes revealed links to differentiation, interferon signaling, and Notch related pathways (Perera *et al.*, 2006). Despite their important contributions to the understanding of epidermal physiology, the above-cited works were not directly intended to explain the effects of aging on epidermis. Several conclusions on epidermal aging could of course be drawn from analyses of senescent keratinocytes, but important considerations must be taken into account when comparing cell biology mechanisms of *in vitro* senescence with those of *in vivo* aging (Hwang *et al.*, 2009). Other studies used *in vivo* human biopsy samples for global molecular analyses of skin aging; these studies, however, fail to supply specific information about how epidermis ages, since skin biopsies also contain (confounding) dermal material (Laimer *et al.*, 2010; Lener *et al.*, 2006). Gromov *et al.* (2003) conducted the only work that targeted analysis of *in vivo* epidermal aging by adopting an “omics” approach. By isolating an enriched epidermis portion of skin biopsies from young and old individuals, they analyzed protein profiling of the human epidermis from elderly persons and substantiated the argument that aging is associated with increased severe oxidative stress and alterations in the signaling of apoptosis. Therefore, platforms based on global analyses at different molecular levels represents a promising alternative to define new pathways inscribed in the aging of the epidermis. In addition, mechanisms other than the regulation of epidermal process, such as differentiation and cornification, have begun to be

understood and interconnected with functional and/or clinical signs in the elderly. Specifically for this purpose, study of premature aging and associated comorbidities, such as the Hutchinson-Gilford progeria syndrome and the Werner syndrome, offers an alternative for understanding key molecular components in the aging process (Capell *et al.*, 2009; Coppedè, 2013; Navarro *et al.*, 2006).

Effects of physical, chemical and biological agents on the aging of the epidermis might provide a powerful way to find new therapeutic opportunities that are more effective and directed to specific pathways or molecular targets. Epidermal keratinocytes are complex cells that create a unique three-dimensional structure, which differentiates through a multistage process and responds to environmental and extracellular stimuli from nearby cells (Gazel *et al.*, 2003). In addition, epidermal keratinocytes have been the target of many studies because they respond to a rich variety of inflammatory and immunomodulating cytokines, hormones, vitamins, ultraviolet (UV) light, toxins, and physical injury (Blumenberg, 2006). Modulation of gene expression, and possibly of many other molecular levels, is a reality that can be applied to fight aging effects on skin tissue (Talbourdet *et al.* 2007). Expression of molecules related to the ability of skin to sense the external environment was identified out of neuronal cells, such as TRV channels in the cell membrane of keratinocytes, suggesting new routes to sensitive properties of epidermis (Denda *et al.*, 2001b). Moreover, a thorough understanding of molecular skin aging may, in a not-too-distant future, permit the efficient application of pharmacogenomics using individualized drug therapies based on genomic biomarker identification, which would avoid potential side effects while maximizing therapeutic response (Greenfield and Maibach, 2012; Rizzo and Maibach, 2012). In this sense, increasing knowledge about epidermal aging, which has a direct influence on response to topic treatments, should result in considerable gains in the field of personalized medicine and drug delivery optimization.

Dynamics of aged skin barrier shows particularities to such an extent that drug pharmacokinetics and pharmacodynamics may be altered in the elderly (Flammiger and Maibach, 2006). Maibach's group has extensively studied

percutaneous drug absorption, including changes promoted by an altered barrier function in aged epidermis (Harvell and Maibach, 1994; Konda *et al.*, 2012a and 2012b; Roskos *et al.*, 1986, 1989 and 1990). It is a common misconception, for example, that older skin has a diminished barrier capacity, and that percutaneous absorption is therefore greater (Oriba *et al.*, 1996). A better understanding of the changes affecting epidermal barrier with age is fundamental for the development of more efficient treatments and reduction of dermatotoxicological effects in elderly individuals (Ngo and Maibach, 2010).

Challenges that face elucidation of complex epidermal interactions and even the understanding of functional signaling in the epidermis with aging are far from complete. Several possibilities emerge for future perspectives, including development of functional assays to identify key protein players in epidermal stem cell proliferation and differentiation; of cell sorting and gene expression studies to shed light on age-related changes in homeostasis for each epidermal cell type; and perhaps of an investigation of functional interplay between different cells in epidermis. Epidermal bath model should be continuously revisited and refilled with recent scientific data, not only as a framework for understanding mechanisms involved in skin aging, but also as a helpful tool for the development of improved therapies to improve, reinforce and/or restore the function of healthy skin.

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Conflict of interest

No conflict of interest was involved in the present work.

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7.2. Artigo de revisão II

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Highlights

1) Epidermis and the evolution toward a global understanding of skin aging.

2) Molecular, cell-related, and morphological changes in aged epidermis.

3) Active ingredients in the recovery of specific age-affected epidermal functions.

4) Potential cosmetic and/or dermatological treatments for age-impaired epidermal homeostasis.

Title: Active Ingredients against Human Epidermal Aging

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Abstract

The decisive role of the epidermis in maintaining body homeostasis prompted studies to evaluate the changes in epidermal structure and functionality over the lifetime. This development, along with the identification of molecular mechanisms of epidermal signaling, maintenance, and differentiation, points to a need for new therapeutic alternatives to treat and prevent skin aging. In addition to recovering age- and sun-compromised functions, proper treatment of the epidermis has important aesthetic implications. This study reviews active ingredients capable of counteracting symptoms of epidermal aging, organized according to the regulation of specific age-affected epidermal functions: 1) several compounds, other than retinoids and derivatives, act on the proliferation and differentiation of keratinocytes, supporting the protective barrier against mechanical and chemical insults; 2) natural lipidic compounds, as well as glycerol and urea, are described as agents for maintaining water-ion balance; 3) regulation of immunological pathogen defense can be reinforced by natural extracts and compounds, such as resveratrol; and 4) antioxidant exogenous sources enriched with flavonoids and vitamin C, for example, improve solar radiation protection and epidermal antioxidant activity. The main objective is to provide a functional classification of active ingredients as regulatory elements of epidermal homeostasis, with potential cosmetic and/or dermatological applications.

Keywords: epidermis; aging; skin; treatment; active ingredients

1. Introduction

Epidermis, the most exposed skin part, directly contacts the external environment. It is assembled by multiple superposed cell layers that form an effective protection barrier (Baroni et al., 2012; Madison, 2003). As a complex system, which also captures environmental stimuli, epidermis is composed of several cell types such as keratinocytes, melanocytes, Langerhans cells, and Merkel cells (Boulais and Misery, 2008). Keratinocytes are the most abundant cell type constituting 80-95% of epidermal cells (Brohem et al., 2011; Ulmann et al., 2007).

Due to constant desquamation, epidermis needs continuous renewal, which begins with multiplication of proliferative cells in the innermost layer, generating keratinocytes that undergo differentiation as they are driven outwards with cell divisions (Fuchs and Raghavan, 2002; Milstone, 2004). Keratinocyte differentiation is marked by molecular, structural, and functional changes, resulting in a stratified epidermis in which the different strata, arranged from the inner to the outer surface, constitute the basal layer (BL), spinous layer (SL), granular layer (GL), and stratum corneum (SC), respectively (Fuchs and Raghavan, 2002; Simpson et al., 2011). The palms and soles possess an additional layer – stratum lucidum (SL) – between GL and SC (Brohem et al., 2011). In SC, keratinocytes reach their highest level of differentiation and are then known as corneocytes – dead, enucleated, and morphologically flat cells composed of protein and lipid blocks bonded to one another and immersed in a lipid matrix (Eckhart et al., 2013).

More than just a barrier for mechanical protection, epidermis is a metabolically active tissue in constant dynamic balance and periodically undergoes complete renewal cycles (Fuchs and Raghavan, 2002). The working of the epidermis seems paradoxical, since it is highly stable in protecting the organism from external aggression and, at the same time, allows its cell components the required flexibility to ensure tissue renewal and capability of response to different stimuli (Simpson et al., 2011). This ability makes the epidermis a decisive component for maintaining body homeostasis. Over the years, however, epidermal primary functions may gradually falter (Elias and Ghadially, 2002). Physiological wear from skin aging is a consequence of damage that accumulates throughout the organism's life and is caused both by intrinsic factors (physiological components and genetic predisposition) and extrinsic factors (external insults, particularly from solar radiation) (El-Domyati et al., 2002; Farage et al., 2008a). Molecular, cell-related, and morphological changes in aged epidermis not only compromise its protective role, but also contribute to the appearance of skin symptoms, including excessive dryness and pruritus (White-Chu and Reddy, 2011), as well as increased predisposition to formation or deepening wrinkles (Kuwazuru et al., 2012), dyspigmentation (Longo et al., 2013), fragility and difficulty to heal injuries (Bourguignon et al., 2013; Calleja-Agius et al., 2007), alteration in skin permeability to drugs (Bourguignon et al., 2013), impaired ability to sense and respond to mechanical stimuli (Wu et al., 2011), skin irritation (Bourguignon et al., 2013), and tumor incidence (Farage et al., 2008b; Wolf et al., 2013) (**Figure 1**).

Skin aging involves systemic changes as well as changes in the entire skin (Waller and Maibach, 2006 and 2005; for details, refer to Farage et al., 2010). Although most investigations still concern dermis, mainly because of its abundant content in extracellular matrix (ECM), recent studies have targeted epidermal aging and possible therapeutic options. In addition to their health-related implications, epidermal alterations can lead to changes in appearance or image that may have a high aesthetic and psychosocial impact (Jiang and DeLaCruz, 2011). Moreover, search for therapeutic alternatives that include the epidermis is an additional step toward an integrating approach to skin aging treatment and prevention.

This manuscript overviews active ingredients identified for the treatment of skin aging. They are grouped according to their specific activity in the recovery of epidermal functions and include the following major topics: 1) protective barrier against mechanical and chemical insults (Lulevich et al., 2010; Kirschner et al., 2013), 2) maintenance of water-ion balance in the organism (Kirschner et al., 2013; Proksch et al., 2008), 3) immunological defense and toxin elimination (Baroni et al., 2012; Geusau et al., 2001; Polak et al., 2014), and 4) solar radiation protection and antioxidant activity (Shindo et al., 1994; Yamaguchi et al., 2006). Overall, current active ingredients were searched for potential cosmetic and/or dermatological applications, according to their biological and biophysical effects on the regulation of age-impaired epidermal homeostasis.

2. Protective Barrier against Mechanical and Chemical Insults

Protection against mechanical and chemical insults depends directly on the structural epidermal integrity – a stratified arrangement of superposed cell layers with keratinocytes bonded by means of intercellular junctions and extracellular matrix components (Ishida-Yamamoto et al., 2011; Kirschner et al., 2013; Lulevich et al., 2010). A primary factor for preserving skin barrier is its capability for cell renewal, affected by the keratinocyte proliferation rate and differentiation (Cangkrama et al., 2013). Distinct mechanical properties of keratinocytes, including their high deformation resistance, which may be up to seventy times that of other cells in the organism, contribute significantly to their protective action (Lulevich et al., 2010). This resistance is largely due to the keratin cytoskeleton acquired along the epidermal cell differentiation process: complete keratin deletion causes significant biomechanical deficiencies in keratinocytes (Bragulla and Homberger, 2009; Kim et al., 2012b; Ramms et al., 2013). Chemical composition of the epidermis, which also plays a part in the protection against mechanical and chemical insults, will be discussed more detailedly in **Section 3** due to its high relevance to maintenance of the water-ion balance in the organism.

Reduction in epidermal thickness – one of the morphological characteristics of age-affected skin – results from lower cell renewal rates due both to intrinsic and extrinsic factors (Crisan et al., 2012; Shlivko et al., 2013; Tsugita et al., 2013; Waaijer et al., 2012). The number of layers containing viable cells diminishes with

epidermal aging, and keratinocyte proliferation and differentiation are significantly impaired in elderly persons' epidermis (Bourguignon et al., 2013; Levakov et al., 2012; Lock-Andersen et al., 1997). Senescent cell build-up may also play a role in the diminishing regenerative capacity of aged biological tissues, including epidermis (Cordisco et al., 2010). In addition, changes that occur in the cells and extracellular matrix suggest a more porous and less effective structural organization of the aged epidermis as regards its barrier function against external chemical agents (Elias and Ghadially, 2002).

Active ingredients that regulate the protection against mechanical and chemical insults should be capable of restoring cell renewal in aged epidermis and thus ensure integrity in the skin barrier. In addition to the possibilities here identified, physical treatments such as photodynamic (Orringer et al., 2008), high-energy pulsed CO_2 laser (Ratner et al., 1998; Stuzin et al., 1997), and fractional CO_2 laser (Sasaki et al., 2009) therapies are suggested as options for epithelium renewal and keratinocyte proliferation incitement action. **Table 1** lists ingredients capable of supporting the protective epidermal barrier against mechanical and chemical insults, including literature-enshrined elements, such as retinoids and their derivatives (for recent review, see Babamiri and Nassab, 2010), as well as alpha-hydroxy acids (AHAs) (for recent review, see Babilas et al., 2012) and several other compounds.

Regarding retinoic acids, a large set of data has already been published describing their effect on the proliferation and differentiation of keratinocytes, that directly affects wrinkles appearance and formation (Bellemère et al., 2009; Skazik et al., 2013). Retinoids are also used for photoaged skin treatment, since they reduce skin hyperpigmentation (Gold et al., 2013; Kircik, 2012) and inhibit metalloproteinases expression (Jurzak et al., 2008). Besides these well-known properties, retinoids have recently been described in the regeneration of hair follicles by promoting functional differentiation of dermal papilla cells (Aoi et al., 2012) and, in association with minoxidil, they prevent apoptosis of dermal papilla cells (Kwon et al., 2007). Side effects upon use of retinoic acids are related to their potential to cause skin irritation. Another potential inconvenience of retinoic acids involves its instability in topical formulations. Interestingly, these problems have led to the development of retinoid derivatives and similar compounds with superior properties (Kim et al., 2011 and 2010). AHAs, such as glycolic and lactic acid, are also used to treat photodamaged skin (Rendl et al., 2001) and to stimulate epidermal renewal, with clinical improvements in skin thickness, firmness, and softness, as well as in the appearance of fine lines and wrinkles (Bhattacharyya et al., 2009; Yamamoto et al., 2006). They reduce the calcium ion concentration in the epidermis and remove calcium ions by chelation, disrupting cell adhesions and resulting in desquamation (Wang, 1999).

3. Maintenance of Water-Ion Balance in the Organism

Epidermis plays a fundamental part in sustaining internal homeostasis in the organism by controlling the exchange of substances, especially water and ions, with the external environment (Tzaphlidou, 2004). Hydration also determines the general aspect of the skin; since the entire cell metabolism can be affected by the amount of water it contains (Jiang and DeLaCruz, 2011). To preserve this functionality, in addition to the cell structure discussed previously, epidermis shows an arrangement of biochemical components with selective properties. In SC, for example, the extracellular matrix contains 75-80% of proteins, 5-15% of lipids, and 5-10% of other constituents (Förster et al., 2009). Lipid fraction consists primarily of ceramides, fatty acids, cholesterol, esters, triglycerides, and phospholipids (Lampe et al., 1983). Part of the highly insoluble and resistant SC proteins, such as loricrin and involucrin, corresponds to corneocyte envelope (Hansen et al., 2009; Kalinin et al., 2001; Nishifuji and Yoon, 2013). Moreover, to preserve water and soluble ions, epidermis has differentiated molecular mechanisms, such as natural moisturizing factors (NMFs) derived from profilaggrin proteolysis, which form an intensely hygroscopic mixture composed of peptides, amino acids and their derivatives (such as urocanic acid (UCA) and 2-pyrrolidone-5-carboxylic acid (PCA)), minerals, urea, and sugars (Bouwstra et al., 2008; Kezic et al., 2009; Zhang et al., 2006). Aquaporins (AQPs) are channels that run along epidermal cell membranes to carry water and small molecules of solute, which are essential for maintaining water-ion balance of the cell. Of the thirteen AQP types described in humans, the most extensively studied AQP in the skin is AQP3, found chiefly in epidermal basal cells (Hara and Verkman, 2003; Takata et al., 2004). Recently, AQP10 has also been

identified in human epidermis, specifically in SC corneocytes (Boury-Jamot et al., 2006; Jungersted et al., 2013). AQP3 and AQP10 belong to the same aquaglyceroporin subclass; they are known to transport water and glycerol – the latter being an important agent for the hydration, resilience and repair of the skin barrier (Fluhr et al., 2008).

Aging significantly affects the epidermal function of controlling the balance of water and ions in the body. Lipid synthesis diminishes with age, as does the secretion of lamellar bodies in SC which generates an extracellular matrix that is more porous and less efficient in controlling the water-ion balance in the organism (Elias and Ghadially, 2002; Ghadially et al., 1995). Many molecular pathways related to SC lipid metabolism are downregulated in aged skin; and cholesterol seems to be the most affected lipid class (Ghadially et al., 1996; Jarrold et al., 2009). In specific cases, such as solar lentigo (an aging mark in photoexposed skin areas), a reduction occurs in the expression of cornified envelope-related genes, such as filaggrin and involucrin (Aoki et al., 2007). Free amino acid content of NMF's seems lower in the SC of senile epidermis (Jacobson et al., 1990). Expression AQP3 levels diminish with the aging of human epidermis and also in isolated keratinocytes, probably related to the development of xerosis (excessive skin dryness commonly seen in the elderly) (Li et al., 2010).

As therapeutic alternatives for recovering the epidermal function that preserves the water-ion balance in the organism, active ingredients should promote

replenishment or stimulate the endogenous synthesis of affected biochemical components. **Table 2** lists the most frequently used components for this specific function, such as waxes, natural oils and derivatives, whose lipid composition either mimics that of SC elements or acts complementarily on skin hydration (for critical considerations, see Draelos, 2013), as well as compounds that stimulate endogenous synthesis of epidermal biomolecules, including glycerol and urea (for details, refer to Lodén and Maibach, 1999).

Among the compounds widely used for maintenance of water-ion balance are glycerol and urea, as they are able to sustain the physical properties of hydrated lipid systems under dry conditions (Björklund et al., 2013). Comparison of the effects of these compounds on water distribution in the SC of human skin equivalents suggested distinct patterns of action. While water domains were mainly located in the intercellular regions under urea treatment, water was observed both in intercellular regions and in corneocytes following glycerol treatment (Bouwstra et al., 2012). A fine-tuned regulation of AQPs expression is also involved in the maintenance of water and solute balance in the skin (Hara and Verkman 2003). It has been shown that mice lacking AQP3 have impaired SC hydration and skin elasticity and a threefold reduction in their glycerol content. However, all these effects were compensated with orally administered glycerol, restoring the epidermal barrier function (Hara and Verkman 2003). Peptides and standardized plant extracts have already been reported to increase expression of the AQP3

gene in cultures of human keratinocytes, but such studies usually lack consistent clinical trials to confirm their function *in vivo*.

4. Immunological Defense and Toxin Elimination

Regulation of epidermal defense mechanisms is crucial for local and systemic homeostasis of the organism. Existence of a complex, unified skin defense system, described as a cutaneous neuroimmunoendocrinological system, has been suggested (Brazzini et al., 2003; Misery, 2000; O'Sullivan et al., 1998). Epidermal cells – including keratinocytes, melanocytes, and Langerhans cells – can produce, either constitutionally or by activation, an arsenal of cytokines (**Table 3**) and thus reinforce the action of epidermis as a tissue that is immunocompetent and active in creating an immunological barrier (Corsini and Galli, 2000; Kupper and Fuhlbrigge, 2004; Williams and Kupper, 1996). Langerhans cells act as sentries for epidermis and ensure the activation of adaptive immune response by presenting antigens to T-cells (Cumberbatch et al., 2003). Epidermis also acts as an adjuvant in the potentiation of inflammatory pathways and in the preparation of more efficient systemic immune responses with improved B- and T-cell activation (Gutowska-Owsiak and Ogg, 2012; Liu et al., 2010). In addition, the epidermal surface exhibits particular properties for a defense strategy against potential pathogens. The strategy includes maintenance of commensal microorganisms capable of producing competitor-inhibiting substances, secretion of antimicrobial peptides named defensins, and maintenance of acid pH levels to hinder the installation and

growth of certain microorganisms (Harder et al., 2013; Namjoshi et al., 2008; Niyonsaba et al., 2009). Although scantily reported to date, there are indications that epidermal desquamation helps to eliminate toxins such as 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) (Geusau et al., 2001).

As the skin ages, agents that stimulate the epidermal immune defense system undergo significant changes: total number of Langerhans cells diminishes, as does their functional capability (Ogden et al., 2011; Xu et al., 2012); secretion level of IL-1 is reduced and affects mitotic capacity and epidermal lipid synthesis (Ye et al., 2002); and SC surface pH tends to become more basic (Choi et al., 2007; Hachem et al., 2005). Furthermore, in addition to activating epidermal immune response, constant exposure to toxins and/or pollutants accelerates skin aging (Vierkötter and Krutmann, 2012). Toxins present in cigarettes damage healing processes, trigger onset of diseases, increase hair loss, and cause premature skin aging and formation of deep wrinkles (Morita et al., 2009). Organic particles released by burning tobacco's smoke induce apoptosis in keratinocytes (Pedata et al., 2012). Exposure to air pollution showed significant correlation with signs of aging, such as dark spots and fine lines on the skin of 400 Caucasian women (Vierkötter et al., 2010). Moreover, capacity of response to pollutants has been suggested to diminish with age (Valacchi et al., 2012).

Active ingredients capable of regulating the immune defense function of the epidermis include those that can modulate inflammatory responses or stimulate the

synthesis of natural defense compounds, such as antimicrobial peptides. **Table 4** covers natural extracts and compounds of various origins which have been described for this type of application, such as resveratrol and its widely studied anti-inflammatory properties (for recent review, see Baur and Sinclair, 2006).

We were unable to identify any effectively proven therapeutic opportunities for epidermal regulation of toxin removal. It is therefore advisable to avoid excessive exposure to polluting or toxic substances and to pursue a healthier lifestyle. An example of this approach is a survey using future projections of the appearance of women who used tobacco led many female volunteers to stop smoking (Grogan et al., 2011). Indeed, cigarette smoking represents an environmental stressor that can damage SC, modifying its lipid composition by increasing the expression of scavenger receptor B1 (SR-B1), related to cholesterol uptake. Resveratrol was recently described as a SR-B1 inhibitor in keratinocytes in a dose-dependent manner, suggesting a skin protective potential against cigarette smoking (Sticozzi et al., 2014). Resveratrol is also able to induce phosphorylation of EGFR (epidermal growth factor receptor), whose signaling pathway regulates the expression of interleukins (IL) by human keratinocytes, such as IL-8 (Pastore et al., 2013). Moreover, in association with its natural precursor polydatin, resveratrol modulates gene expression of IL-6, IL-8 and tumor necrosis factor-alpha (TNF-α), and augments the release of human beta-defensin 2 whose combined action might mediate a positive outcome related to the skin response to toxins (Ravagnan et al., 2013).

5. Solar Radiation Protection and Antioxidant Activity

Solar radiation is a leading environmental factor that affects human skin, particularly radiation in the ultraviolet (UV) region of the spectrum, which is divided into UVA (320-400 nm), UVB (280-320 nm) and UVC (100-280 nm, mostly absorbed by the ozone layer) (Hockberger, 2002). In addition to UV rays, infrared radiation (IR, above 800 nm) may also lead to biological changes in living organisms (Polefka et al., 2012). As the amount of energy is inversely proportional to the wavelength, UVB delivers more energy than UVA. However, UVA has a higher penetration rate and reaches the deepest epidermal layers, while UVB affects primarily epidermis and papillary dermis (Hoffmann et al., 2000). UVB is harmful to biological tissues in that it causes direct injury in molecules such as nucleic acids and proteins, whereas the action of UVA is less understood and involves oxidative stress and production of reactive oxygen species (ROS) that may damage different cell components through propagation reactions (Césarini et al., 2003; Dröge, 2002; Hockberger, 2002). ROS may originate from processes such as cell respiration, or from exogenous agents such as UV radiation, which intensify the formation of such oxygen species in the skin (Burke, 2010; Palmer and Kitchin, 2010; Puizina-Ivić et al., 2010; Rahimpour and Hamishehkar, 2012). UV acts as a broad activator of cell surface receptors, inducing multiple downstream signaling pathways that regulate expression of multiple genes (Rittié and Fisher, 2002). Epidermal cells – and keratinocytes in particular – have an

internal machinery capable of preventing, to a certain extent, the occurrence of UVB-induced mutations by eliminating ROS and inducing cell cycle arrest for subsequent DNA repair. However, if the levels of accumulated damage in DNA become critical, or ROS amounts come to be excessive, an apoptosis-inducing mechanism is activated to prevent malignant changes from taking place in the cells (Kulms et al., 2002). The closer to BL, the greater the chances for a keratinocyte to undergo a malignant transformation, which is why the epidermis is endowed with additional protective mechanisms, such as pigmentation and higher cell susceptibility to UVB-induced apoptosis (Schäfer et al., 2010).

Endogenous components for the removal of ROS are in place all over the body. Transcription factor Nrf2 (NF-E2-related factor 2) is an important cytoprotector that induces production of enzymatic and non-enzymatic elements for antioxidant defense (Beyer et al., 2007; Schäfer et al., 2010). In human skin, antioxidant capacity of epidermis is much greater than that of dermis. Several antioxidant components in the epidermis have higher (enzymatic) activity or (non-enzymatic) concentration percentages than the corresponding components in dermis: superoxide dismutase (126%), glutathione peroxidase (61%), glutathione reductase (215%), glucose-6-phosphate dehydrogenase (111%), isocitrate dehydrogenase (313%), α-tocopherol (90%), ubiquinol 10 (900%), ascorbic acid (425%), uric acid (488%), reduced glutathione (513%), and total glutathione (471%) (Shindo et al., 1994).

UV radiation effects are the main cause of extrinsic skin aging or photoaging, a condition that may be aggravated when combined with IR exposure (Kligman, 1982; Polefka et al., 2012). Skin defenses against oxidative damage become vulnerable with age (Keogh et al., 1996). Elimination of DNA damage, such as removal of UVB-induced pyridine dimers, is slower in the epidermis of older individuals (Yamada et al., 2006). By the same token, antioxidant capacity of epidermal cells declines with age following reduction of α-tocopherol, ascorbic acid and glutathione concentrations (Rhie et al., 2001). As a result, aged skin shows increasing levels of oxidized proteins that become inactive and accumulate inside the cells (Sander et al. 2002).

Table 5 lists active ingredients described in the literature as capable of acting on the regulation of protection against solar radiation, as well as for their antioxidant activity. Exogenous antioxidant supplementation is currently the most explored therapeutic alternative (for review, see Dreher and Maibach, 2001). Topical and oral antioxidant use may reinforce the action of endogenous molecules in protection against ROS. Cosmetics formulated with antioxidants are among the most popular antiage products in the market worldwide (Palmer and Kitchin, 2010; Stamford, 2012). In addition, the use of sunscreens in cosmetic formulations is a preventive measure to avoid damaging effects of excessive solar radiation (for critical considerations, see Lodén et al., 2011). In view of the ample exposure of epidermis to sunlight and its fundamental role as the first barrier in the fight against

ROS, numerous studies have been investigating and proposing options of active ingredients with this protective function.

Among the widely characterized compounds that are capable of protecting skin from solar radiation are green tea extract and resveratrol (Nichols and Katiyar, 2010). Green tea extract and its main polyphenols – notably epigallocatechin-3-gallate and epicatechin-3-gallate – have shown positive effects against inflammation, oxidative stress and DNA damage, with potential to nullify several biochemical processes induced or mediated by UV radiation, such as erythema and premature skin aging (Nichols and Katiyar, 2010; Türkoğlu et al., 2010). Protective effects of polyphenols were also observed due to inhibition of UVA-induced ROS production, mitogen-activating protein kinase activation, and expression of ciclooxigenase-2 (Chan et al., 2008). However, an evaluation of different commercial green tea extracts, used to enrich cosmetic formulations, revealed that photoprotective properties can be affected by the methodologies employed for production of the herbal mixtures (Silva et al., 2013). Therefore, the use of standardized extracts, at least in terms of polyphenols content, seems to be essential to assure the efficacy of products containing such ingredients. Resveratrol, another well-known antioxidant molecule (Bastianetto et al., 2010), is a phytoalexin isolated mainly from grapes (Jagdeo et al., 2010). As a very promising natural drug, resveratrol has been widely explored in the last years to fight aging and age-associated disturbes with consistent *in vivo* apllications (for recent review, see Baur and Sinclair, 2006) and different mechanisms of action,

including: 1) reduction of intracellular hydrogen peroxide-upregulated ROS (Jagdeo et al., 2010), 2) activation of sirtuin – in special SIRT1 that is capable of deacetylate histones promoting increased DNA stability and persistent survival in mammals – and cellular protection against UV damages via modulation of p53 and JNK pathways (Cao et al., 2009), and 3) significant cancer chemopreventive potential (Qian et al., 2009).

6. Concluding Topics and Prospects

With the growing lifespan and quality of life of the population worldwide, appearance of skin becomes increasingly important for people to feel safe and confident in their social interactions. Skin products currently in use are based on new standards of personal hygiene and health, in addition to transmitting a significant aesthetic appeal. Moreover, skin care represents an additional benefit for the elderly, since it also helps to prevent skin disorders and cancer development (Farage et al., 2008a). In its efforts to meet the escalating demand for treatments, development of products keeps abreast of the rapidly evolving knowledge of skin physiology and its functional deterioration with age. Two work fronts cooperate for these advances in knowledge: 1) identification of new biological mechanisms associated with skin aging, and 2) continuous discoveries of new forms of acting to prevent the appearance of or recover signs of aging.

New active ingredients, formulations and suitable delivery systems that may induce the recovery of biological functions affected by age are being sought both by cosmetic and pharmaceutical industries (Kaur et al., 2007). Moreover, a growing movement is under way to customize treatments by taking specific needs of each individual into account. This is the development of tailored medicine, whereby ingredients and their combinations are optimized in a unique composition intended for a specific person (Rizzo and Maibach, 2012; Squassina et al., 2010). If this movement is to become feasible for skin treatment, it would be highly useful to have an extensive portfolio of active ingredients capable of acting on cells, pathways or specific molecules, in addition to refined skin diagnoses. Lists of potential candidates for epidermal aging treatment were organized according to this innovative concept. Mechanisms of action were discussed for key ingredients, evidencing the importance of in depth scientific assessment for specific compounds before their use, considering not just individual needs, but also specific biological and physicochemical properties, compatibility with intended formulation, as well as the availability of robust pre-clinical and clinical trials.

Another scientific trend is related to a holistic approach for the treatment of skin aging. If the skin is to be viewed as a complex biological system, emergence and advance of research involving different skin layers or cell types are essential for the development of more complete and comprehensive therapies. In this sense, it is important to note that our review was focused on active ingredients available for topic applications, but new opportunities have been described for dietary

supplements. Distinct possible applications of ingredients in the treatment of phenotypes like aging gave origin to new terminologies that has been more and more difused in the market, including cosmeceuticals (topically applied products capable of making changes in the skin status that are not considered drugs, nor cosmetics, that decorate the skin), nutraceuticals (any substance that is a food or part of a food that provides medical or health benefits, including the prevention and treatment of disease), and nutricosmetics (a new concept formed by the intersection of cosmeceuticals and nutraceuticals and referring to oral supplementation of nutrients formulated and marketed specifically for beauty purposes) (Anunciato and da Rocha Filho, 2011). This nomenclature is not aligned across legal regulations in different countries but, independently of the adopted term, it points to a trend that involves the development of interdisciplinary activities focused on health and well-being promotion (Anunciato and da Rocha Filho, 2011; Vranesić-Bender, 2010). A good example of that is the use of probiotics for improvements in the photoprotection capacity of the skin (Guéniche et al., 2009). Supplementation with the oral probiotic bacteria *Lactobacillus johnsonii* (La1) maintains cutaneous immune homeostasis after UV exposure, evidenced through substantial experimental protocols, including randomized, double-blind and placebo controlled clinical trials (Guéniche et al., 2006 and 2008; Peguet-Navarro et al., 2008; Yang et al., 2011). If combined with nutriotinal doses of carotenoids, La1 intake reduced early UV-induced skin damage, suggesting a beneficial influence on skin photoaging (Bouilly-Gauthier et al., 2010). Cutaneous carotenoids can be enriched in the skin by nutrition and topically applied antioxidants, indicated

for the prevention of cell damage, premature skin aging, and skin cancer (Meinke et al., 2013). Indeed, anti-aging substances derived from food includes different categories of ingredients, but special attention has been dedicated to those with antioxidant properties, such as coenzyme Q10, phytoestrogens, probiotics and omega-3 fatty acids (Vranesić-Bender, 2010).

This work addresses the issues specifically associated with epidermal aging and was conducted with the intention of providing a comprehensive list of therapeutic approaches to complement those that are currently in use and chiefly concerned with the dermis. This scientific scenario is undergoing rapid expansion with opportunities for future developments. Growing advances in research in the fields of molecular biology and skin stem cells are examples of the next steps to be taken by cosmetology and dermatology (Fu and Sun, 2009). For many of actives considered here, well controlled and executed efficacy and safety studies in man are few or none. The integrity of interpretation of these therapeutic and/or preventive actions will – in the end – rest on such information.

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Conflict of Interest

No conflict of interest was involved in the present work.

Figure captions

Figure 1. Molecular, cell and morphological changes associated with epidermal aging. As the epidermis ages, it undergoes a series of structural modifications (Bergman et al., 2000; Choi et al., 2007; Chu and Kollias, 2011; Denda et al. 2003; Hachem et al., 2005; Levakov et al., 2012; Scharffetter-Kochanek et al., 2000; Zouboulis and Makrantonaki, 2011) that directly impact its physiological functions, compromising the natural protective barrier of the organism. Diagram indicating calcium distribution points to a higher ion concentration in the granular layer (GL), darker colored, region in young epidermis (1). In older epidermis (2) calcium gradient is lost and calcium is possibly distributed homogeneously among the skin layers. Possible therapeutic alternatives are different forms of action of active ingredients or compounds capable of helping to recover age-affected physiological functions to an extent that will approximate them as nearly as possible to those in young epidermis.

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Table 1. Active ingredients for regulation of epidermal protection barrier against mechanical and chemical insults.

Active Ingredients	Action Mechanisms	References
Achillea millefolium extract*	As the human epidermis ages, expression of receptors of PMOC, a precursor of neuropeptides including ACTH and β-endorphin, gradually diminishes. In human keratinocytes, *A. millefolium* extract increased the synthesis of mRNA and proteins for POMC, MC-2R e MOR-1 receptors. In biopsies of skin in culture, the extract helped to improve the expression of K10, transglutaminase-1 and filaggrin, and to increase epidermal thickness. In vivo, it improved appearance of wrinkles and pores significantly in comparison with placebo.	Pain et al., 2011
Adapalene*	Adapalene is a synthetic retinoid commonly used in acne treatment. In vitro and in vivo studies found it active in the regulation of epidermal cell proliferation and differentiation. Action of adapalene on keratinocytes takes place via RAR – specifically γRAR.	Jain, 2004; Michel et al., 1998
Alpha-hydroxy acids*	AHA's are widely used in chemical peeling and cosmetic formulations as cell renewal stimulants. A lotion containing 25% of AHA promoted a 25% increase in skin thickness as well as a reduction in melanin content, which diminished skin spots. Treatment with glycolic acid increased epidermal cell proliferation rate and thickness in mice, as well as the nuclear volume of keratinocytes in the basal, spinous, and granular layers. Treatment with lactic acid results in increased firmness and thickness of both the epidermis and the dermis, as well as clinical improvement in the softness of the skin and in the appearance of fine lines and wrinkles.	Babilas et al., 2012; Bhattacharyya et al., 2009; Ditre et al., 1996; Smith, 1996; Yamamoto et al., 2006
Arotinoid ethyl ester	AEE stimulated cell proliferation in the epidermis of embryonic and adult mice. AEE inhibited epidermal differentiation in embryonic mice and stimulated it in the adult animal.	Tsambaos et al., 1985
Ethyl-α-D-glucoside	α-EG, the main component in Japanese sake, increases loricrin content significantly by acting on keratinocyte differentiation, while reducing the number of SC layers in aged mice, improving their functionality.	Nakahara et al., 2007

Green tea polyphenols	Green tea polyphenols, especially EGCG, were tested on primary human keratinocytes and stimulated their proliferation and differentiation via induction of p57/KIP2, with higher expression of K1 and filaggrin and increased transglutaminase activity. In aged keratinocytes with reduced cell activity rates, treatment with green tea polyphenols renewed DNA synthesis and succinate dehydrogenase activation. EGCG also exhibited a potential for the modulation of caspase 14, a unique regulator of terminal differentiation of keratinocytes associated with cornification.	Hsu et al., 2005 and 2003
Hesperidin	Hesperidin is found in orange rind extract. Its topical application on mice stimulated proliferation, differentiation and secretion of lamellar bodies in the epidermis, as well as activation of PPAR-α and PPAR-γ in keratinocytes.	Hou et al., 2012
Hyaluronic acid*	HA has been extensively studied in epidermal renewal as a component of formulations, or injected intradermically as an alternative antiage treatment. There are also treatments with active ingredients that induce HA production in the skin, as well as research on the therapeutic potential of HA with different molecular weights. A regimen of topical treatment with low molecular weight HA followed by high molecular weight HA increases proliferation and epidermal thickness, and stimulates cell differentiation in aged mice skin. HA acts on CD44 activation, inducing a series of effects on epidermal processes via Rho GTPase.	Bourguignon et al., 2013; Farwick et al., 2011
Jasmonic acid derivative (LR2412)	Treatment with LR2412 induces hyperplasia in epidermis reconstructed in vitro, with an increase in Ki67-positive cells and in epidermal thickness. LR2412 also stimulates HAS2 and HAS3 expression, as well as HA deposition. Treatment with this compound did not modify the expression of the main proteins involved in late terminal differentiation steps, such as filaggrin e transglutaminase 1, indicating that it is devoid of skin irritant potential.	Michelet et al., 2012
Imiquimod*	Therapy using 5% IMI for actinic keratosis results in less compact hyperkeratosis, more homogeneous pattern of epidermal crystals, ordered epidermal proliferation, less sun-damaged melanocytes, and better overall aspect of the skin.	Smith et al., 2007
L-fucose	Percutaneous application of 1% L-fucose in rats during four weeks results in increased skin thickness in 13% of the test group, in addition to significant improvements in the dermis.	Fodil-Bourahla et al., 2003
Lutein	Lutein, zeaxanthin and astaxanthin induced increased expression of HAS3, with an increase in hyalurinan synthesis. Lutein significantly increased RARE transcript activity. In addition, lutein-derived metabolites were reported to act as RAR ligands in keratinocytes, which makes lutein a potential substitute for retinoids.	Sayo et al., 2013

Myristyl nicotinate*	MN, a nicotinic acid derivative, was developed for treating photodamaged skin. Treatment of photodamaged face skin increases the content of NAD in the skin by 25%, in addition to increasing the stratum corneum thickness by 70% and of the whole epidermis by 20%. MN causes the epidermal renewal rate to increase by 6 to 11% and the TEWL rate to decrease by about 20%. These results indicate that MN improves differentiation and epidermal barrier function, suggesting that MN can play a significant part in the treatment of the progression of skin lesions caused by photoexposure.	Jacobson et al., 2007
Oxysterols	Treatment of primary human keratinocytes with oxysterols induced differentiation, stimulating the expression of involucrin and transglutaminase with an inhibitory effect on cell proliferation. Action pathway of oxysterols in the keratinocytes involves activation of liver X receptor-beta. Similar results have been obtained from topical treatments of mice with oxysterols, indicating increased levels of mRNA and protein for involucrin, loricrin and profilaggrin. The treatment of hyperproliferative epidermis with oxysterols proved capable to restore epidermal homeostasis.	Hanley et al., 2000; Kömüves et al., 2002
p-Dodecylaminophenol	With a more potent antioxidant action than retinoic acid, p-DDAP suppresses MMP expression and stimulates K16 synthesis without causing skin irritation or desquamation. p-DDAP also regulates keratinocyte differentiation, promotes increase in epidermal thickness, and may improve wrinkles and freckles in mice.	Takahashi and Fujiu, 2010
Retinyl retinoate*	Retinyl retinoate is a less irritating retinol derivative than other retinoids. A study of primary human and mice keratinocyte cultures indicates that retinyl retinoate has a potential for expressing retinoic acid, as well as its receptor CD44 and the enzyme HAS2.TEWL rates induced by retinyl retinoate were lower than the rates induced by retinol, retinoic acid and retinaldehyde. When used in topical formulations, retinyl retinoate decreased wrinkles.	Kim et al., 2011 and 2010
Simarouba amara extract*	Immunohistochemical analysis of involucrin and activation of transglutaminase in skin fragments treated with this extract demonstrated its potential to increase the expression of these markers. Results were proven with clinical and instrumental methodologies which showed it to have an effect on the improvement of barrier function and skin hydration.	Bonté et al., 1996
Triterpenes*	Purified TE's particularly rich in betulin were demonstrated to act on the proliferation, apoptosis and differentiation of human keratinocytes in vitro, ex vivo, and in vivo. TE activity in human keratinocytes occurred by means of increased calcium influx, which led to an increase in the expression of genes such as TRPC6 and several differentiation markers, including K10.	Woelfle et al., 2010

Valproic acid	Application of VPA on lesions in the skin of mice assisted the scarring process by stimulating the expression of β-catenin and terminal differentiation markers in keratinocytes, as well as the expression of proliferation markers such as Ki67. In vitro, VPA increased the mobility of HaCaT-lineage keratinocytes by activating signaling pathways involving Wnt/β-catenin, ERK and PI3-kinase/Akt.	Lee et al., 2012
Vitamin A*	Vitamin A or retinoic acid is the most widely studied compound for epidermal renewal because of its effect on the proliferation and differentiation of keratinocytes. However, there have been reports of instability and degradation in cosmetic formulas, and also of incidence of skin irritation, prompting the production of similar compounds to avoid such unwanted effects. Retinoids are lipophilic molecules that penetrate easily in the epidermis; their biologically active forms modulate the expression of genes involved in cell differentiation and proliferation by way of nuclear receptors. Mechanisms of retinoid action include RAR and RXR activation, increased CRABP2 and HBEGF gene expression, enhanced keratinocyte proliferation, and increased epidermal thickness. Their proliferative effect was also noted in human keratinocytes via P2Y2 activation.	Babamiri and Nassab, 2010; Bellemère et al., 2009; Fujishita et al., 2006; Sorg et al., 2006 and 2005; Tur et al., 1995; Wang et al., 2011
Vitamin B3*	Topical application of vitamin B3 (niacinamide or nicotinic acid), has a stabilizing effect on the epidermal barrier function by reducing TEWL and improving the moisture content of the cornified layer. Niacinamide leads to increased synthesis of proteins with keratin, stimulation of ceramide synthesis, acceleration of keratinocyte differentiation, and increased intercellular NADP levels. In skin aging treatments, topical application of niacinamide results in improvement of skin surface structure, softening of wrinkles, and photocarcinogenesis inhibition.	Gehring, 2004

* Active ingredients with placebo/vehicle controlled studies in vivo in man. α-EG (ethyl-α-D-glucoside), ACTH (adrenocorticotropic hormone), AEE (arotinoid ethyl ester), AHA (alpha-hydroxy acids), Akt (a serine/threonine-specific protein kinase), CD44 (cluster of differentiation 44), CRABP2 (cellular retinoic-acid-binding protein II), EGCG (epigallocatechin-3-gallate), ERK (extracellular-signal-regulated kinases), HA (hyaluronic acid), HAS (hyaluronan synthase), HBEGF (heparin-binding epidermal growth factor), IMI (imiquimod), K (keratin), Ki67 (nuclear protein Ki-67), MC-2R (melanocortin 2 receptor), MMP (matrix metalloproteinases), MN (myristyl nicotinate), MOR-1 (μ-opioid receptor), NAD (nicotinamide adenine dinucleotide), NADP (nicotinamide adenine dinucleotide phosphate), P2Y2 (P2Y purinoceptor 2), p57/KIP2

(cyclin-dependent kinase inhibitor), p-DDAP (p-Dodecylaminophenol), POMC (pro-opiomelanocortin), PPAR (peroxisome proliferator-activated receptor), PI3 (phosphatidylinositol 3), RAR (retinoic acid receptors), RARE (retinoic acid responsive element), RXR (retinoid receptor X), SC (stratum corneum), TE (triterpenes), TEWL (transepidermal water loss), TRPC6 (transient receptor potential canonical subtype 6), VPA (valproic acid), Wnt (a group of signal transduction pathways).

Table 2. Active ingredients in epidermal regulation for maintenance of water-ion balance in the organism.

Active Ingredients	Action Mechanisms	References
Ajuga turkestanica hydroalcoholic extract*	*A. turkestanica* extract increased AQP3 and filaggrin expression compared with non-treated groups in studies with experimental human keratinocyte models and cocultures of human keratinocytes and fibroblasts. These results led to the application of the extract in formulations; a significant increase hydration was observed in human skin, which strengthens the role of these water channels and small solutes in the skin as a regulation mechanism for the hydration of the skin.	Dumas et al., 2007 and 2002
Botryococcus braunii microalgae	Extract of these microalgae increased significantly the AQP3 gene expression in human keratinocyte cultures in vitro. Furthermore, it inhibited hormone-sensitive lipase activity in adipocytes and increased the biosynthesis of collagen I and III in fibroblasts. To an important extent, the extract increased expression of cornified envelope proteins, such as filaggrin and involucrin, and exhibited a powerful antioxidant activity, for example in reducing nitric oxide production.	Buono et al., 2012
Coffea arabica L. seed oil	*C. arabica* L. seed oil induces TGF-β and GM-CSF increase in cell culture; both are associated with increased synthesis of extracellular matrix and recovery of neurological response, and also with increased AQP3 gene expression in culture and ex-vivo skin.	Velazquez Pereda et al., 2009
Eucalyptus extract (standardized in macrocarpal A)*	Addition of eucalyptus extract to a culture of human keratinocytes increased ceramide levels in a dose-dependent manner, as well as glucosylceramide and sphingomyelin biosynthesis. Topical application of the extract on dry human skin promoted increase in SC ceramide levels, reduction of TEWL, and improved barrier function of the skin. Addition of macrocarpal A, the chief phytochemical in eucalyptus extract, promoted an increase in the amount of ceramide, as well as the expression of acid palmitoyl-transferase, sphingomyelinase, glucosylceramide synthase and glucocerebrosidase. Results indicate a possible therapeutic application of this extract for a variety of skin disorders.	Ishikawa et al., 2012
Glycerol*	Glycerol promotes a significant increase of AQP3 and AQP10 gene expression in human keratinocyte culture in vitro. Moreover, in skin exposed to UVB radiation, which reduces the presence of these proteins in the skin, glycerol has been shown to promote the preservation of this expression, contributing to the maintenance of hydric homeostasis in the skin when confronted with this type of environmental aggression.	Jungersted et al., 2013; Lodén and Maibach, 1999; Xie et al., 2013

Gypsum fibrosum extract (standardized in 0.3% of $CaSO_4$)	Animals treated with oral doses of 0.3% *G. fibrosum* extract or 0.3% of $CaSO_4$ revealed a significant increase in AQP3 expression relatively to non-treated groups. This shows that both the extract and its main active ingredient by itself are capable of stimulating AQP3 expression, contributing positively to the maintenance of hydric homeostasis in the skin.	Ikarashi et al., 2012
Kanglaite (mixture of extractions of coix seed)	In a photoaging study using different experimental models, including in vitro and skin-equivalent models, kanglaite increased AQP3 gene expression. It was also capable of inhibiting the reduction of the expression of this protein caused by keratinocyte exposure to UVB radiation.	Shan et al., 2012
Lithospermum erythrorhizon aqueous extract	Aqueous gromwell (*L. erythrorhizon*) extract induced more intense keratinocyte and fibroblast migration with increased lipid synthesis in an experimental model that simulates wound healing. Cell groups treated with the extract showed a significant increase in phospholipids, sphingolipids (ceramides and glucosylceramides), and neutral lipids. These findings indicate that the aqueous *L. erythrorhizon* extract has an important mechanism linked to the improvement of barrier function and consequent maintenance of skin hydration.	Kim et al., 2012a
Natural oils, waxes or derivatives*	There are countless available possibilities of using natural compounds whose lipid composition mimics SC elements, or else acts as an adjutant in skin hydration. The following stand out: amaranth oil, apricot oil, argan oil, candelilla wax, canola oil, carnauba wax, castor oil, coconut oil, corn oil, jojoba oil, jojoba wax, lanolin, lecithin, olive oil, palm oil, rice bran oil, safflower oil, sesame oil, shea butter, soybean oil, squalane, sunflower oil, sweet almond oil, wheat-germ oil, and yellow beeswax, among others.	Budai et al., 2012; de Waroux Yle, 2013; Huang et al., 2009
Piptadenia colubrina extract*	*P. colubrina* hydroglycolic extract, standardized for total arabinogalactans, increased AQP3 gene and protein expression in keratinocyte culture and ex-vivo skin. Extract also increased the expression of the cornified envelope proteins filaggrin and involucrin. These skin-hydration related results were substantiated with findings from clinical studies, in which formulations containing the extract increased the corneometric indices and reduced TEWL.	Pereda et al., 2010

Rice-derived glucosylceramide	Rice-derived GCFr significantly changed the SC ceramide profile in a human skin-equivalent model. Oral administration of this GCFr fraction in mice (3 and 10 mg/kg/day) reduced TEWL in the group exposed to sodium lauryl sulfate. In the skin fragments, ceramide I had increased, while GlcCer (EOS) and the mixture of the GlcCer + GlcCer A/B complex had diminished. These shifts were followed by an increase in GCSase and glucocerebrosidase expression. On the other hand, the expression of GlcCer (d18:2), ceramides 1 and 2, GlcCer (EOS), and GlcCer A/B increased in skin equivalent and was followed by the expression of GCSase and epidermal maturation markers for these ceramides. These results suggest that oral administration of GCFr counterbalanced epidermal ceramide loss by increasing GlcCer metabolism, which resulted in TEWL reduction and barrier function improvement.	Shimoda et al., 2012
Simarouba amara extract*	Immunohistochemical analysis of skin fragments treated with *S. amara* extract demonstrated an increase in involucrin expression and transglutaminase activation. These results were corroborated by clinical and instrumental methodologies which provided evidence of effects related to improvement of barrier function and skin hydration.	Bonté et al., 1996
Urea*	Urea was shown to stimulate significantly the expression of AQP3, AQP7 and AQP9, as well as of cornified envelope proteins (filaggrin, loricrin and involucrin), in addition to promoting increase in the activity of transglutaminase-1 and other enzymes involved in skin lipid synthesis.	Grether-Beck et al., 2012; Lodén and Maibach, 1999

* Active ingredients with placebo/vehicle controlled studies in vivo in man. AQP (aquaporin), GCSase (glucosylceramide synthase), GlcCer (EOS) (esterified ω-hydroxy fatty acid and sphingosine [EOS]), GM-CSF (granulocyte-macrophage colony-stimulating factor), GCFr (glucosylceramide fraction), SC (stratum corneum), TGF-β (transformation growth factor β), TEWL (transepidermal water loss), UVB (ultraviolet B).

Table 3. Cytokines produced by epidermal cells, with constitutive or induced expression.

Cells	Cytokines
Keratinocytes	G-CSF, GM-CSF, IFN-γ, IL-1α, IL-1β, IL-3, IL-6, IL-7, IL-8, IL-10, IL-12, IL-15, IL-18, IP-10, M-CSF, MCP-1, MIP-1α, TGF-α, TGF-β, TNF-α
Langerhans Cells	IFN-γ, IL-1α, IL-1β, IL-6, IL-15, IL-18, MIP-1α, MIP-2, TGF-β
Melanocytes	G-CSF, GM-CSF, IL-1α, IL-1β, IL-6, IL-7, IL-8, IL-10, IL-12, MCSF, MIP-1α, MCP-1, TGF-α, TGF-β, TNF-α

G-CSF (granulocyte colony-stimulating factor), GM-CSF (granulocyte-macrophage colony-stimulating factor), IFN (Interferon), IL (interleukin), IP (IFN-γ inducible protein), M-CSF (macrophage colony-stimulating factor), MCP (monocyte chemoattractant protein), MIP (macrophage inflammatory protein), TGF (transformation growth factor), TNF (tumor necrosis factor).

Table 4. Active ingredients regulating epidermal immunological defense.

Active Ingredients	Action Mechanisms	References
Association of standardized *Pfaffia paniculata*, *Ptychopetalum olacoides* B. and *Lilium candidum* extracts	Association of standardized plant extracts of *P. paniculata*, *P. olacoides* B. and *L. candidum* promotes significant anti-inflammatory action by reducing PGE2, LTB4 and histamine production in a model of cultivated normal human keratinocyte cells stimulated with LPS.	Eberlin et al., 2009
Butea monosperma (Lam.) Taub. flowers extract	Hydroglycolic *B. monosperma* flower extract is capable of reducing secretion of pro-inflammatory cytokines IL-1β, IL-6 and IL-8 in cell culture of normal human keratinocyte by approximately 32, 33 and 18%, respectively. In addition, the extract also inhibits the production of PGE2 and secretion of MMP-1, MMP-2, MMP-9 e MMP-10.	Krolikiewicz-Renimel et al., 2013
Coffea arabica L. seed oil	*C. arabica* L. seed oil induces increase of TGF-β and GM-CSF in keratinocyte cell culture; both are associated with increased extracellular matrix synthesis and immune response recovery.	Velazquez Pereda et al., 2009
Imiquimod	Topical application of imiquimod in a murine model revealed a potential for recovery of the epidermal barrier following treatment with tacrolimus. The potential was determined by stimulating IL-1α production, and also by an increase in the gene expression of mBD3 and CRAMP, two important antimicrobial peptides.	Jung et al., 2011
Korean red ginseng extract	Treatment of human keratinocyte cells with Korean red ginseng extract indicated its capability to control LPS-stimulated inflammatory response with a dose-dependent decrease of TNF-α and IL-8 production.	Hong and Lyu, 2011
Leontopodium alpinum extract	*L. alpinum* extract inhibited IL-8, IP-10, MCP-1, GM-CSF, TNF-α, and IFN-γ levels, dose-dependently, in human keratinocyte cell cultures exposed to radiation or LPS. Results demonstrate anti-inflammatory and immunomodulating activities of this extract.	Daniela et al., 2012
Natural extracts of arnica flowers, betel nuts, black elder bark, and mugwort root	Natural extracts of arnica (*Arnica montana*) flowers, betel (*Areca catechu*) nuts, black elder (*Sambucus nigra*) bark, and mugwort (*Artemisia vulgaris*) root stimulated gene expression of defensins (hBD2 and/or hBD3) in a normal human keratinocyte culture model. In some cases or at specific concentrations, the extracts also induced secretion of cytokines, including MIP-3a, IL-8, and IL-1α.	Pernet et al., 2005

Red orange extract	Red orange extract (*Citrus sinensis* varieties: Moro, Tarocco, Sanguinello) has high levels of anthocyanins, flavanones, hydroxycinnamic acids, and ascorbic acid. Its anti-inflammatory activity was assessed in human keratinocytes (lineage NCTC 2544) exposed to IFN-γ and histamine. Treatment with red orange extract at different concentrations inhibited expression of ICAM-1 and secretion of MCP-1 and IL-8.	Cardile et al., 2010
Resveratrol*	Resveratrol or its natural precursor, polydatin, on human keratinocytes (lineage HaCaT) promoted the modulation of gene expression of cytokines IL-6, IL-8, and TNF-α, and also stimulated the expression of Hsp70B (important for cytoprotection and cell repair) and hBD2.	Baur and Sinclair, 2006; Ravagnan et al., 2013

* Active ingredients with placebo/vehicle controlled studies in vivo in man. CRAMP (cathelin related antimicrobial peptide), GM-CSF (granulocyte-macrophage colony-stimulating factor), Hsp (heat shock protein), hBD (human beta defensin), ICAM-1 (intercellular adhesion molecule 1), IFN-γ (Interferon γ), IL (interleukin), LPS (lipopolysaccharide), LTB4 (leukotriene B4), mBD (mouse beta-defensin), MCP-1 (monocyte chemoattractant protein-1), MIP-3a (macrophage inflammatory protein 3a), MMP (matrix metalloproteinases), PGE2 (prostaglandin E2), TGF-β (transformation growth factor β), Th (T helper cell), TNF-α (tumor necrosis factor α).

Table 5. Active ingredients for regulation of epidermal protection against solar radiation and antioxidant activity.

Active Ingredients	Action Mechanisms	References
Astaxanthin*	Astaxanthin, derived from the microalga *Haematococcus pluvialis* and administered both orally and topically in humans, provided significant inhibition of melanogenesis in age spots by suppressing oxidative melanocyte polymerization and inflammation of the epidermis. Treatment with astaxanthin also acts by protecting keratinocytes from differentiation and cornification induced by oxidative damage.	Tominaga et al., 2012
Apigenin and luteolin	Apigenin and luteolin jointly inhibited the production of ROS in, and increased the viability of, HaCaT cells irradiated with UVA. Pretreatment of the keratinocytes with these flavonoids also inhibited UVA-induced production of MMP-1 and suppressed the expression of c-jun and c-fos, as well as MAPK phosphorylation. Flavonoids also diminished the calcium influx and Ca2+/CaMKs phosphorylation.	Hwang et al., 2011
β-carotene	β-carotene inhibited UVA-induced gene modulation in a HaCaT human keratinocyte lineage. In non-irradiated cells, the gene regulation suggests that β-carotene significantly reduced signs of stress and degradation of the extracellular matrix, in addition to promoting the differentiation of the keratinocytes. These effects occur via singlet oxygen sequestration.	Wertz et al., 2005
Calluna vulgaris extract	Topical application of *C. vulgaris* extract (4 mg polyphenols/cm^2) on mice during 30 minutes before exposure to UVB radiation, for 10 days, provided protection to the skin, reducing the levels of TNF-α and IL-6 cytokines and pirimidin dimers, and the formation of UVB-induced sunburn cells. Therefore, *C. vulgaris* extract protects the skin from sun-induced DNA damage.	Olteanu et al., 2012
Cocoa powder*	Female volunteers who took these flavonoids during 12 weeks showed reduced UV radiation-induced erythema, improved skin appearance and hydration, increased skin layer thickness, and lower TEWL.	Heinrich et al., 2006; Katz et al., 2011
Cynaropicrin	Cynaropicrin prevents photoaging of micel by suppressing photo-induced (especially UVB radiation-induced) transactivation of NF-kB.	Tanaka et al., 2013
Epicatechin-3-gallate	ECG inhibits keratinocyte death induced by UVA and UVB in a dose-dependent manner. For UVA, this mechanism proceeds by inhibiting hydrogen peroxide production. For UVB, ECG inhibited membrane lipid peroxidation in treated cells, in addition to blocking the activation of ERK1/2, p38 and JNK in keratinocytes. Therefore, ECG was demonstrated to have an important antioxidant potential to prevent photodamage.	Huang et al., 2007 and 2005; Nichols and Katiyar, 2010

Epigallocatechin-3-gallate*	EGCG promotes keratinocyte survival and inhibits UV-induced apoptosis with the aid of a dual mechanism: 1) increased Bad phosphorylation through ERK-AKT-dependent pathways; 2) increased Bcl-2/Bax ratio. EGCG treatment of human HaCaT keratinocyte cultures lowered UVB-induced cytotoxicity and also inhibited mRNA expression of apoptosis-regulating genes p53 and p21, and gene c-fos, in addition to blocking the secretion of cytotoxins IL-6 and TNF-α. These data suggest that EGCG may be used for its antiaging effect and as a tumoral inhibitor in human skin. Moreover, EGCG can inhibit/regulate NF-κB action, iNOS gene expression, and NO generation in keratinocytes following UVB exposure. It suggests that EGCG may have an inhibitory effect on photodamage caused by UVB in the epidermis. In human in vivo evaluation, the addition of EGCG to a broad-spectrum sunscreen decreased UV-induced damage compared with sunscreen alone.	Chen et al., 1999; Chung et al., 2003; Luo et al., 2006; Matsui et al., 2009; Song et al., 2006; Tobi et al., 2002
Fucoxantin	Fucoxantin antioxidant activity inhibited vessel formation induced by UVB exposure in a hairless mice model. Expression of VEGF abates with reduction in wrinkle formation, diminishing epidermal hypertrophy caused by UV exposure.	D'Orazio et al., 2012; Urikura et al., 2011; Yasuda et al., 1999
General carotenoids*	Raman spectroscopy showed that, as a defense mechanism against harmful irradiation and environmental factors, topical application of carotenoids enhances the defense potential of the human epidermis. In addition, carotenoids are recognized as excellent nutricosmetics, improving skin resilience and hydration.	Anunciato and da Rocha Filho, 2011; Darvin et al., 2009; Lademann et al., 2011
Grape seed proanthocyanidins	Human keratinocytes irradiated with UVB and treated with GSP's inhibited formation of UVB-induced hydrogen peroxide, lipid peroxidation, protein oxidation, DNA damage, as well as depletion of antioxidant components, such as glutathione peroxidase, catalase, superoxide dismutase, and glutathione. GSP's also inhibit phosphorylation of ERK1/2, JNK, p38 and proteins of MAPK family, as well as UVB-induced activation of NF-κB/p65. These results suggest that GSP may attenuate UV-induced oxidative stress in human skin.	Mantena and Katiyar, 2006
Green tea extract*	Green tea extract enhances skin photoprotection through anti-inflammatory, antioxidant, and DNA repair mechanisms. In mice stimulated by psoralen and UVA (a quite common psoriasis treatment), orally-administered green tea extract inhibited c-fos and p53 protein accumulation. In reconstituted skin model, green tea extract inhibited psoralen plus UVA-induced 8-methoxypsoralen-DNA adduct formation and p53 protein accumulation. Topic treatment of human skin with green tea extract lowered UV-induced p53 expression as well as the number of apoptotic keratinocytes.	Mnich et al., 2009; Nichols and Katiyar, 2010; Zhao et al., 1999

Jacquez grapes wine extract	Jacquez grapes wine extract efficiently prevents the skin from suffering oxidative damage induced by exposure to UVB radiation. This photoprotective effect is attributed to the rich polyphenol content of the extract. Its application, tested on reconstituted skin, helps to maintain the epidermal redox state even after exposure to radiation.	Tomaino et al., 2006
L-carnosine and *Rhodiola rosea* extract association	This association of extracts modulates β-endorphin, enkephalin, CGRP, substance P, IL-1α, TNF-α and IL-10 levels in normal human keratinocytes in basal conditions, as well as under conditions of acute or chronic exposure to UV radiation.	Dieamant et al., 2008
Lycopene*	Employed in several formulations for topical use, lycopene shows hight therapeutic potential to recover epidermal antioxidants lost as a result of UV exposure and, in addition, acts to protect the skin from damage caused by UV. Lycopene was also found to work as a preventive agent by inhibiting the activity of epidermal ornithine decarboxylase, reducing inflammation, maintaining cell proliferation at normal levels and, possibly, preventing damage to DNA from apoptosis blockage (in particular by inhibition of caspase-3), after exposure to UVB.	Andreassi et al., 2004; Fazekas et al., 2003
Mangifera indica L. extract	Mice treated orally with mango (*M. indica* L.) extract exhibited a significant capacity to modulate harmful effects of UV radiation by inhibiting epidermal hypertrophy.	Song et al., 2013
Mangiferin	Mangiferin is a sequestrant of ROS, superoxide radicals, and hidroxyl radicals. In HaCaT human keratinocyte cultures, mangiferin inhibited the induction of MMP-1 generated by hydrogen peroxide, blocking AP-1 DNA binding. In addition, mangiferin inhibited keratinocyte cell death by down-regulating MEK-ERK and SEK-JNK pathways.	Chae et al., 2011
Myricetin	Myricetin inhibits UVB-induced human keratinocyte death in a dose-dependent fashion, by inhibiting hydrogen peroxide build-up and c-jun activation induced by UVB.	Huang et al., 2010
N-acetyl cysteine and genistein*	Pretreatment of human skin with N-acetyl cysteine in conjunction with genistein blocked UV-induction of collagenase, indicating a photoprotective potential for this ingredient.	Kang et al., 2003
Naringenin	Treatment of HaCaT human keratinocytes with naringenin extended the long-term survival of the cells after irradiation with UVB. UVB-induced PARP-1 cleavage, caspase activation, and Bax/Bcl2 ratio were modulated after the naringenin treatment, indicating an antiapoptotic effect for this active ingredient. Also, when HaCaT cells are irradiated with UVB, naringenin increases CPD removal, which indicates that the active ingredient has a protective effect against DNA damage.	El-Mahdy et al., 2008

Phenylpropanoid glycosides	Phenylpropanoid glycosides (verbascoside, forsythoside B, echinacoside and campneoside I) induced Nrf2 and cytoprotective enzyme activity, and exhibited antioxidant activity in HaCaT human keratinocyte cultures.	Sgarbossa et al., 2012
Polyphenol-rich pomegranate fruit extract	POMx effect on photoaging and UVB-induced oxidative stress was evaluated on HaCaT human keratinocytes. Pretreatment with POMx modulated UVB effects related to reduction in cell viability and intracellular glutathione content, and increase in lipid peroxidation. POMx was also capable of inhibiting increases in MMP-1, -2, -9, and -7, reduction of TIMP-1, and UV-induced phosphorylation of MAPK and c-jun.	Zaid et al., 2007
Polypodium leucotomos exctract	Oral administration of *P. leucotomos* extract in mice during 5 days prior to UV exposure and 2 days following irradiation reduced the number of proliferating cells in the epidermis by 13%, promoted an increase in p53-positive cells, and increased the antioxidant capacity of plasma by 30%. The beneficial effect of *P. leucotomos* extract is probably due to its antioxidant and anti-ROS properties.	Rodríguez-Yanes et al., 2012
Red orange extract	Red orange extract was able to neutralize UVB-induced response efficiently in HaCaT human keratinocytes and, in particular, some of the events associated with inflammation and apoptosis, such as NF-kB and AP-1 translocation and procaspase-3 cleavage. This activity is probably due to a blockage of events related to cell oxidative stress, showing that red orange extract may be useful for the photoprotection of the skin.	Cimino et al., 2007
Resveratrol*	Human skin has specific bonding sites for resveratrol, which has a potential to delay, or even arrest, the normal course of skin aging by blocking apoptotic events and mitochondrial disfunctions in keratinocytes. Studies with the HaCaT human keratinocyte lineage have shown trans-resveratrol to be able to inhibit hydrogen peroxide production. In humans, in addition to providing a protective effect against UVA radiation, trans-resveratrol even improves clinical signs of aging when used in association with β-cyclodextrin excipient.	Bastianetto et al., 2010; Baur and Sinclair, 2006; Chen et al., 2006; Moyano-Mendez et al., 2013
Rheum rhaponticum L. rhizome extract	Rhubarb extract (*R. rhaponticum* L.) showed antiradical characteristics and antioxidant properties against lipid peroxidation in vitro; the extract also reduced tirosinase activity. In addition, it inhibited the production of IL-1α, TNF-α, and α-MSH, and the activity of tyrosine kinase in human melanocytes subjected to UV radiation.	Silveira et al., 2013
Sea buckthorn fruit blend	UV-irradiated mice were treated orally with a blend of sea buckthorn fruit extract, blueberry extract and collagen. Oral ingestion of SFB reduced formation of wrinkles and helped to maintain skin thickness. SFC-treated mice showed inhibited TEWL and increased skin moisture content. SFB application reduced MMP-1 and -9 expressions, and regulated SOD activity levels.	Hwang et al., 2012

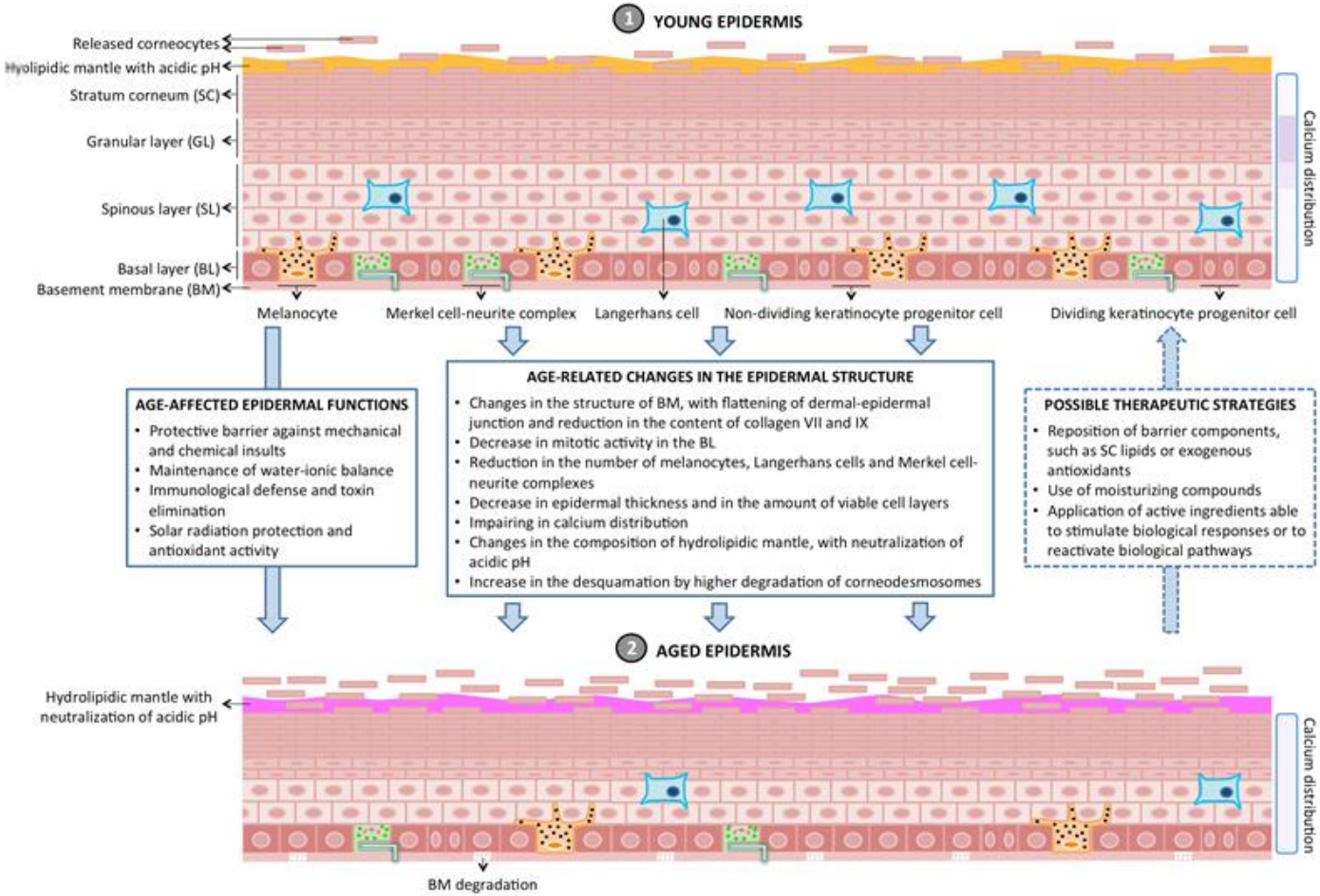
Silk lutein	Protection against harmful effects of UVB was evaluated for lutein extracted from yellow silk cocoons, in comparison with plant-derived lutein, in primary human keratinocytes or lineage CCD 1102 KERTr. Silk lutein was not cytotoxic for keratinocytes, and also protected the cells that received treatment prior to UVB iradiation, reducing the cytotoxicity and the levels of cell apoptosis.	Pongcharoen et al., 2013
Soybean extract	Soybean extract, rich in isoflavones, inhibited UVB-induced cell death in HaCaT human keratinocytes, as well as p38, JNK and ERK1/2 phosphorylation. In mice, topic application prior to UV irradiation was shown to diminish epidermal thickness and COX-2 and PCNA expression, and also to increase catalase concentration.	Chiu et al., 2009
Tannase-converted green tea extract	Tannase, an enzyme produced by fungi, yeasts and bacteria, hydrolyzes catechin gallates (EGCG and ECG) from green tea and enhance its potential application for elimination of radicals, such as hydrogen superoxide and peroxide. A formulation containing tannase-converted green tea extract was used to inhibit UV-induced oxidative damage in mice epidermis. Formulation acted by preventing glutathione reduction and controlling hydrogen peroxide levels. Mice treated with FTGE displayed a significant reduction in the levels of thiobarbituric acid reactive substances by lipid peroxidation, in comparison with non-UVB-irradiated controls, which indicates that this formulation is effective in protecting the skin against photoaging.	Hong et al., 2012
Tectroside	Tectroside or lactone inhibits UVB-induced production of proinflammatory cytokines (IL-6 and IL-8) in HaCaT human keratinocyte cultures, in a dose-dependent manner. It also inhibits COX-2 expression and JNK phosphorylation. These results suggest that this compound has the potential to protect the skin against UVB-induced inflammation.	Kim et al., 2013
Vitamin C*	Vitamin C or ascorbic acid reduces effects of aging, such as deep and superficial wrinkles, and increases skin elasticity, firmness, roughness, and hydration. Evaluation of ascorbic acid and its derivatives, AA 2-phosphate e AAS 2-glucoside, on UVB-induced cytotoxicity in HaCaT human keratinocytes showed that, unlike its derivatives, ascorbic acid was unable to inhibit cytotoxicity.	Haftek et al., 2008; Raschke et al., 2004; Yasuda et al., 2004
Vitamin E*	One of the forms of vitamin E, α-tocopherol, is widely known for its antioxidant potential. The inhibitory role of α-tocopherol in the regulation of IL-8 and AP-1 production in human keratinocyte exposed to UVA was assessed and shown to inhibit significantly the activity of NADPH oxidase, which would be responsible for the activation of IL-8 and AP-1; α-tocopherol also inhibited malondialdehyde-thiobarbituric acid formation in cells exposed to UVA radiation.	Wu et al., 2008

Vitis vinifera shoot extract	*V. vinifera* shoot extract shows a higher in vitro antioxidant capability than vitamin C or E. An aquous *V. vinifera* L. tendril extract, applied in human keratinocytes (NCTC 2544) was able to increase the concentration of reduced glutathione and the activity of trans plasma membrane oxido reductase, in a time- and dose-dependent fashion, which demonstrates that the extract has a relevant antioxidant activity.	Cornacchione et al., 2007; Fraternale et al., 2011
Zeaxanthin and lutein*	Increased intake of lutein improved the health of the skin when supplemented orally or applied topically (zeaxanthin and lutein), as assessed on the basis of the following five physiological parameters: skin surface lipids, skin hydration, photoprotective activity, skin elasticity, and lipid peroxidation. Oral or topical administration improved such measurements significantly: oral administration resulted in better protection against changes in lipid peroxidation and in photoprotective activity following UV irradiation. Nevertheless, combined oral and topic administration provide a higher degree of protection. Other studies have also demonstrated the protective effect of this combination against epidermal hyperproliferation and inflammation after UVB exposure in mice.	Evans and Johnson, 2010; González et al., 2003; Palombo et al., 2007

* Active ingredients with placebo/vehicle controlled studies in vivo in man. AKT (protein kinase B), AP-1 (activator protein 1), Bad (Bcl-2-associated death promoter), Bax (Bcl-2-associated X protein), Bcl-2 (B-cell lymphoma 2), c-fos (cellular oncogene fos), c-jun (cellular oncogene jun), CaMKs (calmodulin-dependent protein kinases), CGRP (calcitonin gene-related peptide), COX-2 (ciclooxigenase-2), ECG (epicatechin-3-gallate), EGCG (epigallocatechin-3-gallate), ERK (extracellular-signal-regulated kinases), FTGE (tannase-converted green tea extract), GSP (grape seed proanthocyanidins), IL (interleukin), iNOS (inducible nitric oxide synthase), JNK (c-Jun NH2-terminal kinase), MAPK (mitogen-activated protein kinases), MEK (mitogen-activated protein kinase kinase), MMP (matrix metalloproteinases), NF-κB (nuclear factor kappa B), Nrf2 (NF-E2-related factor 2), p21 (cyclin-dependent kinase inhibitor 1), p53 (protein 53), p65 (transcription factor p65), PARP-1 (Poly [ADP-ribose] polymerase 1), PCNA (proliferating cell nuclear antigen), POMx (polyphenol-rich pomegranate fruit extract), ROS (reactive oxygen species), SEK (stress-activated protein kinase/extracellular signal-regulated kinase), Ser (serine), SFB (sea buckthorn fruit blend), SOD (superoxide dismutase), TEWL

(transepidermal water loss),TIMP (tissue inhibitors of metalloproteinases), TNF-α (tumor necrosis factor α), UV (ultraviolet).

Figure 1


1 YOUNG EPIDERMIS
Released corneocytes
Hyolipidic mantle with acidic pH
Stratum corneum (SC)
Granular layer (GL)
Spinous layer (SL)
Basal layer (BL)
Basement membrane (BM)
Calcium distribution
Melanocyte
Merkel cell-neurite complex
Langerhans cell
Non-dividing keratinocyte progenitor cell
Dividing keratinocyte progenitor cell
AGE-AFFECTED EPIDERMAL FUNCTIONS
• Protective barrier against mechanical and chemical insults
• Maintenance of water-ionic balance
• Immunological defense and toxin elimination
• Solar radiation protection and antioxidant activity
AGE-RELATED CHANGES IN THE EPIDERMAL STRUCTURE
• Changes in the structure of BM, with flattening of dermal-epidermal junction and reduction in the content of collagen VII and IX
• Decrease in mitotic activity in the BL
• Reduction in the number of melanocytes, Langerhans cells and Merkel cell-neurite complexes
• Decrease in epidermal thickness and in the amount of viable cell layers
• Impairing in calcium distribution
• Changes in the composition of hydrolipidic mantle, with neutralization of acidic pH
• Increase in the desquamation by higher degradation of corneodesmosomes
POSSIBLE THERAPEUTIC STRATEGIES
• Reposition of barrier components, such as SC lipids or exogenous antioxidants
• Use of moisturizing compounds
• Application of active ingredients able to stimulate biological responses or to reactivate biological pathways
2 AGED EPIDERMIS
Hydrolipidic mantle with neutralization of acidic pH
Calcium distribution
BM degradation

7.3. Aprovação do Comitê de Ética em Pesquisa

UNIVERSIDADE
POSITIVO
Comitê de Ética em Pesquisa.
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Curitiba – PR, 24 de outubro de 2011.

Carta de Aprovação Ética

O Comitê de Ética em Pesquisa da UP recebeu a emenda de 19 de outubro de 2011, referente ao protocolo 188/09 "Estudo dos Marcadores Biológicos Envolvidos no Envelhecimento Cutâneo Por Faixa Etária", elaborado pela professora Camila Miranda de Carvalho, não foram identificadas falhas éticas na emenda proposta, portanto essa comissão ética opina pela aprovação.

Atenciosamente,

Juliana Londero
Vice-coordenadora do CEP - UP

7.4. Produtividade técnico-científica do aluno ao longo do curso de Doutorado

Patentes

1) **Título**: Process for preparing a plant extract of Passiflora alata and use of said extract in cosmetic and pharmaceutical compositions
Inventores: Ana Paula Pedroso de Oliveira, Cintia Rosa Ferrari, Elaine Cristina de Oliveira, Gilson Paulo Manfio, Jean-Luc Gesztesi, João Batista Calixto, Márcio Lorencini, Patricia da Luz Moreira, Rodrigo Collina Romanhole, Sandra Patricia Hurtado Medina, Sergio Delarcina Junior, Simone Soares Esteves, Thiago Braz
Código: FR07/06151 / **Abrangência:** França / **Data depósito:** 03/09/2007 / **Publicação:** não publicada
Código: WO/2009/030008 / **Abrangência:** Mundial / **Data depósito:** 03/09/2008 / **Publicação:** 12/03/2009
Código: EP2185166 / **Abrangência:** Europa / **Data depósito:** 03/09/2008 / **Publicação:** 19/05/2010
Código: CA2696566 / **Abrangência:** Canadá / **Data depósito:** 15/02/2010 / **Publicação:** não publicada
Depositante: Natura Cosméticos S.A., Universidade Federal de Santa Catarina
Resumo: The present invention relates to the use of plant extracts of Passiflora alata as an anti-inflammatory agent in cosmetic and pharmaceutical compositions. The present invention further relates to a process for obtaining a plant extract of Passiflora alata comprising the steps of submitting the leaves of the Passiflora alata plants to an extraction with water to obtain an aqueous extract and submitting the aqueous extract thus obtained to at least one elution with an aqueous solution of ethanol in a specific column and later drying of said extract by spray-drying.

2) **Título**: Cosmetic composition comprising siliconed sapucainha ester and a cosmetic product comprising said composition
Inventores: Daisy de Fátima Scarparo de Sanctis, Débora Figueiredo Beda, Érica Dadario Brugnollo, Leandra Moraes Santos, Márcio Lorencini, Vanessa de Moura Sá Rocha
Código: US20110097290 / **Abrangência:** Estados Unidos / **Data depósito:** 27/10/2009 / **Publicação:** 28/04/2011
Código: EP2493448 / **Abrangência:** Europa / **Data depósito:** 27/08/2010 / **Publicação:** 05/09/2012
Código: WO/2011/050433 / **Abrangência:** Mundial / **Data depósito:** 27/10/2010 / **Publicação:** 05/05/2011
Código: US20120328547 / **Abrangência:** Estados Unidos / **Data depósito:** 26/03/2012 / **Publicação:** 27/12/2012
Código: CA2779151 / **Abrangência:** Canadá / **Data depósito:** 27/04/2012 / **Publicação:** não publicada
Depositante: Natura Cosméticos S.A.
Resumo: The present invention relates to a cosmetic composition comprising siliconed sapucainha ester, compound which can be used as a cosmetic excipient replacing silicones for several applications. The present invention further relates to cosmetic products comprising said composition.

3) **Título**: Process for obtaining a standardised extract of quercetin and 3-0-methylquercetin from flowers of macela (Achyrocline satureioides), and cosmetic and pharmaceutical compositions comprising said extract
Inventores: Alan Passero, Débora Figueiredo Beda, Márcio Lorencini, Sergio Delarcina Junior, Tiago Costa Beber, Vanessa de Moura Sá Rocha

Código: FR09/59012 / **Abrangência:** França / **Data depósito:** 15/12/2009 / **Publicação:** não publicada
Código: WO/2011/073961 / **Abrangência:** Mundial / **Data depósito:** 06/01/2011 / **Publicação:** 23/06/2011
Código: EP2512495 / **Abrangência:** Europa / **Data depósito:** 06/01/2011 / **Publicação:** 24/10/2012
Código: US20130012577 / **Abrangência:** Estados Unidos / **Data depósito:** 06/01/2011 / **Publicação:** 10/01/2013
Depositante: Natura Cosméticos S.A.
Resumo: It describes an extraction process for obtaining a standardized extract of quercetin and 3-0-methylquercetin from inflorescences of macela-do-campo (Achyrocline satureioides) characterized by comprising of the following steps: A) grinding the inflorescences of Achyrocline satureioides to obtain a material of ground plant; B) submitting the ground plant to at least four sequential stages of hydro-alcoholic extraction at a temperature from 60°C to 80°C1 for 3 to 4 hours for each stage, in order to obtain 4 intermediary hydro-alcoholic extracts; C) combining the 4 intermediary hydro-alcoholic extracts; D) concentrating the intermediary hydro-alcoholic extracts mixture; in order to obtain up to a maximum of 20% of the initial mass of the intermediary hydro-alcoholic extracts; E) drying the material obtained in (D). It also describes cosmetic, pharmaceutical and veterinary compositions containing the aforesaid extract of macela-do-campo, destined for the prevention and treatment of the damages arising from inflammatory, microbial and oxidation/lypoperoxidation reactions. The use and method of application of the aforesaid extract of macela are also described.

4) **Título**: Composição antienvelhecimento e formulação cosmética e/ou dermatológica contendo a mesma
Inventores: Carlos Eduardo de Oliveira Praes, Marcela Contador Baptista, Márcio Lorencini, Ruandro Victor Knapik
Código: PI 1005274-7 A2 / **Abrangência:** Brasil / **Data depósito:** 15/12/2010 / **Publicação:** publicada em 09/04/2013
Depositante: Botica Comercial Farmacêutica Ltda.
Resumo: Descreve-se a presente invenção como uma composição antienvelhecimento e formulação cosmética e/ou dermatológica contendo a mesma que, de acordo com as suas características gerais, propicia uma composição antienvelhecimento a partir de uma combinação de otimizada de ingredientes contendo sais minerais, com vistas a propiciar por meio da combinação otimizada destes ingredientes um aumento da produção de colágeno e, por conseguinte, a firmeza da pele, de modo a promover a minimização de rugas e linhas da pele e uma melhora efetiva do aspecto geral da pele, ambos obtidos diretamente pela ação balanceada destes ingredientes ricos em sais minerais.

5) **Título:** Composição farmacêutica para aplicação na pele
Inventores: Alessandro Afornali, Camila Miranda de Carvalho, Carlos Eduardo de Oliveira Praes, Fernanda Lourenço Angelucci, Márcio Lorencini, Priscila Fernanda Campos de Menezes, Ruandro Victor Knapik
Código: PI 1010479-8 / **Abrangência:** Brasil / **Data depósito:** 27/12/2010 / **Publicação:** notificação de depósito de pedido de patente em 15/05/2012
Depositante: Botica Comercial Farmacêutica Ltda.
Resumo: Conteúdo ainda não publicado pelo INPI.

6) **Título:** Composição cosmética e/ou dermatológica e formulação cosmética e/ou dermatológica contendo a referida composição
Inventores: Alessandro Afornali, Camila Miranda de Carvalho, Carlos Eduardo de Oliveira Praes, Márcio Lorencini, Priscila Fernanda Campos de Menezes
Código: PI 1005496-0 A2 / **Abrangência:** Brasil / **Data depósito:** 29/12/2010 / **Publicação:** publicada em 16/04/2013
Depositante: Botica Comercial Farmacêutica Ltda.

Resumo: A presente invenção refere-se a uma composição antienvelhecimento e formulação cosmética e/ou dermatológica contendo a referida composição. Esta mistura otimizada de ingredientes ativos é capaz de atuar positivamente sobre processos biológicos relacionados ao envelhecimento da pele, conferindo proteção e minimização dos sinais do relevo cutâneo. Este conjunto de características é obtido pela combinação de dois peptídeos e um polissacarídeo.

7) **Título:** Ingrediente cosmético e/ou dermatológico e formulação cosmética e/ou dermatológica contendo o mesmo
Inventores: Alessandro Afornali, Alexandre Roberto Silva, Bruna Bastos Swinka, Camila Miranda de Carvalho, Carlos Eduardo de Oliveira Praes, Luiza Fernanda Schier, Márcio Lorencini, Priscila Fernanda Campos de Menezes
Código: PI 1102721-5 A2 / **Abrangência:** Brasil / **Data depósito:** 10/06/2011 / **Publicação:** publicada em 16/07/2013
Depositante: Botica Comercial Farmacêutica Ltda.
Resumo: A presente invenção refere-se a um ingrediente e formulação cosmética e/ou dermatológica que apresenta ações de preservação da longevidade de células dérmicas (fibroblastos) e células-tronco adultas, de aumento do metabolismo celular, sustentação e adesão das células da pele e melhoria da função barreira, garantindo assim uma atividade antienvelhecimento diferenciada, com minimização dos sinais de envelhecimento da pele. Este conjunto de benefícios é proporcionado por uma fração obtida a partir de Malus sp.

8) **Título:** Composição nutritiva e formulação cosmética e/ou dermatológica contendo a mesma
Inventores: Alessandro Afornali, Alexandre Roberto Silva, Camila Miranda de Carvalho, Carlos Eduardo de Oliveira Praes, Márcio Lorencini, Priscila Fernanda Campos de Menezes, Ruandro Victor Knapik, Vanessa Vitoriano da Silva
Código: PI 1104880-8 / **Data depósito:** 27/10/2011 / **Abrangência:** Brasil / **Publicação:** notificação de depósito de pedido de patente em 14/08/2012
Depositante: Botica Comercial Farmacêutica Ltda.
Resumo: Conteúdo ainda não publicado pelo INPI.

9) **Título:** Ingrediente protetor da barreira cutânea e formulação cosmética e/ou dermatológica contendo o mesmo
Inventores: Alessandro Afornali, Bruna Bastos Swinka, Carla Abdo Brohem, Gustavo de Campos Diaemant, Israel Henrique Stokfisz Feferman, Marcela Contador Baptista, Márcio Lorencini, Tammy Proença Zagonel Nichele
Código: BR 10 2012 032898 4 / **Data depósito:** 21/12/2012 / **Abrangência:** Brasil / **Publicação:** notificação de depósito de pedido de patente em 11/06/2013
Depositante: Botica Comercial Farmacêutica Ltda.
Resumo: Conteúdo ainda não publicado pelo INPI.

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