UNIVERSIDADE ESTADUAL DE CAMPINAS
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Caracterização do proteoma mitocondrial e nuclear de células neurais derivadas de iPSCs de pacientes com esquizofrenia

Characterization of the mitochondrial and nuclear proteome of neural cells derived from iPSCs from schizophrenia patients

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GIULIANA DA SILVA ZUCCOLI

CARACTERIZAÇÃO DO PROTEOMA MITOCONDRIAL E NUCLEAR DE CÉLULAS NEURAIS DERIVADAS DE IPSCS DE PACIENTES COM ESQUIZOFRENIA

CHARACTERIZATION OF THE MITOCHONDRIAL AND NUCLEAR PROTEOME OF NEURAL CELLS DERIVED FROM IPSCS FROM SCHIZOPHRENIA PATIENTS

Dissertação apresentada ao Instituto de Biologia da Universidade Estadual de Campinas como parte dos requisitos exigidos para a obtenção do título de Mestra em Biologia Funcional e Molecular, na área de Bioquímica

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RESUMO

A esquizofrenia é um transtorno psiquiátrico grave que pode atingir até 1% da população mundial e geralmente se manifesta no final da adolescência/início da idade adulta. Segundo a hipótese do neurodesenvolvimento, disfunções precoces no cérebro em desenvolvimento, devido a fatores genéticos e ambientais, resultam no surgimento da esquizofrenia. Estudos realizados com o intuito de elucidar os mecanismos da doença mostram que processos celulares importantes estão alterados, tais como função mitocondrial, resposta a espécies reativas de oxigênio e outros. Afim de estabelecer se existem alterações relacionadas ao metabolismo energético e função mitocondrial em estágios iniciais do neurodesenvolvimento e suas possíveis implicações para o estabelecimento da esquizofrenia, no presente trabalho foram analisados os proteomas mitocondriais e nucleares de células-tronco neurais (NSCs) e neurônios derivados de células-tronco de pluripotência induzida (iPSCs) de pacientes com esquizofrenia e controles saudáveis. Por conseguinte, a análise comparativa das amostras foi realizada através de proteômica em larga escala baseada em espectrometria de massas. Posteriormente, as proteínas encontradas com diferenças significativas ao comparar esquizofrenia e controle foram submetidas a análise de biologia de sistemas *in silico* para obtenção das vias bioquímicas relacionadas a cada condição. Processos celulares e vias canônicas associados à função mitocondrial, controle do ciclo celular, reparo ao DNA e neuritogênese foram encontrados alterados em esquizofrenia revelando que processos-chave do neurodesenvolvimento podem estar afetados, como diferenciação neuronal e orientação axonal, e dar origem às alterações fenotípicas observadas em pacientes adultos. Dessa forma, os dados gerados nesta dissertação de mestrado auxiliarão na identificação de mecanismos que podem estar alterados durante o neurodesenvolvimento em pacientes com esquizofrenia e contribuir para um melhor entendimento do estabelecimento da doença.

ABSTRACT

Schizophrenia is a severe psychiatric disorder that can affect up to 1% of the world's population and usually manifests itself at the end of adolescence/beginning of adult life. According to the neurodevelopment hypothesis, early dysfunctions in the developing brain, due to genetic and environmental factors, lead to the appearance of schizophrenia. Studies conducted with the purpose of elucidating the mechanisms of the disorder show that important cellular processes are altered, such as mitochondrial function, response to reactive oxygen species and others. To stablish if there are alterations related to energy metabolism and mitochondrial functions in early stages of neurodevelopment and their possible implications to the stablishment of schizophrenia, in the present work the mitochondrial and nuclear proteomes of neural stem cells (NSCs) and neurons derived from induced pluripotent stem cells (iPSCs) from schizophrenia patients and healthy controls were analyzed. The comparative analysis was conducted through large-scale mass spectrometry-based proteomics. Subsequently, the proteins found to be significantly different in schizophrenia when compared to controls were submitted to an *in silico* systems biology analysis to obtain the biochemical pathways related to each condition. Cellular processes and canonical pathways related to mitochondrial function, cell-cycle control, DNA repair and neuritogenesis were found altered in schizophrenia revealing that key processes of neurodevelopment may be affected, such as neuronal differentiation and axonal guidance, and give rise to the phenotypic alterations observed in adult patients. In this way, the data generated in this dissertation will contribute to the identification of mechanisms that can potentially be altered during neurodevelopment in schizophrenia patients and contribute to a better understanding of the disorder's stablishment.

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ÍNDICE DE TABELAS

ABREVIATURAS

2DE – Eletroforese em gel bi-dimensional

2D-DIGE – Eletroforese em gel bi-dimensional fluorescente

AA – Arachidonic acid

ACC – Anterior cingulate cortex

AMPK – AMP-activated protein kinase

APC – Anterior prefrontal cortex

ATL – Anterior temporal lobe

ATP – Adenosine triphosphate

BPD – Bipolar disorder

CA – Cornu ammonis

CC – Corpus callosum

CID – Collision-induced dissociation

CNS – Central nervous system

DA – Dopamina

DG – Dentate gyrus

DIA - Data-independent analysis

DLPFC – Dorsolateral prefrontal cortex

DMEM – Dulbecco's Modified Eagle Medium

DSM-5 – Manual Diagnóstico e Estatístico de Transtornos Mentais

EDTA – Ethylenediamine tetraacetic acid

EPA – Eicosapentaenoic acid

ESI – Ionização por eletrospray

FC – Frontal cortex

FDR – False discovery rate

GIP – Glucose-dependent insulinotropic polypeptide

GLP-1 – Glucagon-like peptide 1

GLU – Glutamato

GSH – Glutationa

GSH-Px – Glutathione peroxidase

GSK3 – Glycogen synthase kinase 3

HDMSe – High Definition Mass Spectrometry

HP – Hippocampus

IC – Insular cortex

IMS – Mobilidade iônica de alta eficiência

IPA – Ingenuity Pathway Analysis

iPSCs – Induced pluripotent stem cells; Células tronco pluripotente induzidas

LC/MS – Cromatografia líquida acoplada a espectrômetro de massas

LSD – Ácido D-lisérgico

MALD – Matrix Assisted Laser Desorption Ionization

MDD – Major depressive disorder

MDT – Mediodorsal thalamus

MRI – Magnetic resonance imaging

MRS – Magnetic resonance spectroscopy

MS – Espectrômetro de massas; mass spectrometry

mtDNA – Mitochondrial DNA

mTOR – Mammalian target of rapamycin

NPC – Neural progenitor cells

NSC – Neural stem cells

OXPHOS – Oxidative phosphorylation

PET – Positron emission tomography

PLA2 – Phospholipase A2

PPP – Pentose phosphate pathway

ROS – Reactive oxygen species

RT – Tempo de retenção; retention time

SCZ – Schizophrenia

SDS-PAGE – Sodium docecylsulfate polyacrylamide gel electrophoresis

SNC – Sistema Nervoso Central

SOD – Superoxide dismutase

TCA – Tricarboxylic acid

TOF – time of flight

WA – Wernicke's area

SUMÁRIO

6. INTRODUÇÃO

6.1 A esquizofrenia

A esquizofrenia é um distúrbio cerebral que se expressa na forma de anormalidades das funções mentais e distúrbios comportamentais (LEWIS; LIEBERMAN, 2000). Seus sintomas podem ser divididos em três categorias. Sintomas produtivos incluem delírios (crenças falsas), alucinações (percepções falsas) e desorganização do pensamento. Sintomas negativos referem-se à síndrome amotivacional, caracterizada pelo isolamento social, inabilidade de sentir prazer e iniciativa e energia diminuídas. Sintomas cognitivos incluem distúrbios de atenção, funções executoras e memória de trabalho (KAHN et al., 2015; LEWIS; LIEBERMAN, 2000). A esquizofrenia tende a se desenvolver por volta dos 16 a 30 anos de idade e persiste durante toda a vida do paciente, consistindo em um dos mais importantes problemas de saúde pública do mundo afetando mais de 21 milhões de pessoas (OWEN; SAWA; MORTENSEN, 2016; “WHO | Schizophrenia”, 2016).

Atualmente, o diagnóstico da esquizofrenia é baseado em entrevistas realizadas entre médico e paciente, envolvendo a comunicação dos sintomas subjetivos e relato da história do paciente. A categorização deste é realizada utilizando-se o Manual Diagnóstico e Estatístico de Transtornos Mentais (DSM-5) ou através da Classificação Estatística Internacional de Doenças e Problemas Relacionados à Saúde (“WHO | Schizophrenia”, 2016). O tratamento da esquizofrenia deve abordar a multifatorialidade da doença por meio da integração de drogas e tratamentos psicossociais para lidar com uma pessoa cronicamente desabilitada (SPOHN, 1985). Consistem da administração de anti-psicóticos que são capazes de diminuir a ocorrência de delírios e alucinações. A eficácia desses medicamentos é baixa e apenas 40% dos pacientes respondem positivamente ao tratamento inicial com essas drogas (THOMPSON, IAN M, LUCIA et al., 2009). Essa resposta é heterogênea devido a variações individuais da doença em conjunto com o conhecimento limitado em relação à sua causa e fisiopatologia, dificultando o diagnóstico e escolha adequada de tratamento (NASCIMENTO; MARTINS-DE-SOUZA, 2015). Por conseguinte, diversos trabalhos vem sendo realizados a fim de compreender as bases moleculares relacionadas ao estabelecimento e progressão da doença, assim permitindo uma melhor intervenção diagnóstica e terapêutica.

6.2 As causas da esquizofrenia

Inúmeros estudos genéticos e epidemiológicos demonstraram durante os últimos anos que fatores genéticos possuem uma grande contribuição, porém não exclusiva, com as causas da esquizofrenia (OWEN; SAWA; MORTENSEN, 2016). Estudos genéticos utilizando gêmeos, adoção e históricos familiares demonstraram que o risco para desenvolvimento da doença é elevado nos indivíduos que possuem uma relação biológica com a desordem, com uma herdabilidade de aproximadamente 80% em estudos realizados com gêmeos, indicando que quanto mais próximo o nível da relação genética, maior a probabilidade do desenvolvimento do transtorno (SULLIVAN; DALY; O'DONOVAN, 2012; VAN OS; KAPUR, 2009).

Dada a importância e severidade da doença, diversos estudos foram realizados afim de tentar elucidar os mecanismos relacionados às causas da esquizofrenia. Dessa forma, foram criadas teorias sobre o desenvolvimento da doença, que estão centradas em desregulações nos neurotransmissores. A hipótese dopaminérgica foi proposta depois de observações que indicaram que drogas usadas recreativamente como anfetamina e cocaína, que são agonistas de receptores dopaminergicos, causam psicoses semelhantes às que os pacientes vivenciam (MELTZER; STAHL, 1976). A teoria seretonérgica também foi formulada a partir de sintomas psicóticos que LSD (ácido D-lisérgico), uma droga recreativa, causava. Essa substância possui a ação agonista em receptores de serotonina, ou seja, o mal funcionamento desse receptor, induzido pela droga, pode causar sintomas parecidos com os da SCZ (SHAW; WOOLLEY, 1956). A hipótese glutamatérgica foi baseada na possibilidade de antagonistas dos receptores de glutamato do tipo N-metil D-Aspartato (NMDA), também induzirem psicose semelhante a que ocorre em pacientes com esquizofrenia (JAVITT; ZUKIN, 1991). No entanto, a hipótese do neurodesenvolvimento representa a união das hipóteses citadas anteriormente e postula que a convergência de pequenos fatores leva à deficiência sináptica, causando os sintomas relacionados à esquizofrenia.

6.2.1 Hipótese do neurodesenvolvimento

Desde a publicação dos artigos de Weinberger (WEINBERGER, 1987) e Murray (MURRAY, 1987) há trinta anos, a hipótese do neurodesenvolvimento tem sido uma das principais teorias para a explicação do surgimento da esquizofrenia (OWEN; O'DONOVAN, 2017). Essa hipótese baseia-se na proposta de que o surgimento do transtorno no final da adolescência/início da idade adulta possa ser explicado por disfunções precoces no cérebro

em desenvolvimento, devido a fatores genéticos e ambientais. Os precursores da esquizofrenia são sutis e não-específicos, mas a consistência dos relatos suporta a hipótese de que a psicose não se manifesta a partir de um cérebro completamente saudável (INSEL, 2010). Supõe-se que a interação genética associada ao acometimento do desenvolvimento neurológico promove uma conexão defeituosa entre regiões do cérebro, como mesencéfalo, tálamo e córtex pré-frontal. Este circuito neural defeituoso fica vulnerável à disfunção quando revelado pelos processos de desenvolvimento e eventos relacionados à adolescência, como mielinização, poda sináptica e efeitos hormonais da puberdade no sistema nervoso central (SNC) (LEWIS; LIEBERMAN, 2000).

Por exemplo, já se foi observado alterações no hipocampo e córtex pré-frontal durante o neurodesenvolvimento de pacientes com esquizofrenia (WEINBERGER, 1987). Ademais, alterações no neurodesenvolvimento também vem sendo relacionadas a problemas durante a gravidez como a desnutrição materna antes e durante a gravidez. Análise de dados obtidos durante dois grandes períodos de fome, sendo uma a *Dutch Hunger winter* de 1944 a 1945 e a outra na China durante 1959 a 1961 demonstrou um aumento de cerca de 2 vezes na taxa de esquizofrenia nos filhos de mães nascidas durante este período (MCGRATH; BROWN; ST CLAIR, 2011; XU et al., 2009). Todos esses fatores levaram a busca de quais sistemas neuroquímicos estão envolvidos e podem mediar as alterações progressivas observadas durante as fases iniciais da esquizofrenia e também no decorrer da vida do indivíduo afetado.

6.3 Fisiopatologia da esquizofrenia

Ao contrário de outros distúrbios neurodesenvolvimentais, pessoas com esquizofrenia parecem funcionar normalmente até que os sintomas mais severos, como a psicose, aparecem no final da adolescência ou início da vida adulta. No entanto, ao se fazer o histórico destas pessoas, é possível identificar que elas apresentavam pequenos déficits sociais, motores e cognitivos durante a infância e adolescência que podem representar fatores pré-morbidos da doença (JONES, 1997). Sintomas e comportamentos prodromais podem incluir, entre outros, sintomas positivos atenuados, ansiedade, irritabilidade, sintomas cognitivos e afastamento social. Como essas características podem estar presentes em outras doenças psiquiátricas, elas não podem ser consideradas diagnósticas (LEWIS; LIEBERMAN, 2000).

Inúmeros estudos de imagem e neuropatológicos cerebrais tentaram relacionar as alterações observadas na esquizofrenia e funções alteradas do cérebro (JARSKOG; MIYAMOTO; LIEBERMAN, 2007; LINDEN, 2012). Estudos indicam que a fisiopatologia do transtorno envolvem uma conectividade sináptica interrompida que afeta tanto os circuitos

excitatórios quanto inibitórios (JARSKOG; MIYAMOTO; LIEBERMAN, 2007). Dessa forma, grande número de evidências sugere que alterações em vários sistemas de neurotransmissores estão envolvidos na sintomatologia do transtorno. Dentre estes, os sistemas de dopamina (DA) e glutamato (GLU) receberam maior foco, embora outros sistemas também sejam implicados como GABAérgicos, serotonérgicos e opióides (LARUELLE; KEGELES; ABI-DARGHAM, 2003).

Diversos estudos de tecido *post mortem*, farmacológicos e genéticos apontaram anormalidades na rede neural e mudanças em neurotransmissão, além de, entre outros, alterações na resposta inflamatória, metabolismo energético, disfunção mitocondrial e desbalanço das espécies reativas de oxigênio (ERO) (NASCIMENTO; MARTINS-DE-SOUZA, 2015).

6.4 Metabolismo energético - Estresse oxidativo - Disfunção mitocondrial

Os processos realizados pelo cérebro demandam um gasto energético elevado. Mesmo representando apenas 2% do total de peso corpóreo, este órgão requer 20% da energia total do organismo (ATTWELL; LAUGHLIN, 2001). Glicose é o substrato energético obrigatório do cérebro e é totalmente oxidada a CO_2 e água através de seu processamento sequencial na glicólise, ciclo de Krebs e fosforilação oxidativa (MAGISTRETTI; ALLAMAN, 2013).

6.3.1 Evidências de comprometimento em esquizofrenia

Estudos proteômicos de diferentes regiões do cérebro de pacientes com esquizofrenia coletados *post mortem* revelaram que enzimas-chave da via glicolítica estão diferencialmente expressas quando comparadas com controles saudáveis. A enzima mais diferencialmente expressa é a aldolase C. Esta enzima da glicólise catalisa a clivagem da frutose-1,6-bifosfato e frutose-1-fosfato em diidroxiacetona fosfato e/ou gliceraldeído-3-fosfato. Ao analisar a região do tálamo do cérebro de pacientes com esquizofrenia, foi observado que os níveis de piruvato, que é o produto final da glicólise, estavam menores do que quando comparado com controles (MARTINS-DE-SOUZA et al., 2011).

A produção de acetil-CoA e oxaloacetato a partir do piruvato acontece no ciclo de Krebs e estudos mostraram que essa reação está desregulada em pacientes com esquizofrenia (MARTINS-DE-SOUZA et al., 2010a). Por sua vez, como o ciclo de Krebs tem a função de produzir o potencial redox da célula, alterações em seus componentes causariam uma

perturbação na produção de doadores de íons, afetando a fosforilação oxidativa (MARTINS-DE-SOUZA et al., 2010b).

As mitocôndrias desempenham um papel-chave na energética neural, apresentam uma complexa rede enzimática que é altamente regulada para otimizar processos metabólicos. Diversos componentes dos complexos mitocondriais I e V da fosforilação oxidativa se mostram alterados em esquizofrenia. O complexo I é composto de 45 subunidades, está localizado na membrana interna mitocondrial e apresenta atividade de NADH desidrogenase e oxiredutase, e está envolvido na transferência de elétrons do NADH para a cadeia respiratória. O complexo V representa o complexo enzimático que sintetiza ATP a partir de ADP e fosfato inorgânico. Portanto, essas perturbações na rede enzimática mitocondrial podem contribuir para as características observadas na patologia da esquizofrenia (MARTINS-DE-SOUZA et al., 2011). Muitos estudos observaram alteração na fosforilação oxidativa mitocondrial em cérebro de pacientes com esquizofrenia.

Além de promover energia para as células, as mitocôndrias também desempenham o papel de garantir o tamponamento de cálcio (Ca^{2+}) nelas. O Ca^{2+} liberado no citosol por fontes externas é capturado pela mitocôndria e liberado lentamente, evitando que altos níveis de Ca^{2+} no citosol induzam estresse e excitotoxicidade. Essa homeostase de cálcio se mostra alterada em esquizofrenia (CLAY; SILLIVAN; KONRADI, 2011). Estudos observaram alterações na morfologia, densidade e volume dessas organelas, quando comparada com controles. Portanto, a disfunção mitocondrial se mostra presente em esquizofrenia e teoriza-se que outros processos relacionados à organela são afetados, como morte celular, transporte de neurotransmissores, plasticidade sináptica e produção de EROs, podendo contribuir para a fisiopatologia da esquizofrenia (MARTINS-DE-SOUZA et al., 2011).

As perturbações nas vias energéticas e mitocondriais citadas anteriormente podem promover uma produção exacerbada de espécies reativas de oxigênio (EROs), que por sua vez podem danificar as membranas celulares e o DNA (MARTINS-DE-SOUZA et al., 2011). Para que o estresse oxidativo se estabeleça é necessário haver um desbalanço entre a superprodução de EROs e as defesas antioxidantes enzimáticas e não-enzimáticas da célula (DO et al., 2009). O cérebro é particularmente vulnerável ao dano oxidativo devido a seu elevado consumo de oxigênio, seu elevado conteúdo de ácidos graxos poli-insaturados oxidáveis e à presença de metais redox-ativos, como cobre e ferro (DO et al., 2009).

Os mecanismos de defesa contra o estresse oxidativo consistem em enzimas como a superóxido dismutase, glutationa peroxidase, catalase e antioxidantes não enzimáticos como glutationa (GSH), ácido ascórbico, carotenóides e flavonóides. O tripeptídeo GSH tem um

importante papel antioxidante e de tampão redox na célula, e está presente em abundância no citosol, núcleo e mitocôndria (DO et al., 2009). Estudos mostram que existe um déficit na produção de GSH em esquizofrenia e que, em conjunto com a superprodução de EROs, contribui para o aparecimento do estresse oxidativo. A expressão de enzimas da família glutationa redutase também se mostrou alterada na região do tálamo de pacientes com esquizofrenia (MARTINS-DE-SOUZA et al., 2011). É proposto que esse fator de estresse durante o neurodesenvolvimento prejudique o processo de maturação neural, resultando na deficiência de conectividade e sincronização neural observada em esquizofrenia (DA SILVEIRA PAULSEN et al., 2013).

É importante ressaltar que os estudos de esquizofrenia mencionados anteriormente em grande parte foram realizados em amostras de pacientes que apresentavam tratamento à longo prazo com antipsicóticos, então sempre há a ressalva que as características observadas podem ser devido à medicação e não à doença. Estes estudos contribuíram significativamente para o melhor entendimento, mesmo que parcial, das características neuroquímicas e neuropatológicas associadas à doença (HARRISON, 2000). No entanto, essa abordagem não permite a observação dos mecanismos da doença em células vivas e representa o tecido após uso prolongado de medicamentos (MARCHETTO et al., 2011). Além disso, não é possível estudar o tecido na fase do surgimento da doença, que é neurodesenvolvimental, uma vez que o tecido representa o estágio mais avançado da doença (PEDROSA et al., 2011). Dessa forma, estudos conduzidos afim de estabelecer se as alterações observadas são de fato relacionadas a doença e se estão presentes durante o neurodesenvolvimento são de extrema importância. Neste contexto, o desenvolvimento de células tronco de pluripotência induzida abre muitas possibilidades para o estudo de doenças do neurodesenvolvimento e de difícil acesso *in vivo*.

6.5 iPSCs

Em 2006, o pesquisador Shinia Yamanaka desenvolveu uma técnica para produção de células pluripotentes através da reprogramação genética de células somáticas de camundongos e em 2007 realizou a técnica com células humanas. Essa reprogramação ocorre a partir da transdução de quatro fatores de transcrição (oct-4, sox-2, Klf-4 e c-Myc) através do uso de fatores virais (TAKAHASHI et al., 2007; TAKAHASHI; YAMANAKA, 2006). Essas células são chamadas de células tronco de pluripotência induzida e são conhecidas como iPSCs (da

sigla em inglês *induced pluripotent stem cells*). A partir do momento que adquirem o estado pluripotente, podem gerar células dos três folhetos embrionários (YU; THOMSON, 2008).

6.5.1 iPSC no estudo de doenças psiquiátricas

Para doenças que afetam o cérebro, como doenças psiquiátricas por exemplo, a tecnologia das iPSCs é de extrema importância, uma vez que pode ajudar a contornar a inacessibilidade do cérebro humano, através da geração de células neurais (PEDROSA et al., 2011). Outro grande benefício da utilização das iPSCs é a possibilidade de estudar as fases desenvolvimentais de células neurais humanas antes delas se diferenciarem em células maduras. Essa característica é particularmente interessante no estudo de doenças neurodesenvolvimentais, como a esquizofrenia. Desta forma, a partir de um protocolo de indução neural é possível diferenciar iPSCs para células-tronco neurais, conhecidas como NSCs (da sigla em inglês *neural stem cells),* que representam o estágio anterior à formação de progenitores neurais e posteriormente células maduras e em cultura podem dar origem a populações gliais e neuronais, que por sua vez podem se diferenciar em subtipos de glia e subtipos de neurônio, respectivamente (MARCHETTO; WINNER; GAGE, 2010).

Estudos utilizando iPSCs derivadas de pacientes com esquizofrenia apontaram que tais alterações mitocondriais e de estresse oxidativo poderiam ser encontradas nestes modelos. Paulsen et al. (2012) produziu IPSCs a partir de fibloblastos de um paciente com esquizofrenia. Não foi observada nenhuma diferença entre fibroblastos e iPSCs de esquizofrenia e controle. No entanto, céulas progenitoras neurais, conhecidas como NPCs (da sigla em inglês *neural progenitor cells)* derivadas de esquizofrenia apresentaram um aumento no consumo extramitocondrial de oxigênio e elevados níveis de EROs, quando comparado com o controle (PAULSEN et al., 2012). Brennand et al. (2015) também analisou NPCs derivadas de iPSCs de pacientes com esquizofrenia e observou dano mitocondrial e aumento de EROs nessas células, quando comparado com o controle. As mitocôndrias observadas em NPCs de esquizofrenia eram menores, desconexas e distribuídas distalmente, enquanto que em NPCs controle elas eram mais conectadas, tubulares e agregadas na região perinuclear (BRENNAND et al., 2015)

Dessa forma, ao gerar células afetadas na doença a partir de células somáticas do próprio paciente é possível estudar a relação entre genótipo e fenótipo levando em consideração seu histórico pessoal (HAGGARTY; PERLIS, 2014; MARCHETTO; WINNER; GAGE, 2010). Portanto, o uso de iPSCs pode ser de extrema valia para se fazer decisões de tratamento no contexto da medicina personalizada, permitindo a avaliação da

eficácia do tratamento nas células em cultura antes de administrá-lo ao paciente (AVIOR; SAGI; BENVENISTY, 2016). A possibilidade de investigar os mecanismos específicos à doença anteriormente e durante o seu estabelecimento permitem a detecção de assinaturas moleculares da doença em células vivas, abrindo possibilidades de intervenção antecipada e descoberta de potenciais biomarcadores para novas ferramentas de diagnóstico. (NASCIMENTO; MARTINS-DE-SOUZA, 2015). Nesse contexto, estudar a expressão proteíca destas células traz informações sobre o perfil functional e fisiológico da interação entre genes e ambiente.

6.4 Proteômica

Um proteoma compreende todo o conjunto de proteínas em um sistema biológico (célula, tecido ou organismo) em um determinado estado e momento (WILKINS et al., 1996). Técnicas de proteômica têm contribuído para o melhor entendimento das bases relacionadas à esquizofrenia em um nível celular e tecidual através da identificação de proteínas diferentemente expressas e suas respectivas vias bioquímicas. Essa abordagem permite revelar a expressão global de proteínas ou grupos de proteínas em um dado momento e local, independentemente do tipo de célula ou situação fisiológica. Mesmo os estudos proteômicos detectando menos proteínas expressas do que os estudos de transcriptoma detectam genes expressos, a expressão protéica revela um perfil funcional preciso e o estado fisiológico não enviesado relacionado à complexa interação entre genes e ambiente (NASCIMENTO; MARTINS-DE-SOUZA, 2015).

Nas primeiras décadas do surgimento da proteômica, o principal método quantitativo utilizado era baseado em gel, como a eletroforese em gel bi-dimensional (2DE) e a eletroforese em gel bi-dimensional fluorescente (2D-DIGE) (OLIVEIRA; COORSSEN; MARTINS-DE-SOUZA, 2014). Apesar de muito utilizado, as técnicas baseadas em gel foram sendo substituídas após a introdução do conceito de proteômica em larga escala, que faz uso da cromatografia líquida acoplada a um espectrômetro de massas (LC/MS) (LINK et al., 1999). A proteômica com base na espectrometria de massas foi a responsável por oferecer informações sobre a abundância de proteínas, perfis de expressão de acordo com o tipo celular, uma organela específica, modificações pós-traducionais e interações proteínas-proteínas, aumentando a possibilidade de se estudar as modificações a nível protéico (JENSEN, 2006).

6.4.1 Espectrometria de massas

A espectrometria de massas consiste em uma técnica de análise qualitativa e quantitativa, que se baseia na medida da razão massa/carga (*m/z*) dos íons das moléculas, ou seja, precisam ser ionizadas para que seja possível sua identificação. A ionização é a conversão de um átomo ou molécula em um íon pela adição ou remoção de partículas carregadas, ocorrendo através da permuta de elétrons ou outros íons. Inúmeras técnicas de ionização são utilizadas em espectrometria de massas. Os fatores mais importantes a serem considerados referem-se a energia interna transferida para o íon durante o processo de ionização e as propriedades físico-químicas do analito que podem ser ionizados. Algumas técnicas são altamente energéticas e causam fragmentação extensiva, enquanto que outras são mais suaves e produzem apenas íons das espécies moleculares. As principais técnicas de ionização utilizadas em proteômica são a ionização dessorção a laser auxiliada por matriz (Matrix Assisted Laser Desorption Ionization, MALDI) e a ionização por eletrospray (ESI).

Existem vários tipos de analisadores, cada um possuindo vantagens e desvantagens. De maneira geral, todos os analisadores de massa utilizam energia elétrica estática ou dinâmica e campos magnéticos isolados ou combinados. As diferenças entre os tipos residem basicamente na maneira como esses campos são utilizados para alcançar a separação. Dois exemplos de analisadores largamente utilizados em proteômica são o analisador por tempo de voo (time of flight, TOF) e o quadrupolo. O TOF analisa os espectros de massa através do tempo de vôo dos íons por um tubo, que dependendo das relações *m/z* evidenciam diferentes tempos de voo. Já o analisador de quadrupolo utiliza da trajetória em campos elétricos oscilantes para separar os íons de acordo com suas *m/z* (HOFFMANN; STROOBANT, 2007). Finalmente, quando o detector de MS registra o momento de chegada dos feixes de íons, estes serão convertidos em sinais elétricos que geram espectros de massas.

As técnicas baseadas em espectrometria de massas são capazes de quantificar milhares de proteínas em grandes números de amostras, gerando grandes conjuntos de dados que podem ser extraídos por ferramentas computacionais específicas, como MASCOT®, PLGS®, MaxQuant e Progenesis®.

6.4.2 Synapt G2-Si

O espectrômetro de massas (MS) utilizado para as análises realizadas nesta dissertação de mestrado foi o Synapt G2-Si HDMS (Waters Corp., Milford, EUA), que consiste em um MS com uma fonte de ionização do tipo ESI e analisador do tipo Q-TOF, ou seja, possui dois

analisadores hibridizados: um quadrupolo (Q) seguido de um analisador do tipo TOF. Ademais, o Synapt G2-Si também está equipado com uma cela de mobilidade iônica de alta eficiência (IMS). Com esse equipamento é possível fazer experimentos do tipo análise independente de dados (data-independent analysis-DIA), que consiste em espectrometria de massas sequencial (MSe, ou tandem MS) envolvendo a fragmentação de peptídeos seguida da posterior análise de sua sequência de aminoácidos. O processo de fragmentação mais utilizado em MSe é a técnica de dissociação induzida por colisão (Collision Induced Dissociation-CID); nela os peptídeos são selecionados em um primeiro analisador, nesse caso o quadrupolo, e acelerados em uma região do espectrômetro de massas com um gás inerte (hélio, argônio ou nitrogênio), o que acarreta na colisão entre os íons e as moleculas desse gás fazendo com que a energia dessa colisão seja transferida para as ligações presentes nos íons, os quais são fragmentados. Este ciclo de aquisições de MS e MS/MS continua ao longo do tempo de execução. Os dados então gerados *m/z* e tempo de retenção (RT) para os íons de precursores e fragmentos são então extraídos e processadas para identificação de peptídeos e proteínas (LEVIN; HRADETZKY; BAHN, 2011).

Como mencionado anteriormente, o Synapt G2-Si possui uma cela IMS, que confere mais uma dimensão para separação dos íons. Dessa forma, para cada valor de *m/z* há um espectro de *drift time*, ou seja, a velocidade com que um íon se desloca em uma câmara contendo um gás inerte, influenciado por um campo elétrico. A cela IMS é dividida em três partes: a TRAP, onde os íons são acumulados e lançados em períodos regulares para a câmara de mobilidade, na qual ocorre a separação em função da mobilidade; e a TRANSFER, que conduz os íons para o analisador TOF. A junção das técnicas de IMS e MS^E confere o modo de *High Definition Mass Spectrometry* (HDMSe), que foi utilizada neste trabalho.

6.4.3 Proteômica de organelas

Estima-se que o número de genes expressos no genoma humano em um tipo celular particular pode chegar a 10000. Por conseguinte, o número de proteínas no corpo humano representa diversas vezes esse número, uma vez que modificações protéicas e taxas de splicing alternativo devem ser levadas em consideração. Um desafio enfrentado pelo campo da protêomica é manter a capacidade de alta cobertura de identificação e quantificação de proteínas sem perder informações de proteínas menos abundantes na amostra. Proteínas muito abundantes acabam mascarando proteínas menos abundantes. O fracionamento e enriquecimento de amostras biológicas pode permitir a identificação e quantificação destas

proteínas menos abundantes (HUBER; PFALLER; VIETOR, 2003). Neste contexto, a separação de organelas é uma ferramenta valiosa para análise do proteoma celular, pois o conteúdo proteico das amostras é reduzido representando um conjunto moléculas específicas e direcionadas (TAYLOR; FAHY; GHOSH, 2003).

7. OBJETIVOS

A presente dissertação teve como objetivo avaliar se existem alterações nos proteomas mitocondriais e nucleares de células neurais derivadas de pacientes com esquizofrenia quando comparadas com controles saudáveis. Os objetivos específicos foram cultivar células-tronco neurais derivadas de células-tronco de pluripotência induzida de pacientes com esquizofrenia e controles, diferenciar estas células em neurônios, realizar um protocolo de enriquecimento das frações mitocondriais e nucleares e analisar por espectrometria de massas os proteomas enriquecidos de células-tronco neurais e neurônios, além do proteoma total de neurônios. Dessa forma, ao cumprir os objetivos propostos pretendemos corroborar a hipótese que alterações relacionadas a processos mitocondriais estão presentes em esquizofrenia durante o neurodesenvolvimento.

8. CAPÍTULO 1

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The Energy Metabolism Dysfunction in Psychiatric Disorders Postmortem Brains: Focus on Proteomic Evidence

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REVIEW
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Abstract

Psychiatric disorders represent a great medical and social challenge and people suffering from these conditions face many impairments regarding personal and professional life. In addition, a mental disorder will manifest itself in approximately one quarter of the world's population at some period of their life. Dysfunction in energy metabolism is one of the most consistent scientific findings associated with these disorders. With this in mind, this review compiled data on disturbances in energy metabolism found by proteomic analyses of postmortem brains collected from patients affected by the most prevalent psychiatric disorders: schizophrenia (SCZ), bipolar disorder (BPD), and major depressive disorder (MDD). We searched in the PubMed database to gather the studies and compiled all the differentially expressed proteins reported in each work. SCZ studies revealed 92 differentially expressed proteins related to energy metabolism, while 95 proteins were discovered in BPD, and 41 proteins in MDD. With the compiled data, it was possible to determine which proteins related to energy metabolism were found to be altered in all the disorders as well as which ones were altered exclusively in one of them. In conclusion, the information gathered in this work could contribute to a better understanding of the impaired metabolic mechanisms and hopefully bring insights into the underlying neuropathology of psychiatric disorders.

Keywords: proteome, schizophrenia, depression, bipolar disorder, mass spectrometry

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1 Introduction

Psychiatric disorders represent a great medical and social challenge and people suffering from those conditions face many impairments regarding personal and professional life. Many of those disorders have an onset on early adult life and can severely affect a person's well-being and ability to be functional (Hyman, 2008). Approximately one quarter of the world's population will manifest a mental disorder at some period of their life (World Health Organization, 2008b), and people affected by psychiatric disorders have amortality rate 2.22 times higher than the general population, with a 10-year shorter lifespan (Walker et al., 2015). Worldwide, 4 out of 10 estimated causes of disability are neuropsychiatric disorders, and among the most prevalent are schizophrenia (SCZ), bipolar disorder (BPD), and major depressive disorder (MDD) (WorldHealthOrganization, 2008b). Despite the great burden related to psychiatric disorders and the extensive research made on the topic, the mechanisms and risk-factors associated with them have not yet been elucidated.

Over the years, the brain has been extensively studied in attempts to understand these disorders, searching for possible causes and treatments. SCZ, BPD, and MDD are characterized as disorders brought on by small flaws in several brain areas rather than a greater damage in an individual brain region. This implies that those disorders could derive from flawed connections between components of the neural system (Fornito and Harrison, 2012). The recurring presence of metabolic alterations related to energy pathways has been suggested as one of the most important physiological features of SCZ, BPD, and MDD (Shao et al., 2008).

The human brain constitutes 2% of the whole body weight and, paradoxically, is responsible for ∼25% of total body glucose utilization (Bélanger et al., 2011). Glucose is the obligatory energy substrate of the brain and it goes through many reactions in order to produce adenosine triphosphate (ATP) through sequential processing by glycolysis, the tricarboxylic acid (TCA) cycle, and oxidative phosphorylation (OXPHOS) (Magistretti, 2004). Oxidative metabolism is a crucial process in maintaining cell viability as it generates great amounts of ATP, however, this accelerated rate of oxidation within the cell culminates in the production of potentially detrimental by-products, called reactive oxygen species (ROS) (Magistretti, 2008). These highly ROS, if not neutralized by the action of antioxidant enzymes, can cause damage to carbohydrates, lipids, proteins, and DNA, potentially resulting in functional deficits and even cell death (Manji et al., 2012).

Glucose also plays an important role in entering the metabolic pathways that lead to the synthesis of glutamate, acetylcholine, gamma-aminobutyric acid (GABA), all three being key neurotransmitters (Deutch and Roth, 2004; Magistretti, 2004). Mitochondria, which are responsible for playing an important role in cellular energy generation, also promotes calcium buffering, ROS neutralization (Clay et al., 2011) and are intimately involved with aminoacid metabolism. The brain's high energy demand is mainly due to the myriad of energy-intensive processes, including axonal action potentials, cell signaling, presynaptic Ca^{2+} entry, uptake and recycling of neurotransmitters and synaptic vesicle releasing (Attwell and Laughlin, 2001; Alle et al., 2009). In regions of gray matter, there is a majority of excitatory synapses compared to inhibitory synapses, suggesting that excitatory neurotransmission accounts for most of the energy demands at the cortical level (Bélanger et al., 2011). Depending on the activity performed at the time, energy consumption in the related brain region is stimulated, and for that reason there is an increase on blood flow to that particular area, since energy substrates reach their targets by the circulatory system (Magistretti and Allaman, 2013).

The possibility to study postmortem brain tissue derived from patients with psychiatric disorders have provided valuable insights into the physiopathology of those disorders, since the brain is rarely if ever accessible for biopsies from living patients. Many studies have been conducted on postmortem brain tissue from patients suffering from neuropsychiatric disorders. Proteomic studies have the advantage to provide valuable information on which proteins were present at the time of the course of illness and their expression level (Bayés and Grant, 2009; Gottschalk et al., 2015). Given the importance of energy metabolism in the brain and its important role in the pathophysiology of neuropsychiatric disorders, this review aims to compile data on energy metabolism dysfunction found on postmortem brain tissue revealed by proteomics in SCZ, BPD, and MDD.

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2 Psychiatric disorders and evidences of overall metabolic dysfunction

2.1. Schizophrenia

SCZ is known to affect ~1% of the world population. As a complex syndrome thought to be of neurodevelopmental origin (Rapoport et al., 2005), is manifested through a wide range of severe symptoms, and patients experience a combination of what are classified as positive, negative, and cognitive symptoms. Positive symptoms are related to the loss of touch with reality, represented by auditory hallucinations and delusions, negative symptoms include

the inability to feel pleasure, flattening of affect, and social withdrawal. Cognitive dysfunction is also an important characteristic of schizophrenia and includes a decreased ability to focus as well as attention and memory deficiencies (Wood and Freedman, 2003). The onset of the illness, often not recognized as such, begins with decline in cognitive and social functioning in early adolescence and precedes the onset of psychosis by ~10 years (Kahn et al., 2015). SCZ is thought to be one of the most severe mental disorders and the average life expectancy is ~20 years below that of the general population (Laursen et al., 2014).

Blood sample analyses of antipsychotic SCZ patients have detected elevated levels of insulin (Guest et al., 2010) and increased insulin resistance (Venkatasubramanian et al., 2007; van Nimwegen et al., 2008). In addition, there was a higher prevalence of hyperglycemia and impaired glucose tolerance in schizophrenia patients when compared to healthy controls (Ryan et al., 2003; Spelman et al., 2007; Fernandez-Egea et al., 2008, 2009).

Many investigators have found correlations between the occurrence of psychosis and altered blood flow and metabolism in different brain regions (Cleghorn et al., 1989; Gur et al., 1989; Andreasen et al., 1992; Siegel et al., 1993). Unmedicated patients with schizophrenia were studied with ^{18}F-fluorodeoxyglucose positron emission tomography (PET) and magnetic resonance imaging (MRI) to evaluate glucose metabolism and to obtain volumetric measurements, respectively. This study revealed that, when compared to controls, SCZ patients displayed lower relative glucose metabolic rates and volumetric reductions in an area of the cingulate gyrus related to higher executive functions (Haznedar et al., 2004). In a similar study that focused on three thalamic nuclei, it was observed that reduced relative glucose metabolism in the pulvinar nucleus was associated with more hallucinations and positive symptoms, while metabolic reductions in the mediodorsal nucleus were associated predominantly with negative symptoms (Hazlett et al., 2004). There have also been reports of significantly lower levels of pyruvate in the mediodorsal thalamus of patients with SCZ (Martins-De-Souza et al., 2010a).

Schizophrenia has also been associated with mitochondrial dysfunction and the presence of mutations and polymorphisms in mitochondrial DNA (Rollins et al., 2009; Clay et al., 2011). Mitochondrial hypoplasia has also been observed (Uranova et al., 2001) in addition to significant alterations in the enzymatic activity of Complex I located in the mitochondrial inner membrane, which together point to a dysfunction of the oxidative phosphorylation system (Dror et al., 2002) and decreased ATP production (Volz et al., 2000) in schizophrenia patients. Disturbances due to oxidative stress disturbance are evident in schizophrenia, such as the higher activity levels of superoxide dismutase (SOD) and

glutathione peroxidase (GSH-Px) show higher activity levels when compared to healthy controls (Mahadik et al., 2001; Kuloglu et al., 2002). Another important cellular process related to mitochondria is the maintenance of calcium homeostasis, and studies have shown impairment of calcium homeostasis and signaling in schizophrenia (Bojarski et al., 2010). All the aforementioned processes altered in schizophrenia are implicated in synaptic remodeling, and their dysfunction may induce a wide range of harmful effects, and consequently affect brain plasticity (Martins-de-Souza et al., 2011).

2.2. Major depressive disorder

MDD is a heterogeneous, debilitating, and at times, life-threatening psychiatric disorder that affects ~350 million people worldwide (World Health Organization, 2008a) and the lifetime incidence of depression is more than 12% in men and 20% in women (Kessler et al., 2003). Patients with MDD present a lasting feeling of sadness or irritability and, in addition, can present several psychological and physiological disturbances, such as flattening of affect, reductions in appetite and libido, suicidal thoughts and slowing of speech and action (Belmaker and Agam, 2008).

Some factors related to metabolic syndrome including obesity, diabetes, and hyperglycemia have been associated with the presence of depression; and there are also reports of insulin resistance in MDD patients (Everson-Rose et al., 2004; Skilton et al., 2007).

PET measurements from MDD patients revealed a reduction in both blood flow and glucose metabolism in the caudate nucleus, anterior cingulate cortex and prefrontal cortex during tests that were conducted both in a resting state and under stressful situations (Videbech, 2000). However, analysis of the orbital cortex, medial thalamus, and amygdala displayed increased blood flow and glucose metabolism (Drevets, 2001). Another study made use of the administration of a stable isotope (^{13}C) that is detected by magnetic resonance spectroscopy (MRS) to evaluate the processes associated with neurotransmission and metabolism in MDD patients. It was possible to observe that glutamatergic neurons displayed hampered TCA cycle rates when compared to controls, implicating that the glutamatergic system and mitochondrial energy metabolism may have an important role in the pathology of this disorder (Abdallah et al., 2014).

In concordance with these data, significant impairment of mitochondrial ATP production and lower activity levels of mitochondrial enzymes have been reported in MDD patients compared to controls. Additionally, an increased proportion of patients displayed

deletions in mitochondrial DNA (mtDNA) indicating the presence of mitochondrial dysfunction (Gardner et al., 2003).

2.3. Bipolar disorder

BPD is a chronic mood disorder characterized by transitions between manic and depressive episodes, which is estimated to affect up to 4% of the population (Merikangas et al., 2011). Manic episodes can be described as an overall exacerbation of emotions, such as euphoria and elevated optimism. Those characteristics, together with sleep deprivation caused by overactivity may become extreme and hamper a patient's well-being and decision-making ability (Belmaker, 2004).

Individuals with BPD have high rates of disability and often experience persistent neurocognitive deficits and poor psychosocial functioning (Kapczinski et al., 2014). They present a higher incidence of metabolic syndrome in comparison to the general population (Fagiolini et al., 2005; Taylor and MacQueen, 2006; Garcia-Portilla et al., 2008). By compiling data from the prevalence of metabolic syndrome, it was observed that the rate of metabolic syndrome varied from 17 to 67% in BPD patients (Grover et al., 2012). This syndrome is a high-risk factor for cardiovascular disease and type-2 diabetes mellitus. Studies reported that individuals with BPD are more affected by hyperglycemia, type-2 diabetes mellitus and insulin resistance than the general population (Grover et al., 2012). Medical conditions that are chronic and stress-sensitive, such as cardiovascular disease, obesity, and type-2 diabetes mellitus are the most prominent causes of mortality among individuals with BPD (Brietzke et al., 2011; Vancampfort et al., 2013).

The observation of cerebral blood flow in individuals experiencing mania symptoms revealed that there was a flow decrease in different brain regions, such as the right ventral lobe and frontal regions, when compared to healthy controls (Migliorelli et al., 1993; Blumberg et al., 1999). Interestingly, in a different study it was verified that manic patients presented higher cerebral blood flow in the left dorsal anterior cingulate cortex when compared to not-manic BPD patients (Blumberg et al., 2000).

The evaluation of markers normally linked to metabolic dysfunctions revealed lower serum levels of glucagon, glucagon-like peptide-1 (GLP-1), ghrelin, and higher levels of glucose-dependent insulinotropic polypeptide (GIP) in BPD patients (Rosso et al., 2015). Glucagon is known to act on the system for psychological stress response (Perry et al., 2014). GLP-1 and GIP receptors are expressed in brain areas predominantly involved in mood and cognitive function (Alvarez et al., 2005). Therefore, these markers could be pivotal to the

association between bipolar and metabolic disorders (Czepielewski et al., 2013) as they perform an important role in mechanisms of brain synaptic plasticity and neuroprotection, which were found to be altered in neuroimaging studies of BPD patients (Canales-Rodríguez et al., 2014).

Gray matter analysis of medication-free BPD patients revealed elevated levels of lactate and decreased intracellular pH in the prefrontal cortex. These characteristics suggest that cells are relying mainly on glycolysis rather than OXPHOS to acquire energy, which in turn may indicate that mitochondrial functionality is hampered in BPD (Dager et al., 2004; Weber et al., 2013). Abnormalities in mitochondrion structure and mutations and polymorphisms in mitochondrial DNA (mtDNA) have been reported in patients with BPD (Shao et al., 2008; Cataldo et al., 2010), which could compromise the integrity and functionality of mitochondria, the efficiency of OXPHOS, the Ca^{2+} buffering, and neutralization of ROS in BPD (Clay et al., 2011).

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3. Evidence of compromised energy metabolism in neuropsychiatric disorders revealed by proteomics

Proteomics has the goal to obtain a global view of the proteins present in a given cell or tissue at a determined moment and state; only this snapshot is possible because the proteome is dynamic, with different proteins being constantly degraded and produced in response to various internal and external stimuli (Graves and Haystead, 2002). The proteome represents the genetic information that has been transcribed and translated, after any modifications at the epigenetic, mRNA, and post-translational levels (Nascimento and Martins-de-Souza, 2015). By understanding the information obtained from these studies, it has been proposed that proteomics may provide more accurate information about the pathophysiology of a disease than other approaches such as genomics and transcriptomics, as it represents what proteins are present at any important moment during the course of the illness (Bayés and Grant, 2009; Gottschalk et al., 2015). Therefore, mass spectrometry (MS)-based proteomics methods have been widely used in several studies, as they have the ability to identify, as well as quantify innumerous disease-associated protein changes in a given sample (Föcking et al., 2014)

3.1 Proteomic Techniques

Proteomic methods employed in the study of neuropsychiatric disorders began with the development of two-dimensional gel electrophoresis (2DE) (O'Farrell, 1975). By late 1990s it was developed the differential two-dimensional electrophoresis (2D-DIGE) (Unlu et al., 1997). The major limitation of the 2DE and 2D-DIGE techniques is the separation of proteins with more extreme characteristics, including those that are hydrophobic, too large or too small, or extremely basic or acidic. Despite the limitations, these techniques represent a very high-quality top-down method of total proteome resolution, resolving protein isoforms and post-translational modifications (O'Farrell, 2008; Oliveira et al., 2014).

In 1999, a technique was described to perform protein identification by first using liquid chromatography (LC) and then tandem mass spectrometry (MS/MS) to separate and fragment peptides. From this, the term "shotgun proteomics" was coined (Link et al., 1999). This approach is under continuous development to achieve a better coverage of a sample's whole proteome. Considering recent developments, proteomic studies consist of the analysis of a digested proteome, which goes through chromatographic separation, of one or more dimensions, followed by MS/MS analysis (Aebersold and Mann, 2003; Taylor et al., 2009).

Due to methods developed using mass-spectrometry based approaches for quantitative proteomics, currently is possible to monitor global protein expression and to obtain important quantitative data (Ong et al., 2003).

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4. What can proteomics tell us about energy metabolism dysfunction?

This review searched and analyzed every postmortem brain tissue-based proteomic work published so far regarding patients with SCZ, BPD and MDD. We searched in the PubMed database (www.ncbi.nlm.nih.gov/pubmed) to gather the studies and compiled all the differentially expressed proteins reported in each work. The proteins were searched for individually in the Human Protein Reference Database (http://hprd.org) to determine their biological process and in which cellular component(s) they are normally present. Twenty-two articles on SCZ were found (Johnston-Wilson et al., 2000; Prabakaran et al., 2004; Beasley et al., 2006; Clark et al., 2006; Sivagnanasundaram et al., 2007; Pennington et al., 2008a,b; Behan et al., 2009; English et al., 2009; Martins-de-Souza et al., 2009a,b,c,d; Martins-De-Souza et al., 2010a,b; Föcking et al., 2011, 2014; Wesseling et al., 2014; Gottschalk et al., 2015; Saia-Cereda et al., 2015, 2016; Schubert et al., 2015), 10 on BPD (Johnston-Wilson et

al., 2000; Beasley et al., 2006; Pennington et al., 2008a; Behan et al., 2009; Föcking et al., 2011, 2016; Wesseling et al., 2014; Gottschalk et al., 2015; Schubert et al., 2015; Stelzhammer et al., 2015), and seven on MDD (Johnston-Wilson et al., 2000; Beasley et al., 2006; Martins-de-Souza et al., 2012a,b; Wesseling et al., 2014; Gottschalk et al., 2015; Stelzhammer et al., 2015). After annotating biological processes and cellular components, we selected those that were related to metabolism and energy pathways and compiled this data in with information on up- or down-regulation, when available, from which specific brain region was the postmortem tissue and what was the proteomic technique used in the study (Tables 1, 2 and 3). SCZ studies revealed 92 differentially expressed proteins related to energy metabolism, while 95 proteins were discovered in BPD and 41 proteins in MDD (Tables 1, 2 and 3). Information regarding sample size, gender, age, drug treatment, and brain pH from each study compiled on SCZ, BPD, and MDD can be found in Tables 5, 6 and 7.

It is important to highlight that all the studies mentioned above have been performed using brain tissue collected from patients treated with a wide range of drugs and for that reason it cannot be ruled out that at least some findings could be attributed to a drug-derived artifact rather than the disorder itself. However, as the results will be discussed in the upcoming section, this potential bias could be elucidated as there are evidences suggesting that alterations of energy metabolism described in SCZ, BPD, and MDD are a component of the diseases themselves and not an effect of the treatments used

4.1 Similarities among SCZ, BPD, and MDD

Five proteins overlapped as differently expressed in all three disorders (Figure 1 and Table 4): aldolase C, citrate synthase, malate dehydrogenase, cytochrome bc1 core protein 1, and ATP synthase subunit beta (Figure 2). Aldolase C is a crucial enzyme in glycolysis responsible for the conversion of fructose-1,6-bisphosphate to glyceraldehyde-3- phosphate and dihydroxyacetone phosphate. Citrate synthase is a key enzyme of the TCA cycle and catalyzes the reaction in which citrate is formed by the condensation of the acetate residue from acetyl-CoA with oxaloacetate. Malate dehydrogenase is another enzyme of the TCA cycle and catalyzes the NAD^+/NADH-dependent interconversion of the substrates malate and oxaloacetate. Cytochrome bc1 core protein 1 is located within the mitochondrial matrix and the full cytochrome bc1 complex is a key component of the respiratory electron transport chain embedded in the inner membrane of mitochondria. The beta subunit of ATP synthase is the portion that is responsible for the conversion of ADP to ATP, which occurs due to the proton gradient across the membrane formed by OXPHOS reactions.

These differences involve the main axis of metabolic pathways for ATP production, with a slight focus on oxidative phosphorylation. The common differential expression of citrate synthase and malate dehydrogenase may hypothetically connect these disorders to lipid production impairment. Citrate synthase is downregulated in SCZ and upregulated in BPD and MDD whereas malate dehydrogenase in downregulated in BPD and upregulated in SCZ and MDD. This disruption in ATP production may switch the metabolic demand of the cell to obtain energy by lipid breakdown in the brain.

Phospholipase A2 (PLA2), which catalyzes the cleavage of membrane phospholipids, was found to have increased activity levels in the blood of SCZ patients (Gattaz et al., 1987; Gattaz and Brunner, 1996; Ross, 1997). There have been reports of increased phospholipid turnover rates in the thalamus and frontal lobe (Gattaz and Brunner, 1996) and lower levels of docosapentaenoic acid (EPA) and phosphatidylcholine in the hippocampus of SCZ patients (Hamazaki et al., 2010). In addition, there is evidence of lower levels of arachidonic acid (AA) in erythrocytes and brain tissue of SCZ patients (Horrobin, 1996; Laugharne et al., 1996).

There have been reports of elevated rates of hydrolysis for serum phospholipids in BPD (Lieb et al., 1983; Hibbeln et al., 1989) and increased levels of prostaglandins - compounds derived from AA metabolism- in serum, saliva and cerebrospinal fluid from BPD patients, suggesting dysregulated AA metabolism (Lieb et al., 1983; Linnoila, 1983; Nishino et al., 1989). Also, upregulation of calcium-dependent cytosolic phospholipase A2 (cPLA2) was reported, an enzyme involved in AA metabolism, as well as lower concentrations of AA in the frontal cortex of BPD patients (McNamara et al., 2008; Rapoport, 2008). Further studies should be conducted in order to evaluate larger sample sizes, taking into consideration any potentially confounding factors like the dietary profile of patients and their general health status (Igarashi et al., 2010).

Cholesterol located in the myelin sheath that surrounds axons is effectively immobilized because of the slow turnover of myelin. Studies conducted on mood disorder patients revealed lower cholesterol levels when compared to controls (Beasley et al., 2005). A significant association between AA to EPA ratios present in erythrocytes and severity of depression has been stablished (Adams et al., 1996). Compared with healthy controls, patients suffering from MDD displayed significantly higher serum levels of PLA2 activity (Noponen et al., 1993) and the mRNA expression of PLA2 was significantly increased when compared with healthy controls (Mueller et al., 2015).

Several studies have shown the effects of antidepressants, antipsychotics, and mood-stabilizers on PLA2 activity (Gattaz et al., 1987; Bosetti et al., 2003; Tavares et al., 2003). The antipsychotic drug clozapine was reported to elevate the erythrocyte levels of AA and docosahexaenoic acid (DHA) in SCZ patients (Glen et al., 1996). This could indicate an additional mechanism that contributes to the therapeutic effects of clozapine (Horrobin, 1998). Lithium, at therapeutic concentrations, was shown to strongly inhibit PLA2 activity (Horrobin and Bennett, 1999).

This reveals a connection between serious psychiatric disorders — SCZ, MDD, and BPD — which have a different range of debilitating symptoms and prognosis yet show similar alterations in energy metabolism processes. Several key components of the three pivotal processes in energy metabolism are altered in these disorders, which highlights the importance of proper functioning of how the brain handles energy production. Nevertheless, is important trying to assess whether brain metabolism dysfunction is a cause or consequence in the establishment of psychiatric disorders. Reports have shown that people suffering from mitochondrial diseases frequently show psychiatric symptoms such as psychosis, depression, personality change, and BPD (Manji et al., 2012). In fact, major depression has been described as being the initial symptom of mitochondrial disease in a large sample size of adult patients (Fattal et al., 2007). Mitochondrial function and energy metabolism were shown to play an important role in regulating social behaviors (Hollis et al., 2015). In addition, limited energy production may impair adaptive neuronal capacity and contribute as one of the causes to the development of psychopathologies such as SCZ, BPD, and MDD under stressful stimulus (Koene et al., 2009).

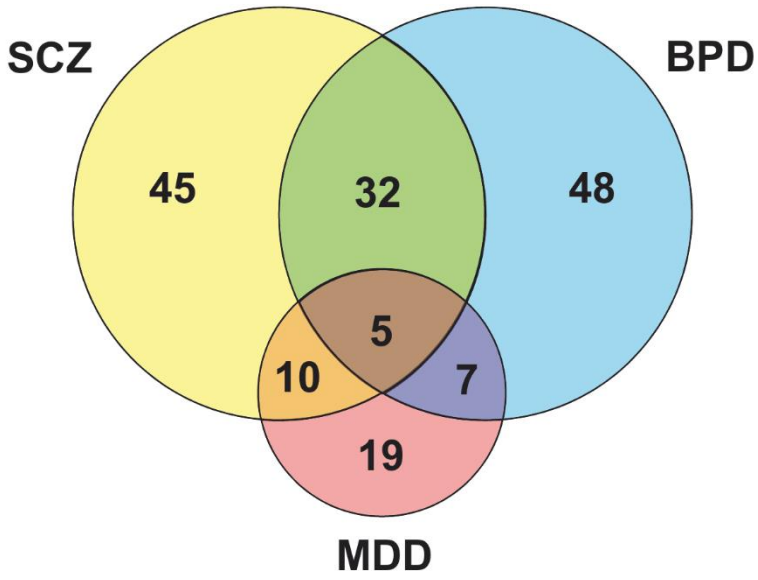

Figure 1: Venn diagram evidencing peculiarities and similarities among the major psychiatric disorders.

4.2 Similarities between Disorders

Data show that SCZ and BPD share 32 altered proteins (Figure 1 and Table 4), which are mostly related to mitochondrial electron transport, response to ROS and glycolysis (Figure 2). Even though SCZ and BPD represent two distinct types of psychiatric disorders, the first being of thought or cognition and the second being of emotion, they share some pathophysiological traits such as chronic and relapsing illness trajectories (Iwamoto et al., 2005). Alterations in components of the electron transport chain, such as subunits from NADH dehydrogenase, or glycolytic enzymes, as pyruvate kinase and phosphofructokinase, reveal an overall energy metabolism dysregulation that may relate to dysfunctions in mitochondrial processes. Oxidative damage to the brain may be partially responsible for the pathophysiological process in BPD and SCZ (Wang et al., 2009).

Oxygen and ROS metabolism pathways were found to be significantly increased, which indicates the presence of increased levels of ROS and oxidative stress generation in SCZ patients (Prabakaran et al., 2004), and the level of tyrosine nitration, which reflects the level of endogenous ROS, was significantly higher in BPD patients than in unaffected controls (Kunz et al., 2008). As was previously explored, disturbances in lipid metabolism are present in SCZ and BPD and this could, in turn, hypothetically contribute to the establishment of oxidative stress establishment since ROS are a natural by-product of lipid metabolism (Martins-de-Souza et al., 2011). With this is mind, is important to stress that further studies

ought to be conducted to confirm the relation between oxidative stress and membrane phospholipid breakdown in consequence of impaired energy metabolism.

Our results showed that enzymes such as peroxiredoxins (1,2,5,6), glutathione S-transferase and superoxide dismutase are involved in protecting the cell against oxidative damage and were found to be altered in the disorders (Martins-de- Souza et al., 2009a). In situations where free radical formation surpasses the cell's antioxidant defense capacity, oxidative stress may cause direct injuries to cellular lipids, DNA and proteins, thus affecting proper cellular functioning (Cochrane, 1991). It has been proposed that oxidative damage to the brain may contribute to some extent to the development of these disorders, and associating compounds with antioxidative properties with existing treatment may be a possible approach to complement pharmacological treatment of SCZ and BPD (Wang et al., 2009).

The enzyme creatine kinase B was found to be differentially regulated in SCZ and BPD when compared to controls. This enzyme catalyzes the reversible transfer of phosphate between ATP and creatine, generating phosphocreatine (Hemmer and Wallimann, 1994). Creatine is taken up by neurons and oligodendrocytes by creatine transporters and the circuit of converting creatine to phosphocreatine by creatine kinase acts as a bioenergetic sensor that rapidly reloads ATP in the area to maintain stable levels when there are significant energy demands (Wyss and Schulze, 2002; Allen, 2012). There have been reports of decreased brain phosphocreatine levels in BPD patients in the depressed state, as compared with normal controls (Manji et al., 2012). In SCZ, levels of phosphocreatine were found to be asymmetrical in the temporal lobe of patients and lower levels of phosphocreatine were observed in the frontal brain region of patients and their first-degree relatives (Klemm et al., 2001). For that reason, decreases of phosphocreatine and ATP reported in patients with psychiatric disorders reinforces the importance of impaired energy production in those conditions (Kato, 2006).

SCZ and MDD share 10 altered proteins (Figure 1 and Table 4), such as phosphoglucomutase 1 (Figure 2) which is an enzyme involved in glycolysis and succinyl-CoA:3-ketoacid CoA transferase which is a key enzyme in ketone body catabolism. Carbonic anhydrase I and II were also altered both in MDD and SCZ. Carbonic anhydrase I and II are expressed in erythrocytes and glial cells, respectively (Hayes, 1994). Carbonic anhydrase II is also present in myelin and the choroid plexus (Hayes, 1994) and represents one of the core determining factors of pH fluxes in neural cells (Chesler and Kaila, 1992). In schizophrenia patients, treatment with acetazolamide, which inhibits the action of carbonic anhydrase, promoted an increase in blood flow throughout the brain (Taylor et al., 1999).

Data analysis revealed seven proteins altered both in BPD and MDD (Figure 1 and Table 4), while five of those are different subunits of the NADH dehydrogenase complex in the electron transport chain (Figure 2). This is consistent with previous reports of impaired functioning of OXPHOS complexes in MDD (Ben-Shachar, 2009; Moylan et al., 2012) and decreased nuclear expression of genes coding for mitochondrial respiratory mechanisms in BPD (Konradi et al., 2004) both of which lead to reduced mitochondrial energy production. Peroxiredoxin 5 was also altered in both disorders, which may be evidence of an increase in ROS due to poor mitochondrial functioning (Manji et al., 2012). Antidepressants used in the treatment of MDD, along with lithium which is generally used in BPD treatment, have an effect on the upregulation of mitochondrial energy generation (Scaini et al., 2011).

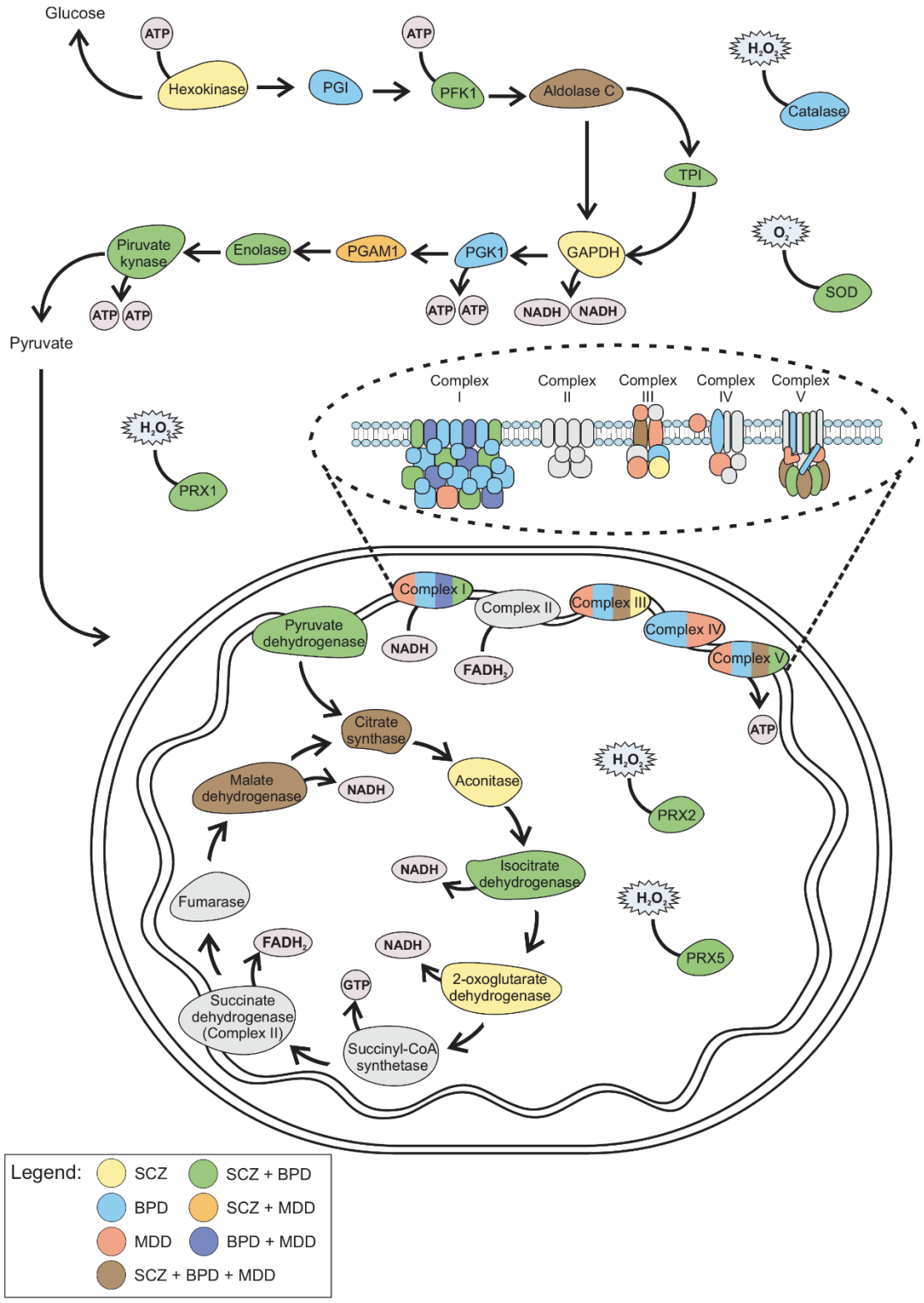

Figure 2: Schematic representation of the altered proteins in SCZ, BPD, and MDD. Color from each disorder and combination of disorders correlates with the Venn diagram (Figure 1). GAPDH, Glyceraldehyde 3-phosphate dehydrogenase; PFK1, Phosphofructokinase 1; PGAM, Phosphoglycerate mutase; PGI, Phosphoglucose isomerase; PGK1, Phosphoglycerate kinase 1; PRX, Peroxiredoxin; SOD, Superoxide dismutase; TPI, Triosephosphate isomerase.

5. SCZ Exclusive

Proteins altered exclusively in SCZ (45) (Figure 1 and Table 4) were related mostly to glycolysis and the TCA cycle (Figure 2). Hexokinase and glyceraldehyde-3-phosphate dehydrogenase are key enzymes in the handling of glucose. The alteration of these proteins along with glycolytic enzymes previously mentioned to be altered in SCZ is consistent with impaired glycolysis being an important attribute of SCZ. An approach to pharmacologically model schizophrenia in cell culture is treating cells with MK-801, which acts on the glutamatergic system. Treatment of cultured neurons, oligodendrocytes and astrocytes with MK-801 promoted a significant alteration in the level of enzymes related to glycolysis in the three cell types. Notably, of the three cell types, oligodendrocytes were the ones with more metabolic differences (Guest et al., 2015). Oligodendrocytes are glial cells responsible for neuron myelination, which is fundamental for neuronal connectivity (Davis et al., 2003) and it has been documented that oligodendrocyte dysfunction and abnormal metabolic activity are present in SCZ (Tkachev et al., 2003; Uranova et al., 2004; Bernstein et al., 2015). Most of the therapeutic targets of SCZ have been related to connectivity and synaptic transmission. Notably, clozapine is an antipsychotic drug with great clinical efficacy shown to improve glucose uptake in oligodendrocytes, indicating that in addition to rebalancing neurotransmission, this drug acts on the energy metabolism of those cells, which may in turn improve neuronal connectivity (Steiner et al., 2014; Cassoli et al., 2016). This evidence indicates that SCZ may be, at least in part, a glial cell metabolic disorder, opening doors to new therapeutic targets (Bernstein et al., 2009).

Another important and informative approach in proteomics is the analysis of post-translational modifications, such as phosphorylation. While some proteins are constitutively phosphorylated, the majority present transitory phosphorylation, depending on the cellular conditions at a given time. Proteome analyses of the corpus callosum, the largest white matter structure in the human brain, rich in glial cells revealed that several proteins were differentially phosphorylated (Saia- Cereda et al., 2016). Among them was the mammalian target of rapamycin (mTOR), a kinase that is a component of the mTORC1 pathway, and it plays a role in regulating protein synthesis, mainly by direct and indirect phosphorylation (Hay and Sonenberg, 2004), as well as being an important regulator of intracellular communicatory mechanisms in glial cells (Lisi et al., 2011). The AMP-activated protein kinase (AMPK) is a cellular energy sensor and signal transducer that is regulated by a wide

variety of metabolic stresses and AMPK directly phosphorylates multiple components in the mTORC1 pathway (Inoki et al., 2012). The relationship between mTOR and AMPK signaling pathways would make mTOR sensitive to even the lowest ATP depletion (Tokunaga et al., 2004). Therefore, the observation of changes in phosphorylation profile in mTOR emphasizes impaired energy production in glial cells of SCZ patients.

Transketolase and 6-phosphogluconolactonase are related to oxidation-reduction process and were altered in SCZ. They are key enzymes in the pentose phosphate pathway (PPP), which synthesizes the reduced form of nicotinamide adenine dinucleotide phosphate (NADPH) and ribose-5-phosphate (Horecker, 2002; Zhao et al., 2014). Alterations in NADPH levels and a potential imbalance in the NADP+/NADPH ratio have been reported in SCZ patients (Martins-De-Souza et al., 2010a). This evidence, along with the lower levels of pyruvate reported, points to glycolysis being a key pathway in the pathophysiological processes of SCZ (Martins-De-Souza et al., 2010a).

Furthermore, aconitase, isocitrate dehydrogenase, malate dehydrogenase and oxoglutarate dehydrogenase have been found to be altered in SCZ and are related to the TCA cycle. This points to alterations in mitochondrial pathways which are consistent with the concept that the broad mitochondrial processes are affected in the disorder (Ben-Shachar, 2009; English et al., 2011). Whether it is mitochondrial function or glucose metabolism that is affected first in the establishment of SCZ has yet to be elucidated (Martins-de-Souza et al., 2011).

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6. MDD Exclusive

Proteins altered in MDD (19) (Figure 1 and Table 4) are predominantly related to oxidative phosphorylation (Figure 2). In fact, the great majority of the proteins are subunits of cytochrome c, ATP synthase, or NADH dehydrogenase. An animal model of depression revealed that complexes from the electron transport chain were inhibited in the cerebellum and cortex when the animals were submitted to conditions of chronic mild stress (Rezin et al., 2008), while a human postmortem study of mRNA and protein levels revealed the reduced expression of three subunits of NADH dehydrogenase in the cerebellum of depressed patients (Ben- Shachar and Karry, 2008). Therefore, the poor functioning of oxidative phosphorylation due to decreased electron transport chain activity (Hroudová et al., 2013) promotes a biochemical imbalance in the processes leading to ATP production.

Mitochondrial dysfunction has been linked to depression and may be explained by deficiencies in both concentration and activity of proteins required for the proper functioning of the electron transport chain (Gardner and Boles, 2011). According to clinical studies, adults as well as children diagnosed with a primary OXPHOS disease present a higher incidence of major depression when compared to unaffected controls (Koene et al., 2009; Morava et al., 2010). Also, significant decreases of mitochondrial ATP production rates and mitochondrial enzymes ratios were observed in MDD patients (Gardner et al., 2003). Antidepressants, such as citalopram and venlafaxine promote changes in NADH dehydrogenase and cytochrome c oxidase, which indicates that those electron transport chain complexes are desirable drug targets and potential markers for MDD (Hroudova and Fisar, 2010).

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7. BPD Exclusive

Proteins found to be altered in BPD (48) (Figure 1 and Table 4) are mostly related to the TCA cycle and the electron transport chain (Figure 2). Microarray analyses on postmortem brain tissue revealed that several mRNAs linked to the production of mitochondrial electron transport chain complexes I–V were expressed in lower levels in BPD (Sun et al., 2006). Those findings agree with an important association between BPD and mitochondrial dysfunction (Konradi et al., 2004). As the mitochondrial electron transport chain is responsible for OXPHOS, consequently, it accounts for most of the oxygen consumption by the cell and also is responsible for substantial ROS production (Wang et al., 2009). Since polyunsaturated fatty acids, which constitute neuronal cell membranes, are very vulnerable to damage by ROS, BPD mitochondrial dysfunction may lead to overproduction of those reactive compounds, resulting in oxidative stress (Wang et al., 2009). Catalase and other previously mentioned antioxidant enzymes, such as peroxiredoxins, glutathione S-transferase and superoxide-dismutase, were found to be altered in BPD, which confirms the theory that oxidative stress plays a role in BPD occurrence. Hence, valproate and lithium, which are the most commonly used mood stabilizers in the treatment of BPD, were shown to have neuroprotective effects when oxidative stress was induced in rat brains (Cui et al., 2007; Shao et al., 2008). It has been reported that chronic treatment with those drugs results in an increased expression of cellular glutathione S-transferase (Wang et al., 2004). Additionally, treatment with N-acetylcysteine, a precursor of antioxidant glutathione, led to a significant improvement in the course of BPD treatment (Berk et al., 2008).

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8 Concluding remarks

Psychiatric disorders are highly prevalent worldwide and can have an early onset. This allows for substantial impairment for patients in both productive and social aspects of life, resulting in low level of education, work absenteeism, unemployment, social isolation, marital disruption, and the need for caregiving in many cases (Kessler et al., 1997, 1998; Wu et al., 2005; Hyman, 2008). One of the main underpins in psychiatry is the diagnosis, which relies entirely on a clinical evaluation when symptoms become evident. Although, when the disorder reaches this stage, it is usually already fully established, which indicates a higher severity in combination with less effective treatments (Saia-Cereda et al., 2017). The underlying pathophysiology of these disorders remains undetermined and studies aiming to help in early detection and early intervention could yield substantial improvements to the outcome of the disorders (Insel, 2010). For that reason, the use of quantitative proteomics to investigate disease-specific protein and pathway signatures can improve the understanding of psychiatric disorders (Filiou et al., 2011). The presence of metabolic alterations related to energy pathways have been recurrently implied as one of the physiological features of SCZ, BPD, and MDD (Shao et al., 2008). By collecting information acquired from patient postmortem brain proteomic research, with a focus on energy metabolism, we could establish molecular similarities among the disorders, in addition to highlighting which pathways were most affected in each one. This study highlights the importance of the connection between psychiatrists and researchers to facilitate access to patient samples and stimulate a more comprehensible knowledge base acquired in this field. Consequently, the constant update and increase of data deposited in postmortem brain banks will contribute to a better comprehension of the pathophysiological mechanisms of psychiatric disorders, which can in turn improve the diagnosis, treatment, and potential to overcome these conditions, resulting in improvements in quality of life for the patients.

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9. CAPÍTULO 2

Artigo a ser submetido

Proteomic findings in iPSC-derived neural cells from schizophrenia patients point to alterations associated with energy metabolism in neurodevelopment

Abstract

Schizophrenia is a severe psychiatric disorder of neurodevelopmental origin that affects around 1% of the world's population. Proteomic studies and other approaches have provided evidences of compromised cellular processes in the disorder, including mitochondrial function. Most of the studies so far have been conducted on postmortem brain tissue from patients, and therefore don't allow the evaluation of the neurodevelopmental aspect of the disorder. To circumvent that, we studied the mitochondrial and nuclear proteomes of neural stem cells (NSCs) and neurons derived from induced pluripotent stem cells (iPSCs) from schizophrenia patients versus healthy controls to assess possible alterations related to energy metabolism and mitochondrial function during neurodevelopment in the disorder. Our results revealed differentially expressed proteins in pathways related to mitochondrial function, cell cycle control, DNA repair and neuritogenesis and their possible implication in key process of neurodevelopment, such as neuronal differentiation and axonal guidance signaling. Hence, this study shows evidences that alterations in important cellular processes are present during neurodevelopment and could be involved with the stablishment of schizophrenia, as well as, the phenotyphic traits observed in adult patients.

Keywords: Schizophrenia, neurodevelopment, proteomics, iPSCs, neural cells, mitochondrion, nucleus

Introduction

Schizophrenia is a complex syndrome expressed by the combination of psychotic symptoms, such as hallucinations and delusions, with cognitive and motivational dysfunctions (Kahn et al., 2015). The disorder affects approximately 1% of the world's population and is thought to have a neurodevelopmental origin, which indicates that the combination of genetic and environmental factors would promote an early insult accompanied by a latent period throughout neurodevelopment, leading to the appearance of psychosis on late adolescence (Insel, 2010).

Proteomic studies conducted on postmortem brain tissue have provided insights on cellular processes that may be altered in the disorder, such as inflammation, glucose handling, mitochondrial function and response to reactive oxygen species (ROS) (Martins-de-Souza et al., 2011; Nascimento and Martins-de-Souza, 2015; Zuccoli et al., 2017). Organelle proteomics is a valuable tool and is based on the enrichment of a specific organelle in a given sample prior to MS analysis, which allows a better coverage of the subcellular proteome, enabling the identification of less abundant proteins which wouldn't otherwise be identified (Taylor et al., 2003).

Most of the studies so far have been conducted on postmortem brain tissue from schizophrenia patients, which makes it impossible to investigate the disorder in living cells and during the different developmental stages of the disease (Pedrosa et al., 2011). The use of induced pluripotent stem cells (iPSCs) (Takahashi et al., 2007; Takahashi and Yamanaka, 2006) derived from patients with schizophrenia has provided the possibility to study different neural cell types as well as the neurodevelopmental aspect of the disorder (Marchetto et al., 2011). The use of neural stem cells (NSCs) makes possible to study the process of neurons and radial glia given rise to more defined neuronal and glial populations (Marchetto et al., 2010). Studies performed on NSCs and neural progenitor cells (NPCs) derived from iPSCs from schizophrenia patients showed increased oxygen consumption, mitochondrial alterations, elevated ROS levels, decreased angiogenic factors, synaptic alterations and migration changes (Brennand et al., 2011, 2015; Casas et al., 2018; Paulsen et al., 2012, 2014). These characteristics indicate that this model can help recapitulate the phenotypic traits of schizophrenia, but the specific proteins and patways involved in the changes observed have not yet been elucidated.

Hence, in this work we proposed to study the mitochondrial and nuclear proteome of NSCs and neurons derived from iPSCs from patients with schizophrenia as well as the whole

proteome of neurons. The nucleus is responsible for the storage of genetic material in eukaryotic organisms and exerts key cellular functions such as gene expression, splicing, DNA repair and generation of gene products (Narula et al., 2013). Mitochondria provide most of the energy for the cell and are involved in ATP production, lipid metabolism, Ca^{2+} buffering and ROS production. In stem cells, the role for mitochondrial function is key for neurogenesis and neural stem cell fate decisions (Khacho and Slack, 2018) and it is proposed that a component of mitochondrial dysfunction might be involved in schizophrenia (Hroudová and Fišar, 2011; Rezin et al., 2009). For that reason, we propose to identify the proteins and pathways related to mitochondrial and nuclear function altered in the disorder and provide further information regarding the possible alterations related to energy metabolism and mitochondrial function affected in the disorder and its consequences to the neurodevelopmental course of schizophrenia.

Experimental Procedures

Generation of iPSCs from schizophrenia patients and controls

Schizophrenia cell lines used in this study were obtained from three subjects diagnosed with the schizophrenia spectrum, GM23760B, GM23761B and EZQ4 (clone 1). Patient 1 (GM23760B) and patient 2 (GM23761B) are siblings (Brennand et al., 2011; available at Coriell). Three control cell lines were used GM23279A (available at Coriell), CF1 (clone 10) and CF2 (clone 2). Cell lines EZQ4, CF1 and CF2 were reprogrammed at the D'Or Institute for Research and Education (Sochacki et al., 2016). Cells were cultured in mTeSR1 media (Stemcell Technologies, Vancouver, Canada) or E8 (Thermo Fisher Scientific, Carlsbad, CA, USA) on Matrigel (BD Biosciences, San Jose, CA, USA)-coated surface. Colonies were manually passaged every five-seven days and maintained at 37°C in humidified air with 5% CO_2.

Neural differentiation

iPSCs lines derived from schizophrenia patients and controls were adapted to E8 medium (Thermo Fisher Scientific, Carlsbad, CA, USA) for a minimum of 4 passages and the cells were then split. After 24 h of splitting the cells, we maintained them in Pluripotent Stem Cells (PSC) Neural Induction Medium (Thermo Fisher Scientific, Carlsbad, CA, USA), composed by Neurobasal medium and PSC supplement, according to the manufacturer's protocol. After seven days, changing the medium every other day, cells were then maintained in Neural

Induction Medium (NEM, Advanced DMEM/F12 and Neurobasal medium (1:1) with Neural Induction Supplement; Thermo Fisher Scientific, Carlsbad, CA, USA).

NSCs differentiation into neurons

NSCs were plated on poly-ornithine/laminin coated plates and then the NEM medium was used on the first day. After two days, which is considered as day 0, the medium was changed to neuronal differentiation (DMEM/F12 and Neurobasal medium (1:1) with B27 supplement; Thermo Fisher Scientific, Carlsbad, CA, USA). The change in medium happened every five days, we only removed half of the content on the plate and added fresh medium to reach the final volume. The factors secreted by the differentiating cells are important for a successful differentiation. We kept this process for 30 days from day 0.

Subcellular fractionation

Mitochondrial and nuclear fractions were obtained from NSCs and neurons according to an adaptation of the protocol described by Clayton and Shadel (Clayton and Shadel, 2014). Approximately 10^7 cells from each group were homogenized on ice in a buffer containing 210 mM Mannitol (Sigma-Aldrich, St. Louis, MO, USA), 70 mM Sucrose (Sigma-Aldrich), 5 mM Tris-HCl (Sigma-Aldrich), 1 mM EDTA (Sigma-Aldrich) and one tablet of protease cocktail inhibitor (Roche Diagnostics, Indianapolis, IN, USA) per 25 ml of buffer. The homogenized samples were then centrifuged at 2000xg for 5 minutes. The resulting pellets consisted of the nuclear fraction. The supernatant was then centrifuged at 13000xg for 20 minutes and the resulting pellets were the mitochondrial fraction.

In-gel digestion

Mitochondrial, nuclear and whole-cell pellets were subjected to a brief sodium docecylsulfate polyacrylamide gel electrophoresis (SDS-PAGE) to enhance the protein separation in each sample and optimize the digestion into peptides. Gel sections containing the proteins were subjected to reduction, alkylation, and overnight digestion with trypsin as described by (Shevchenko et al., 2007). The resulting peptide mixtures were removed from the gel by addition of acetonitrile and the solution with peptides were dried and posteriorly resuspended in ammonium formate pH 10 to posterior LC-MS/MS analysis.

LC-MS/MS

Qualitative and quantitative proteomic analyses were performed in a bidimensional nanoUPLC tandem nanoESI-HDMSE platform by multiplexed data-independent acquisitions (DIA) experiments. The peptides (1 μg) were injected into a 2D-RP/RPAcquity UPLC M-Class System (Waters Corporation, Milford, MA) coupled to a Synapt G2-Si mass spectrometer (Waters Corporation, Milford, MA). The samples were fractionated in first dimension chromatography with an XBridge Peptide BEH C18 NanoEase Column (Waters Corporation, Milford, MA). Peptide elutions were performed by using discontinuous steps of acetonitrile. After each step, peptide loads were carried to second dimension separation in an ACQUITY UPLC HSS T3 nanoACQUITY Column (Waters Corporation, Milford, MA). Peptide elutions were achieved by using an acetonitrile gradient from 7% to 40% (v/v) for 95 min at a flow rate of 500 nL/min directly into a Synapt G2-Si. MS/MS analyses were performed by nano- electrospray ionization in positive ion mode nanoESI (+) and a NanoLock Spray (Waters, Manchester, UK) ionization source. The mass spectrometer was calibrated with an MS/MS spectrum of [Glu1]-Fibrinopeptide B human (Glu-Fib) solution that was delivered through the reference sprayer of the NanoLock Spray source.

Database search and Protein identification

Spectra processing and database searching conditions were performed on the Progenesis® QI version 3.1 software package with Apex3D, peptide 3D, and ion accounting informatics (Waters). Proteins were identified and quantified by searching on the Uniprot human proteomic database, version 2017/10. The following parameters were considered in the identification of peptides: 1) digestion by trypsin with one missed cleavage maximum; 2) variable modifications by oxidation (M) and fixed modification by carbamidomethyl (C); 3) false discovery rate (FDR) less than 1%; and 4) peptides/proteins (N) equal to 3 in the quantification of proteins by the method of relative quantification with HI\N. Identifications that did not meet these criteria were rejected.

Systems biology analysis in silico

Biological processes and cellular compartments from each protein were searched in the David Protein networks (https://david.ncifcrf.gov/). Canonical pathways associated with differentially expressed proteins were identified by Ingenuity Pathway Analysis (IPA, Ingenuity Systems, Qiagen, Redwood, CA, USA; www.ingenuity.com). This program is based on an algorithm that uses curated connectivity information from the literature to

determine the network of interactions among the differentially expressed proteins and canonical pathways in which they are involved (Calvano et al., 2005).

Results

Mitochondrial proteome from NSCs and Neurons derived from SCZ iPSC

In the mitochondrial proteome of NSCs, we identified a total of 1354 and of those 1104 were quantified. A total of 84 proteins were found to be differentially regulated when compared SCZ and controls. In the mitochondrial proteome of neurons, we identified a total of 1043 proteins and of those 949 were quantified. Here, 169 proteins were found to be differentially regulated when compared SCZ and controls. Those differentially regulated proteins were analyzed in the online human protein reference database (http://www.hprd.org/) to find the biological processes with which they are related and the cellular compartment where they are located (Table 8 and 9)

By analyzing the gene ontology of those differentially regulated proteins using the David database (http://david.abcc.ncifcrf.gov), we could have an overrepresentation of biological processes significantly related to the differentially regulated proteins in each condition. The NSC's mitochondrial proteome analysis revealed that the proteins are related to processes such as oxidative phosphorylation, calcium homeostasis and cristae formation. The neuron's mitochondrial proteome analysis revealed that the proteins are related to processes such as calcium transport, mitochondrial location, tricarboxylic acid cycle, cell redox homeostasis and apoptotic changes.

We also conducted analyzes on the Ingenuity Pathway Analysis software (IPA, www.ingenuity.com) to determine the canonical pathways related to the differentially expressed proteins found in our data. With this information, it was possible to compare the levels of activation and inhibition of the canonical pathways related to the mitochondrial proteome of NSC and neurons and contribute to an overview of the altered pathways in the course of neurodevelopment in schizophrenia (Figure 3).

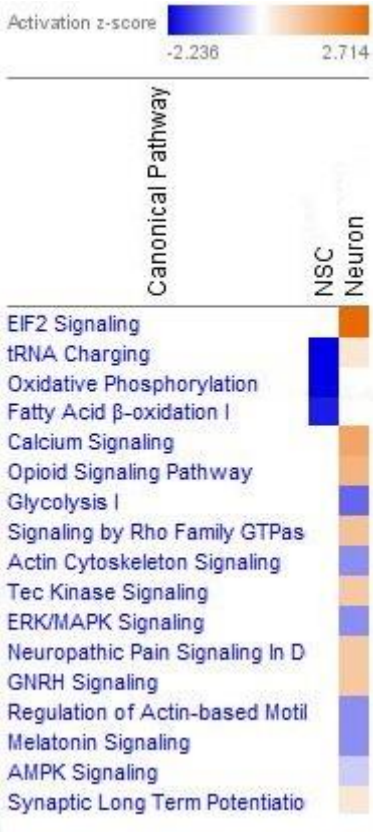

Figure 3: Comparison analysis of the levels of activation and inhibition of the canonical pathways related to the mitochondrial proteome of NSC and neurons derived from iPSCs from schizophrenia patients

Nuclear proteome from NSCs and Neurons derived from SCZ iPSC

In the nuclear proteome of NSCs, we identified a total of 1360 and of those 1152 were quantified. A total of 215 proteins were found to be differentially regulated when compared SCZ and controls. In the nuclear proteome of neurons, we identified a total of 1056 proteins and of those 888 were quantified. Here, 144 proteins were found to be differentially regulated when compared SCZ and controls. Those differentially regulated proteins were then analyzed in the online human protein reference database (http://www.hprd.org/) (Table 8 and 9) and in the David database (http://david.abcc.ncifcrf.gov).

The nuclear NSC analysis revealed that the differentially expressed proteins are related to cellular processes such as DNA repair, mRNA splicing, translation and histone phosphorylation. In the case of the nuclear proteome from neurons, the differentially expressed proteins are related to processes such as response do DNA damage, translation, mRNA stability and cell cycle.

We also conducted analyzes on the Ingenuity Pathway Analysis software (IPA, www.ingenuity.com) to determine the canonical pathways related to the differentially expressed proteins found in our data. With this information, it was possible to compare the levels of activation and inhibition of the canonical pathways related to the nuclear proteome of NSC and neurons and contribute to an overview of the altered pathways in the course of neurodevelopment in schizophrenia (Figure 4).

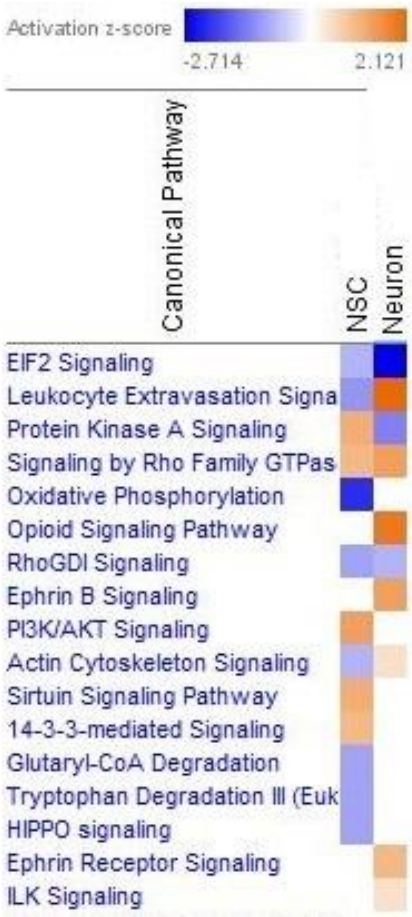

Figure 4: Comparison analysis of the levels of activation and inhibition of the canonical pathways related to the nuclear proteome of NSC and neurons derived from iPSCs from schizophrenia patients

Proteome of neurons derived from SCZ iPSCs

We identified a total of 1389 and of those 1285 were quantified. A total of 311 proteins were found to be differentially regulated when compared SCZ and controls. We then analyzed the

differentially regulated proteins in the online human protein reference database (http://www.hprd.org/) (Table 10) and in the David database (http://david.abcc.ncifcrf.gov). Our analyzes revealed that the differentially expressed proteins are related to processes such as glycolytic processes, tricarboxylic acid cycle, response to reactive oxygen species, mRNA splicing and neuron projection development. We also conducted analyzes on the Ingenuity Pathway Analysis software (IPA, www.ingenuity.com) to determine the canonical pathways and their activation levels related to the differentially expressed proteins found in our data (Figure 5). In addition, we performed the comparison analysis of the levels of activation or inhibition of the canonical pathways found altered in the mitochondrial and nuclear proteome of NSCs and neurons as well as in the total proteome of neurons to have a broad view of the activation or inhibition levels of the canonical pathwas found in our analysis (Figure 6)

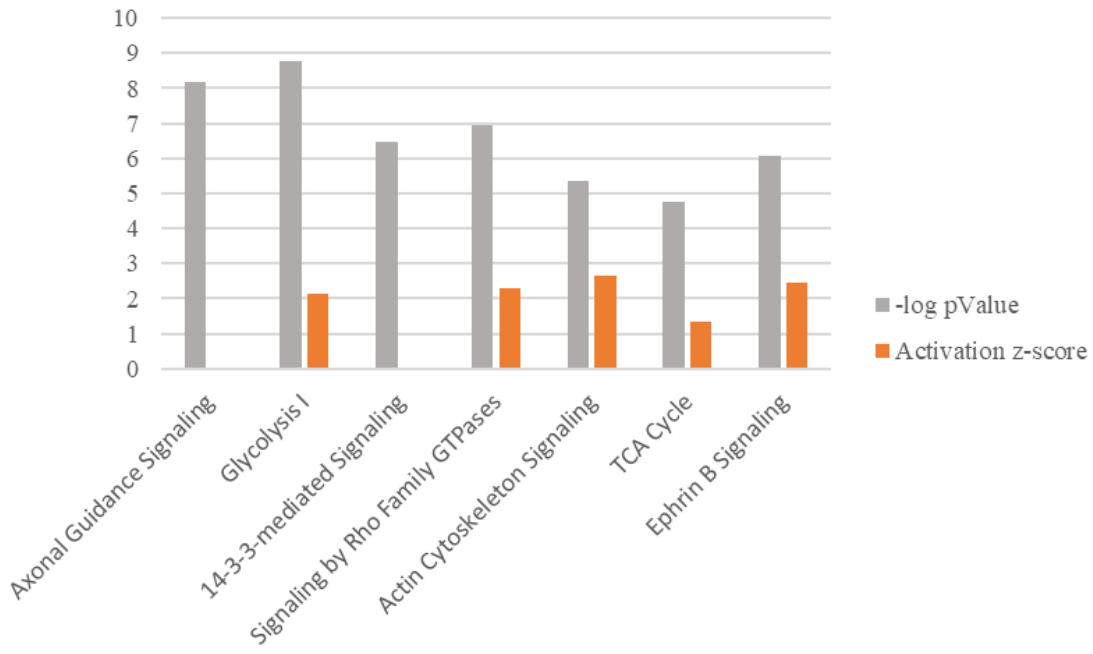

Figure 5: Analysis of the canonical pathways related to the total proteome of neurons derived from iPSCs from schizophrenia patients and their levels of activation.

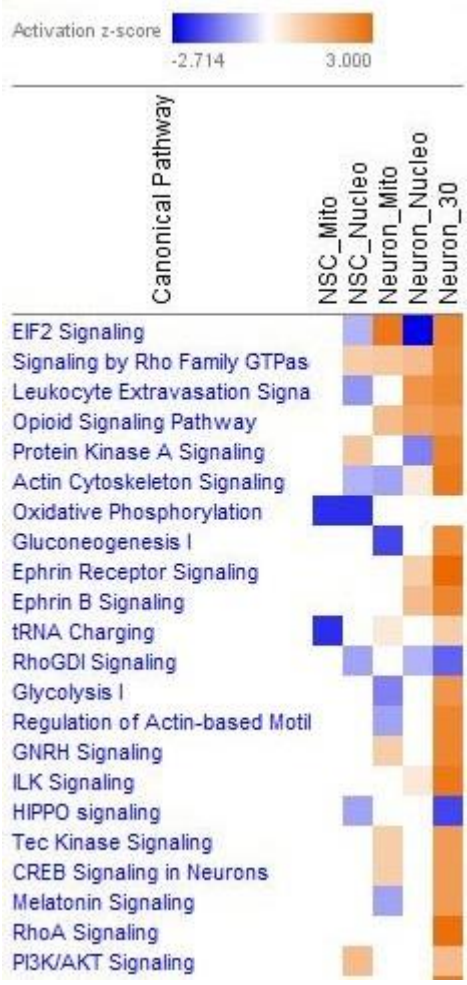

Figure 6: Comparison analysis of the levels of activation and inhibition of the canonical pathways related to the total proteome of neurons and nuclear and mitochondrial proteomes of NSCs and neurons derived from iPSCs from schizophrenia patients.

Discussion

Role of differentially expressed mitochondrial proteins in NSC and Neurons

In this study, proteins related to the pyruvate dehydrogenase complex, complex III of the electron transport chain and ATP synthase were found altered in schizophrenia and the canonical pathway mitochondrial dysfunction was significantly dysregulated in NSC, as shown by the analysis of the differentially expressed proteins according to IPA (p=5,04E-05). Our findings indicate the mitochondrial proteins that could be involved in the neurodevelopment of schizophrenia, as it has been revealed by recent studies that mitochondrial function, besides having an important role in mature neurons, also plays a key

part in neurodevelopmental processes, such as NSC fate commitment and neurogenesis (Beckervordersandforth et al., 2017; Khacho and Slack, 2018). In one study that used the deletion of the mitochondrial oxidoreductase protein AIF as a model of mitochondrial dysfunction in NSC it was observed the loss of NSC self-renewal capacity and defects in neuronal differentiation and cell cycle exit (Khacho et al., 2017). Our results show that the expression levels of proteins related to cristae formation, such as AFG3-like protein 2, proton/calcium exchanger protein and MICOS complex subunit MIC60 are altered in schizophrenia and it has been shown that changes in mitochondrial morphology in NSCs act as an upstream regulatory mechanism for stem cell fate decisions through modification of ROS signaling to activate developmental pathways, leading to commitment and differentiation (Khacho et al., 2016; Steib et al., 2014). Changes in mitochondrial morphology were observed in neural progenitor cells derived from iPSC from schizophrenia patients where the mitochondria were smaller, disconnected and distally distributed when compared to controls (Brennand et al., 2015). The gene Disrupted-in-Schizophrenia 1 (DISC1) is one of the major susceptibility genes related to schizophrenia and it has been reported that, in association with MICOS complex subunit MIC60 (Mitofilin), whose expression levels were found altered in our analysis, plays an important role in mitochondrial function, regulating mitochondrial cristae morphology and the maintenance of mitochondrial DNA (Park and Park, 2012). Therefore, alterations found in our work point to compromised function in key mitochondrial proteins that could potentially implicate in abnormalities related to neurodevelopment in schizophrenia.

In our study, the canonical pathway TCA cycle was significantly altered in neurons (p=8,06E-04) as well as mitochondrial dysfunction (p=1,05E-02). We also found alterations the expression levels of components of the Complex I and ATP synthase. The differentiation from NSCs to neurons is related to the shift in metabolism of those cells, the energy supply that relied mostly on glycolysis to attend the energetic demands of NSC changes to mostly mitochondrial metabolism in neurons (Bélanger et al., 2011; Kim et al., 2014). Neurons heavily rely on mitochondrial function to establish membrane excitability and to perform complex processes, such as neurotransmission and plasticity (Kann and Kovács, 2007). Mitochondria play an important role in axonogenesis and trafficking of the organelle in the developing brain supports the formation of axons and dendrites (Rajasekaran et al., 2015). For that reason, mitochondrial alterations could affect pivotal neuronal processes, such as neural maturation, neurite outgrowth and neurotransmitter release (Levy et al., 2003; Nicholls and

Budd, 2000). In fact, studies conducted on neurons derived from schizophrenia-patient iPSCs showed reduced neuronal connectivity, a decrease in number of neurites and impaired ability to differentiate into dopaminergic and mature glutamatergic neurons (Brennand et al., 2011; Robicsek et al., 2013). Our work has provided information regarding the proteins that could be directly involved in the phenotypic alterations mentioned previously and could, therefore, help in the understanding of the stablishment of schizophrenia. Also, by comparing the proteins found altered in the mitochondrial proteome of neurons (Table 9) with proteomics findings of postmortem brain tissue from schizophrenia patients (Table 1) we could identify that dihydrolipoyl dehydrogenase, citrate synthase, isocitrate dehydrogenase, malate dehydrogenase and glutamate dehydrogenase are altered in both analyzes, which is an important indicator that there are similarities between altered proteins found in a model of neurodevelopment and in the adult brain of schizophrenia patients.

Role of differentially expressed nuclear proteins in NSC and Neurons

In our study, we found canonical pathways related to cell cycle control and DNA damage repair to be significantly altered in NSC: cell cycle control of chromosomal replication (p=1,18E-06), DNA double-strand break repair by non-homologous end joining (p= 8,15E-06) and mismatch repair (p=1.46E-05). DNA replication licensing factor MCM7, Replication protein A and components of the DNA polymerase complex were found altered in our analysis and are essential for the proper functioning of DNA replication and DNA damage repair. The proper control of cell cycle progression is crucial for the generation of appropriate cell fates during neurodevelopmental processes that transform undifferentiated cells into differentiated brain structures (Cremisi et al., 2003). Microarray analyses of the anterior cingulate gyrus of schizophrenia patients revealed alterations in genes associated with canonical cell cycle pathways (Katsel et al., 2008). One study conducted on neural stem cell culture derived from nasal biopsies from patients with schizophrenia revealed alterations in genes and proteins related to cell cycle control pathways, hypothesizing that subtle alterations in cell cycle dynamics and shortening of the cell cycle in neural stem cells could contribute to the neurodevelopmental aspect of the disorder (Fan et al., 2012). Postmortem analyses have revealed increased levels of DNA damage markers in midbrain, caudate putamen and hippocampus in schizophrenia patients (Raza et al., 2017). Several studies have linked polymorphisms in genes related to DNA repair to the development of schizophrenia (Odemis et al., 2016; Saadat et al., 2008). Analysis of the DNA double-strand break marker γH2AX in immortalized lymphoblasts from schizophrenia patients by flow cytometry revealed

significantly higher baseline levels of this marker, which indicates higher occurrence of DNA double-strand damage may be due to replication stress and/or oxidative stress (Markkanen et al., 2016). In this way, our work identified alterations in expression levels of proteins that play an important part in the DNA repair processes. Deficiencies in DNA repair mechanisms in the nervous system could compromise the proper developmental dynamics of this complex system (Lee and McKinnon, 2007), but whether DNA damage and DNA repair are causally linked to schizophrenia remains unknown (Markkanen et al., 2016).

Our analysis revealed a potential link between nuclear proteins found altered in NSCs and the involvement of Akt and GSK3 in this stage of neurodevelopment in schizophrenia (Figure 7). Akt is a member of the serine/threonine protein kinase AGC family, has three isoforms and acts as a positive regulator of several signaling pathways such as cell proliferation, growth, survival, and metabolism (Engelman et al., 2006). Glycogen synthase kinase 3 (GSK3) proteins are serine/threonine kinases that were originally identified as regulatory enzymes in glucose metabolism (Woodgett and Cohen, 1984) but have emerged as key regulators of neurodevelopmental processes, including neurogenesis, neuronal migration and axonal guidance (Hur and Zhou, 2010). GSK3 is hypothesized to be an important coordinator of those processes, as it can respond to and integrate upstream signals, as well as phosphorylate a wide range of downstream substrates. Transcription factors play important parts in the regulation of gene expression during neurodevelopment and GSK3 regulates them by controlling their protein levels, DNA binding activities and nuclear localization (Hur and Zhou, 2010). Akt regulates the processes mentioned previously due to its ability to phosphorylate key proteins leading these processes, and one of those targets is GSK3, that is inhbited when phosphorylated (Bijur and Jope, 2003). Evidences suggest a critical role for Akt/GSK3 in the preservation of mitochondrial integrity and function, with Akt interacting with mitochondrial proteins such as Mitofusin-1 and affecting mitochondrial morphology (Ong et al., 2015; Wang et al., 2017), which was previously discussed as being a key factor in proper neurodevelopment (Khacho et al., 2016). Several studies have provided evidences of the involvement of the Akt/GSK3 signaling pathway in schizophrenia (Emamian, 2012) and our work has linked the proteins involved in this pathway to neurodevelopment in the disorder. In addition, our work indicates an important connection between the nuclear and mitochondrial alterations observed in NSCs, given the wide range of targets related to Akt and GSK3.

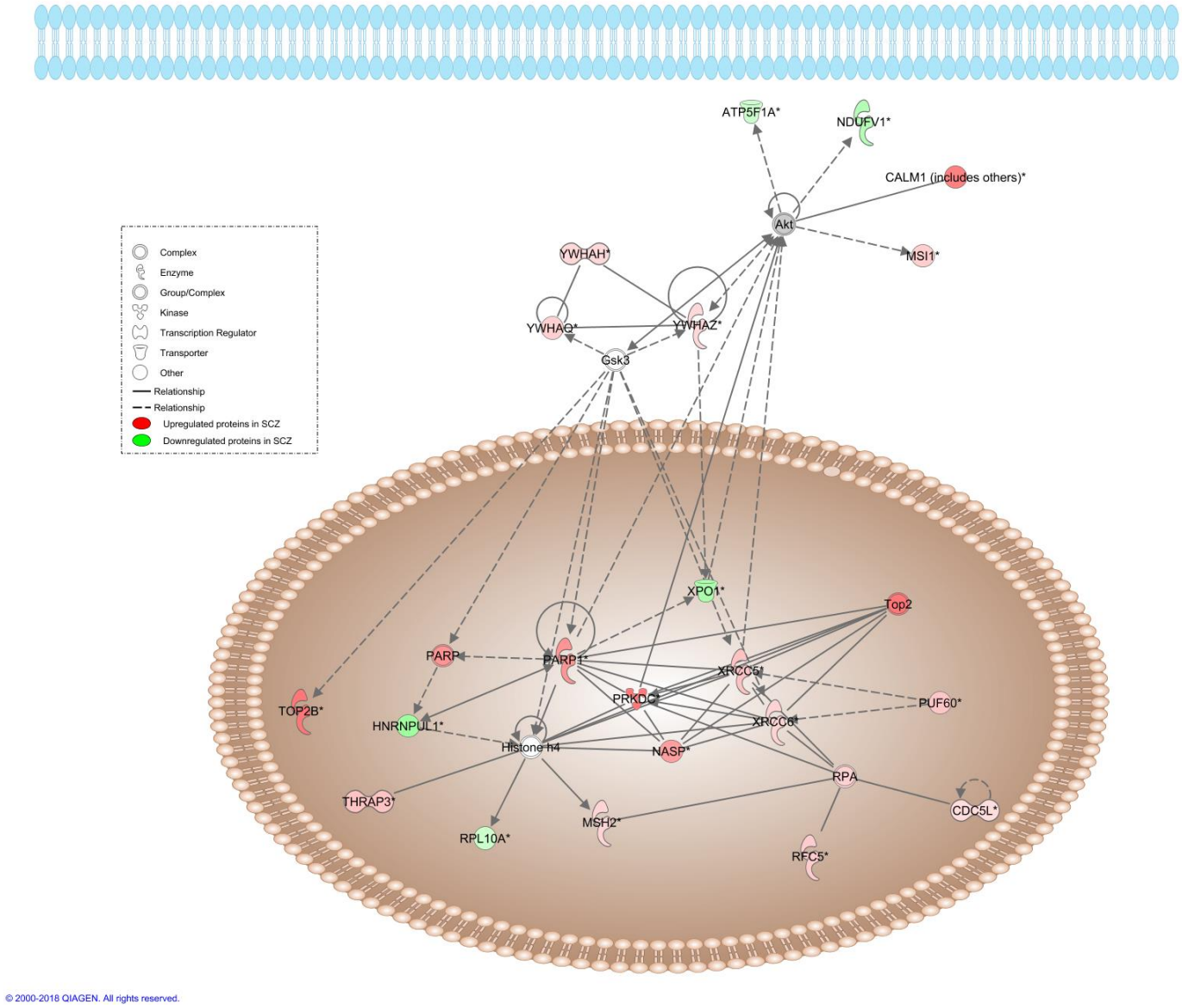

Figure 7: Network analysis of the differentially expressed proteins in the nuclear proteome of NSCs. Colored interactors represent proteins previous found in the proteome. Full and dashed lines depict direct and indirect connections, respectively

In our study we identified that the expression levels of proteins related to neuritogenesis (p=5,78E-07) and axonogenesis (p=2,03E-06) were altered in neurons. The formation of neurites is an important process in neurodevelopment, since is linked to the formation of axons and dendrites in early neuronal development (Polleux and Snider, 2010). Neuritogenesis starts after neuronal commitment and involves activation of membrane receptors, cytoskeleton rearrangements and regulation of gene transcription (Da Silva and Dotti, 2002). Genes that have been associated with schizophrenia, such as DISC-1, Akt and

NRG1 are hypothesized to be involved in the processes related to neurite formation in cell models of neurodevelopment (Bellon, 2007). In one of those studies, transfection of mutant DISC-1 in PC12 cells, which is one of those models, resulted in reduced neurite extension and by lowering the function of endogenous DISC-1 it was observed decreased levels of neurite outgrowth (Kamiya et al., 2005; Ozeki et al., 2003). Our findings of the presence of neuritogenesis alterations are consistent with other studies mentioned previously that observed reduced neurite outgrowths in neurons derived from schizophrenia patients (Brennand et al., 2011; Brennand and Gage, 2011) and in postmortem schizophrenia brain tissue (Jones et al., 2002; Kalus et al., 2000). Therefore, our results reveal the specific targets related to those processes that are altered in schizophrenia-patient's iPSC derived neurons and can contribute to a better understanding of the phenotypic alterations discussed previously.

Role of differentially expressed proteins in neurons

We decided to analyze the total proteome of neurons derived from iPSCs from schizophrenia patients to try to stablish the effects of the differentially regulated proteins and associated altered pathways. In this way, we could see the whole-cell impacts of alterations in mitochondrial and nuclear proteins since NSC until neuronal formation (Figure 8). The canonical pathways axonal guidance signaling (p=6,87E-09) and glycolysis (p=1,72E-09) were significantly altered in our analysis. During neurodevelopment, there is a transition in energy metabolism and what was predominantly glycolytic in NSCs changes to rely mostly in oxidative phosphorylation in neurons (Bélanger et al., 2011). This transition is tightly coupled to neuronal differentiation, as it was observed the dramatic decrease in the expression levels of key glycolytic proteins, such as hexokinase, glyceraldehyde 3-phosphate dehydrogenase and phosphoglycerate kinase 1. In fact, constitutive expression of glycolytic enzymes during differentiation leads to neuronal cell death, indicating that the decrease in aerobic glycolysis is essential for neuronal survival (Zheng et al., 2016). Our analysis revealed alteration in the expression levels of proteins related to glycolysis in neurons derived from schizophrenia patient's iPSC and those proteins were mostly upregulated when compared to controls. This indicates that the process of neuronal differentiation and, therefore, neurodevelopment could be affected in schizophrenia.

The establishment of neuronal connections during neurodevelopment requires the proper functioning of axonal guidance and pathfinding (Nugent et al., 2012). Alterations in those processes during brain development could lead to profound changes in neuronal circuits (Korecka et al., 2016). One study employed a computational approach that allowed the

integrative analysis of diverse schizophrenia-related genetic data and identified several gene networks related to axon guidance (Gilman et al., 2012). This is consistent with observations of defective neural connectivity between different brain regions in schizophrenia (Lewis and Lieberman, 2000). As discussed previously, mitochondrial function is an important contributor to proper formation of neurites and the establishment of connectivity, with fundamental roles in axon extension and guidance (Smith and Gallo, 2018). We also found proteins related to response to ROS altered in schizophrenia, such as superoxide dismutase, peroxiredoxins and thioredoxin. Oxidative stress, caused by impaired antioxidant defenses and/or by an exacerbated production of ROS, is related to risk factors for neurodevelopmental disorders (Do et al., 2009) and changes in the redox system have been identified in diverse models of schizophrenia (Behrens et al., 2008; Pedrini et al., 2012). One study that measured ROS levels in NPCs observed higher levels in cells derived from iPSCs from patients than controls (Paulsen et al., 2012). Hence, in the developing embryo, the occurrence of oxidative stress may alter development by damaging lipids, DNA and proteins, potentially altering signal transduction (Wells et al., 2009) and at least partially explain the phenotypic traits observed in schizophrenia. In addition, there is a link between the alterations found in the redox system, mitochondrial and nuclear proteins with cytoskeleton components (Figure 8). These alterations could interfere with the proper organization of actin filaments and microtubules, which are important for the formation and development of neuronal processes (Liu and Dwyer, 2014; Pacheco and Gallo, 2016).

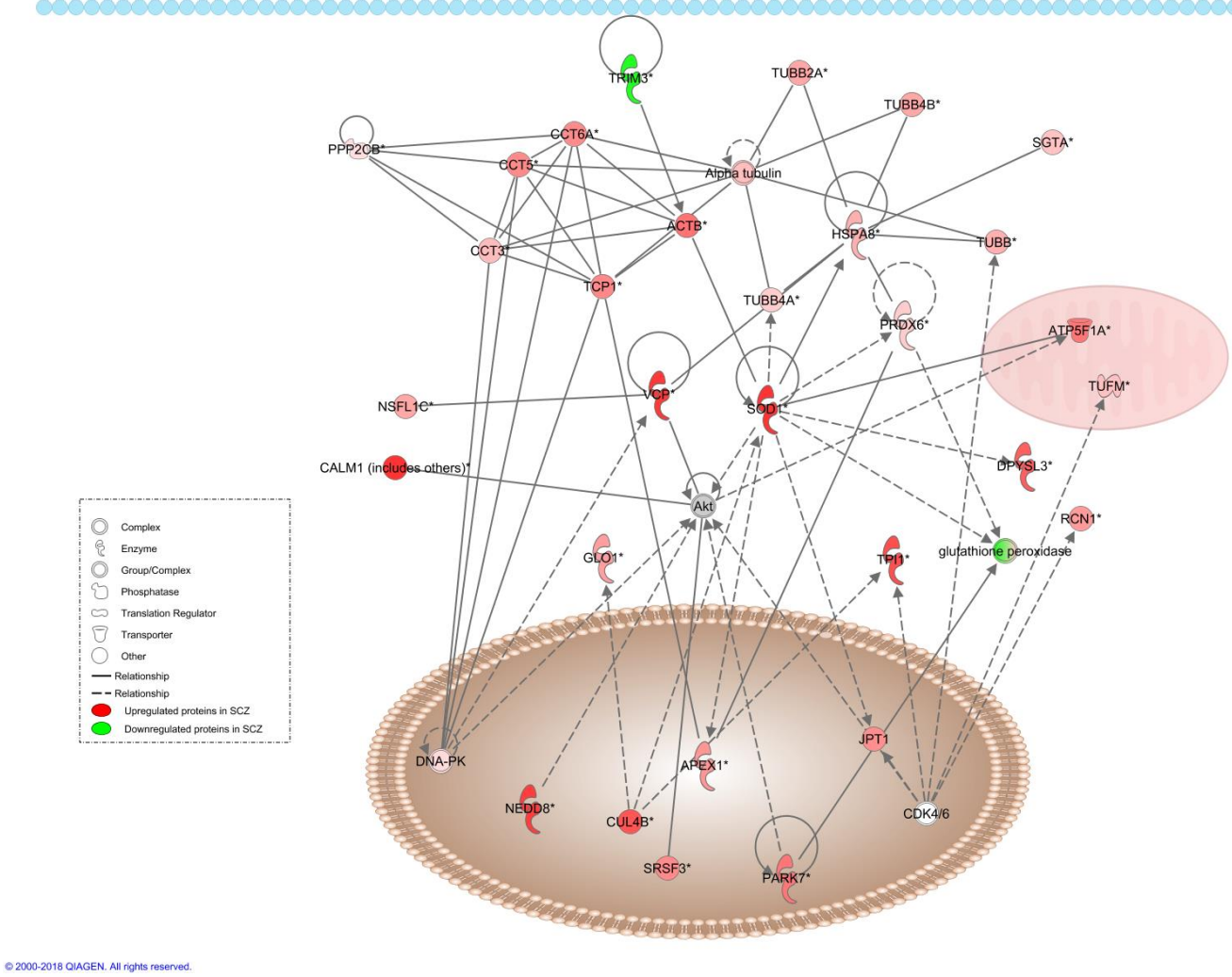

Figure 8: Network analysis of the differently expressed proteins in neurons derived from schizophrenia patients, showing their interactions and interactors. The network was generated from differentially expressed proteins by IPA. Colored interactors represent proteins previous found in the proteome. Full and dashed lines depict direct and indirect connections, respectively

Conclusion

Considering the results discussed above, this study has led to the identification of proteins and theirs associated pathways that are altered in neural cells derived from schizophrenia-patients's iPSCs. It was possible to observe that proteins related to TCA cycle, oxidative phosphorylation, mitochondrial morphology, cell cycle control and DNA repair are altered in neural stem cells and neurons derived from schizophrenia patients, which indicates that dysfunctions in key processes related to cell function and development are already present

during neurodevelopment and are not restricted to the adult brain or an exclusive effect of the medication is postmortem brain tissue analyzes. Hence, the alterations found reveal the potential targets involved with compromised neurodevelopment in schizophrenia, since processes such as neuronal differentiation, neuritogenesis and axonal guidance signaling are linked to our findings. In this way, this work shows evidences that alterations in key cellular processes related to energy metabolism and mitochondrial function during neurodevelopment could be involved with the stablishemt of schizophrenia and phenotypic traits observed in adult patients. Future studies ought to be conducted to determine the functional implications of the proteins found altered in our analyzes in the course of neurodevelopment. In conclusion, this work reveals the importance of combining proteomic approaches with cells derived from iPSCs from schizophrenia patients in the study of the disorder to bring insights into the mechanisms related to the neurodevelopment of schizophrenia.

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10. CONCLUSÃO FINAL

Como já descrito ao longo desta dissertação, a esquizofrenia consiste em um transtorno complexo de caráter multifatorial e associado ao neurodesenvolvimento. Desta forma, o estudo desta doença requer não apenas a compreensão de parâmetros clínicos e biológicos, mas é necessário também compreender as mudanças que ocorrem na biologia celular. Estudos com tecidos *post mortem*, genéticos e de imagem identificaram uma série de potenciais processos moleculares que precisam ser olhados no contexto celular, com vias relacionadas a metabolismo energético sendo constantemente encontradas alteradas na doença. Desta forma, na primeira etapa deste trabalho foi realizada a revisão da literatura e compilação de alterações em vias metabólicas encontradas em trabalhos que analisaram o proteoma de diferentes regiões cerebrais de pacientes com esquizofrenia e outras doenças psiquiátricas. Isto posto, através deste artigo de revisão, visamos contribuir para uma visão geral das evidências de alterações no metabolismo energético, estabelecendo as alterações relacionadas exclusivamente à esquizofrenia e aquelas em comum com outras doenças.

A esquizofrenia é uma doença psiquiátrica que acredita-se estar relacionada ao neurodesenvolvimento, o que significa que disfunções precoces no cérebro em desenvolvimento, devido a fatores genéticos e ambientais resultam no aparecimento da doença no final da adolescência/início da vida adulta. Visto a importância de se estudar aspectos neurodesenvolvimentais relacionados à esquizofrenia e inúmeras evidências de comprometimento do metabolismo energético na doença, a segunda parte deste trabalho se baseou em análises dos proteomas mitocondriais e nucleares de células-tronco neurais e neurônios derivados de células-tronco de pluripotência induzida obtidas por reprogramação de fibroblastos de pacientes com esquizofrenia para determinar se alterações relacionadas à função mitocondrial e metabolismo energético estão presentes em estágios iniciais do neurodesenvolvimento e suas potenciais consequências no contexto da esquizofrenia. Este modelo é de extrema valia para o estudo de doenças neurodesenvolvimentais, como a esquizofrenia, pois permite a observação de tipos celulares que são de difícil acesso *in vivo* em diferentes estágios de desenvolvimento. As análises dos proteomas mitocondriais e nucleares de células-tronco neurais e neurônios e também do proteoma total de neurônios revelaram diversas proteínas alteradas em esquizofrenia, quando comparado com controles saudáveis. Através dos dados obtidos, evidenciamos a presença de alterações em proteínas relacionadas a processos como metabolismo energético, função mitocondrial, controle do ciclo celular e reparo de DNA, durante o neurodesenvolvimento. Estas alterações presentes

em estágios iniciais do desenvolvimento estão ligadas ao possível comprometimento de processos-chave, como neuritogênese, orientação axonal e reorganização do citoesqueleto em neurônios, que podem afetar profundamente a organização e funcionamento cerebral. Dessa forma, ao identificar proteínas e suas respectivas vias que já se encontram alteradas durante o neurodesenvolvimento em esquizofrenia, podemos estabelecer uma relação com as alterações fenotípicas encontradas em pacientes adultos. Assim, pretendemos contribuir para o melhor entendimento dos mecanismos relacionados ao estabelecimento e fisiopatologia da esquizofrenia.

11. PERSPECTIVAS

Este trabalho apresentou uma revisão sobre evidências de alterações metabólicas em tecido cerebral *post mortem* de pacientes com doenças psiquiátricas e a análise dos proteomas mitocondriais e nucleares de células-tronco neurais e neurônios derivados de pacientes com esquizofrenia. Destas análises, foi possível identificar proteínas e suas vias associadas alteradas nestas células, evidenciando que é possível estabelecer a presença de alterações em processos relacionados ao neurodesenvolvimento na doença. Desta forma, trabalhos futuros buscarão, por análises dos aspectos funcionais destas células, estabelecer os efeitos das proteínas e vias encontradas alteradas neste estudo, buscando compreender o envolvimento destas no mecanismo neurodesenvolvimental e como se relacionam com a fisiopatologia da esquizofrenia.

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13. ANEXOS

Table 1: List of proteins related to energy metabolism found altered in SCZ

Protein	Acession number	Regulation	Biological Process	Cellular Component	Brain Region	Proteome Reference
Dihydropyrimidinase-like 4 (DPYSL4)	O14531	Up	Metabolism; Energy pathways	Cytoplasm	DLPFC	10.1038/sj.mp.4001532
Phosphoglycerate dehydrogenase	O43175	Down	Metabolism; Energy pathways	Extracellular	DLPFC	10.1038/sj.mp.4001532
NADH-ubiquinone oxidoreductase SGDH subunit	O43674	Down	Metabolism; Energy pathways	Mitochondrion	ATL	10.1007/s00702-008-0156-y
NADH-ubiquinone oxidoreductase 13 kDa-A subunit	O75380	Down	Metabolism; Energy pathways	Mitochondrion	ATL	10.1007/s00702-008-0156-y
Citrate synthase	O75390	Down	Metabolism; Energy pathways	Mitochondrion	ACC	10.1038/sj.mp.4001806
NADH-ubiquinone oxidoreductase 30 kDa subunit	O75489	Down	Metabolism; Energy pathways	Mitochondrion	ATL	10.1007/s00702-008-0156-y
Carbonyl reductase 3 (CBR3)	O75828	Up	Metabolism; Energy pathways		DLPFC	10.1038/sj.mp.4001532
ATP synthase, H+ transporting, mitochondrial F0 complex, subunit d isoform a	O75947	Down	Metabolism; Energy pathways	Mitochondrion	DLPFC	10.1016/j.jpsychires.2008.11.006
Dimethylarginine dimethylaminohydrolase 1 (DDAH1)	O94760	Down	Metabolism; Energy pathways	Cytoplasm	ACC, CC	10.1038/sj.mp.4001806; 10.1016/j.jpsychires.2010.03.003; 10.1002/prca.200700230
6-Phosphoglu- conolactonase	O95336	Up	Metabolism; Energy pathways		DLPFC	10.1038/sj.mp.4002098
CDP-DAG synthase 2	O95674	Down	Metabolism; Energy pathways	Mitochondrion	ACC	10.1038/mp.2014.63
Glutamate dehydrogenase	P00367	Up	Metabolism; Energy pathways	Mitochondrion	ACC, CC	10.1002/pmic.200500069; 10.1007/s00406-015-0621-1; 10.1016/j.schres.2015.02.002
Cytochrome c oxidase subunit 2	P00403	Down	Metabolism; Energy pathways	Mitochondrion	ACC, MDT	10.1038/mp.2014.63; 10.1016/j.jpsychires.2010.04.014
Superoxide dismutase [Cu-Zn]	P00441	Down	Metabolism; Energy pathways	Cytoplasm	ACC, CC	10.1002/prca.200700230; 10.1038/sj.mp.4001806; 10.1007/s00406-015-0621-1

Adenylate kinase 1	P00568	Up	Metabolism; Energy pathways	Cytoplasm	DLPFC	10.1007/s00406-008-0847-2
Carbonic anhydrase	P00915	Up	Metabolism; Energy pathways	Cytoplasm	ACC	10.1038/sj.mp.4001806; 10.1002/pmic.200500069
Carbonic anhydrase 2	P00918	Down	Metabolism; Energy pathways	Cytoplasm	ATL	10.1007/s00702-008-0156-y
Aldolase A, fructose-bisphosphate (ALDOA)	P04075	Down	Metabolism; Energy pathways	Cytoplasm	ACC, CC, DLPFC	10.1038/sj.mp.4001532; 10.1002/pmic.200500069; 10.1007/s00406-015-0621-1; 10.1016/j.jpsychires.2010.03.003
Glyceraldehyde-3-phosphate dehydrogenase	P04406	Down	Metabolism; Energy pathways	Cytoplasm	CC, DLPFC, MDT, WA	10.1016/j.jpsychires.2010.04.014; 10.1007/s00406-015-0621-1; 10.1186/1471-244X-9-17; 10.1038/sj.mp.4001532
Aldehydedehydrogenase, mitochondrial	P05091	Up	Metabolism; Energy pathways	Mitochondrion	ACC	10.1016/j.jpsychires.2010.03.003
ATP synthase beta chain	P06576	Up	Metabolism; Energy pathways	Mitochondrion	ACC, CC	10.1002/pmic.200500069; 10.1002/prca.200700230
Alpha-enolase	P06733	Up	Metabolism; Energy pathways	Cytoplasm	CC, DLPFC	10.1007/s00406-015-0621-1; 10.1038/sj.mp.4001532
L-lactate dehydrogenase B chain	P07195	Down	Metabolism; Energy pathways	Cytoplasm	CC	10.1002/prca.200700230
Pyruvate dehydrogenase E1 component, alpha 1	P08559	Down	Metabolism; Energy pathways	Mitochondrion	DLPFC	10.1038/sj.mp.4001532
Enolase 2, (gamma, neuronal) (ENO2)	P09104	Up	Metabolism; Energy pathways	Cytoplasm	CC, DLPFC, WA	10.1038/sj.mp.4001532; 10.1002/prca.200700230; 10.1038/sj.mp.4002098; 10.1186/1471-244X-9-17; 10.1007/s00406-015-0621-1
Glutathione s- transferase	P09211	Up	Metabolism; Energy pathways	Cytoplasm	CC, MDT	10.1002/prca.200700230; 10.1016/j.jpsychires.2010.04.014
Dihydropteridine reductase	P09417	Up	Metabolism; Energy pathways	Extracellular	DLPFC, MDT, WA	10.1186/1471-244X-9-17; 10.1016/j.jpsychires.2010.04.014; 10.1038/sj.mp.4001532
2',3'-cyclic nucleotide 3' phosphodiesterase (CNP)	P09543	Down	Metabolism; Energy pathways	Cytoplasm	ATL, CC, DLPFC	10.1038/sj.mp.4001532; 10.1007/s00406-015-0621-1; 10.1007/s00702-008-0156-y
Dihydrolipoyl dehydrogenase, mitochondrial precursor	P09622	Up	Metabolism; Energy pathways	Mitochondrion	WA	10.1186/1471-244X-9-17
Aldolase C, fructose-bisphosphate (ALDOC)	P09972	Down	Metabolism; Energy pathways	Mitochondrion	ACC, ATL, DLPFC, IC, WA	10.1016/j.jpsychires.2008.11.006; 10.1038/sj.mp.4001532; 10.1038/sj.mp.4001806; 10.1002/pmic.200900015; 10.1002/pmic.200800415;

						10.1007/s00702-008-0156-y; 10.1186/1471-244X-9-17
Esterase D/formylglutathione hydrolase (ESD)	P10768	Up	Metabolism; Energy pathways	Cytoplasm	DLPFC	10.1038/sj.mp.4001532
Glycogen phosphorylase, brain form	P11216	Down	Metabolism; Energy pathways	Cytoplasm	CC, MDT	10.1016/j.jpsychires.2010.04.014; 10.1007/s00406-015-0621-1
Glycogen phosphorylase, muscle form	P11217	Down	Metabolism; Energy pathways	Extracellular	CC	10.1007/s00406-015-0621-1
Imp dehydrogenase 2	P12268	Up	Metabolism; Energy pathways	Cytosol	DLPFC	10.1002/pmic.200900015
Creatine kinase B chain	P12277	Up	Metabolism; Energy pathways	Cytoplasm	ACC, CC, DLPFC, WA	10.1038/sj.mp.4001806; 10.1002/pmic.200500069; 10.1007/s00406-008-0847-2; 10.1002/prca.200700230; 10.1186/1471-244X-9-17; 10.1038/sj.mp.4001532
Creatine kinase ubiquitous mitochondrial	P12532	Down	Metabolism; Energy pathways	Mitochondrion	ACC	10.1038/sj.mp.4001806
Pyruvate kinase	P14618	Up	Metabolism; Energy pathways	Cytoplasm	CC, DLPFC	10.1007/s00406-015-0621-1; 10.1038/sj.mp.4001532
Aspartate--tRNA ligase, Cytoplasmic	P14868	Up	Metabolism; Energy pathways	Cytoplasm	ACC	10.1038/mp.2014.63
Glutamine synthetase	P15104	Up	Metabolism; Energy pathways	Cytosol	ACC, DLPFC, MDT	10.1038/sj.mp.4001532; 10.1016/j.jpsychires.2010.04.014; 10.1002/pmic.200500069
Phosphoglycerate mutase 2	P15259	Up	Metabolism; Energy pathways	Cytoplasm	DLPFC	10.1038/sj.mp.4001532
Carbonyl reductase 1	P16152	Up	Metabolism; Energy pathways	Cytoplasm	DLPFC, MDT	10.1016/j.jpsychires.2010.04.014; 10.1038/sj.mp.4001532
Phosphofructokinase 1; phosphohexokinase	P17858	Down	Metabolism; Energy pathways	Cytoplasm	ACC	10.1038/mp.2014.63
Phosphoglycerate mutase 1	P18669	Up	Metabolism; Energy pathways	Cytoplasm	DLPFC, MDT, WA	10.1016/j.jpsychires.2008.11.006; 10.1186/1471-244X-9-17; 10.1016/j.jpsychires.2010.04.014; 10.1038/sj.mp.4001532
Hexokinase 1 (HK1)	P19367	Down	Metabolism; Energy pathways	Cytoplasm	ACC, ATL, DLPFC	10.1038/mp.2014.63; 10.1038/sj.mp.4001532; 10.1007/s00702-008-0156-y
Glutathione-S-transferase Mu 3	P21266	Down	Metabolism; Energy pathways	Cytoplasm	DLPFC	10.1038/sj.mp.4001532
Catechol O-methyltransferase	P21964	Up	Metabolism; Energy pathways	Cytoplasm	ACC	10.1038/mp.2014.63

Acetoacetyl-CoA thiolase	P24752	Up	Metabolism; Energy pathways	Mitochondrion	ACC	10.1038/mp.2014.63
ATP synthase subunit alpha, mitochondrial	P25705	Down	Metabolism; Energy pathways	Mitochondrion	CC, DLPFC, WA	10.1007/s00406-015-0621-1; 10.1016/j.jpsychires.2008.11.006; 10.1186/1471-244X-9-17; 10.1016/j.schres.2015.02.002
NADH-ubiquinone oxidoreductase 75 kDa subunit	P28331	Down	Metabolism; Energy pathways	Mitochondrion	WA	10.1186/1471-244X-9-17
Inositol monophosphatase (IMPA1)	P29218	Up	Metabolism; Energy pathways	Cytoplasm	DLPFC	10.1002/pmic.200900015
Transketolase	P29401	Up	Metabolism; Energy pathways	Cytoplasm	MDT, DLPFC	10.1016/j.jpsychires.2010.04.014; 10.1016/j.jpsychires.2008.11.006
Delta-1-pyrroline-5-carboxylate dehydrogenase, mitochondrial	P30038	Up	Metabolism; Energy pathways	Mitochondrion	CC	10.1007/s00406-015-0621-1
Peroxiredoxin 6	P30041	Up	Metabolism; Energy pathways	Lysosome	DLPFC, WA	10.1007/s00406-008-0847-2; 10.1186/1471-244X-9-17
Biliverdin reductase B	P30043	Down	Metabolism; Energy pathways	Cytoplasm	ACC	10.1038/sj.mp.4001806
Peroxiredoxin 5	P30044	Down	Metabolism; Energy pathways	Mitochondrion	HP	10.1016/j.schres.2015.02.002
Aldehyde dehydrogenase	P30838	Up	Metabolism; Energy pathways	Cytoplasm	IC	10.1002/pmic.200800415
Ubiquinol-cytochrome-c reductase complex core protein I	P31930	Down	Metabolism; Energy pathways	Mitochondrion	DLPFC	10.1016/j.jpsychires.2008.11.006; 10.1038/sj.mp.4001532
Peroxiredoxin 2	P32119	Up	Metabolism; Energy pathways	Cytoplasm	ACC, CC, DLPFC	10.1002/prca.200700230; 10.1038/sj.mp.4001532; 10.1038/mp.2014.63
ATP synthase, gamma	P36542	Up	Metabolism; Energy pathways	Mitochondrion	IC	10.1002/pmic.200800415
Phosphoglucomutase-1	P36871	Down	Metabolism; Energy pathways	Cytoplasm	IC	10.1002/pmic.200800415
V-type proton ATPase catalytic subunit A	P38606	Down	Metabolism; Energy pathways	Endosome	DLPFC	10.1038/mp.2008.7
Malate dehydrogenase 1, NAD (soluble) (MDH1)	P40925	Down	Metabolism; Energy pathways	Cytoplasm	CC, DLPFC	10.1016/j.jpsychires.2008.11.006; 10.1038/sj.mp.4001532; 10.1007/s00406-015-0621-1
Malate dehydrogenase, mitochondrial precursora	P40926	Up	Metabolism; Energy pathways	Mitochondrion	ACC	10.1002/pmic.200500069
Isoleucyl tRNA synthetase, Cytoplasmic	P41252	Up	Metabolism; Energy pathways	Mitochondrion	ACC	10.1038/mp.2014.63

N- ethylmaleimide-sensitive factor	P46459	Up	Metabolism; Energy pathways	Cytoplasm	ACC, DLPFC	10.1038/sj.mp.4001532; 10.1038/sj.mp.4001806
Isocitrate dehydrogenase 2 (NADP+), mitochondrial variant	P48735	Down	Metabolism; Energy pathways	Mitochondrion	ACC	10.1038/mp.2014.63
Serine--tRNA ligase, Cytoplasmic	P49591	Up	Metabolism; Energy pathways	Cytoplasm	CC	10.1007/s00406-015-0621-1
Isocitrate dehydrogenase (NAD) subunit a	P50213	Down	Metabolism; Energy pathways	Mitochondrion	ACC	10.1038/sj.mp.4001806
Palmitoyl protein thioesterase 1	P50897	Up	Metabolism; Energy pathways	Lysosome	DLPFC	10.1007/s00406-008-0847-2
Tyrosyl-ttRNA synthetase (YARS)	P54577	Down	Metabolism; Energy pathways	Cytoplasm	DLPFC	10.1038/sj.mp.4001532
Succinyl coenzyme A:3 ketoacid CoA transferase	P55809	Up	Metabolism; Energy pathways	Mitochondrion	ACC	10.1002/pmic.200500069; 10.1016/j.jpsychires.2010.03.003
Triosephosphate isomerase	P60174	Up	Metabolism; Energy pathways	Cytoplasm	CC, DLPFC, IC, MDT, WA	10.1007/s00406-015-0621-1; 10.1186/1471-244X-9-17; 10.1002/pmic.200900015; 10.1002/pmic.200800415; 10.1016/j.jpsychires.2010.04.014
Phosphoribosyl pyrophosphate synthase isoform I	P60891	Up	Metabolism; Energy pathways		ACC	10.1038/mp.2014.63
Glutathione transferase omega	P78417	Down	Metabolism; Energy pathways	Nucleus	DLPFC	10.1038/sj.mp.4001532
Oxoglutarate (alpha-ketoglutarate) dehydrogenase	Q02218	Up	Metabolism; Energy pathways	Mitochondrion	ACC	10.1038/mp.2014.63
Fk506-binding protein 4	Q02790	Up	Metabolism; Energy pathways	Cytoplasm	IC	10.1002/pmic.200800415
Peroxiredoxin 1	Q06830	Up	Metabolism; Energy pathways	Cytoplasm	ACC, CC, DLPFC	10.1016/j.jpsychires.2010.03.003; 10.1038/mp.2014.63; 10.1007/s00406-015-0621-1; 10.1038/sj.mp.4001532
Peroxiredoxin 4	Q13162	Down	Metabolism; Energy pathways	Cytoplasm	DLPFC	10.1002/pmic.200900015
Cytoplasmic dynein 1 heavy chain 1, cytosolic	Q14204	Down	Metabolism; Energy pathways	Cytoplasm	ACC	10.1038/mp.2014.63
NADH oxidoreductase (ubiquinone) 1 a subcomplex, 5, 13kDa	Q16718	Down	Metabolism; Energy pathways	Mitochondrion	ACC	10.1038/sj.mp.4001806
Hydroxyacylglutathione hydrolase (Glx II)	Q16775	Down	Metabolism; Energy pathways	Cytoplasm	ACC	10.1038/sj.mp.4001806
NADH-ubiquinone oxidoreductase 39 kDa subunit	Q16795	Up	Metabolism; Energy pathways	Mitochondrion	ACC	10.1038/mp.2014.63

Malic enzyme 3	Q16798	Up	Metabolism; Energy pathways	Mitochondrion	MDT	10.1016/j.jpsychires.2010.04.014
Ectonucleotide pyrophosphatase/phosphodiesterase family member 6	Q6UWR7	Down	Metabolism; Energy pathways		CC	10.1007/s00406-015-0621-1
Pyridoxal phosphatase	Q96GD0	Up	Metabolism; Energy pathways		DLPFC	10.1002/pmic.200900015
Inositol polyphosphate 4-phosphatase type I	Q96PE3	Up	Metabolism; Energy pathways	Cytoplasm	ACC	10.1038/mp.2014.63
Aconitase 2, mitochondrial	Q99798	Up	Metabolism; Energy pathways	Mitochondrion	ACC, DLPFC, WA	10.1016/j.jpsychires.2008.11.006; 10.1038/sj.mp.4001532; 10.1186/1471-244X-9-17; 10.1002/pmic.200500069
Acetyl CoA acetyltransferase cytosolic	Q9BWD1	Down	Metabolism; Energy pathways	Cytoplasm	ACC	10.1038/sj.mp.4001806; 10.1038/mp.2014.63
Methyltransferase-like protein 7A; protein AAM-B	Q9H8H3	Down	Metabolism; Energy pathways		ACC	10.1038/mp.2014.63
Lambda-crystallin homolog	Q9Y2S2	Down	Metabolism; Energy pathways		CC	10.1007/s00406-015-0621-1
Guanine deaminase	Q9Y2T3	Up	Metabolism; Energy pathways	Cytoplasm	DLPFC, IC, MDT	10.1016/j.jpsychires.2010.04.014; 10.1038/sj.mp.4002098; 10.1002/pmic.200800415
NADH dehydrogenase [ubiquinone] 1 beta subcomplex subunit 9	Q9Y6M9	Up	Metabolism; Energy pathways	Mitochondrion	MDT	10.1016/j.jpsychires.2010.04.014

Table 2: List of proteins related to energy metabolism found altered in MDD

Protein	Acession number	Regulation	Biological Process	Cellular Component	Brain Region	Proteome Reference
NADH dehydrogenase Ubiquinone 1-alpha subcomplex subunit 2	O43678	Up	Metabolism; Energy pathways		DLPFC	10.1038/tp.2012.13
NADH dehydrogenase Ubiquinone iron-sulphur protein 5	O43920	Up	Metabolism; Energy pathways	Mitochondrion	DLPFC	10.1038/tp.2012.13
Citrate synthase	O75390	Up	Metabolism; Energy pathways	Mitochondrial matrix	pituitary gland	10.1016/j.jpsychires.2014.09.022
ATP synthase subunit g mitochondrial short ATPase	O75964	Up	Metabolism; Energy	Mitochondrion	DLPFC	10.1038/tp.2012.13

			pathways			
Carbonic anhydrase 1b	P00915	Up	Metabolism; Energy pathways	Cytoplasm	PFC, ACC	10.1038/sj.mp.4000696; 10.1002/pmic.200500069
Carbonic anhydrase 2	P00918	Up	Metabolism; Energy pathways	Cytoplasm	pituitary gland	10.1016/j.jpsychires.2014.09.022
Fructose bisphosphate aldolase A	P04075	Up	Metabolism; Energy pathways	Cytoplasm	ACC	10.1002/pmic.200500069
Aldehyde dehydrogenase, mitochondrial	P05091		Metabolism; Energy pathways	Mitochondrion	APC	10.1093/ijnp/pyu019
ATP synthase b chain, mitochondrial precursor a	P06576	Up	Metabolism; Energy pathways	Mitochondrion	ACC	10.1002/pmic.200500069
Glycogen phosphorylase, liver form	P06737		Metabolism; Energy pathways		APC	10.1093/ijnp/pyu019
Beta-hexosaminidase subunit beta	P07686		Metabolism; Energy pathways	Lysosome	APC	10.1093/ijnp/pyu019
Fructose-bisphosphate aldolase C	P09972	Up	Metabolism; Energy pathways	Mitochondrion	PFC	10.1038/sj.mp.4000696
Cytochrome c oxidase subunit 5B mitochondrial	P10606	Up	Metabolism; Energy pathways	Mitochondrion	DLPFC	10.1038/tp.2012.13
Cytochrome c oxidase subunit 4 isoform 1 mitochondrial	P13073	Up	Metabolism; Energy pathways	Mitochondrion	DLPFC	10.1038/tp.2012.13
Cytochrome c oxidase polypeptide 7A2 mitochondrial	P14406	Up	Metabolism; Energy pathways	Mitochondrion	DLPFC	10.1038/tp.2012.13
Glutamine synthetase a	P15104	Down	Metabolism; Energy pathways	Cytosol	ACC	10.1002/pmic.200500069
Carbonyl reductase [NADPH] 1	P16152		Metabolism; Energy pathways	Cytoplasm	APC	10.1093/ijnp/pyu019
Serine--pyruvate aminotransferase	P21549		Metabolism; Energy pathways	Peroxisome	APC	10.1093/ijnp/pyu019
Alpha-(1,3)-fucosyltransferase 4	P22083		Metabolism; Energy pathways	Golgi apparatus	APC	10.1093/ijnp/pyu019

Thioredoxin-dependent peroxide reductase	P30048		Metabolism; Energy pathways	Mitochondrion	pituitary gland	10.1016/j.jpsychires.2014.09.022
Ubiquinol cytochrome c reductase complex core Protein 1	P31930	Down	Metabolism; Energy pathways	Mitochondrion	PFC	10.1038/sj.mp.4000696
Phosphoglucomutase-1	P36871		Metabolism; Energy pathways	Cytoplasm	APC	10.1093/ijnp/pyu019
Malate dehydrogenase, mitochondrial precursor a	P40926	Up	Metabolism; Energy pathways	Mitochondrion	ACC	10.1002/pmic.200500069
Platelet-activating factor acetylhydrolase IB subunit alpha	P43034		Metabolism; Energy pathways	Cytoplasm	APC	10.1093/ijnp/pyu019
Cytochrome b-c1 complex subunit Rieske, mitochondrial	P47985		Metabolism; Energy pathways	Mitochondrion	APC	10.1093/ijnp/pyu019
Biotin protein ligase	P50747	Up	Metabolism; Energy pathways	Cytoplasm	pituitary gland	10.1016/j.jpsychires.2014.09.022
Succinyl-CoA ligase [ADP/GDP-forming] subunit alpha, mitochondrial	P53597		Metabolism; Energy pathways	Mitochondrion	APC	10.1093/ijnp/pyu019
Succinyl coenzyme A:3 ketoacid CoA transferase	P55809	Down	Metabolism; Energy pathways	Mitochondrion	ACC	10.1002/pmic.200500069
NADH dehydrogenase [ubiquinone] flavoprotein 3, mitochondrial	P56181		Metabolism; Energy pathways	Mitochondrion	APC	10.1093/ijnp/pyu019
ATP synthase subunit e mitochondrial	P56385	Up	Metabolism; Energy pathways	Mitochondrion	DLPFC	10.1038/tp.2012.13
NADH dehydrogenase Ubiquinone 1 alpha subcomplex subunit 6	P56556	Up	Metabolism; Energy pathways	Mitochondrion	DLPFC	10.1038/tp.2012.13
Glutathione S-transferase omega-1	P78417		Metabolism; Energy pathways	Nucleus	APC	10.1093/ijnp/pyu019
Cytochrome c	P99999	Up	Metabolism; Energy pathways	Mitochondrion	DLPFC	10.1038/tp.2012.13
Glucosamine fruct 6 phos aminotransferase 1	Q06210	Down	Metabolism; Energy pathways	Cytoplasm	pituitary gland	10.1016/j.jpsychires.2014.09.022
Dihydropyrimidinase-related protein 3	Q14195	Up	Metabolism; Energy pathways	Cytoplasm	DLPFC	10.1038/tp.2012.13

Neutrophil cytosol factor 4	Q15080		Metabolism; Energy pathways	Cytoplasm	APC	10.1093/ijnp/pyu019
Hydroxyacylglutathione hydrolase, mitochondrial	Q16775		Metabolism; Energy pathways	Cytoplasm	APC	10.1093/ijnp/pyu019
NADH dehydrogenase [ubiquinone] 1 alpha subcomplex subunit 11	Q86Y39		Metabolism; Energy pathways	Mitochondrion	APC	10.1093/ijnp/pyu019
NADH dehydrogenase [ubiquinone] 1 beta subcomplex subunit 11, mitochondrial	Q9NX14		Metabolism; Energy pathways		APC	10.1093/ijnp/pyu019
NADH dehydrogenase Ubiquinone 1-alpha subcomplex subunit 13	Q9P0J0	Up	Metabolism; Energy pathways	Mitochondrion	DLPFC	10.1038/tp.2012.13
Beta enolase	P13929		Metabolism; Energy pathways	Extracellular	DLPFC	10.1007/s00406-012-0301-3

Table 3: List of proteins related to energy metabolism found altered in BPD

Protein	Acession number	Regulation	Biological Process	Cellular Component	Brain Region	Proteome Reference
Hydroxyacylglutathione hydrolase, mitochondrial	H3BPK3	Down	Metabolism; Energy pathways		ACC	10.1038/tp.2016.224
ATPase (transitional ER)	O14983	Up	Metabolism; Energy pathways	Sarcoplasmic reticulum	DLPFC	10.1038/sj.mp.4002098
D-3 Phosphoglycerate dehydrogenase	O43175	Up	Metabolism; Energy pathways	Extracellular	DLPFC	10.1038/sj.mp.4002098
Proline dehydrogenase 1, mito	O43272	Up	Metabolism; Energy pathways		APC	10.1093/ijnp/pyu015
NADH dehydrogenase [ubiquinone] 1 beta subcomplex subunit 3	O43676	Up	Metabolism; Energy pathways		ACC	10.1038/tp.2016.224
NADH dehydrogenase [ubiquinone] 1 alpha subcomplex subunit 2	O43678	Up	Metabolism; Energy pathways		ACC	10.1038/tp.2016.224
Isocitrate dehydrogenase [NAD] subunit beta, mitochondrial	O43837	Up	Metabolism; Energy pathways	Mitochondrion	ACC	10.1038/tp.2016.224
NADH dehydrogenase [ubiquinone] iron-sulfur protein 5	O43920	Up	Metabolism; Energy pathways	Mitochondrion	ACC	10.1038/tp.2016.224
NADH dehydrogenase [ubiquinone] iron-sulfur protein 2, mitochondrial	O75306	Up	Metabolism; Energy pathways	Mitochondrion	ACC	10.1038/tp.2016.224
NADH dehydrogenase [ubiquinone] iron-sulfur protein 6, mitochondrial	O75380	Up	Metabolism; Energy pathways	Mitochondrion	ACC	10.1038/tp.2016.224
Citrate synthase, mito	O75390	Up	Metabolism; Energy pathways	Mitochondrial matrix	APC	10.1093/ijnp/pyu015
NADH dehydrogenase [ubiquinone] 1 beta subcomplex subunit 1	O75438	Up	Metabolism; Energy pathways	Integral to membrane	ACC	10.1038/tp.2016.224
NADH dehydrogenase [ubiquinone] iron-sulfur protein 3,	O75489	Up	Metabolism; Energy	Mitochondrion	ACC	10.1038/tp.2016.224

mitochondrial			pathways			
ATP synthase subunit d, mitochondrial	O75947	Up	Metabolism; Energy pathways	Mitochondrial membrane	CA2/3, CA4, DG, ACC	10.1001/archgenpsychiatry.2011.43; 10.1038/tp.2016.224
Dimethylarginine Dimethylaminohydrolase 1	O94760	Down	Metabolism; Energy pathways	Cytoplasm	CA2/3, CA4, DG, DLPFC	10.1001/archgenpsychiatry.2011.43; 10.1038/sj.mp.4002098
NADH dehydrogenase [ubiquinone] 1 beta subcomplex subunit 4	O95168	Up	Metabolism; Energy pathways	Integral to membrane	ACC	10.1038/tp.2016.224
NADH dehydrogenase [ubiquinone] 1 alpha subcomplex subunit 7	O95182	Up	Metabolism; Energy pathways	Mitochondrion	ACC	10.1038/tp.2016.224
NADH dehydrogenase [ubiquinone] 1 subunit C2;NADH dehydrogenase [ubiquinone] 1 subunit C2, isoform 2	O95298	Up	Metabolism; Energy pathways	Mitochondrion	ACC	10.1038/tp.2016.224
NADH dehydrogenase [ubiquinone] 1 alpha subcomplex subunit 10, mitochondrial	O95299	Up	Metabolism; Energy pathways	Mitochondrion	ACC	10.1038/tp.2016.224
Phosphatidate cytidylyltransferase 2	O95674	Up	Metabolism; Energy pathways	Mitochondrion	ACC	10.1038/tp.2016.224
Glutamate dehydrogenase 1, mitochondrial	P00367	Up	Metabolism; Energy pathways	Mitochondrion	ACC	10.1038/tp.2016.224; 10.1016/j.schres.2015.02.002
Superoxide dismutase [Cu-Zn]	P00441		Metabolism; Energy pathways	Cytoplasm	CA1, CA2/3, CA4, DG	10.1001/archgenpsychiatry.2011.43
Aspartate aminotransferase, mitochondrial	P00505	Down	Metabolism; Energy pathways	Mitochondrion	ACC	10.1038/tp.2016.224
Phosphoglycerate kinase 1	P00558	Down	Metabolism; Energy	Cytoplasm	APC	10.1093/ijnp/pyu015

			pathways			
NADH-ubiquinone oxidoreductase chain 4	P03905	Up	Metabolism; Energy pathways	Mitochondrion	ACC	10.1038/tp.2016.224
NADH-ubiquinone oxidoreductase chain 5	P03915	Up	Metabolism; Energy pathways	Mitochondrion	ACC	10.1038/tp.2016.224
Catalase	P04040		Metabolism; Energy pathways	Cytoplasm	APC	10.1093/ijnp/pyu015
ATP synthase subunit beta, mitochondrial	P06576	Up	Metabolism; Energy pathways	Mitochondrion	CA2/3, ACC	10.1001/archgenpsychiatry.2011.43; 10.1038/tp.2016.224
ATP synthase beta chain	P06576	Up	Metabolism; Energy pathways	Mitochondrion	DLPFC	10.1038/sj.mp.4002098
Alpha-enolase	P06733	Down	Metabolism; Energy pathways	Cytoplasm	CA1, CA2/3, DG	10.1001/archgenpsychiatry.2011.43
Glucose-6-phosphate isomerase	P06744	Down	Metabolism; Energy pathways	Cytoplasm	ACC	10.1038/tp.2016.224
Cytochrome b-c1 complex subunit 6, mitochondrial	P07919	Up	Metabolism; Energy pathways	Mitochondrion	ACC	10.1038/tp.2016.224
Pyruvate dehydrogenase E1 component subunit alpha, somatic form, mitochondrial	P08559	Up	Metabolism; Energy pathways	Mitochondrion	ACC	10.1038/tp.2016.224
Cytochrome c1, heme protein, mitochondrial	P08574	Up	Metabolism; Energy pathways	Mitochondrion	ACC	10.1038/tp.2016.224
Gamma enolase	P09104	Up	Metabolism; Energy pathways	Cytoplasm	DLPFC	10.1038/sj.mp.4002098
Glutathione S-Transferase Pi 1	P09211		Metabolism; Energy pathways	Cytoplasm	CA2/3, CA4	10.1001/archgenpsychiatry.2011.43
2',3'-cyclic-nucleotide 3'-phosphodiesterase CNPase	P09543	Down	Metabolism; Energy pathways	Cytoplasm	APC	10.1093/ijnp/pyu015

Dihydrolipoyl dehydrogenase, mitochondrial	P09622	Up	Metabolism; Energy pathways	Mitochondrion	ACC	10.1038/tp.2016.224
Dihydrolipoyl dehydrogenase	P09622	Up	Metabolism; Energy pathways	Mitochondrion	DLPFC	10.1038/sj.mp.4002098
Fructose-bisphosphate aldolase C	P09972	Up	Metabolism; Energy pathways	Mitochondrion	CA2/3	10.1001/archgenpsychiatry.2011.43
Dihydrolipoyllysine-residue acetyltransferase component of pyruvate dehydrogenase complex, mitochondrial	P10515	Up	Metabolism; Energy pathways	Mitochondrion	ACC	10.1038/tp.2016.224
Pyruvate dehydrogenase E1 component subunit beta, mitochondrial	P11177	Up	Metabolism; Energy pathways	Mitochondrion	ACC	10.1038/tp.2016.224
Glucose-6-phosphate 1-dehydrogenase	P11413	Up	Metabolism; Energy pathways	Cytoplasm	ACC	10.1038/tp.2016.224
Creatine kinase B chain	P12277	Down	Metabolism; Energy pathways	Cytoplasm	DLPFC	10.1038/mp.2008.7
Pyruvate kinase PKM;Pyruvate kinase	P14618	Down	Metabolism; Energy pathways	Cytoplasm	ACC	10.1038/tp.2016.224
NAD(P)H Dehydrogenase, Quinone 2	P16083		Metabolism; Energy pathways	Cytoplasm	CA2/3	10.1001/archgenpsychiatry.2011.43
6-phosphofructokinase, liver type	P17858	Down	Metabolism; Energy pathways	Cytoplasm	ACC	10.1038/tp.2016.224
NADH dehydrogenase [ubiquinone] flavoprotein 2, mitochondrial	P19404	Up	Metabolism; Energy pathways	Mitochondrion	ACC	10.1038/tp.2016.224
Glutathione S-transferase Mu 3	P21266	Down	Metabolism; Energy pathways	Cytoplasm	ACC	10.1038/tp.2016.224
Catechol O-methyltransferase	P21964	Down	Metabolism; Energy pathways	Cytoplasm	APC	10.1093/ijnp/pyu015
ATP synthase F(0) complex subunit B1, mitochondrial ATP synthase subunit b	P24539	Up	Metabolism; Energy pathways	Mitochondrion	APC	10.1093/ijnp/pyu015; 10.1038/tp.2016.224

ATP synthase subunit alpha, mitochondrial	P25705	Up	Metabolism; Energy pathways	Mitochondrion	ACC	10.1038/tp.2016.224
NADH-ubiquinone oxidoreductase 75 kDa subunit, mitochondrial, Complex I-75 kDa	P28331	Up	Metabolism; Energy pathways	Mitochondrion	APC; ACC	10.1093/ijnp/pyu015; 10.1038/tp.2016.224
Peroxiredoxin 6	P30041	Up	Metabolism; Energy pathways	Lysosome	DLPFC	10.1038/sj.mp.4002098
Peroxiredoxin 5	P30044	Down	Metabolism; Energy pathways	Mitochondrion	HP	10.1016/j.schres.2015.02.002
Peroxiredoxin 3	P30048	Up	Metabolism; Energy pathways	Mitochondrion	APC; ACC	10.1093/ijnp/pyu015; 10.1038/tp.2016.224
Ubiquinol-cytochrome C reductase complex	P31930	Down	Metabolism; Energy pathways	Mitochondrion	DLPFC	10.1038/sj.mp.4002098
Peroxiredoxin 2	P32119	Down	Metabolism; Energy pathways	Cytoplasm	DLPFC	10.1038/sj.mp.4002098
ATP synthase subunit gamma, mitochondrial	P36542	Up	Metabolism; Energy pathways	Mitochondrion	ACC	10.1038/tp.2016.224
ATP synthase gamma chain (splice isoforms of liver)	P36542	Up	Metabolism; Energy pathways	Mitochondrion	DLPFC	10.1038/sj.mp.4002098
Dihydrolipoyllysine-residue succinyltransferase component of 2-oxoglutarate dehydrogenase complex, mitochondrial	P36957	Up	Metabolism; Energy pathways	Mitochondrion	ACC	10.1038/tp.2016.224
Vacuolar ATP synthase subunit A	P38606	Down	Metabolism; Energy pathways	Endosome	DLPFC	10.1038/mp.2008.7
Malate dehydrogenase	P40926	Down	Metabolism; Energy pathways	Mitochondrion	APC, ACC	10.1093/ijnp/pyu015; 10.1038/tp.2016.224; 10.1016/j.schres.2015.02.002
Trifunctional enzyme subunit alpha, mitochondrial;Long-chain enoyl-CoA hydratase;Long chain 3-hydroxyacyl-CoA dehydrogenase	P40939	Up	Metabolism; Energy pathways	Mitochondrion	ACC	10.1038/tp.2016.224

Glycerol-3-phosphate dehydrogenase, mitochondrial	P43304	Up	Metabolism; Energy pathways	Mitochondrion	ACC	10.1038/tp.2016.224
ATP synthase subunit O, mitochondrial	P48047	Up	Metabolism; Energy pathways		ACC	10.1038/tp.2016.224
4-Trimethylamino- butyraldehyde dehydrogenase	P49189	Up	Metabolism; Energy pathways	Cytoplasm	DLPFC	10.1038/sj.mp.4002098
Aldehyde dehydrogenase 7A1	P49419	Up	Metabolism; Energy pathways		DLPFC	10.1038/sj.mp.4002098
NADH dehydrogenase [ubiquinone] flavoprotein 1, mitochondrial	P49821	Up	Metabolism; Energy pathways	Mitochondrion	ACC	10.1038/tp.2016.224
Glycogen synthase kinase-3 β	P49841	Up	Metabolism; Energy pathways	Cytoplasm	APC	10.1093/ijnp/pyu015
Isocitrate dehydrogenase subunit alpha	P50213	Up	Metabolism; Energy pathways	Mitochondrion	DLPFC	10.1038/sj.mp.4002098
NADH dehydrogenase [ubiquinone] 1 alpha subcomplex subunit 8	P51970	Up	Metabolism; Energy pathways	Mitochondrion	ACC	10.1038/tp.2016.224
ATP-citrate synthase	P53396	Up	Metabolism; Energy pathways	Cytoplasm	ACC	10.1038/tp.2016.224
Trifunctional enzyme subunit beta, mitochondrial;3-ketoacyl-CoA thiolase	P55084	Up	Metabolism; Energy pathways	Mitochondrion	ACC	10.1038/tp.2016.224
NADH dehydrogenase [ubiquinone] 1 alpha subcomplex subunit 6	P56556	Up	Metabolism; Energy pathways	Mitochondrion	ACC	10.1038/tp.2016.224
Triosephosphate isomerase	P60174	Up	Metabolism; Energy pathways	Cytoplasm	APC	10.1093/ijnp/pyu015; 10.1016/j.schres.2015.02.002
Peptidyl-prolyl cis-trans isomerase FKBP3	Q00688	Down	Metabolism; Energy pathways	Nucleus	ACC	10.1038/tp.2016.224
Peroxiredoxin 1	Q06830	Down	Metabolism; Energy pathways	Cytoplasm	DG, ACC	10.1001/archgenpsychiatry.2011.43; 10.1038/tp.2016.224

Peptidyl-prolyl cis-trans isomerase NIMA-interacting 1	Q13526	Down	Metabolism; Energy pathways	Nucleus	ACC	10.1038/tp.2016.224
Tubulin--tyrosine ligase-like protein 12	Q14166	Down	Metabolism; Energy pathways	Nucleus	ACC	10.1038/tp.2016.224
Dihydropyrimidinase- related protein-3	Q14195	Up	Metabolism; Energy pathways	Cytoplasm	DLPFC, CA2/3	10.1038/sj.mp.4002098; 10.1001/archgenpsychiatry.2011.43
Platelet-activating factor acetylhydrolase IB subunit gamma	Q15102	Down	Metabolism; Energy pathways	Cytoplasm	CA2/3	10.1001/archgenpsychiatry.2011.43
[Pyruvate dehydrogenase [lipoamide]] kinase isozyme 2, mitochondrial	Q15119	Up	Metabolism; Energy pathways	Mitochondrion	ACC	10.1038/tp.2016.224
Inorganic pyrophosphate	Q15181	Down	Metabolism; Energy pathways	Cytoplasm	DLPFC	10.1038/sj.mp.4002098
2,4-dienoyl-CoA reductase, mitochondrial	Q16698	Up	Metabolism; Energy pathways	Mitochondrion	ACC	10.1038/tp.2016.224
NADH dehydrogenase [ubiquinone] 1 alpha subcomplex subunit 5	Q16718	Up	Metabolism; Energy pathways	Mitochondrion	ACC	10.1038/tp.2016.224
NADH dehydrogenase [ubiquinone] 1 alpha subcomplex subunit 9, mitochondrial	Q16795	Up	Metabolism; Energy pathways	Mitochondrion	ACC	10.1038/tp.2016.224
Serine/threonine-protein phosphatase PGAM5, mitochondrial	Q96HS1	Up	Metabolism; Energy pathways	Cytosol	ACC	10.1038/tp.2016.224
Prostaglandin E synthase 2;Prostaglandin E synthase 2 truncated form	Q9H7Z7	Up	Metabolism; Energy pathways	Nucleus	ACC	10.1038/tp.2016.224
Acyl-CoA dehydrogenase family member 9, mitochondrial	Q9H845	Up	Metabolism; Energy pathways	Mitochondrion	ACC	10.1038/tp.2016.224
NADH dehydrogenase [ubiquinone] 1 beta subcomplex subunit 11, mitochondrial	Q9NX14	Up	Metabolism; Energy pathways		ACC	10.1038/tp.2016.224
NADH dehydrogenase [ubiquinone] 1 alpha subcomplex subunit 13	Q9P0J0	Up	Metabolism; Energy pathways	Mitochondrion	ACC	10.1038/tp.2016.224

NADH-ubiquinone oxidoreductase (13 kDa)-B subunit	Q9UI09	Up	Metabolism; Energy pathways	Mitochondrion	DLPFC, ACC	10.1038/mp.2008.7; 10.1038/tp.2016.224
Acyl-coenzyme A thioesterase 9, mitochondrial	Q9Y305	Up	Metabolism; Energy pathways	Mitochondrion	ACC	10.1038/tp.2016.224
NADH dehydrogenase [ubiquinone] 1 beta subcomplex subunit 9	Q9Y6M9	Up	Metabolism; Energy pathways	Mitochondrion	ACC	10.1038/tp.2016.224

Table 4: Compilation of data from the SCZ, MDD and BPD used to construct the Venn Diagram

Protein	Acession	SCZ	MDD	BPD
Citrate synthase, mito	O75390	X	X	X
ATP synthase beta chain	P06576	X	X	X
Aldolase C, fructose-bisphosphate (ALDOC)	P09972	X	X	X
Ubiquinol-cytochrome-c reductase complex core protein I	P31930	X	X	X
Malate dehydrogenase, mitochondrial precursora	P40926	X	X	X
NADH dehydrogenase [ubiquinone] 1 alpha subcomplex subunit 2	O43678		X	X
NADH dehydrogenase [ubiquinone] iron-sulfur protein 5	O43920		X	X
Peroxiredoxin 3	P30048		X	X
NADH dehydrogenase Ubiquinone 1 alpha subcomplex subunit 6	P56556		X	X
Dihydropyrimidinase- related protein-3	Q14195		X	X
NADH dehydrogenase [ubiquinone] 1 beta subcomplex subunit 11, mitochondrial	Q9NX14		X	X
NADH dehydrogenase [ubiquinone] 1 alpha subcomplex subunit 13	Q9P0J0		X	X
Carbonic anhydrase	P00915	X	X	
Carbonic anhydrase 2	P00918	X	X	
Aldolase A, fructose-bisphosphate (ALDOA)	P04075	X	X	
Aldehydedehydrogenase, mitochondrial	P05091	X	X	
Glutamine synthetase	P15104	X	X	

Carbonyl reductase 1	P16152	X	X	
Phosphoglucomutase-1	P36871	X	X	
Succinyl coenzyme A:3 ketoacid CoA transferase	P55809	X	X	
Glutathione transferase omega	P78417	X	X	
Hydroxyacylglutathione hydrolase (Glx II)	Q16775	X	X	
ATP synthase subunit g mitochondrial short ATPase	O75964		X	
Glycogen phosphorylase, liver form	P06737		X	
Beta-hexosaminidase subunit beta	P07686		X	
Cytochrome c oxidase subunit 5B mitochondrial	P10606		X	
Cytochrome c oxidase subunit 4 isoform 1 mitochondrial	P13073		X	
Cytochrome c oxidase polypeptide 7A2 mitochondrial	P14406		X	
Serine--pyruvate aminotransferase	P21549		X	
Alpha-(1,3)-fucosyltransferase 4	P22083		X	
Platelet-activating factor acetylhydrolase IB subunit alpha	P43034		X	
Cytochrome b-c1 complex subunit Rieske, mitochondrial	P47985		X	
Biotin protein ligase	P50747		X	
Succinyl-CoA ligase [ADP/GDP-forming] subunit alpha, mitochondrial	P53597		X	
NADH dehydrogenase [ubiquinone] flavoprotein 3, mitochondrial	P56181		X	
ATP synthase subunit e mitochondrial	P56385		X	
Cytochrome c	P99999		X	
Glucosamine fruct 6 phos aminotransferase 1	Q06210		X	
Neutrophil cytosol factor 4	Q15080		X	
NADH dehydrogenase [ubiquinone] 1 alpha subcomplex subunit 11	Q86Y39		X	
Beta enolase	P13929		X	
D-3 Phosphoglycerate dehydrogenase	O43175	X		X
NADH dehydrogenase [ubiquinone] iron-sulfur protein 6, mitochondrial	O75380	X		X
NADH-ubiquinone oxidoreductase 30 kDa subunit	O75489	X		X

ATP synthase, H+ transporting, mitochondrial F0 complex, subunit d isoform a	O75947	X		X
Dimethylarginine dimethylaminohydrolase 1 (DDAH1)	O94760	X		X
CDP-DAG synthase 2	O95674	X		X
Glutamate dehydrogenase	P00367	X		X
Superoxide dismutase [Cu-Zn]	P00441	X		X
Alpha-enolase	P06733	X		X
Pyruvate dehydrogenase E1 component subunit alpha, somatic form, mitochondrial	P08559	X		X
Gamma enolase	P09104	X		X
Glutathione S-Transferase Pi 1	P09211	X		X
2',3'-cyclic nucleotide 3' phosphodiesterase (CNP)	P09543	X		X
Dihydrolipoyl dehydrogenase, mitochondrial precursor	P09622	X		X
Creatine kinase B chain	P12277	X		X
Pyruvate kinase	P14618	X		X
Phosphofructokinase 1; phosphohexokinase	P17858	X		X
Glutathione S-transferase Mu 3	P21266	X		X
Catechol O-methyltransferase	P21964	X		X
ATP synthase subunit alpha, mitochondrial	P25705	X		X
NADH-ubiquinone oxidoreductase 75 kDa subunit	P28331	X		X
Peroxiredoxin 6	P30041	X		X
Peroxiredoxin 5	P30044	X		X
Peroxiredoxin 2	P32119	X		X
ATP synthase, gamma	P36542	X		X
V-type proton ATPase catalytic subunit A	P38606	X		X
Isocitrate dehydrogenase subunit alpha	P50213	X		X
Triosephosphate isomerase	P60174	X		X
Peroxiredoxin 1	Q06830	X		X
NADH dehydrogenase [ubiquinone] 1 alpha subcomplex subunit 5	Q16718	X		X

NADH-ubiquinone oxidoreductase 39 kDa subunit	Q16795	X		X
NADH dehydrogenase [ubiquinone] 1 beta subcomplex subunit 9	Q9Y6M9	X		X
Hydroxyacylglutathione hydrolase, mitochondrial	H3BPK3			X
ATPase (transitional ER)	O14983			X
Proline dehydrogenase 1, mito	O43272			X
NADH dehydrogenase [ubiquinone] 1 beta subcomplex subunit 3	O43676			X
Isocitrate dehydrogenase [NAD] subunit beta, mitochondrial	O43837			X
NADH dehydrogenase [ubiquinone] iron-sulfur protein 2, mitochondrial	O75306			X
NADH dehydrogenase [ubiquinone] 1 beta subcomplex subunit 1	O75438			X
NADH dehydrogenase [ubiquinone] 1 beta subcomplex subunit 4	O95168			X
NADH dehydrogenase [ubiquinone] 1 alpha subcomplex subunit 7	O95182			X
NADH dehydrogenase [ubiquinone] 1 subunit C2;NADH dehydrogenase [ubiquinone] 1 subunit C2, isoform 2	O95298			X
NADH dehydrogenase [ubiquinone] 1 alpha subcomplex subunit 10, mitochondrial	O95299			X
Aspartate aminotransferase, mitochondrial	P00505			X
Phosphoglycerate kinase 1	P00558			X
NADH-ubiquinone oxidoreductase chain 4	P03905			X
NADH-ubiquinone oxidoreductase chain 5	P03915			X
Catalase	P04040			X
Glucose-6-phosphate isomerase	P06744			X
Cytochrome b-c1 complex subunit 6, mitochondrial	P07919			X
Cytochrome c1, heme protein, mitochondrial	P08574			X
Dihydrolipoyllysine-residue acetyltransferase component of pyruvate dehydrogenase complex, mitochondrial	P10515			X
Pyruvate dehydrogenase E1 component subunit beta, mitochondrial	P11177			X
Glucose-6-phosphate 1-dehydrogenase	P11413			X
NAD(P)H Dehydrogenase, Quinone 2	P16083			X
NADH dehydrogenase [ubiquinone] flavoprotein 2, mitochondrial	P19404			X
ATP synthase F(0) complex subunit B1, mitochondrial ATP synthase subunit b	P24539			X

Dihydrolipoyllysine-residue succinyltransferase component of 2-oxoglutarate dehydrogenase complex, mitochondrial	P36957			X
Trifunctional enzyme subunit alpha, mitochondrial;Long-chain enoyl-CoA hydratase;Long chain 3-hydroxyacyl-CoA dehydrogenase	P40939			X
Glycerol-3-phosphate dehydrogenase, mitochondrial	P43304			X
ATP synthase subunit O, mitochondrial	P48047			X
4-Trimethylamino- butyraldehyde dehydrogenase	P49189			X
Aldehyde dehydrogenase 7A1	P49419			X
NADH dehydrogenase [ubiquinone] flavoprotein 1, mitochondrial	P49821			X
Glycogen synthase kinase-3 β	P49841			X
NADH dehydrogenase [ubiquinone] 1 alpha subcomplex subunit 8	P51970			X
ATP-citrate synthase	P53396			X
Trifunctional enzyme subunit beta, mitochondrial;3-ketoacyl-CoA thiolase	P55084			X
Peptidyl-prolyl cis-trans isomerase FKBP3	Q00688			X
Peptidyl-prolyl cis-trans isomerase NIMA-interacting 1	Q13526			X
Tubulin--tyrosine ligase-like protein 12	Q14166			X
Platelet-activating factor acetylhydrolase IB subunit gamma	Q15102			X
[Pyruvate dehydrogenase [lipoamide]] kinase isozyme 2, mitochondrial	Q15119			X
Inorganic pyrophosphate	Q15181			X
2,4-dienoyl-CoA reductase, mitochondrial	Q16698			X
Serine/threonine-protein phosphatase PGAM5, mitochondrial	Q96HS1			X
Prostaglandin E synthase 2;Prostaglandin E synthase 2 truncated form	Q9H7Z7			X
Acyl-CoA dehydrogenase family member 9, mitochondrial	Q9H845			X
NADH-ubiquinone oxidoreductase (13 kDa)-B subunit	Q9UI09			X
Acyl-coenzyme A thioesterase 9, mitochondrial	Q9Y305			X
Dihydropyrimidinase-like 4 (DPYSL4)	O14531	X		
NADH-ubiquinone oxidoreductase SGDH subunit	O43674	X		
Carbonyl reductase 3 (CBR3)	O75828	X		
6-Phosphoglu- conolactonase	O95336	X		

Cytochrome c oxidase subunit 2	P00403	X		
Adenylate kinase 1	P00568	X		
Glyceraldehyde-3-phosphate dehydrogenase	P04406	X		
L-lactate dehydrogenase B chain	P07195	X		
Dihydropteridine reductase	P09417	X		
Esterase D/formylglutathione hydrolase (ESD)	P10768	X		
Glycogen phosphorylase, brain form	P11216	X		
Glycogen phosphorylase, muscle form	P11217	X		
Imp dehydrogenase 2	P12268	X		
Creatine kinase ubiquitous mitochondrial	P12532	X		
Aspartate--tRNA ligase, Cytoplasmic	P14868	X		
Phosphoglycerate mutase 2	P15259	X		
Phosphoglycerate mutase 1	P18669	X		
Hexokinase 1 (HK1)	P19367	X		
Acetoacetyl-CoA thiolase	P24752	X		
Inositol monophosphatase (IMPA1)	P29218	X		
Transketolase	P29401	X		
Delta-1-pyrroline-5-carboxylate dehydrogenase, mitochondrial	P30038	X		
Biliverdin reductase B	P30043	X		
Aldehyde dehydrogenase	P30838	X		
Malate dehydrogenase 1, NAD (soluble) (MDH1)	P40925	X		
Isoleucyl tRNA synthetase, Cytoplasmic	P41252	X		
N- ethylmaleimide-sensitive factor	P46459	X		
Isocitrate dehydrogenase 2 (NADP+), mitochondrial variant	P48735	X		
Serine--tRNA ligase, Cytoplasmic	P49591	X		
Palmitoyl protein thioesterase 1	P50897	X		
Tyrosyl-ttRNA synthetase (YARS)	P54577	X		

Phosphoribosyl pyrophosphate synthase isoform I	P60891	X		
Oxoglutarate (alpha-ketoglutarate) dehydrogenase	Q02218	X		
Fk506-binding protein 4	Q02790	X		
Peroxiredoxin 4	Q13162	X		
Cytoplasmic dynein 1 heavy chain 1, cytosolic	Q14204	X		
Malic enzyme 3	Q16798	X		
Ectonucleotide pyrophosphatase/phosphodiesterase family member 6	Q6UWR7	X		
Pyridoxal phosphatase	Q96GD0	X		
Inositol polyphosphate 4-phosphatase type I	Q96PE3	X		
Aconitase 2, mitochondrial	Q99798	X		
Acetyl CoA acetyltransferase cytosolic	Q9BWD1	X		
Methyltransferase-like protein 7A; protein AAM-B	Q9H8H3	X		
Lambda-crystallin homolog	Q9Y2S2	X		
Guanine deaminase	Q9Y2T3	X		

Table 5: Compilation of demographic and clinical data from the samples used in SCZ studies

Article	Sample size (control:patient)	Brain region	Drug treatment Yes/No (control:patient)	Average age in years (control:patient)	Gender M/F (control:patient)	Brain pH (control:patient)
Prabakaran et al. 2004	10:10	FC	0/10:10/0	45,6:39,6	7/3:8/2	6,49:6,43
Clark et al. 2006	10:10	ACC	0/10:10/0	48,6:48	8/2:8/2	6,45:6,39
Beasley et al. 2006	15:15	ACC	0/15:15/0	48,1:44,2	9/6:9/6	
Sivagnanasundaram et al. 2007	10:10	CC	0/10:10/0	48,6:48	8/2:8/2	6,47:6,4
Pennington et al. 2008a	30:34	DLPFC	0/30:34/0	44:42	23/7:25/9	6,59:6,47
Pennington et al. 2008b	13:12	IC	0/13:12/0	50,7:45,8	8/5:8/4	6,3:6,3
English et al. 2009	35:35	DLPFC	0/35:35/0	44,2:42,6	26/9:26/9	6,6:6,5
Martins-De-Souza et al. 2009a	7:9	DLPFC	0/7:9/0	62,8:71,1	5/2:5/4	6,68:6,74

Martins-De-Souza et al. 2009b	6:9	WA	0/6:9/0	64:66,7	6/0:3/6	6,8:6,76
Martins-de-Souza et al. 2009c	7:9	FC	0/7:9/0	62,8:71	5/2:5/4	
Martins-de-Souza et al. 2009d	4:5	ATL	0/4:5/0	72,2:68	3/1:4/1	6,8:6,7
Martins-de-Souza et al. 2010a	8:11	MDT	0/8:11/0	64,8:65,9	6/2:5/6	6,62:6,63
Martins-de-Souza et al. 2010b	8:11	ACC	0/8:11/0	64,8:65,9	6/8:5/6	6,65:6,6
Föcking et al. 2014	20:20	ACC	0/20:20/0	43,6:41,9	15/5:16/4	6,59:6,48
Saia-Cereda et al. 2015	7:9	CC	0/7:9/0	64,7:68,3	5/2:5/4	6,62:6,62
Schubert et al. 2015	10:10	HP	0/10:10/0	40,4:41,1	6/4:6/4	6,6:6,58
Saia-Cereda et al. 2016	5:5	CC	0/5:5/0	59,2:66,2	5/0:4/1	6,72:6,68
Gottschalk et al. 2015	23:23	APC	0/23:23/0	42,7:41	8/15:8/15	6,59:6,53
Johnston-Wilson et al. 2000	23:24	FC				
Föcking et al. 2011	20:20	HP	0/20:20/0	43,6:41,9	15/5:16/4	6,59:6,48
Behan et al. 2009	20:20	DLPFC	0/20:20/0	44,1:46,8	14/6:11/9	6,5:6,6
Wesseling et al. 2014	22:22	APC	0/22:22/0	42,3:40,8	8/14:8/14	6,59:6,53

Table 6: Compilation of demographic and clinical data from the samples used in MDD studies

Article	Sample size (control:patient)	Brain region	Drug treatment Yes/No (control:patient)	Average age in years (control:patient)	Gender M/F (control:patient)	Brain pH (control:patient)
Johnston-Wilson et al. 2000	23:19	FC	0/23:19/0			
Beasley et al. 2006	15:15	ACC	0/15:15/0	48,1:46,4	9/6:9/6	
Martins-de-Souza et al. 2012a	12:24	DLPFC	0/12:24/0	47:42	8/4:13/11	6,6:6,7
Martins-de-Souza et al. 2012b	12:24	DLPFC	0/12:24/0	47:42	8/4:13/11	6,6:6,7
Gottschalk et al. 2015	23:23	APC	0/23:23/0	42,6:41,2	8/15:12/11	6,59:6,65
Stelzhammer et al. 2015	15:13	Pituitary gland	0/15:13/0	48:46,3	6/9:6/7	6,27:6,17
Wesseling et al. 2014	22:22	APC	0/22:22/0	42,3:42,3	8/14:13/9	6,59:6,63

Table 7: Compilation of demographic and clinical data from the samples used in BPD studies

Article	Sample size (control:patient)	Brain region	Drug treatment Yes/No (control:patient)	Average age in years (control:patient)	Gender M/F (control:patient)	Brain pH (control:patient)
Pennington et al. 2008a	30:32	DLPFC	0/30:32/0	44:45,1	7/23:15/17	6,59:6,42
Behan et al. 2009	20:20	DLPFC	0/20:20/0	44,1:41	14/6:14/6	6,5:6,5
Föcking et al. 2011	20:20	HP	0/20:20/0	43,6:45,7	15/5:10/10	6,59:6,41
Wesseling et al. 2014	22:23	APC	0/22:23/0	42,3:42,4	8/14:13/10	6,59:6,43
Föcking et al. 2016	20/16	ACC	0/20:16/0	43,6:46,6	15/5:10/6	6,59:6,46
Schubert et al. 2015	20:20	HP	0/20:20/0	43,6:45,7	15/5:10/10	6,59:6,41
Beasley et al. 2006	15:15	ACC	0/15:15/0	48,1:42,3	9/6:9/6	
Stelzhammer et al. 2015	15:13	Pituitary gland	0/15:13:0	48:41,5	6/9:5/7	6,27:6,19
Gottschalk et al. 2015	23:23	APC	0/23:23/0	42,7:42,4	8/15:13/10	6,59:6,43
Johnston-Wilson et al. 2000	23:23	FC	0/23:23/0			

Tabel 8: List of proteins found altered in the mitochondrial and nuclear proteomes of NSCs

Accession	Description	Biological Process	Cellular component	p-Value	SCZ/CTRL ratio	Fraction
A5YKK6	CCR4-NOT transcription complex subunit 1	Transcription	Nucleus	0,0009237	1,595361022	Mitochondrion
O00264	Membrane-associated progesterone receptor component 1	Cell communication	Plasma membrane	0,0294786	1,777994311	Mitochondrion
O43615	Mitochondrial import inner membrane translocase subunit TIM44	Transport	Mitochondrion	0,0045313	0,431193395	Mitochondrion
O43776	Asparagine--tRNA ligase_ cytoplasmic	Protein metabolism	Cytoplasm	0,0414845	0,77188705	Mitochondrion
O60749	Sorting nexin-2	Transport	Endosome	0,0075918	0,769199618	Mitochondrion
O75390	Citrate synthase_ mitochondrial	Metabolism; Energy pathways	Mitochondrion	0,0428382	0,793084926	Mitochondrion
O75534	Cold shock domain-containing protein E1	Regulation of gene expression	Cytoplasm	0,0474248	3,734627541	Mitochondrion
O75569	Interferon-inducible double-stranded RNA-dependent protein kinase activator A	Regulation of nucleotide metabolism	Cytoplasm	0,0468766	1,733078696	Mitochondrion
O75643	U5 small nuclear ribonucleoprotein 200 kDa helicase	Regulation of nucleotide metabolism	Mitochondrion; Nucleus	0,0489081	1,482607097	Mitochondrion
O95202	Mitochondrial proton/calcium exchanger protein	Cell communication	Mitochondrion	0,0119772	0,514952979	Mitochondrion
O95573	Long-chain-fatty-acid--CoA ligase 3	Fatty acid metabolism	Peroxisome; Mitochondrion	0,0035945	0,664969567	Mitochondrion
P05062	Fructose-bisphosphate aldolase B	Metabolism; Energy pathways	Cytoplasm	0,001422	0,763814165	Mitochondrion
P05091	Aldehyde dehydrogenase_ mitochondrial	Metabolism; Energy pathways	Mitochondrion	0,047609	1,5275866	Mitochondrion
P05186	Alkaline phosphatase_ tissue-nonspecific isozyme	Metabolism; Energy pathways	Plasma membrane	0,0343502	0,464951135	Mitochondrion
P06576	ATP synthase subunit beta_ mitochondrial	Metabolism; Energy pathways	Mitochondrion	0,0001346	0,7809306	Mitochondrion
P08133	Annexin A6	Cell communication; Signal transduction	Endoplasmic reticulum; Mitochondrion	0,002184	0,324697452	Mitochondrion
P08559	Pyruvate dehydrogenase E1 component subunit alpha_ somatic form_ mitochondrial	Metabolism; Energy pathways	Mitochondrion	0,0001175	0,790939034	Mitochondrion
P09110	3-ketoacyl-CoA thiolase_ peroxisomal	Metabolism; Energy pathways	Peroxisome; Mitochondrion	0,0185633	0,61827695	Mitochondrion
P11177	Pyruvate dehydrogenase E1 component subunit beta_ mitochondrial	Metabolism; Energy pathways	Mitochondrion	0,0021535	0,737384348	Mitochondrion
P12268	Inine-5'-monophosphate dehydrogenase 2	Metabolism; Energy pathways	Cytoplasm	0,0150328	0,547608564	Mitochondrion
P12814	Alpha-actinin-1	Cell growth	Cytoplasm;	0,0146274	0,766394171	Mitochondrion

			Mitochondrion			
P13591	Neural cell adhesion molecule 1	Cell communication	Plasma membrane	0,0068742	1,575555504	Mitochondrion
P13637	Sodium/potassium-transporting ATPase subunit alpha-3	Transport	Plasma membrane	0,014996	1,758689192	Mitochondrion
P13645	Keratin_ type I cytkeletal 10	Cell growth	Cytoplasm	0,0403162	3,361262859	Mitochondrion
P13674	Prolyl 4-hydroxylase subunit alpha-1	Metabolism; Energy pathways	Endoplasmic reticulum	0,0225059	0,67316565	Mitochondrion
P14868	Aspartate--tRNA ligase_ cytoplasmic	Metabolism; Energy pathways	Cytoplasm	0,0002214	0,713013807	Mitochondrion
P16401	Histone H1.5	Regulation of nucleotide metabolism	Mitochondrion; Nucleus	0,0261905	1,855863056	Mitochondrion
P18206	Vinculin	Cell growth	Cytoplasm; Nucleus	0,0127546	0,498951774	Mitochondrion
P22695	Cytochrome b-c1 complex subunit 2_ mitochondrial	Metabolism; Energy pathways	Mitochondrion	0,0056558	0,770080063	Mitochondrion
P26232	Catenin alpha-2	Cell growth	Cytoplasm	0,0491726	1,442861808	Mitochondrion
P26639	Threonine--tRNA ligase_ cytoplasmic	Metabolism; Energy pathways	Cytoplasm; Mitochondrion	0,0221601	0,509631713	Mitochondrion
P31930	Cytochrome b-c1 complex subunit 1_ mitochondrial	Metabolism; Energy pathways	Mitochondrion	0,0166592	0,443311936	Mitochondrion
P32322	Pyrroline-5-carboxylate reductase 1_ mitochondrial	Metabolism; Energy pathways	Cytoplasm; Mitochondrion	0,0036904	0,564038754	Mitochondrion
P35637	RNA-binding protein FUS	RNA localization	Mitochondrion; Nucleus	0,0360421	1,304864405	Mitochondrion
P36542	ATP synthase subunit gamma_ mitochondrial	Metabolism; Energy pathways	Mitochondrion	0,0078833	0,825763421	Mitochondrion
P37837	Transaldolase	Metabolism; Energy pathways	Nucleus	0,0222407	4,88239712	Mitochondrion
P38646	Stress-70 protein_ mitochondrial	Protein metabolism	Mitochondrion	0,0151956	0,628961503	Mitochondrion
P40926	Malate dehydrogenase_ mitochondrial	Metabolism; Energy pathways	Mitochondrion	0,0401738	0,562047494	Mitochondrion
P41091	Eukaryotic translation initiation factor 2 subunit 3	Protein metabolism	Cytoplasm	0,0238845	1,836136991	Mitochondrion
P42696	RNA-binding protein 34	Regulation of nucleotide metabolism	Nucleus	0,0360053	0,841860042	Mitochondrion
P42765	3-ketoacyl-CoA thiolase_ mitochondrial	Metabolism; Energy pathways	Mitochondrion	0,0027423	0,496185903	Mitochondrion
P47897	Glutamine--tRNA ligase	Metabolism; Energy pathways	Cytoplasm	0,0214663	0,76349697	Mitochondrion
P50454	Serpin H1	Protein metabolism	Endoplasmic reticulum	0,0264448	0,545857348	Mitochondrion
P54136	Arginine--tRNA ligase_ cytoplasmic	Protein metabolism	Cytoplasm	0,0002228	0,514482809	Mitochondrion
P54886	Delta-1-pyrroline-5-carboxylate synthase	Metabolism; Energy pathways	Mitochondrion	0,0144135	0,657968022	Mitochondrion

P55010	Eukaryotic translation initiation factor 5	Protein metabolism	Cytoplasm	0,0383736	0,733990998	Mitochondrion
P55011	Solute carrier family 12 member 2	Transport	Plasma membrane	0,0111084	1,183295731	Mitochondrion
P55084	Trifunctional enzyme subunit beta_ mitochondrial	Metabolism; Energy pathways	Mitochondrion	0,0024346	0,80172129	Mitochondrion
P56134	ATP synthase subunit f_ mitochondrial	Electron transport	Mitochondrion	0,002477	0,573219618	Mitochondrion
P61221	ATP-binding cassette sub-family E member 1	Transport	Cytoplasm; Mitochondrion	0,0134555	0,791770593	Mitochondrion
Q00325	Phosphate carrier protein_ mitochondrial	Transport	Mitochondrion	0,0205585	0,74524321	Mitochondrion
Q02246	Contactin-2	Cell communication	Plasma membrane	0,0489403	2,218740561	Mitochondrion
Q04637	Eukaryotic translation initiation factor 4 gamma 1	Protein metabolism	Cytoplasm	0,0041499	1,80805722	Mitochondrion
Q07666	KH domain-containing_ RNA-binding_ signal transduction-associated protein 1	Regulation of nucleotide metabolism	Nucleus	0,0191996	0,751173806	Mitochondrion
Q08211	ATP-dependent RNA helicase A	Regulation of nucleotide metabolism	Nucleus	0,022207	1,765286881	Mitochondrion
Q08945	FACT complex subunit SSRP1	Regulation of nucleotide metabolism	Nucleus	0,0009606	0,428124422	Mitochondrion
Q13867	Bleomycin hydrolase	Metabolism; Energy pathways	Cytoplasm	0,0178838	1,879747103	Mitochondrion
Q15758	Neutral amino acid transporter B(0)	Transport	Plasma membrane	0,0486491	0,674360422	Mitochondrion
Q16891	MICOS complex subunit MIC60	Cell growth	Mitochondrion	0,0486491	0,583447916	Mitochondrion
Q2VWP7	Protogenin		Plasma membrane	0,015688	0,363221456	Mitochondrion
Q53H12	Acylglycerol kinase_ mitochondrial	Cell communication	Mitochondrion	0,0413518	0,380615229	Mitochondrion
Q5IJ48	Protein crumbs homolog 2	Cell growth	Plasma membrane	4,555E-05	2,143476668	Mitochondrion
Q5T9A4	ATPase family AAA domain-containing protein 3A	Metabolism; Energy pathways	Mitochondrion	0,001546	0,502840027	Mitochondrion
Q6UB35	Monofunctional C1-tetrahydrofolate synthase_ mitochondrial	Metabolism	Mitochondrion	0,0011758	0,627346579	Mitochondrion
Q8WVM8	Sec1 family domain-containing protein 1	Transport	Plasma membrane	0,0078008	0,803623286	Mitochondrion
Q92692	Nectin-2	Cell communication	Plasma membrane	0,0047758	0,523042969	Mitochondrion
Q92896	Golgi apparatus protein 1		Golgi apparatus; Mitochondrion	0,0274554	0,764505822	Mitochondrion
Q92900	Regulator of nonsense transcripts 1	Regulation of translation	Cytoplasm	0,0114718	1,55156945	Mitochondrion
Q96A65	Exocyst complex component 4	Transport	Plasma membrane	0,0070869	1,810996959	Mitochondrion
Q96AE4	Far upstream element-binding protein 1	Regulation of nucleotide	Nucleus	0,0067549	0,583002797	Mitochondrion

		metabolism				
Q96JA1	Leucine-rich repeats and immunoglobulin-like domains protein 1	Cell communication	Plasma membrane	0,0390648	0,528261854	Mitochondrion
Q96L92	Sorting nexin-27	Vesicle-mediated transport	Cytoplasm	0,0494936	0,708765926	Mitochondrion
Q96PQ0	VPS10 domain-containing receptor SorCS2	Cell communication	Plasma membrane	0,0076851	4,348269313	Mitochondrion
Q9BSJ8	Extended synaptotagmin-1	Cell communication	Mitochondrion; Plasma membrane	0,0283158	0,676389776	Mitochondrion
Q9H2U1	ATP-dependent RNA helicase DHX36	Regulation of nucleotide metabolism	Plasma membrane	0,0445643	0,594746642	Mitochondrion
Q9H9A5	CCR4-NOT transcription complex subunit 10			0,0152181	1,288597547	Mitochondrion
Q9H9B4	Sideroflexin-1	Transport	Mitochondrion	0,0266244	0,418704228	Mitochondrion
Q9NYU2	UDP-glucose:glycoprotein glucyltransferase 1	Metabolism; Energy pathways	Endoplasmic reticulum; Mitochondrion	0,0225234	1,927624966	Mitochondrion
Q9UDR5	Alpha-aminoadipic semialdehyde synthase_ mitochondrial	Metabolism; Energy pathways	Mitochondrion	0,002785	1,443959595	Mitochondrion
Q9UH03	Neuronal-specific septin-3	Cell communication	Plasma membrane	0,0368229	1,726913948	Mitochondrion
Q9UHB9	Signal recognition particle subunit SRP68	Protein metabolism	Nucleus	0,0091205	0,758969829	Mitochondrion
Q9UKV8	Protein argonaute-2	Protein metabolism	Cytoplasm	0,0219266	2,285783341	Mitochondrion
Q9UQE7	Structural maintenance of chromosomes protein 3	DNA repair	Mitochondrion; Nucleus	0,0117422	1,541625914	Mitochondrion
Q9Y4W6	AFG3-like protein 2	Transport	Mitochondrion	0,006184	1,249977102	Mitochondrion
O00217	NADH dehydrogenase [ubiquinone] iron-sulfur protein 8_ mitochondrial	Metabolism; Energy pathways	Mitochondrion; Nucleus	0,0306479	0,605321736	Nucleus
O00231	26S proteasome non-ATPase regulatory subunit 11	Protein metabolism	Nucleus	0,0043536	1,281018966	Nucleus
O00299	Chloride intracellular channel protein 1	Transport	Nucleus	0,021777	0,756513069	Nucleus
O00410	Importin-5	Transport	Cytoplasm; Nucleus	0,0424261	1,440367442	Nucleus
O00487	26S proteasome non-ATPase regulatory subunit 14	Protein metabolism	Cytoplasm; Nucleus	0,0120854	0,844216146	Nucleus
O14579	Coatomer subunit epsilon	Transport	Cytoplasm	0,017233	0,753035955	Nucleus
O14980	Exportin-1	Cell communication	Nucleus	0,0051921	0,722022511	Nucleus
O15042	U2 snRNP-associated SURP motif-containing protein	RNA binding	Nucleus	0,0017928	1,76349104	Nucleus
O15523	ATP-dependent RNA helicase DDX3Y	Regulation of nucleotide	Nucleus	0,001938	1,444579811	Nucleus

		metabolism				
O43347	RNA-binding protein Musashi homolog 1	Regulation of nucleotide metabolism	Cytoplasm	0,0174603	1,31910785	Nucleus
O43399	Tumor protein D54	Cell proliferation	Cytoplasm	0,0020641	0,872310662	Nucleus
O60664	Perilipin-3	Transport	Cytoplasm	0,0056275	0,64528828	Nucleus
O60716	Catenin delta-1	Cell communication	Nucleus	0,0352407	0,796004824	Nucleus
O75376	Nuclear receptor corepressor 1	Regulation of nucleotide metabolism	Nucleus	0,0074645	0,661967125	Nucleus
O75400	pre-mRNA processing factor 40 homolog A	Regulation of nucleotide metabolism	Nucleus	0,0204413	1,446789233	Nucleus
O75521	Enoyl-CoA delta isomerase 2_ mitochondrial	Fatty acid metabolism	Peroxisome	0,0009043	0,59778388	Nucleus
O75643	U5 small nuclear ribonucleoprotein 200 kDa helicase	Regulation of nucleotide metabolism	Mitochondrion; Nucleus	0,0055332	1,842977912	Nucleus
O75874	Isocitrate dehydrogenase [NADP] cytoplasmic	Metabolism; Energy pathways	Cytoplasm	0,0046762	1,472463678	Nucleus
O76094	Signal recognition particle subunit SRP72	Protein metabolism	Nucleus	0,0007327	0,785876404	Nucleus
O95292	Vesicle-associated membrane protein-associated protein B/C	Transport	Plasma membrane	0,0107871	0,768013028	Nucleus
O95373	Importin-7	Transport	Nucleus	0,0002003	1,929225039	Nucleus
O95831	Apoptis-inducing factor 1_ mitochondrial	Cell communication	Mitochondrion; Nucleus	3,864E-06	0,729113552	Nucleus
O95865	N(G)_N(G)-dimethylarginine dimethylaminohydrolase 2	Metabolism; Energy pathways	Cytoplasm	0,0064616	1,481259417	Nucleus
O96008	Mitochondrial import receptor subunit TOM40 homolog	Transport	Mitochondrion	0,0067282	0,784513783	Nucleus
O96019	Actin-like protein 6A	Regulation of nucleotide metabolism	Nucleus	0,0014446	1,222279174	Nucleus
P02768	Serum albumin			0,0137512	1,967135865	Nucleus
P05186	Alkaline phosphatase_ tissue-nonspecific isozyme	Metabolism; Energy pathways	Plasma membrane	0,0489548	0,654321155	Nucleus
P05388	60S acidic ribomal protein P0	Protein metabolism	Nucleus; Ribosome	4,641E-05	0,873161677	Nucleus
P06493	Cyclin-dependent kinase 1	Cell communication	Nucleus	0,0382183	1,24979603	Nucleus
P06748	Nucleophosmin	Protein metabolism	Nucleus	0,012087	0,718519823	Nucleus
P07195	L-lactate dehydrogenase B chain	Metabolism; Energy pathways	Cytoplasm	0,0100615	1,240578646	Nucleus
P07196	Neurofilament light polypeptide	Cell growth	Cytoplasm	0,0253412	0,761379621	Nucleus

P07305	Histone H1.0	Regulation of nucleotide metabolism	Nucleus	0,0155675	0,414628093	Nucleus
P07355	Annexin A2	Cell communication; Signal transduction	Nucleus	0,0199679	0,386828239	Nucleus
P08133	Annexin A6	Cell communication; Signal transduction	Endoplasmic reticulum	0,0063335	0,533839253	Nucleus
P08195	4F2 cell-surface antigen heavy chain	Transport	Plasma membrane	0,0071986	0,741756518	Nucleus
P09211	Glutathione S-transferase P	Metabolism; Energy pathways	Cytoplasm	0,0066129	1,441695885	Nucleus
P09874	Poly [ADP-ribe] polymerase 1	Protein metabolism	Nucleus	0,0233723	1,839690387	Nucleus
P09936	Ubiquitin carboxyl-terminal hydrolase isozyme L1	Protein metabolism	Cytoplasm	0,0199742	1,349334094	Nucleus
P0DP23	Calmodulin-1	Cell communication	Cytoplasm; Nucleus	0,0173871	2,059206212	Nucleus
P10809	60 kDa heat shock protein_ mitochondrial	Apoptosis	Cytoplasm; Mitochondrion	0,0121135	0,737504613	Nucleus
P11137	Microtubule-associated protein 2	Cell growth	Cytoplasm	0,0405392	1,391334025	Nucleus
P11216	Glycogen phosphorylase_ brain form	Metabolism; Energy pathways	Cytoplasm; Nucleus	0,0127037	1,54782519	Nucleus
P11279	Lysosome-associated membrane glycoprotein 1		Lysossome	0,0023436	1,91244341	Nucleus
P11766	Alcohol dehydrogenase class-3	Metabolism; Energy pathways	Cytoplasm; Nucleus	0,0272111	1,262381341	Nucleus
P12277	Creatine kinase B-type	Metabolism; Energy pathways	Cytoplasm	0,0235189	1,340169861	Nucleus
P12956	X-ray repair crs-complementing protein 6	Regulation of nucleotide metabolism	Nucleus	0,0359676	1,286150284	Nucleus
P13010	X-ray repair crs-complementing protein 5	Regulation of nucleotide metabolism	Nucleus	0,0351366	1,416605281	Nucleus
P13645	Keratin_ type I cytoskeletal 10	Cell growth	Cytoplasm	0,0006093	1,918803251	Nucleus
P15121	Aldose reductase	Metabolism; Energy pathways	Cytoplasm	0,0004901	1,557729445	Nucleus
P16401	Histone H1.5	Regulation of nucleotide metabolism	Nucleus	0,000231	3,302855205	Nucleus
P18206	Vinculin	Cell growth	Cytoplasm; Nucleus	0,0483305	0,835594344	Nucleus
P18754	Regulator of chromosome condensation	Chromosome organization	Nucleus	0,0313523	1,852513166	Nucleus
P19022	Cadherin-2	Cell communication	Plasma membrane	0,0020416	1,588244438	Nucleus
P21796	Voltage-dependent anion-selective channel protein 1	Transport	Mitochondrion;	0,0012501	0,748755784	Nucleus

			Nucleus			
P22570	NADPH:adrenodoxin oxidoreductase_ mitochondrial	Metabolism; Energy pathways	Mitochondrion	0,0003428	0,454797616	Nucleus
P23193	Transcription elongation factor A protein 1	Transcription regulation	Nucleus	0,0058946	1,294542341	Nucleus
P24752	Acetyl-CoA acetyltransferase_ mitochondrial	Metabolism; Energy pathways	Cytoplasm; Mitochondrion	0,0072783	0,578772433	Nucleus
P24941	Cyclin-dependent kinase 2	Regulation of nucleotide metabolism	Nucleus	0,0495074	1,544028849	Nucleus
P25205	DNA replication licensing factor MCM3	Regulation of nucleotide metabolism	Nucleus	0,0078507	1,739156286	Nucleus
P25705	ATP synthase subunit alpha_ mitochondrial	Metabolism; Energy pathways	Mitochondrion	9,23E-05	0,827332138	Nucleus
P26232	Catenin alpha-2	Cell growth	Cytoplasm	0,0236046	0,751298556	Nucleus
P27348	14-3-3 protein theta	Cell communication	Cytoplasm; Nucleus	0,0079458	1,296587065	Nucleus
P27694	Replication protein A 70 kDa DNA-binding subunit	Regulation of nucleotide metabolism	Nucleus	0,0487831	1,286814621	Nucleus
P27816	Microtubule-associated protein 4	Cell growth	Cytoplasm	0,0076435	1,700514421	Nucleus
P29762	Cellular retinoic acid-binding protein 1	Cell growth	Cytoplasm	0,0127374	0,605029271	Nucleus
P29966	Myristoylated alanine-rich C-kinase substrate	Cell growth	Plasma membrane	0,006199	1,474818866	Nucleus
P30086	Phosphatidylethanolamine-binding protein 1	Cell communication	Cytoplasm	0,0099211	1,694175893	Nucleus
P30154	Serine/threonine-protein phphatase 2A 65 kDa regulatory subunit A beta isoform	Cell communication	Cytoplasm; Nucleus	0,0348075	0,779649087	Nucleus
P30566	Adenyluccinate lyase	Metabolism; Energy pathways	Cytoplasm	0,000569	0,650299071	Nucleus
P30837	Aldehyde dehydrogenase X_ mitochondrial	Metabolism; Energy pathways	Mitochondrion	0,0355562	0,697917353	Nucleus
P31150	Rab GDP dissociation inhibitor alpha	Cell communication	Cytoplasm	0,0085507	1,461240665	Nucleus
P31153	S-adenylmethionine synthase isoform type-2	Metabolism; Energy pathways	Cytoplasm	0,0143085	1,300154834	Nucleus
P31689	DnaJ homolog subfamily A member 1	Protein metabolism	Nucleus	0,030291	0,808453948	Nucleus
P32119	Peroxiredoxin-2	Metabolism; Energy pathways	Cytoplasm	0,003068	1,579909952	Nucleus
P33991	DNA replication licensing factor MCM4	Regulation of nucleotide metabolism	Nucleus	0,0006213	1,891175997	Nucleus
P34932	Heat shock 70 kDa protein 4	Protein metabolism	Cytoplasm; Nucleus	0,0037123	1,464130294	Nucleus
P35221	Catenin alpha-1	Cell growth	Cytoplasm	0,0280463	1,250977204	Nucleus

P35232	Prohibitin	Cell communication	Nucleus; Mitochondrion	5,583E-05	0,699925527	Nucleus
P35241	Radixin	Cell growth	Plasma membrane	0,0404667	1,516744115	Nucleus
P35580	Myosin-10	Cell growth	Cytoplasm	0,0002724	2,899764052	Nucleus
P35611	Alpha-adducin	Cell growth	Nucleus	0,0254077	1,885491379	Nucleus
P35613	Basigin	Cell communication	Plasma membrane	0,013047	0,772952753	Nucleus
P36507	Dual specificity mitogen-activated protein kinase kinase 2	Cell communication	Cytoplasm; Nucleus	0,0356278	0,706223679	Nucleus
P37837	Transaldolase	Metabolism; Energy pathways	Nucleus	0,0152573	1,385335869	Nucleus
P38646	Stress-70 protein_ mitochondrial	Protein metabolism	Mitochondrion; Nucleus	0,0063581	0,731543193	Nucleus
P40925	Malate dehydrogenase_ cytoplasmic	Metabolism; Energy pathways	Cytoplasm; Mitochondrion	0,0211028	1,329279095	Nucleus
P40926	Malate dehydrogenase_ mitochondrial	Metabolism; Energy pathways	Mitochondrion; Nucleus	0,0001451	0,697438257	Nucleus
P40937	Replication factor C subunit 5	DNA replication	Nucleus	0,0037681	1,338074733	Nucleus
P40939	Trifunctional enzyme subunit alpha_ mitochondrial	Metabolism; Energy pathways	Mitochondrion; Nucleus	9,028E-05	0,699501609	Nucleus
P43243	Matrin-3	Regulation of nucleotide metabolism	Nucleus	0,0065288	1,543260217	Nucleus
P43246	DNA mismatch repair protein Msh2	Regulation of nucleotide metabolism	Nucleus	0,0249427	1,278087689	Nucleus
P43307	Translocon-associated protein subunit alpha	Transport	Endoplasmic reticulum	0,0013172	0,62395124	Nucleus
P45880	Voltage-dependent anion-selective channel protein 2	Transport	Mitochondrion; Nucleus	0,0043666	0,757043367	Nucleus
P46821	Microtubule-associated protein 1B	Cell growth	Cytoplasm; Nucleus	8,784E-05	1,424403531	Nucleus
P47985	Putative cytochrome b-c1 complex subunit Rieske-like protein 1	Metabolism; Energy pathways	Mitochondrion	0,0131561	0,804110554	Nucleus
P48681	Nestin	Cell growth	Cytoplasm; Nucleus	0,0068516	1,372493825	Nucleus
P49321	Nuclear autoantigenic sperm protein	Cell communication	Nucleus	0,0164462	1,741410424	Nucleus
P49411	Elongation factor Tu_ mitochondrial	Protein metabolism	Mitochondrion; Nucleus	0,0040793	0,748386235	Nucleus

P49721	Proteasome subunit beta type-2	Protein metabolism	Cytoplasm	0,0137118	1,238550987	Nucleus
P49736	DNA replication licensing factor MCM2	Regulation of nucleotide metabolism	Nucleus	6,134E-05	2,899562015	Nucleus
P49821	NADH dehydrogenase [ubiquinone] flavoprotein 1_ mitochondrial	Metabolism; Energy pathways	Mitochondrion	0,0002183	0,750661135	Nucleus
P50402	Emerin	Cell growth	Nucleus	0,0010072	0,67209495	Nucleus
P50454	Serpin H1	Protein metabolism	Endoplasmic reticulum	0,0021153	0,480225844	Nucleus
P51398	28S ribomal protein S29_ mitochondrial	Apoptosis	Mitochondrion; Nucleus	0,0234592	0,704110044	Nucleus
P52701	DNA mismatch repair protein Msh6	DNA repair	Nucleus	0,0089123	2,357547614	Nucleus
P52735	Guanine nucleotide exchange factor VAV2	Cell communication	Cytoplasm; Nucleus	0,0389437	0,740101524	Nucleus
P53396	ATP-citrate synthase	Metabolism; Energy pathways	Cytoplasm; Nucleus	0,0007074	1,356341786	Nucleus
P53597	Succinate--CoA ligase [ADP/GDP-forming] subunit alpha_ mitochondrial	Metabolism; Energy pathways	Mitochondrion	0,0044326	0,789923219	Nucleus
P53990	IST1 homolog	Cell division	Nucleus	0,0167539	0,827505198	Nucleus
P54709	Sodium/potassium-transporting ATPase subunit beta-3	Transport	Plasma membrane	0,0041801	0,848523462	Nucleus
P54886	Delta-1-pyrroline-5-carboxylate synthase	Metabolism; Energy pathways	Mitochondrion	0,0238918	0,826681518	Nucleus
P55786	Puromycin-sensitive aminopeptidase	Protein metabolism	Cytoplasm; Nucleus	0,0096514	1,435377913	Nucleus
P60174	Triosephosphate isomerase	Metabolism; Energy pathways	Cytoplasm	0,0283189	1,253797993	Nucleus
P60900	Proteasome subunit alpha type-6	Protein metabolism	Cytoplasm; Nucleus	0,0461687	1,097990517	Nucleus
P61254	60S ribomal protein L26-like 1	Protein metabolism	Ribosome	0,0136037	1,276488666	Nucleus
P61604	10 kDa heat shock protein_ mitochondrial	Protein metabolism	Mitochondrion	0,0145687	0,456229448	Nucleus
P62136	Serine/threonine-protein phosphatase PP1-alpha catalytic subunit	Cell proliferation	Cytoeskeleton	0,0108403	0,888525723	Nucleus
P62280	40S ribosomal protein S11	Protein metabolism	Ribosome; Nucleus	0,0009815	1,468008271	Nucleus
P62333	26S proteasome regulatory subunit 10B	Protein metabolism	Cytoplasm	0,0150883	0,881464707	Nucleus
P62495	Eukaryotic peptide chain release factor subunit 1	Protein metabolism	Ribosome; Nucleus	2,602E-05	0,842095085	Nucleus
P62906	60S ribosomal protein L10a	Protein metabolism	Ribosome; Nucleus	0,0110262	0,82339368	Nucleus
P62913	60S ribosomal protein L11	Protein metabolism	Ribosome; Nucleus	0,01699	1,40601326	Nucleus
P63104	14-3-3 protein zeta/delta	Regulation of cell cycle	Cytoplasm	0,026998	1,237409863	Nucleus
P78344	Eukaryotic translation initiation factor 4 gamma 2	Protein metabolism	Cytoplasm	0,0105219	0,875849295	Nucleus
P78527	DNA-dependent protein kinase catalytic subunit	Cell communication	Nucleus	0,0097186	2,155032306	Nucleus

P98172	Ephrin-B1	Cell communication	Plasma membrane	0,0285825	0,631650926	Nucleus
Q00341	Vigilin	Transport	Cytoplasm	0,0266754	1,425695984	Nucleus
Q01581	Hydroxymethylglutaryl-CoA synthase_ cytoplasmic	Metabolism; Energy pathways	Cytoplasm	0,0070479	1,540424666	Nucleus
Q02880	DNA topoisomerase 2-beta	Regulation of nucleotide metabolism	Nucleus	0,0208909	2,206810337	Nucleus
Q04760	Lactoylglutathione lyase	Metabolism; Energy pathways	Cytoplasm	0,0015114	1,373978859	Nucleus
Q04917	14-3-3 protein eta	Cell communication	Cytoplasm; Nucleus	0,0085051	1,239102838	Nucleus
Q12874	Splicing factor 3A subunit 3	Protein metabolism	Nucleus	0,0158199	1,145014629	Nucleus
Q12931	Heat shock protein 75 kDa_ mitochondrial	Protein metabolism	Mitochondrion	0,0005252	0,697217074	Nucleus
Q13084	39S ribomal protein L28_ mitochondrial	Protein metabolism	Mitochondrion	0,0060977	0,840295686	Nucleus
Q13148	TAR DNA-binding protein 43	Regulation of nucleotide metabolism	Nucleus	3,507E-05	1,186731352	Nucleus
Q13247	Serine/arginine-rich splicing factor 6	Regulation of nucleotide metabolism	Nucleus	0,0015214	1,327529017	Nucleus
Q14194	Dihydropyrimidinase-related protein 1	Cell growth	Cytoplasm	0,0009313	1,206753794	Nucleus
Q14195	Dihydropyrimidinase-related protein 3	Metabolism; Energy pathways	Cytoplasm; Nucleus	0,0006223	1,602860636	Nucleus
Q14204	Cytoplasmic dynein 1 heavy chain 1	Metabolism; Energy pathways	Cytoplasm; Nucleus	0,0059347	1,887803685	Nucleus
Q14974	Importin subunit beta-1	Transport	Cytoplasm; Nucleus	0,0255627	1,190805069	Nucleus
Q14980	Nuclear mitotic apparatus protein 1	Cell growth	Nucleus	0,0120603	1,649404355	Nucleus
Q15046	Lysine--tRNA ligase	tRNA aminoacylation	Cytoplasm	0,03484	0,464919535	Nucleus
Q15050	Ribosome biogenesis regulatory protein homolog	Cell growth	Nucleus	0,0184416	0,664757067	Nucleus
Q15758	Neutral amino acid transporter B(0)	Transport	Plasma membrane	0,0327203	0,796822203	Nucleus
Q15785	Mitochondrial import receptor subunit TOM34	Transport	Cytoplasm; Mitochondrion	0,0093709	0,630439497	Nucleus
Q16352	Alpha-internexin	Cell growth	Cytoplasm	0,030307	1,329020331	Nucleus
Q16555	Dihydropyrimidinase-related protein 2	Cell communication	Cytoplasm; Nucleus	0,0014631	1,474487689	Nucleus
Q16658	Fascin	Cell growth	Cytoplasm	0,03986	1,309283779	Nucleus
Q16698	2_4-dienoyl-CoA reductase_ mitochondrial	Metabolism; Energy pathways	Mitochondrion	0,0007467	0,602903539	Nucleus
Q16795	NADH dehydrogenase [ubiquinone] 1 alpha subcomplex subunit 9_ mitochondrial	Metabolism; Energy pathways	Mitochondrion	0,0035356	0,794531574	Nucleus

Q16836	Hydroxyacyl-coenzyme A dehydrogenase_ mitochondrial		Mitochondrion	0,0001593	0,728036577	Nucleus
Q3ZCQ8	Mitochondrial import inner membrane translocase subunit TIM50	Cell communication	Mitochondrion	0,0040656	0,767693723	Nucleus
Q53GS9	U4/U6.U5 tri-snRNP-associated protein 2	Protein metabolism	Nucleus	0,0135297	1,214631464	Nucleus
Q5JTV8	Torsin-1A-interacting protein 1		Nucleus	0,0175815	1,232698256	Nucleus
Q5SSJ5	Heterochromatin protein 1-binding protein 3	Regulation of nucleotide metabolism	Nucleus	0,0192131	1,375047374	Nucleus
Q6NUK1	Calcium-binding mitochondrial carrier protein SCaMC-1	Transport	Mitochondrion	0,0132478	0,668198619	Nucleus
Q6P2Q9	Pre-mRNA-processing-splicing factor 8	Regulation of nucleotide metabolism	Nucleus	0,0128968	4,755357163	Nucleus
Q6YN16	Hydroxysteroid dehydrogenase-like protein 2			0,0236716	0,680714392	Nucleus
Q7Z434	Mitochondrial antiviral-signaling protein			0,0016091	0,633838308	Nucleus
Q7Z7K6	Centromere protein V	Regulation of nucleotide metabolism	Nucleus	0,0023226	1,831354051	Nucleus
Q8N0Y7	Probable phosphoglycerate mutase 4	Metabolism		0,0086863	1,246332337	Nucleus
Q8N163	Cell cycle and apoptis regulator protein 2	Signal transduction	Nucleus	0,0137423	1,406215794	Nucleus
Q8N1F7	Nuclear pore complex protein Nup93	Transport	Nucleus	0,0354165	0,847694533	Nucleus
Q8N684	Cleavage and polyadenylation specificity factor subunit 7	RNA binding	Nucleus	0,0002926	1,133214292	Nucleus
Q8NBS9	Thioredoxin domain-containing protein 5	Protein metabolism	Endoplasmic reticulum	0,0333698	0,759042926	Nucleus
Q8NHW5	60S acidic ribomal protein P0-like	Ribosome biogenesis	Ribosome	0,0025482	0,87203174	Nucleus
Q8TAQ2	SWI/SNF complex subunit SMARCC2	Regulation of nucleotide metabolism	Nucleus	3,484E-05	2,00947324	Nucleus
Q8WXF1	Paraspeckle component 1	Regulation of nucleotide metabolism	Nucleus	0,0137757	1,115269529	Nucleus
Q92552	28S ribomal protein S27_ mitochondrial	Protein metabolism	Mitochondrion	0,0181253	0,648163702	Nucleus
Q92598	Heat shock protein 105 kDa	Protein metabolism	Cytoplasm; Nucleus	0,0285091	1,107484066	Nucleus
Q92618	Zinc finger protein 516	Regulation of nucleotide metabolism	Nucleus	0,0033606	0,68524731	Nucleus
Q92922	SWI/SNF complex subunit SMARCC1	Regulation of nucleotide metabolism	Nucleus	0,000721	1,458669976	Nucleus
Q969Z0	Protein TBRG4	Cell communication	Mitochondrion;	0,0028361	0,741844881	Nucleus

			Nucleus			
Q96A33	Coiled-coil domain-containing protein 47		Mitochondrion	0,0173569	0,866674419	Nucleus
Q96AG4	Leucine-rich repeat-containing protein 59		Plasma membrane	0,0233578	0,841720393	Nucleus
Q96EY1	DnaJ homolog subfamily A member 3_ mitochondrial	Apoptosis	Mitochondrion; Nucleus	0,0154667	0,526020764	Nucleus
Q96EY7	Pentatricopeptide repeat domain-containing protein 3_ mitochondrial		Mitochondrion	0,0069085	0,748401004	Nucleus
Q96P70	Importin-9	Transport	Cytoplasm	0,0466024	1,66941413	Nucleus
Q96T88	E3 ubiquitin-protein ligase UHRF1	Regulation of nucleotide metabolism	Nucleus	0,0222728	1,302288276	Nucleus
Q99439	Calponin-2	Cell growth	Cytoplasm; Nucleus	0,018401	0,750387588	Nucleus
Q99459	Cell division cycle 5-like protein	Cell communication	Nucleus	0,0002151	1,206470185	Nucleus
Q99497	Protein/nucleic acid deglycase DJ-1	Regulation of nucleotide metabolism	Cytoplasm; Nucleus	0,0075854	1,406807462	Nucleus
Q99623	Prohibitin-2	Regulation of nucleotide metabolism	Nucleus	0,0001981	0,766223336	Nucleus
Q99996	A-kinase anchor protein 9	Cell communication	Centrosome	0,0487522	0,697610123	Nucleus
Q9BPU6	Dihydropyrimidinase-related protein 5		Cytoplasm	0,0287043	1,240979888	Nucleus
Q9BPW8	Protein NipSnap homolog 1		Mitochondrion	0,0087752	0,830263397	Nucleus
Q9BUF5	Tubulin beta-6 chain	Cell growth		0,0473765	0,572346461	Nucleus
Q9BUJ2	Heterogeneous nuclear ribonucleoprotein U-like protein 1	Regulation of nucleotide metabolism	Nucleus	0,0192897	0,690952946	Nucleus
Q9BXP5	Serrate RNA effector molecule homolog		Nucleus	0,0003402	1,30904196	Nucleus
Q9BY77	Polymerase delta-interacting protein 3	Cell growth	Nucleus	0,0432273	1,189206549	Nucleus
Q9BYD2	39S ribomal protein L9_ mitochondrial	Protein metabolism	Mitochondrion	0,0014386	0,721458906	Nucleus
Q9H9B4	Sideroflexin-1	Transport	Mitochondrion	0,0266244	0,814175432	Nucleus
Q9H9Z2	Protein lin-28 homolog A	Regulation of nucleotide metabolism	Nucleus	0,01425	0,528350834	Nucleus
Q9NP92	39S ribomal protein S30_ mitochondrial	Protein metabolism	Mitochondrion	0,0121391	0,525371976	Nucleus
Q9NPH2	Inositol-3-phosphate synthase 1	Metabolism; Energy pathways		0,0265981	1,425305828	Nucleus
Q9NRY4	Rho GTPase-activating protein 35	Cell communication	Nucleus	0,0147827	1,394853418	Nucleus

Q9NTX5	Ethylmalonyl-CoA decarboxylase			0,0062588	0,662810499	Nucleus
Q9NX20	39S ribosomal protein L16_ mitochondrial	Protein metabolism	Mitochondrion	0,0018707	0,631669254	Nucleus
Q9NX40	OCIA domain-containing protein 1			0,0005792	0,526127108	Nucleus
Q9NZL9	Methionine adenyltransferase 2 subunit beta	Metabolism	Cytoplasm	0,0471674	1,29811784	Nucleus
Q9P0L0	Vesicle-associated membrane protein-associated protein A	Transport	Endoplasmic reticulum	0,0017612	0,758079853	Nucleus
Q9P2K5	Myelin expression factor 2	Regulation of nucleotide metabolism	Nucleus	0,0195714	1,157117411	Nucleus
Q9UH03	Neuronal-specific septin-3	Cell communication	Plasma membrane	0,0024981	1,796795236	Nucleus
Q9UHX1	Poly(U)-binding-splicing factor PUF60	Regulation of nucleotide metabolism	Nucleus	0,0353126	1,374046301	Nucleus
Q9UI15	Transgelin-3		Cytoplasm	0,0395711	1,659196086	Nucleus
Q9UIG0	Tyrine-protein kinase BAZ1B	Regulation of nucleotide metabolism	Nucleus	0,0311342	1,846011437	Nucleus
Q9UJS0	Calcium-binding mitochondrial carrier protein Aralar2	Transport	Mitochondrion	6,853E-05	0,780551637	Nucleus
Q9UJZ1	Stomatin-like protein 2_ mitochondrial	Transport	Plasma membrane	0,0113586	0,733084258	Nucleus
Q9UKA9	Polypyrimidine tract-binding protein 2	Regulation of nucleotide metabolism	Nucleus	0,0014908	1,570436866	Nucleus
Q9UNW9	RNA-binding protein Nova-2	Regulation of nucleotide metabolism	Nucleus	0,0082712	0,573165702	Nucleus
Q9UQE7	Structural maintenance of chromosomes protein 3	DNA repair	Mitochondrion; Nucleus	0,0041007	1,773885588	Nucleus
Q9Y2W1	Thyroid hormone receptor-associated protein 3	Regulation of nucleotide metabolism	Nucleus	0,0469822	1,40556417	Nucleus
Q9Y3B3	Transmembrane emp24 domain-containing protein 7			0,002251	0,688811445	Nucleus
Q9Y5X3	Sorting nexin-5	Transport	Endosome	0,013653	0,493559358	Nucleus

Table 9: List of proteins found altered in the mitochondrial and nuclear proteomes of neurons

Accession	Description	Biological Process	Cellular component	p-Value	SCZ/CTRL Ratio	Fraction
O00264	Membrane-associated progesterone receptor component 1	Cell communication	Plasma membrane	0,041956435	1,781517241	Mitochondrion
O00425	Insulin-like growth factor 2 mRNA-binding protein 3	Protein Metabolism	Cytoplasm	0,000103789	3,139123808	Mitochondrion
O14983	Sarcoplasmic/endoplasmic reticulum calcium ATPase 1	Metabolism; Energy pathways	Endoplasmic reticulum; Mitochondrion	0,004801781	2,70538634	Mitochondrion
O43157	Plexin-B1	Cell communication	Plasma membrane	0,000381837	3,499203922	Mitochondrion
O43295	SLIT-ROBO Rho GTPase-activating protein 3	Cell communication	Cytoplasm	0,040472563	0,520471903	Mitochondrion
O43854	EGF-like repeat and discoidin I-like domain-containing protein 3	Cell growth	Extracellular	0,015393309	0,448336632	Mitochondrion
O60831	PRA1 family protein 2	Transport	Endosome	7,51068E-05	1,716732982	Mitochondrion
O75110	Probable phospholipid-transporting ATPase IIA	Regulation of enzyme activity	Endosome	0,000426487	1,993766936	Mitochondrion
O75131	Copine-3	Transport	Cytoplasm	0,001100983	5,043723328	Mitochondrion
O75489	NADH dehydrogenase [ubiquinone] iron-sulfur protein 3_ mitochondrial	Metabolism; Energy pathways	Mitochondrion	3,1676E-06	0,574936371	Mitochondrion
O75569	Interferon-inducible double-stranded RNA-dependent protein kinase activator A	Regulation of nucleotide metabolism	Cytoplasm	0,046572176	1,569289619	Mitochondrion
O94856	Neurofascin	Cell communication	Plasma membrane	0,000249579	1,820158646	Mitochondrion
O94874	E3 UFM1-protein ligase 1	Protein Metabolism	Mitochondrion	0,00028529	2,099486341	Mitochondrion
O94979	Protein transport protein Sec31A	Transport	Endoplasmic reticulum	0,039789549	2,504856189	Mitochondrion
O95336	6-phosphogluconolactonase	Metabolism; Energy pathways	Cytoplasm	0,045754671	0,398981332	Mitochondrion
O95573	Long-chain-fatty-acid--CoA ligase 3	Metabolism; Energy pathways	Mitochondrion; Peroxisome	0,036001164	2,745340428	Mitochondrion
O95865	N(G)_N(G)-dimethylarginine dimethylaminohydrolase 2	Metabolism; Energy pathways	Cytoplasm	0,009452516	2,323663442	Mitochondrion
P00387	NADH-cytochrome b5 reductase 3	Metabolism; Energy pathways	Cytoplasm; Mitochondrion	3,06501E-05	1,911969534	Mitochondrion
P00558	Phosphoglycerate kinase 1	Metabolism; Energy pathways	Cytoplasm; Mitochondrion	0,001831699	0,648253339	Mitochondrion
P02768	Serum albumin	Transport	Extracellular	0,008786728	0,264157585	Mitochondrion
P02786	Transferrin receptor protein 1	Transport	Plasma membrane;	0,00815584	1,684719204	Mitochondrion

			Mitochondrion			
P04264	Keratin_ type II cytoskeletal 1	Cell growth	Plasma membrane	0,039765274	0,272095146	Mitochondrion
P04844	Dolichyl-diphosphooligosaccharide--protein glycosyltransferase subunit 2	Protein Metabolism	Endoplasmic reticulum; Mitochondrion	0,003496916	2,374823891	Mitochondrion
P05141	ADP/ATP translocase 2	Metabolism; Energy pathways	Mitochondrion	0,031299548	1,263580596	Mitochondrion
P05455	Lupus La protein	Regulation of nucleotide metabolism	Nucleus	0,00147714	0,008726842	Mitochondrion
P06733	Alpha-enolase	Metabolism; Energy pathways	Cytoplasm	0,001423292	0,669050675	Mitochondrion
P07196	Neurofilament light polypeptide	Cell growth	Cytoplasm	0,029362404	0,622892521	Mitochondrion
P07237	Protein disulfide-isomerase	Protein Metabolism	Endoplasmic reticulum; Mitochondrion	0,000224264	1,829078767	Mitochondrion
P07437	Tubulin beta chain	Cell growth	Cytoplasm	0,004661952	0,340422923	Mitochondrion
P07947	Tyrosine-protein kinase Yes	Cell communication	Cytoplasm	0,000671156	2,516998979	Mitochondrion
P08133	Annexin A6	Cell communication	Endoplasmic reticulum; Mitochondrion	0,023850071	0,623862819	Mitochondrion
P08237	ATP-dependent 6-phosphofructokinase_ muscle type	Metabolism; Energy pathways	Cytoplasm	0,000646564	2,385281801	Mitochondrion
P09104	Gamma-enolase	Metabolism; Energy pathways	Cytoplasm	9,3756E-05	0,518397883	Mitochondrion
P09622	Dihydrolipoyl dehydrogenase_ mitochondrial	Metabolism; Energy pathways	Mitochondrion	0,016103163	1,47064124	Mitochondrion
P0DMV8	Heat shock 70 kDa protein 1A	Protein Metabolism	Nucleus; Mitochondrion	0,000412652	5,595594618	Mitochondrion
P10515	Dihydrolipoyllysine-residue acetyltransferase component of pyruvate dehydrogenase complex_ mitochondrial	Metabolism; Energy pathways	Mitochondrion	0,029589462	2,508495608	Mitochondrion
P10809	60 kDa heat shock protein_ mitochondrial	Protein folding	Mitochondrion	0,044216376	0,628073143	Mitochondrion
P11021	78 kDa glucose-regulated protein	Protein metabolism	Endoplasmic reticulum; Mitochondrion	0,000707879	2,194011802	Mitochondrion
P11171	Protein 4.1	Cell growth	Cytoplasm; Nucleus	0,001055146	2,175784472	Mitochondrion

P11217	Glycogen phosphorylase_ muscle form	Metabolism; Energy pathways	Endoplasmic reticulum	0,002388416	0,121504671	Mitochondrion
P11586	C-1-tetrahydrofolate synthase_ cytoplasmic	Metabolism; Energy pathways	Cytoplasm; Mitochondrion	0,002045822	1,910947493	Mitochondrion
P11940	Polyadenylate-binding protein 1	Regulation of nucleotide metabolism	Cytoplasm; Nucleus	0,001859046	1,610464782	Mitochondrion
P12235	ADP/ATP translocase 1	Transport	Mitochondrion; Nucleus	0,015863198	1,718414432	Mitochondrion
P13010	X-ray repair cross-complementing protein 5	Regulation of nucleotide metabolism	Mitochondrion; Nucleus	0,030430425	1,521233982	Mitochondrion
P13645	Keratin_ type I cytoskeletal 10	Cell growth	Cytoplasm	0,040364322	0,299399243	Mitochondrion
P13667	Protein disulfide-isomerase A4	Protein Metabolism	Endoplasmic reticulum; Mitochondrion	0,008204204	1,983795485	Mitochondrion
P13861	cAMP-dependent protein kinase type II-alpha regulatory subunit	Cell communication	Cytoplasm	0,044099803	0,25113101	Mitochondrion
P15880	40S ribosomal protein S2	Protein Metabolism	Ribosome	0,029035171	1,307456401	Mitochondrion
P16401	Histone H1.5	Regulation of nucleotide metabolism	Mitochondrion; Nucleus	0,017619594	5,606598823	Mitochondrion
P16435	NADPH--cytochrome P450 reductase	Metabolism; Energy pathways	Endoplasmic reticulum; Mitochondrion	0,00672907	1,892326594	Mitochondrion
P16615	Sarcoplasmic/endoplasmic reticulum calcium ATPase 2	Transport	Endoplasmic reticulum; Mitochondrion	0,004799061	2,38561903	Mitochondrion
P17987	T-complex protein 1 subunit alpha	Protein Metabolism	Cytoplasm	0,022713229	1,439285175	Mitochondrion
P18124	60S ribosomal protein L7	Protein Metabolism	Ribosome	0,036041691	1,229173649	Mitochondrion
P19022	Cadherin-2	Cell communication	Plasma membrane	0,005098477	1,900168938	Mitochondrion
P23284	Peptidyl-prolyl cis-trans isomerase B	Protein Metabolism	Endoplasmic reticulum; Mitochondrion	0,022412458	1,50681539	Mitochondrion
P24539	ATP synthase F(0) complex subunit B1_ mitochondrial	Metabolism; Energy pathways	Mitochondrion	0,045643227	1,369621724	Mitochondrion

P25789	Proteasome subunit alpha type-4	Protein Metabolism	Cytoplasm; Endoplasmic reticulum	0,011164883	0,596588579	Mitochondrion
P26232	Catenin alpha-2	Cell growth	Cytoplasm	0,001500401	1,738755892	Mitochondrion
P26378	ELAV-like protein 4	Regulation of nucleotide metabolism	Nucleus	0,007149181	4,321315355	Mitochondrion
P26640	Valine--tRNA ligase	Protein Metabolism	Cytoplasm; Mitochondrion	0,020650588	1,783375436	Mitochondrion
P26641	Elongation factor 1-gamma	Protein Metabolism	Cytoplasm; Mitochondrion	0,016874075	0,559968425	Mitochondrion
P27348	14-3-3 protein theta	Cell communication	Cytoplasm	0,006100222	0,404830226	Mitochondrion
P27797	Calreticulin	Protein Metabolism	Endoplasmic reticulum	0,007835629	1,798114751	Mitochondrion
P27816	Microtubule-associated protein 4	Cell growth	Cytoplasm	0,022758961	1,760011287	Mitochondrion
P29762	Cellular retinoic acid-binding protein 1	Transport	Cytoplasm	0,016028041	0,384281703	Mitochondrion
P30101	Protein disulfide-isomerase A3	Protein metabolism	Endoplasmic reticulum	0,006505876	1,702404378	Mitochondrion
P30566	Adenylosuccinate lyase	Metabolism; Energy pathways	Cytoplasm	0,004156436	0,018234564	Mitochondrion
P31146	Coronin-1A	Cell growth	Cytoplasm; Mitochondrion	0,012384327	1,59683695	Mitochondrion
P31943	Heterogeneous nuclear ribonucleoprotein H	Regulation of nucleotide metabolism	Cytoplasm; Nucleus	0,017331189	0,621465691	Mitochondrion
P32969	60S ribosomal protein L9	Protein Metabolism	Ribosome	0,032647122	1,522673981	Mitochondrion
P35908	Keratin_ type II cytoskeletal 2 epidermal	Cell growth	Cytoplasm	0,048424202	0,289076576	Mitochondrion
P36542	ATP synthase subunit gamma_ mitochondrial	Metabolism; Energy pathways	Mitochondrion	0,003299898	0,468377323	Mitochondrion
P39656	Dolichyl-diphosphooligosaccharide--protein glycosyltransferase 48 kDa subunit	Metabolism; Energy pathways	Endoplasmic reticulum; Mitochondrion	0,041738795	1,389893178	Mitochondrion
P40925	Malate dehydrogenase_ cytoplasmic	Metabolism; Energy pathways	Cytoplasm; Mitochondrion	0,002915161	0,629553239	Mitochondrion
P40939	Trifunctional enzyme subunit alpha_ mitochondrial	Metabolism; Energy pathways	Mitochondrion	0,040077104	1,60570545	Mitochondrion

P41252	Isoleucine--tRNA ligase_ cytoplasmic	Protein metabolism	Cytoplasm; Mitochondrion	0,029308139	0,434344756	Mitochondrion
P42766	60S ribosomal protein L35	Protein metabolism	Ribosome	0,040682623	1,502508997	Mitochondrion
P46977	Dolichyl-diphosphooligosaccharide--protein glycosyltransferase subunit STT3A		Plasma membrane	0,008918957	2,949041997	Mitochondrion
P48637	Glutathione synthetase	Metabolism; Energy pathways	Cytoplasm	0,014073603	0,000262862	Mitochondrion
P49327	Fatty acid synthase	Metabolism; Energy pathways	Cytoplasm; Mitochondrion	0,040971617	0,463236376	Mitochondrion
P49411	Elongation factor Tu_ mitochondrial	Protein metabolism	Mitochondrion; Nucleus	0,000903971	0,071220585	Mitochondrion
P53007	Tricarboxylate transport protein_ mitochondrial	Transport	Mitochondrion	0,004772952	1,735069051	Mitochondrion
P54136	Arginine--tRNA ligase_ cytoplasmic	Protein metabolism	Cytoplasm	0,048267519	1,696283557	Mitochondrion
P54577	Tyrosine--tRNA ligase_ cytoplasmic	Metabolism; Energy pathways	Cytoplasm	0,008575453	0,44524252	Mitochondrion
P54753	Ephrin type-B receptor 3	Cell communication	Plasma membrane	0,013443429	2,179305459	Mitochondrion
P54762	Ephrin type-B receptor 1	Cell communication	Plasma membrane	0,015785663	1,673571721	Mitochondrion
P55060	Exportin-2	Transport	Nucleus; Mitochondrion	0,006735833	0,077173695	Mitochondrion
P55157	Microsomal triglyceride transfer protein large subunit	Transport	Cytoplasm; Endoplasmic reticulum	0,009041321	3,799179662	Mitochondrion
P59998	Actin-related protein 2/3 complex subunit 4	Cell growth	Cytoplasm	0,040623057	0,303683267	Mitochondrion
P60174	Triosephosphate isomerase	Metabolism; Energy pathways	Cytoplasm	0,005830156	0,579485805	Mitochondrion
P60201	Myelin proteolipid protein	Cell growth	Plasma membrane	0,034829337	2,010490815	Mitochondrion
P60709	Actin_ cytoplasmic 1	Cell growth	Cytoplasm; Mitochondrion	0,00316421	0,279350891	Mitochondrion
P61020	Ras-related protein Rab-5B	Cell communication	Plasma membrane	0,015177571	0,304565572	Mitochondrion
P61204	ADP-ribosylation factor 3	Cell communication	Cytoplasm	0,007622368	0,329778543	Mitochondrion
P61266	Syntaxin-1B	Transport	Integral to membrane	0,03150623	0,433259888	Mitochondrion
P61313	60S ribosomal protein L15	Protein Metabolism	Ribosome	0,023308034	1,686487303	Mitochondrion
P62140	Serine/threonine-protein phosphatase PP1-beta catalytic subunit	Cell growth	Nucleus	0,025656329	1,830949891	Mitochondrion
P62424	60S ribosomal protein L7a	Protein Metabolism	Cytoplasm; Nucleus	0,020082076	2,746743149	Mitochondrion

P62495	Eukaryotic peptide chain release factor subunit 1	Protein Metabolism	Ribosome	0,035162562	0,11585024	Mitochondrion
P62753	40S ribosomal protein S6	Protein Metabolism	Ribosome	0,004180199	1,482361256	Mitochondrion
P62820	Ras-related protein Rab-1A	Cell communication	Endoplasmic reticulum; Golgi apparatus	0,017467777	0,416293209	Mitochondrion
P78347	General transcription factor II-I	Regulation of nucleotide metabolism	Nucleus	0,04823097	2,476103884	Mitochondrion
P78371	T-complex protein 1 subunit beta	Protein Metabolism	Cytoplasm; Mitochondrion	0,002477599	0,081906731	Mitochondrion
P83731	60S ribosomal protein L24	Protein Metabolism	Ribosome	0,021746895	1,439347593	Mitochondrion
Q00341	Vigilin	Transport	Cytoplasm	0,007316173	6,463307057	Mitochondrion
Q00534	Cyclin-dependent kinase 6	Cell communication	Cytoplasm; Nucleus	0,019512552	2,605122401	Mitochondrion
Q02878	60S ribosomal protein L6	Protein Metabolism	Mitochondrion; Ribosome	0,00120829	1,580017222	Mitochondrion
Q07020	60S ribosomal protein L18	Protein Metabolism	Mitochondrion; Ribosome	0,015208066	1,517185572	Mitochondrion
Q07065	Cytoskeleton-associated protein 4	Cell growth	Plasma membrane	0,024155273	1,696189012	Mitochondrion
Q08211	ATP-dependent RNA helicase A	Regulation of nucleotide metabolism	Cytoplasm; Nucleus	0,015566351	2,020796014	Mitochondrion
Q12926	ELAV-like protein 2	Regulation of nucleotide metabolism	Cytoplasm; Nucleus	0,030745865	1,521217526	Mitochondrion
Q13098	COP9 signalosome complex subunit 1	Cell communication	Cytoplasm; Nucleus	0,010461326	1,941053905	Mitochondrion
Q13177	Serine/threonine-protein kinase PAK 2	Cell communication	Endoplasmic reticulum	0,036874193	1,528754469	Mitochondrion
Q13228	Selenium-binding protein 1	Protein Metabolism	Cytoplasm	0,040256636	0,047884205	Mitochondrion
Q13423	NAD(P) transhydrogenase_ mitochondrial	Metabolism; Energy pathways	Mitochondrion	0,015457995	2,252984583	Mitochondrion
Q13554	Calcium/calmodulin-dependent protein kinase type II subunit beta	Cell communication	Cytoplasm	0,021349714	1,582436023	Mitochondrion
Q13557	Calcium/calmodulin-dependent protein kinase type II subunit delta	Regulation of cell growth	Cytoplasm; Nucleus	0,003762239	1,785586343	Mitochondrion
Q13838	Spliceosome RNA helicase DDX39B	Regulation of nucleotide metabolism	Nucleus	0,031283379	0,508874002	Mitochondrion
Q13867	Bleomycin hydrolase	Metabolism; Energy pathways	Cytoplasm	0,028741894	0,439729631	Mitochondrion

Q14141	Septin-6		Cytoplasm	0,00686152	1,829772259	Mitochondrion
Q14168	MAGUK p55 subfamily member 2	Cell communication	Plasma membrane	0,009262946	3,437883514	Mitochondrion
Q14203	Dynactin subunit 1	Transport	Cytoplasm; Endoplasmic reticulum	0,002565822	2,383723969	Mitochondrion
Q15084	Protein disulfide-isomerase A6	Protein metabolism	Endoplasmic reticulum; Mitochondrion	0,006800008	1,452874978	Mitochondrion
Q15643	Thyroid receptor-interacting protein 11	Regulation of nucleotide metabolism	Golgi apparatus	0,042479717	0,503954747	Mitochondrion
Q16537	Serine/threonine-protein phosphatase 2A 56 kDa regulatory subunit epsilon isoform	Cell communication	Cytoplasm	0,001348344	2,227729546	Mitochondrion
Q5ZPR3	CD276 antigen			0,007724194	0,568710857	Mitochondrion
Q6P2E9	Enhancer of mRNA-decapping protein 4		Nucleus	0,047087947	0,275246914	Mitochondrion
Q6S8J3	POTE ankyrin domain family member E		Plasma membrane	0,000335496	0,289606564	Mitochondrion
Q6XQN6	Nicotinate phosphoribosyltransferase	Regulation of nucleotide metabolism	Cytoplasm	0,026969894	0,115305526	Mitochondrion
Q71U36	Tubulin alpha-1A chain	Cell growth	Cytoplasm; Nucleus	0,016442503	0,391012742	Mitochondrion
Q8N3J6	Cell adhesion molecule 2	Cell communication		4,80216E-05	2,178052746	Mitochondrion
Q8N9N7	Leucine-rich repeat-containing protein 57			0,001793816	1,504067232	Mitochondrion
Q8NC51	Plasminogen activator inhibitor 1 RNA-binding protein	Regulation of nucleotide metabolism	Cytoplasm	0,015575693	2,180715454	Mitochondrion
Q8NDA2	Hemicentin-2			0,031894072	1,798072069	Mitochondrion
Q92499	ATP-dependent RNA helicase DDX1	Regulation of nucleotide metabolism	Nucleus	0,015459682	1,841998691	Mitochondrion
Q92973	Transportin-1	Transport	Cytoplasm	0,014955752	1,801288606	Mitochondrion
Q96CS3	FAS-associated factor 2		Cytoplasm	0,010165185	2,158472303	Mitochondrion
Q96CW1	AP-2 complex subunit mu	Transport		0,038049452	4,082798388	Mitochondrion
Q96E17	Ras-related protein Rab-3C	Transport	Cytoplasm	0,001939255	2,227435164	Mitochondrion
Q99798	Aconitate hydratase_ mitochondrial	Metabolism; Energy pathways	Mitochondrion	0,02269079	2,215956422	Mitochondrion

Q9BQE3	Tubulin alpha-1C chain	Cell growth	Cytoplasm; Nucleus	0,000122696	0,598538737	Mitochondrion
Q9BUF5	Tubulin beta-6 chain	Cell growth		0,021991092	0,124754562	Mitochondrion
Q9BZF1	Oxysterol-binding protein-related protein 8	Transport	Mitochondrion	0,001967672	0,284492675	Mitochondrion
Q9C0E8	Endoplasmic reticulum junction formation protein lunapark			0,002615647	8,365588447	Mitochondrion
Q9H115	Beta-soluble NSF attachment protein	Transport		0,009873899	3,517510782	Mitochondrion
Q9H270	Vacuolar protein sorting-associated protein 11 homolog	Transport	Endosome	0,047816398	0,581616808	Mitochondrion
Q9HDC9	Adipocyte plasma membrane-associated protein		Plasma membrane	0,024978764	2,203807825	Mitochondrion
Q9NQC3	Reticulon-4	Cell growth	Endoplasmic reticulum; Mitochondrion	0,013811803	1,360480198	Mitochondrion
Q9NSD9	Phenylalanine--tRNA ligase beta subunit	Protein Metabolism	Cytoplasm	0,039754019	2,109187107	Mitochondrion
Q9NTJ5	Phosphatidylinositide phosphatase SAC1	Cell communication	Endoplasmic reticulum	0,028133814	4,765291663	Mitochondrion
Q9NVA2	Septin-11	Cell cycle	Cytoplasm	0,000575627	2,377740197	Mitochondrion
Q9NYU2	UDP-glucose:glycoprotein glucosyltransferase 1	Metabolism; Energy pathways	Endoplasmic reticulum; Mitochondrion	0,004860355	0,33513755	Mitochondrion
Q9NZI8	Insulin-like growth factor 2 mRNA-binding protein 1			0,000457846	1,857132891	Mitochondrion
Q9P121	Neurotrimin			0,000222943	0,595228229	Mitochondrion
Q9UHD8	Septin-9			0,004379017	1,837788151	Mitochondrion
Q9UHG3	Prenylcysteine oxidase 1			0,022543367	1,707597825	Mitochondrion
Q9UI15	Transgelin-3	Regulation of transcription	Cytoplasm; Nucleus	0,017132729	1,650897189	Mitochondrion
Q9UIW2	Plexin-A1	Cell communication	Plasma membrane	0,009879354	0,144275572	Mitochondrion
Q9UKA9	Polypyrimidine tract-binding protein 2			0,048598456	2,387963071	Mitochondrion
Q9UL18	Protein argonaute-1	Protein Metabolism	Cytoplasm	0,017594549	3,572888237	Mitochondrion
Q9ULU8	Calcium-dependent secretion activator 1	Transport	Cytoplasm	5,14431E-08	3,651620072	Mitochondrion
Q9UM54	Unconventional myosin-VI	Cell growth	Golgi apparatus	0,030425256	2,38182267	Mitochondrion
Q9UPZ6	Thrombospondin type-1 domain-containing protein 7A	Cell communication		0,000246963	0,436256441	Mitochondrion
Q9UQ80	Proliferation-associated protein 2G4	Regulation of nucleotide metabolism	Mitochondrion; Nucleus	0,009869115	0,532020767	Mitochondrion

Q9Y265	RuvB-like 1	Regulation of nucleotide metabolism	Cytoplasm; Nucleus	0,016113411	0,148128232	Mitochondrion
Q9Y2A7	Nck-associated protein 1	Cell communication	Cytoplasm; Mitochondrion	0,02506563	0,695673509	Mitochondrion
Q9Y4F1	FERM_ ARHGEF and pleckstrin domain-containing protein 1	Cell growth		0,002056227	2,34627575	Mitochondrion
Q9Y6G9	Cytoplasmic dynein 1 light intermediate chain 1	Cell growth	Cytoplasm	0,021376249	1,425989929	Mitochondrion
Q9Y6M1	Insulin-like growth factor 2 mRNA-binding protein 2	Regulation of nucleotide metabolism	Cytoplasm	0,000884164	2,245365845	Mitochondrion
O00231	26S proteasome non-ATPase regulatory subunit 11	Protein Metabolism	Cytoplasm; Nucleus	0,042674718	0,759190435	Nucleus
O00232	26S proteasome non-ATPase regulatory subunit 12	Protein Metabolism	Cytoplasm	0,006864619	0,646012592	Nucleus
O00299	Chloride intracellular channel protein 1	Transport	Nucleus	0,008515495	0,453071903	Nucleus
O43175	D-3-phosphoglycerate dehydrogenase	Metabolism; Energy pathways	Extracellular	0,042751498	0,633175248	Nucleus
O43488	Aflatoxin B1 aldehyde reductase member 2	Metabolism; Energy pathways	Cytoplasm	0,012044747	0,7203363	Nucleus
O43707	Alpha-actinin-4	Cell growth	Cytoplasm; Nucleus	0,047269207	3,277134376	Nucleus
O43776	Asparagine--tRNA ligase_ cytoplasmic	Protein Metabolism	Cytoplasm	0,011291814	0,55322836	Nucleus
O43854	EGF-like repeat and discoidin I-like domain-containing protein 3	Cell growth	Extracellular	0,046525395	0,098187089	Nucleus
O60282	Kinesin heavy chain isoform 5C	Cell growth	Cytoplasm	0,023907322	2,437747158	Nucleus
O60701	UDP-glucose 6-dehydrogenase	Metabolism; Energy pathways	Nucleus	0,005454333	1,952782372	Nucleus
O60812	Heterogeneous nuclear ribonucleoprotein C-like 1	Protein Metabolism	Nucleus	0,001446525	1,247542424	Nucleus
O75122	CLIP-associating protein 2	Cell growth	Cytoplasm	0,001610965	2,963054274	Nucleus
O75746	Calcium-binding mitochondrial carrier protein Aralar1	Transport	Cytoplasm; Mitochondrion	0,031292387	1,956705671	Nucleus
O94973	AP-2 complex subunit alpha-2	Transport	Plasma membrane	0,04772019	1,694377982	Nucleus
O94986	Centrosomal protein of 152 kDa	Cell growth	Cytoplasm; Nucleus	0,038838029	2,376862093	Nucleus
P00568	Adenylate kinase isoenzyme 1	Metabolism; Energy pathways	Cytoplasm	0,0312693	0,50159433	Nucleus
P04040	Catalase	Metabolism; Energy pathways	Cytoplasm	0,01498074	0,309666879	Nucleus
P05023	Sodium/potassium-transporting ATPase subunit alpha-1	Transport	Plasma membrane	0,042951435	1,759581853	Nucleus
P06744	Glucose-6-phosphate isomerase	Metabolism; Energy pathways	Cytoplasm	0,00151362	2,739221368	Nucleus
P07305	Histone H1.0	Regulation of nucleotide metabolism	Nucleus	0,01003865	0,17174482	Nucleus

P07339	Cathepsin D	Protein Metabolism	Lysosome	0,00971599	1,453197247	Nucleus
P07355	Putative annexin A2-like protein	Signal transduction; Cell communication	Nucleus	0,001676842	0,117188794	Nucleus
P07437	Tubulin beta chain	Cell growth	Cytoplasm; Plasma membrane	0,034092144	0,562841615	Nucleus
P08865	40S ribosomal protein SA	Protein Metabolism	Nucleus	0,028549503	0,537863359	Nucleus
P09471	Guanine nucleotide-binding protein G(o) subunit alpha	Cell communication	Plasma membrane	6,63892E-05	2,281275734	Nucleus
P10909	Clusterin	Protein metabolism	Cytoplasm; Nucleus	0,012455714	2,501360621	Nucleus
P11940	Polyadenylate-binding protein 1	Regulation of nucleotide metabolism	Cytoplasm; Nucleus	0,007646054	0,751427291	Nucleus
P12004	Proliferating cell nuclear antigen	DNA repair	Nucleus	0,012781361	0,392478613	Nucleus
P12235	ADP/ATP translocase 1	Transport	Mitochondrion; Nucleus	0,022048751	1,330283404	Nucleus
P12236	ADP/ATP translocase 3	Transport	Mitochondrion; Nucleus	0,031299549	1,263580596	Nucleus
P13667	Protein disulfide-isomerase A4	Protein Metabolism	Endoplasmic reticulum; Mitochondrion	0,009831539	1,831403121	Nucleus
P14314	Glucosidase 2 subunit beta	Metabolism; Energy pathways	Endoplasmic reticulum	0,005705199	2,070427651	Nucleus
P15311	Ezrin	Cell growth	Cytoplasm	0,019489594	1,64373973	Nucleus
P15586	N-acetylglucosamine-6-sulfatase	Metabolism; Energy pathways	Lysosome	0,008373919	1,943994832	Nucleus
P18621	60S ribosomal protein L17	Protein Metabolism	Ribosome	0,033544525	0,220084069	Nucleus
P19022	Cadherin-2	Cell communication	Plasma membrane	0,002881189	2,752353198	Nucleus
P19367	Hexokinase-1	Metabolism; Energy pathways	Cytoplasm	0,03430051	1,971098315	Nucleus
P21579	Synaptotagmin-1	Cell communication	Cytoplasm	0,012292234	2,422322432	Nucleus
P23526	Adenosylhomocysteinase	Metabolism; Energy pathways	Cytoplasm	0,035066789	0,803159232	Nucleus
P26232	Catenin alpha-2	Cell growth	Cytoplasm	0,016305754	1,569844886	Nucleus
P26378	ELAV-like protein 4	Regulation of nucleotide metabolism	Nucleus	0,007170079	1,856229718	Nucleus

P26640	Valine--tRNA ligase	Protein Metabolism	Cytoplasm; Mitochondrion	0,046815094	3,808227234	Nucleus
P27824	Calnexin	Protein folding	Endoplasmic reticulum	0,042193938	1,633185619	Nucleus
P29323	Ephrin type-B receptor 2	Cell communication	Plasma membrane	0,027360125	1,320946438	Nucleus
P29762	Cellular retinoic acid-binding protein 1	Transport	Cytoplasm	0,012305218	0,436782176	Nucleus
P31150	Rab GDP dissociation inhibitor alpha	Cell communication	Cytoplasm	0,005300074	0,611715363	Nucleus
P31939	Bifunctional purine biosynthesis protein PURH	Metabolism; Energy pathways	Cytoplasm; Mitochondrion	0,001149528	0,724149889	Nucleus
P32969	60S ribosomal protein L9	Protein Metabolism	Ribosome	0,018378246	0,688091323	Nucleus
P35221	Catenin alpha-1	Cell growth	Cytoplasm	0,027020224	2,07107355	Nucleus
P35222	Catenin beta-1	Cell communication	Nucleus; Plasma membrane	0,008298486	3,084534228	Nucleus
P35611	Alpha-adducin	Cell growth	Nucleus	0,003428561	2,265544866	Nucleus
P35612	Beta-adducin	Cell growth	Nucleus	0,004047981	2,744406909	Nucleus
P36578	60S ribosomal protein L4	Protein Metabolism	Nucleus; Ribosome	0,03625426	0,657697261	Nucleus
P36776	Lon protease homolog_ mitochondrial	Protein Metabolism	Mitochondrion	0,013581566	2,149800119	Nucleus
P38159	RNA-binding motif protein_ X chromosome	Regulation of nucleotide metabolism	Nucleus	0,044884793	1,286154056	Nucleus
P41091	Putative eukaryotic translation initiation factor 2 subunit 3-like protein	Protein Metabolism	Cytoplasm; Nucleus	0,045071455	1,610767543	Nucleus
P45880	Voltage-dependent anion-selective channel protein 2	Transport	Mitochondrion; Nucleus	0,02356102	1,272432256	Nucleus
P46776	60S ribosomal protein L27a	Protein Metabolism	Nucleus; Ribosome	0,013756968	0,518782338	Nucleus
P46781	40S ribosomal protein S9	Protein Metabolism	Nucleus; Ribosome	0,004285354	0,674963642	Nucleus
P46783	40S ribosomal protein S10	Protein Metabolism	Nucleus; Ribosome	0,033328552	0,432343805	Nucleus
P48681	Nestin	Protein Metabolism	Cytoplasm; Nucleus	0,001442497	0,514569526	Nucleus
P49591	Serine--tRNA ligase_ cytoplasmic	Metabolism; Energy pathways	Cytoplasm	0,007789969	0,742013578	Nucleus
P49841	Glycogen synthase kinase-3 beta	Metabolism; Energy pathways	Cytoplasm; Nucleus	0,028793336	1,923916175	Nucleus
P50395	Rab GDP dissociation inhibitor beta	Transport	Cytoplasm	0,032959278	1,196666575	Nucleus
P50454	Serpin H1	Protein Metabolism	Endoplasmic	0,001882583	0,273963977	Nucleus

			reticulum; Nucleus			
P50914	60S ribosomal protein L14	Protein Metabolism	Nucleus; Ribosome	0,01397447	0,664602733	Nucleus
P51991	Heterogeneous nuclear ribonucleoprotein A3	Regulation of nucleotide metabolism	Nucleus	0,03162002	0,241198256	Nucleus
P52209	6-phosphogluconate dehydrogenase_ decarboxylating	Metabolism; Energy pathways	Cytoplasm	0,02555359	0,642189831	Nucleus
P52292	Importin subunit alpha-1	Cell communication	Cytoplasm; Nucleus	0,011475161	0,53527724	Nucleus
P52895	Aldo-keto reductase family 1 member C2	Metabolism; Transport	Cytoplasm	0,000233538	1,652717252	Nucleus
P54578	Ubiquitin carboxyl-terminal hydrolase 14	Protein Metabolism	Cytoplasm	0,036102138	0,793014278	Nucleus
P54687	Branched-chain-amino-acid aminotransferase_ cytosolic	Metabolism; Energy pathways	Cytoplasm	0,026474716	0,63455212	Nucleus
P54920	Alpha-soluble NSF attachment protein	Transport	Golgi apparatus	0,041703561	1,250832907	Nucleus
P55265	Double-stranded RNA-specific adenosine deaminase	Regulation of nucleotide metabolism	Nucleus	0,030038645	2,229249735	Nucleus
P55809	Succinyl-CoA:3-ketoacid coenzyme A transferase 1_ mitochondrial	Metabolism; Energy pathways	Mitochondrion; Nucleus	0,003366947	2,312218782	Nucleus
P60953	Cell division control protein 42 homolog	Cell communication	Cytoplasm	0,019566354	1,234811874	Nucleus
P61247	40S ribosomal protein S3a	Protein Metabolism	Cytoplasm; Nucleus	0,007898504	0,587101564	Nucleus
P61313	60S ribosomal protein L15	Protein Metabolism	Ribosome	0,003285851	0,641397739	Nucleus
P61421	V-type proton ATPase subunit d 1	Transport		0,011668732	1,359521955	Nucleus
P62241	40S ribosomal protein S8	Protein Metabolism	Cytoplasm; Nucleus	0,008648868	0,607418512	Nucleus
P62263	40S ribosomal protein S14	Protein Metabolism	Nucleus; Ribosome	0,00155768	0,373603862	Nucleus
P62277	40S ribosomal protein S13	Protein Metabolism	Nucleus; Ribosome	0,032199766	0,464835475	Nucleus
P62280	40S ribosomal protein S11	Protein Metabolism	Nucleus; Ribosome	0,000594412	0,525262296	Nucleus
P62424	60S ribosomal protein L7a	Protein Metabolism	Cytoplasm; Nucleus	0,028859607	0,606764491	Nucleus
P62701	40S ribosomal protein S4_ X isoform	Protein Metabolism	Nucleus; Ribosome	0,032482507	0,599988502	Nucleus
P62736	Actin_ aortic smooth muscle	Cell growth	Cytoplasm	0,019775708	0,599234996	Nucleus
P62826	GTP-binding nuclear protein Ran	Cell communication	Nucleus	0,013095323	0,698407722	Nucleus
P62879	Guanine nucleotide-binding protein G(I)/G(S)/G(T) subunit beta-2	Cell communication	Cytoplasm	0,037159381	1,508968061	Nucleus
P62910	60S ribosomal protein L32	Protein Metabolism	Ribosome	0,018938121	0,707083307	Nucleus
P62913	60S ribosomal protein L11	Protein Metabolism	Nucleus; Ribosome	0,011005093	0,709373454	Nucleus

P62987	Ubiquitin-60S ribosomal protein L40	Protein Metabolism	Ribosome	0,02900742	1,518431693	Nucleus
P63244	Receptor of activated protein C kinase 1	Cell communication	Cytoplasm; Nucleus	0,044191724	0,718381678	Nucleus
P68402	Platelet-activating factor acetylhydrolase IB subunit beta	Cell communication	Cytoplasm	0,005227115	0,077812948	Nucleus
Q00169	Phosphatidylinositol transfer protein alpha isoform	Transport	Cytoplasm	0,00054813	0,649047536	Nucleus
Q01518	Adenylyl cyclase-associated protein 1	Cell growth	Cytoplasm; Nucleus	0,002032923	1,672220377	Nucleus
Q02790	Peptidyl-prolyl cis-trans isomerase FKBP4	Metabolism; Energy pathways	Cytoplasm; Nucleus	0,019691596	1,549846489	Nucleus
Q02978	Mitochondrial 2-oxoglutarate/malate carrier protein	Transport	Mitochondrion; Nucleus	0,018543913	1,596987798	Nucleus
Q07955	Serine/arginine-rich splicing factor 1	Protein Metabolism	Nucleus	0,006410167	0,011706407	Nucleus
Q08209	Serine/threonine-protein phosphatase 2B catalytic subunit alpha isoform	Cell communication	Cytoplasm; Nucleus	0,005333659	1,674281379	Nucleus
Q10567	AP-1 complex subunit beta-1	Transport	Golgi apparatus	0,049241385	1,577211384	Nucleus
Q12906	Interleukin enhancer-binding factor 3	Regulation of gene expression	Nucleus	0,0416942	1,476921817	Nucleus
Q13098	COP9 signalosome complex subunit 1	Cell communication	Cytoplasm; Nucleus	0,00301648	0,460558086	Nucleus
Q14108	Lysosome membrane protein 2	Cell communication	Plasma membrane	0,012894874	2,224613645	Nucleus
Q14117	Dihydropyrimidinase	Regulation of nucleotide metabolism	Cytoplasm; Nucleus	0,031118586	1,770374745	Nucleus
Q14204	Cytoplasmic dynein 1 heavy chain 1	Metabolism; Energy pathways	Cytoplasm; Nucleus	0,00646492	0,822854117	Nucleus
Q15102	Platelet-activating factor acetylhydrolase IB subunit gamma	Metabolism; Energy pathways	Cytoplasm	0,039944965	0,366582625	Nucleus
Q15185	Prostaglandin E synthase 3	Protein Metabolism	Cytoplasm; Nucleus	0,00429819	0,643450664	Nucleus
Q15334	Lethal(2) giant larvae protein homolog 1	Cell growth	Cytoplasm	0,030107933	2,281544421	Nucleus
Q16531	DNA damage-binding protein 1	Regulation of nucleotide metabolism	Nucleus	0,008915944	0,299821511	Nucleus
Q5TF21	Protein SOGA3		Plasma membrane	0,032542655	2,382704942	Nucleus
Q5VTE0	Putative elongation factor 1-alpha-like 3			0,00620493	0,801519443	Nucleus
Q71U36	Tubulin alpha-1A chain	Cell growth	Cytoplasm; Nucleus	0,042963242	0,720965363	Nucleus
Q7L099	Protein RUFY3			0,030921726	1,975790883	Nucleus
Q7Z460	CLIP-associating protein 1	Cell growth	Nucleus	0,024255639	1,959291554	Nucleus
Q86UX7	Fermitin family homolog 3		Plasma membrane	0,035330665	2,750294859	Nucleus
Q8N163	Cell cycle and apoptosis regulator protein 2	Signal transduction	Nucleus	0,01716188	0,656241816	Nucleus

Q8WVM8	Sec1 family domain-containing protein 1	Transport	Nucleus; Plasma membrane	0,010468417	1,740028619	Nucleus
Q8WZA9	Immunity-related GTPase family Q protein			0,043640359	1,488348652	Nucleus
Q92820	Gamma-glutamyl hydrolase	Metabolism; Energy pathways	Lysosome	2,13731E-05	3,403527114	Nucleus
Q96JP2	Unconventional myosin-XVB			0,000665393	2,247191517	Nucleus
Q96KP4	Cytosolic non-specific dipeptidase	Protein Metabolism	Cytoplasm	0,018082124	0,653609793	Nucleus
Q96QT4	Transient receptor potential cation channel subfamily M member 7	Transport	Plasma membrane	0,048510167	1,772793096	Nucleus
Q99460	26S proteasome non-ATPase regulatory subunit 1	Protein Metabolism	Cytoplasm; Nucleus	0,000178441	0,534552509	Nucleus
Q99497	Protein/nucleic acid deglycase DJ-1	Regulation of nucleotide metabolism	Nucleus	0,035666701	1,842977904	Nucleus
Q99873	Protein arginine N-methyltransferase 1	Metabolism; Energy pathways	Nucleus	0,049939145	0,646011394	Nucleus
Q99996	A-kinase anchor protein 9	Cell communication	Cytoplasm	8,85179E-07	2,036444024	Nucleus
Q9BSJ8	Extended synaptotagmin-1			0,02619189	0,614668628	Nucleus
Q9BVA1	Tubulin beta-2B chain	Cell growth	Cytoplasm; Nucleus	0,037178297	0,544267532	Nucleus
Q9H9A6	Leucine-rich repeat-containing protein 40			0,029212075	1,840183043	Nucleus
Q9H9B4	Sideroflexin-1	Transport	Mitochondrion	0,030568829	1,288703449	Nucleus
Q9HDC9	Adipocyte plasma membrane-associated protein			0,007445066	0,822975776	Nucleus
Q9NR30	Nucleolar RNA helicase 2	Transcription	Nucleus	0,042639097	2,016705175	Nucleus
Q9NRF8	CTP synthase 2	Regulation of nucleotide metabolism	Nucleus	0,004050885	0,6756135	Nucleus
Q9NTK5	Obg-like ATPase 1		Nucleus	0,001003329	0,540163112	Nucleus
Q9NVA2	Septin-11	Cell cycle	Cytoplasm	0,029013932	1,526452672	Nucleus
Q9UGL1	Lysine-specific demethylase 5B	Regulation of nucleotide metabolism	Nucleus	0,041021724	2,003951507	Nucleus
Q9UI15	Transgelin-3	Regulation of transcription	Cytoplasm; Nucleus	0,011143049	1,826828779	Nucleus
Q9UJS0	Calcium-binding mitochondrial carrier protein Aralar2	Transport	Mitochondrion	0,009323279	1,509964493	Nucleus
Q9UKX3	Myosin-13	Cell growth	Cytoplasm	0,026295856	0,561942769	Nucleus
Q9UQE7	Structural maintenance of chromosomes protein 3	DNA repair	Nucleus	0,038980862	1,73005412	Nucleus
Q9Y277	Voltage-dependent anion-selective channel protein 3	Transport	Mitochondrion	0,003551196	1,255875827	Nucleus

Q9Y4F4	TOG array regulator of axonemal microtubules protein 1			0,016199351	2,085827533	Nucleus
Q9Y617	Phosphoserine aminotransferase	Metabolism; Energy pathways	Cytoplasm	7,79348E-05	0,482136366	Nucleus
Q9Y6C9	Mitochondrial carrier homolog 2	Cell communication	Mitochondrion	0,007181508	1,545978896	Nucleus

Table 10: List of proteins found altered in the total proteome of neurons

Accession	Description	Biological Process	Cellular component	p-Value	SCZ/CTRL ration	Fractions
A4FU69	EF-hand calcium-binding domain-containing protein 5			0,001101	2,724427411	3
A4UGR9	Xin actin-binding repeat-containing protein 2	Cytoskeletal anchoring	Cytoplasm	0,006756	1,413953388	2;3
A6NCE7	Microtubule-associated proteins 1A/1B light chain 3 beta 2		Cytoplasm	0,001417	1,99612969	2
B2RPK0	Putative high mobility group protein B1-like 1			0,032314	1,590743352	1;2;3
O00231	26S proteasome non-ATPase regulatory subunit 11	Protein metabolism	Cytoplasm; Nucleus	0,000029	1,428664042	2;3
O00232	26S proteasome non-ATPase regulatory subunit 12	Protein metabolism	Cytoplasm	0,008566	1,544545922	2;3
O00264	Membrane-associated progesterone receptor component 1	Cell communication	Plasma membrane	0,001459	2,322924147	1;3
O00429	Dynamin-1-like protein	Mitochondrion organization and biogenesis	Cytoplasm	0,006560	0,06391487	3
O00567	Nucleolar protein 56	Regulation of nucleotide metabolism	Nucleus	0,007330	3,842896338	1;2;3
O14737	Programmed cell death protein 5	Apoptosis	Cytoplasm; Nucleus	0,006358	3,836727237	3
O14818	Proteasome subunit alpha type-7	Protein metabolism	Cytoplasm	0,030521	1,893928387	1;2
O14979	Heterogeneous nuclear ribonucleoprotein D-like	Regulation of nucleotide metabolism	Nucleus	0,000637	2,150005885	1;2;3
O15078	Centrosomal protein of 290 kDa			0,015359	14,26648619	1
O15347	High mobility group protein B3	Regulation of nucleotide metabolism	Nucleus	0,005500	1,364309014	2
O15540	Fatty acid-binding protein_ brain	Transport	Cytoplasm	0,000087	3,125786118	1;2
O43237	Cytoplasmic dynein 1 light intermediate chain 2		Cytoplasm	0,000001	2,899117004	1;2
O43390	Heterogeneous nuclear ribonucleoprotein R	Regulation of nucleotide metabolism	Nucleus	0,008258	3,137959143	2;3
O43765	Small glutamine-rich tetratricopeptide repeat-containing protein	Protein metabolism	Cytoplasm	0,032581	1,576418524	1;3

	alpha					
O60282	Kinesin heavy chain isoform 5C	Transport	Cytoeskeleton	0,000039	1,423144029	1;2;3
O60506	Heterogeneous nuclear ribonucleoprotein Q	Regulation of nucleotide metabolism	Cytoplasm	0,003433	1,530731557	2;3
O75131	Copine-3	Transport	Cytoplasm	0,000171	3,456872861	2;3
O75347	Tubulin-specific chaperone A	Protein metabolism	Cytoskeleton	0,000026	3,840566927	1;2
O75382	Tripartite motif-containing protein 3	Cell growth	Cytoplasm	0,026096	0,076976149	3
O75390	Citrate synthase_ mitochondrial	Metabolism; Energy pathways	Cytoplasm; Mitochondrion	0,004420	2,646990187	1;2;3
O75396	Vesicle-trafficking protein SEC22b	Cell communication	Endoplasmic reticulum; Mitochondrion	0,012905	0,683726194	2
O75475	PC4 and SFRS1-interacting protein	Regulation of nucleotide metabolism	Cytoplasm; Nucleus	0,005454	1,833569047	1;2;3
O75874	Isocitrate dehydrogenase [NADP] cytoplasmic	Metabolism; Energy pathways	Cytoplasm	0,002529	1,683910315	1;2;3
O94986	Centrosomal protein of 152 kDa		Centrosome	0,031185	1,692258676	2
O95084	Serine protease 23	Protein metabolism		0,017703	0,317260583	3
O95232	Luc7-like protein 3	Regulation of nucleotide metabolism	Nucleus	0,018226	0,514816495	2;3
O95336	6-phosphogluconolactonase	Metabolism; Energy pathways		0,046459	5,101197384	2;3
O95747	Serine/threonine-protein kinase R1	Cell communication	Cytoplasm	0,000378	1,525816307	2;3
O95865	N(G)_N(G)-dimethylarginine dimethylaminohydrolase 2	Metabolism; Energy pathways	Cytoplasm	0,000182	3,075603829	1;2;3
O96006	Zinc finger BED domain-containing protein 1	Regulation of nucleotide metabolism	Nucleus	0,007524	2,052376373	3
P00338	L-lactate dehydrogenase A chain	Metabolism; Energy pathways	Cytoplasm	0,006554	1,683082038	2;3
P00367	Glutamate dehydrogenase 1_ mitochondrial	Metabolism; Energy pathways	Mitochondrion	0,047704	1,352938725	1;2;3
P00441	Superoxide dismutase [Cu-Zn]	Metabolism; Energy pathways	Cytoplasm	0,001274	5,280017128	1;2;3
P00558	Phosphoglycerate kinase 1	Metabolism; Energy pathways	Cytoplasm	0,021835	2,656123884	2;3
P00568	Adenylate kinase isoenzyme 1	Metabolism; Energy pathways	Cytoplasm	0,008022	1,675044517	2;3
P02768	Serum albumin	Transport	Extracellular	0,008951	2,143526733	1;2
P04075	Fructose-bisphosphate aldolase A	Metabolism; Energy pathways	Cytoplasm	0,033034	1,533279394	1;2;3

P04350	Tubulin beta-4A chain	Cell growth	Microtubule	0,039634	1,451155651	1;2;3
P04406	Glyceraldehyde-3-phosphate dehydrogenase	Metabolism; Energy pathways	Cytoplasm	0,012201	1,8649441	1;2;3
P05387	60S acidic ribosomal protein P2	Protein metabolism	Cytoplasm	0,000310	4,347939219	2;3
P05937	Calbindin	Cell communication	Cytoplasm; Nucleus	0,000001	5,206278496	2;3
P06733	Alpha-enolase	Metabolism; Energy pathways	Cytoplasm	0,006600	2,257962433	1;2;3
P06744	Glucose-6-phosphate isomerase	Metabolism; Energy pathways	Cytoplasm	0,008231	1,914536761	1;3
P06753	Tropomyosin alpha-3 chain	Cell growth	Cytoplasm	0,002648	1,990681561	1;2
P07195	L-lactate dehydrogenase B chain	Metabolism; Energy pathways	Cytoplasm	0,004090	1,713553818	1;2;3
P07305	Histone H1.0	Regulation of nucleotide metabolism	Nucleus	0,009729	0,194459798	1;3
P07339	Cathepsin D	Protein metabolism	Lysosome	0,004048	1,851891243	1;2;3
P07437	Tubulin beta chain	Cell growth	Cytoplasm	0,004369	1,818524126	1;2;3
P07602	Prosaposin	Cell communication	Lysosome	0,000001	2,641685059	2;3
P07737	Profilin-1	Cell growth	Cytoplasm	0,019891	2,656841125	2;3
P07864	L-lactate dehydrogenase C chain	Metabolism; Energy pathways	Cytoplasm	0,000025	1,825307604	2
P08133	Annexin A6	Cell communication	Endoplasmic reticulum	0,021518	1,900748397	1;2;3
P08727	Keratin_ type I cytoskeletal 19	Cell growth	Cytoplasm	0,046869	0,65532044	1;2
P09104	Gamma-enolase	Metabolism; Energy pathways	Cytoplasm	0,001541	2,244981042	1;2;3
P09429	High mobility group protein B1	Regulation of nucleotide metabolism	Nucleus	0,019200	1,677061838	1;2;3
P09471	Guanine nucleotide-binding protein G(o) subunit alpha	Cell communication	Plasma membrane	0,000006	2,175386959	2;3
P09493	Tropomyosin alpha-1 chain	Cell growth	Cytoskeleton	0,006066	2,550099831	1;2
P09622	Dihydrolipoyl dehydrogenase_ mitochondrial	Metabolism; Energy pathways	Mitochondrion	0,015963	1,753849584	3
P09936	Ubiquitin carboxyl-terminal hydrolase isozyme L1	Protein metabolism	Cytoplasm	0,000670	2,48447248	1;2;3
P0DMV8	Heat shock 70 kDa protein 1A		Cytoplasm; Nucleus	0,020307	1,439327653	1;2;3
P0DP24	Calmodulin-2	Cell communication	Cytoplasm; Nucleus	0,000143	11,36816528	1;2;3
P10155	60 kDa SS-A/Ro ribonucleoprotein	Regulation of nucleotide metabolism	Cytoplasm	0,011398	1,539351353	1;3
P10599	Thioredoxin	Metabolism; Energy pathways	Cytoplasm	0,008225	1,925543807	1;2

P10809	60 kDa heat shock protein_ mitochondrial	Protein folding	Mitochondrion	0,000800	1,673308344	1;2;3
P10909	Clusterin	Immune response	Cytoplasm	0,022458	2,180888369	1;2;3
P11137	Microtubule-associated protein 2	Cell growth	Cytoplasm	0,021320	1,562448768	1;2;3
P11142	Heat shock cognate 71 kDa protein	Protein metabolism	Cytoplasm	0,000927	1,832670037	1;2;3
P11216	Glycogen phosphorylase_ brain form	Metabolism; Energy pathways	Cytoplasm	0,003602	2,629010479	2;3
P11532	Dystrophin	Cell growth	Cytoplasm	0,028536	1,627002621	2
P11940	Polyadenylate-binding protein 1	Regulation of nucleotide metabolism	Cytoplasm; Nucleus	0,002924	0,284578632	3
P12268	Inosine-5'-monophosphate dehydrogenase 2	Metabolism; Energy pathways	Cytoplasm	0,022160	1,311036617	1;2;3
P12277	Creatine kinase B-type	Metabolism; Energy pathways	Cytoplasm	0,000945	2,567288508	1;2;3
P12956	X-ray repair cross-complementing protein 6	Regulation of nucleotide metabolism	Nucleus	0,047675	1,322064867	1;2;3
P13667	Protein disulfide-isomerase A4	Protein metabolism	Endoplasmic reticulum	0,009228	1,900324246	1;2;3
P13861	cAMP-dependent protein kinase type II-alpha regulatory subunit	Cell communication	Cytoplasm	0,012335	1,849934911	1;2;3
P14174	Macrophage migration inhibitory factor	Cell communication	Extracellular	0,000000	5,452247573	3
P14314	Glucosidase 2 subunit beta	Metabolism; Energy pathways	Endoplasmic reticulum	0,039305	1,362863062	1;2;3
P16152	Carbonyl reductase [NADPH] 1	Metabolism; Energy pathways	Cytoplasm	0,041778	2,237760986	2
P16401	Histone H1.5	Regulation of nucleotide metabolism	Nucleus	0,046248	2,036540468	1;2;3
P16949	Stathmin	Cell growth	Cytoplasm	0,000084	3,78954511	1;2;3
P16989	Y-box-binding protein 3	Regulation of nucleotide metabolism	Nucleus	0,022747	1,804122144	1;2
P17844	Probable ATP-dependent RNA helicase DDX5	Regulation of nucleotide metabolism	Nucleus	0,008272	1,449923646	1;2;3
P17987	T-complex protein 1 subunit alpha	Protein metabolism	Cytoplasm	0,021912	2,466740118	1;2;3
P21281	V-type proton ATPase subunit B_ brain isoform	Transport	Endosome	0,000010	1,558344576	1;2;3
P22087	rRNA 2'-O-methyltransferase fibrillarin	Regulation of nucleotide metabolism	Nucleus	0,038911	0,519202443	2;3
P22676	Calretinin	Cell communication	Cytoplasm	0,004405	4,810663523	1;2;3
P23381	Tryptophan--tRNA ligase_ cytoplasmic	Protein metabolism	Cytoplasm	0,024157	0,623273137	2

P23434	Glycine cleavage system H protein_ mitochondrial	Metabolism; Energy pathways	Mitochondrion	0,001400	1,911521005	2
P23528	Cofilin-1	Cell growth	Cytoplasm	0,014625	1,597391059	1;2;3
P24539	ATP synthase F(0) complex subunit B1_ mitochondrial	Metabolism; Energy pathways	Mitochondrion	0,010465	0,540466061	1;3
P25705	ATP synthase subunit alpha_ mitochondrial	Metabolism; Energy pathways	Mitochondrion	0,006083	2,845083522	1;2;3
P25789	Proteasome subunit alpha type-4	Protein metabolism	Cytoplasm	0,000010	2,103730426	2;3
P26038	Moesin	Cell growth	Cytoplasm	0,000106	1,771643573	2;3
P26368	Splicing factor U2AF 65 kDa subunit	RNA metabolism	Cytoplasm; Nucleus	0,032348	1,709346812	2;3
P26378	ELAV-like protein 4	Regulation of nucleotide metabolism	Nucleus	0,012280	4,418087716	2;3
P26641	Elongation factor 1-gamma	Protein metabolism	Cytoplasm	0,003988	2,174778121	1;2;3
P27695	DNA-(apurinic or apyrimidinic site) lyase	Regulation of nucleotide metabolism	Cytoplasm	0,000642	2,233503669	1;2;3
P28070	Proteasome subunit beta type-4	Protein metabolism	Cytoplasm	0,001951	1,817225795	2
P28161	Glutathione S-transferase Mu 2	Metabolism; Energy pathways	Cytoplasm	0,032607	0,122635942	2;3
P30041	Peroxiredoxin-6	Metabolism; Energy pathways	Lysosome	0,029738	1,465155069	2;3
P30086	Phosphatidylethanolamine-binding protein 1	Cell communication	Cytoplasm	0,000235	2,670603154	2;3
P31323	cAMP-dependent protein kinase type II-beta regulatory subunit	Cell communication	Cytoplasm	0,032649	2,395304145	1;2;3
P32119	Peroxiredoxin-2	Metabolism; Energy pathways	Cytoplasm	0,000075	2,150091292	2;3
P33176	Kinesin-1 heavy chain	Cell growth	Mitochondrion	0,027703	2,228651969	1;2;3
P35232	Prohibitin	Cell communication	Mitochondrion	0,000221	1,569493465	1;2;3
P35580	Myosin-10	Cell growth	Cytoplasm	0,009957	1,640637533	1;2;3
P35749	Myosin-11	Cell growth	Cytoplasm	0,017217	1,551931028	1;2
P35998	26S proteasome regulatory subunit 7	Protein metabolism	Cytoplasm	0,000417	2,19289918	2;3
P36405	ADP-ribosylation factor-like protein 3	Cell communication	Cytoplasm	0,000757	2,174710584	3
P37108	Signal recognition particle 14 kDa protein	Protein metabolism	Cytoplasm	0,000015	1,732894835	2;3
P37198	Nuclear pore glycoprotein p62	Transport	Nucleus	0,000745	4,898039289	3
P38159	RNA-binding motif protein_ X chromosome	Regulation of nucleotide metabolism	Nucleus	0,007735	3,010859592	1;3
P39019	40S ribosomal protein S19	Protein metabolism	Nucleus	0,013595	1,74433533	1;3

P39687	Acidic leucine-rich nuclear phosphoprotein 32 family member A	Transcription	Endoplasmic reticulum	0,006737	2,017895473	1;2;3
P40227	T-complex protein 1 subunit zeta	Protein metabolism	Cytoplasm	0,039424	2,424869841	1;2;3
P40925	Malate dehydrogenase_ cytoplasmic	Metabolism; Energy pathways	Cytoplasm	0,001429	2,682650974	1;3
P40926	Malate dehydrogenase_ mitochondrial	Metabolism; Energy pathways	Mitochondrion	0,031708	1,352415375	1;2;3
P42166	Lamina-associated polypeptide 2_ isoform alpha			0,014914	1,582368835	1;2
P43487	Ran-specific GTPase-activating protein	Cell communication	Cytoplasm	0,034649	1,395639023	2
P43686	26S proteasome regulatory subunit 6B	Protein metabolism	Nucleus	0,000172	1,724158552	2;3
P45974	Ubiquitin carboxyl-terminal hydrolase 5	Protein metabolism	Extracellular	0,005219	0,5662373	2;3
P46782	40S ribosomal protein S5	Protein metabolism	Ribosome	0,012027	1,438527599	1;2;3
P46783	40S ribosomal protein S10	Protein metabolism	Ribosome	0,022989	0,279321508	2;3
P46821	Microtubule-associated protein 1B	Cell growth	Cytoplasm	0,004604	5,87930572	1;2;3
P48643	T-complex protein 1 subunit epsilon	Protein metabolism	Centrosome	0,008746	2,456875552	1;2;3
P48723	Heat shock 70 kDa protein 13	Protein metabolism	Endoplasmic reticulum	0,014553	1,586013019	3
P49006	MARCKS-related protein	Cell communication		0,031569	4,963617688	1
P49327	Fatty acid synthase	Metabolism; Energy pathways	Cytoplasm	0,017385	1,627448611	2
P49368	T-complex protein 1 subunit gamma	Protein metabolism	Cytoplasm	0,023073	1,664437048	1;2;3
P49411	Elongation factor Tu_ mitochondrial	Protein metabolism	Mitochondrion; Nucleus	0,002477	1,608616627	1;2;3
P49591	Serine--tRNA ligase_ cytoplasmic	Metabolism; Energy pathways	Cytoplasm	0,000170	6,085902228	1;2;3
P49721	Proteasome subunit beta type-2	Protein metabolism	Cytoplasm	0,023382	0,545905023	2;3
P49915	GMP synthase [glutamine-hydrolyzing]	Metabolism; Energy pathways		0,009031	0,458585862	1;3
P50213	Isocitrate dehydrogenase [NAD] subunit alpha_ mitochondrial	Metabolism; Energy pathways	Mitochondrion	0,000494	0,643514233	2
P50502	Hsc70-interacting protein	Cell communication	Lysosome	0,007255	2,548044191	1;2;3
P50914	60S ribosomal protein L14	Protein metabolism	Ribosome	0,000237	1,678852154	1;3
P51148	Ras-related protein Rab-5C	Cell communication	Endosome	0,020570	1,788211502	1;2;3
P51784	Ubiquitin carboxyl-terminal hydrolase 11	Protein metabolism	Nucleus	0,007860	2,627447501	2
P51858	Hepatoma-derived growth factor	Cell communication	Nucleus	0,009932	1,966736821	1;2
P52907	F-actin-capping protein subunit alpha-1	Cell growth	Cytoplasm	0,023834	1,650442742	1;2;3
P54136	Arginine--tRNA ligase_ cytoplasmic	Protein metabolism	Cytoplasm	0,001387	2,106776597	3
P54577	Tyrosine--tRNA ligase_ cytoplasmic	Metabolism; Energy pathways	Cytoplasm	0,027478	1,422940258	2;3

P54727	UV excision repair protein RAD23 homolog B	Regulation of nucleotide metabolism	Cytoplasm; Nucleus	0,019774	2,387665653	1;3
P55072	Transitional endoplasmic reticulum ATPase	Metabolism; Energy pathways	Cytoplasm	0,016113	4,596795152	1;2;3
P55209	Nucleosome assembly protein 1-like 1	Regulation of nucleotide metabolism	Cytoplasm; Mitochondrion	0,041993	1,638856919	2;3
P55854	Small ubiquitin-related modifier 3	Protein metabolism	Cytoplasm; Nucleus	0,000017	2,902791705	2
P56134	ATP synthase subunit f_ mitochondrial	Metabolism; Energy pathways	Mitochondrion	0,037842	0,385460168	3
P59768	Guanine nucleotide-binding protein G(I)/G(S)/G(O) subunit gamma-2	Cell communication		0,000548	2,434908073	2
P60174	Triosephosphate isomerase	Metabolism; Energy pathways	Cytoplasm	0,000083	3,913742323	1;2;3
P60660	Myosin light polypeptide 6	Cell growth	Cytoplasm	0,003606	2,591649563	2
P60709	Actin_ cytoplasmic 1	Cell growth	Cytoplasm	0,040687	2,932257282	1;2;3
P61026	Ras-related protein Rab-10	Cell communication	Nucleus	0,014351	1,750667202	3
P61088	Ubiquitin-conjugating enzyme E2 N	Protein metabolism	Nucleus	0,000016	1,990869761	3
P61266	Syntaxin-1B	Transport	Plasma membrane	0,028375	2,366590455	1;2
P61586	Transforming protein RhoA	Cell communication	Cytoplasm	0,008164	2,983594687	2;3
P61601	Neurocalcin-delta	Cell communication	Cytoplasm	0,030912	1,634865575	3
P61604	10 kDa heat shock protein_ mitochondrial	Protein metabolism	Mitochondrion	0,000009	2,778461817	1;3
P61981	14-3-3 protein gamma	Cell communication	Cytoplasm	0,048999	1,698868152	1;2;3
P62191	26S proteasome regulatory subunit 4	Protein metabolism	Cytoplasm	0,000278	2,717973768	2;3
P62269	40S ribosomal protein S18	Protein metabolism	Ribosome	0,024500	1,937082342	2;3
P62304	Small nuclear ribonucleoprotein E	Regulation of nucleotide metabolism	Nucleus	0,004857	0,158825875	3
P62328	Thymosin beta-4	Cell growth	Cytoplasm	0,001050	5,688866399	1
P62714	Serine/threonine-protein phosphatase 2A catalytic subunit beta isoform	Cell communication	Cytoplasm; Nucleus	0,032752	1,144638178	2;3
P62829	60S ribosomal protein L23	Protein metabolism	Ribosome	0,017132	1,89542136	3
P62917	60S ribosomal protein L8	Protein metabolism	Nucleus	0,007827	1,373061557	2
P62937	Peptidyl-prolyl cis-trans isomerase A	Protein folding	Cytoplasm; Mitochondrion	0,000006	2,687671822	1;2;3

P62987	Ubiquitin-60S ribosomal protein L40	Protein metabolism	Ribosome	0,000040	2,659383552	2;3
P63000	Ras-related C3 botulinum toxin substrate 1	Cell communication	Cytoplasm	0,000248	1,676853813	2;3
P63104	14-3-3 protein zeta/delta	Regulation of cell cycle	Cytoplasm	0,002786	2,037317413	1;2;3
P63208	S-phase kinase-associated protein 1	Protein metabolism	Nucleus	0,018562	1,484630943	2
P67809	Nuclease-sensitive element-binding protein 1	Regulation of nucleotide metabolism	Nucleus	0,023294	1,868567001	1;2
P67936	Tropomyosin alpha-4 chain	Cell growth	Cytoskeleton	0,014948	3,806361248	1;2;3
P68036	Ubiquitin-conjugating enzyme E2 L3	Protein metabolism	Cytoplasm	0,004306	4,940752027	3
P68371	Tubulin beta-4B chain	Cell growth	Cytoplasm	0,043237	1,940299338	1;2;3
P78559	Microtubule-associated protein 1A	Cell growth	Cytoplasm	0,000460	2,544974871	3
P80404	4-aminobutyrate aminotransferase_ mitochondrial	Metabolism; Energy pathways	Mitochondrion	0,027871	2,210104573	2;3
P83916	Chromobox protein homolog 1	Regulation of nucleotide metabolism	Nucleus	0,000477	1,967504985	3
P84077	ADP-ribosylation factor 1	Signal transduction	Golgi apparatus	0,029483	2,656101013	1;3
P84103	Serine/arginine-rich splicing factor 3	Regulation of nucleotide metabolism	Nucleus	0,004335	2,431538889	3
Q00610	Clathrin heavy chain 1	Cell growth	Cytoplasm	0,030669	1,908022019	2;3
Q02790	Peptidyl-prolyl cis-trans isomerase FKBP4	Metabolism; Energy pathways	Cytoplasm	0,001884	1,332204361	1;2;3
Q04760	Lactoylglutathione lyase	Metabolism; Energy pathways	Cytoplasm	0,001383	2,092829595	3
Q04917	14-3-3 protein eta	Cell communication	Cytoplasm	0,049326	1,871833099	1;2;3
Q05639	Elongation factor 1-alpha 2	Protein metabolism	Cytoplasm	0,019878	1,455816713	1;2;3
Q05682	Caldesmon	Cell growth	Cytoplasm	0,009880	2,705691034	1;2
Q06323	Proteasome activator complex subunit 1	Protein metabolism	Nucleus	0,004605	1,798822628	2
Q06830	Peroxiredoxin-1	Metabolism; Energy pathways	Cytoplasm	0,040068	1,941901288	1;2;3
Q07021	Complement component 1 Q subcomponent-binding protein_ mitochondrial	Immune response	Mitochondrion	0,004835	1,517730954	2;3
Q07866	Kinesin light chain 1	Signal transduction	Cytoplasm	0,001460	1,729718449	1;2;3
Q08043	Alpha-actinin-3	Cell growth	Cytoplasm	0,000317	1,472062324	2
Q09028	Histone-binding protein RBBP4	Regulation of nucleotide metabolism	Nucleus	0,013135	1,320136313	2;3

Q12765	Secernin-1	Immune response	Cytoplasm	0,014923	3,078739534	1;2;3
Q13098	COP9 signalosome complex subunit 1	Cell communication	Nucleus	0,000101	1,94210178	2;3
Q13153	Serine/threonine-protein kinase PAK 1	Cell communication	Plasma membrane	0,004535	6,488271134	2;3
Q13404	Ubiquitin-conjugating enzyme E2 variant 1	Cell differentiation	Nucleus	0,007012	1,516709669	2;3
Q13509	Tubulin beta-3 chain	Cell growth	Cytoplasm	0,009175	2,360523534	1;2;3
Q13620	Cullin-4B	Protein metabolism	Nucleus	0,017783	3,704437199	3
Q13885	Tubulin beta-2A chain			0,000246	1,965593106	1;2;3
Q14008	Cytoskeleton-associated protein 5	Mitosis	Centrosome	0,027123	1,50342356	2
Q14011	Cold-inducible RNA-binding protein	Cell communication	Nucleus	0,009220	2,179301066	1;2;3
Q14117	Dihydropyrimidinase	Regulation of nucleotide metabolism	Cytoplasm	0,000662	1,406999351	3
Q14141	Septin-6		Cytoplasm	0,008088	2,934877417	2;3
Q14195	Dihydropyrimidinase-related protein 3	Metabolism; Energy pathways	Cytoplasm	0,000812	3,428140731	1;2;3
Q14204	Cytoplasmic dynein 1 heavy chain 1	Metabolism; Energy pathways	Cytoplasm	0,004551	1,44211235	2;3
Q14240	Eukaryotic initiation factor 4A-II	Protein metabolism	Cytoplasm	0,000127	2,10519341	1;2;3
Q14247	Src substrate cortactin	Cell growth	Cytoplasm	0,028210	2,004139481	1;2;3
Q14257	Reticulocalbin-2	Cell communication	Endoplasmic reticulum	0,029599	1,651999573	1;2;3
Q14344	Guanine nucleotide-binding protein subunit alpha-13	Cell communication	Plasma membrane	0,032823	1,149779435	2
Q14498	RNA-binding protein 39	Regulation of nucleotide metabolism	Nucleus	0,027667	1,522493816	1;3
Q14576	ELAV-like protein 3	Regulation of nucleotide metabolism	Nucleus	0,001719	0,09289286	2;3
Q15058	Kinesin-like protein KIF14	Cell growth	Microtubule	0,010381	0,162533191	3
Q15063	Periostin	Cell communication		0,003422	0,025271161	3
Q15084	Protein disulfide-isomerase A6	Protein metabolism	Endoplasmic reticulum	0,005007	2,420062454	1;2;3
Q15102	Platelet-activating factor acetylhydrolase IB subunit gamma	Metabolism; Energy pathways	Cytoplasm	0,003112	1,759616448	1;2;3
Q15185	Prostaglandin E synthase 3	Protein metabolism	Cytoplasm	0,010390	1,704979434	1;3
Q15293	Reticulocalbin-1	Cell communication	Endoplasmic reticulum	0,000871	2,150265659	1;2;3
Q15365	Poly(rC)-binding protein 1	Regulation of nucleotide	Nucleus	0,048370	1,565494144	1;2;3

		metabolism				
Q15417	Calponin-3	Cell growth	Cytoplasm	0,000044	2,574997371	3
Q15435	Protein phosphatase 1 regulatory subunit 7	Regulation of nucleotide metabolism	Nucleus	0,000767	5,935875578	1;2;3
Q15631	Translin	Regulation of nucleotide metabolism	Nucleus	0,028200	1,437517269	2
Q15700	Disks large homolog 2	Cell communication	Plasma membrane	0,001751	1,772664327	2
Q15843	NEDD8	Protein metabolism	Nucleus	0,003854	4,456194812	1
Q16181	Septin-7	Cell communication	Cytoskeleton	0,019275	10,44709984	1;2;3
Q16543	Hsp90 co-chaperone Cdc37	Protein metabolism	Cytoplasm	0,000993	1,87419871	1;3
Q16555	Dihydropyrimidinase-related protein 2	Cell communication	Cytoplasm	0,000397	2,421927452	1;2;3
Q16629	Serine/arginine-rich splicing factor 7	Regulation of nucleotide metabolism	Nucleus	0,002531	2,250790013	1;2;3
Q16658	Fascin	Cell growth	Cytoplasm	0,039815	1,644114619	1;2;3
Q16698	2_4-dienoyl-CoA reductase_ mitochondrial	Metabolism; Energy pathways	Mitochondrion	0,003434	0,55541008	1;2;3
Q3ZCM7	Tubulin beta-8 chain	Cell growth		0,017338	1,539927587	1;2;3
Q53GQ0	Very-long-chain 3-oxoacyl-CoA reductase	Metabolism; Energy pathways	Endoplasmic reticulum	0,002213	0,652490858	2
Q53GS9	U4/U6.U5 tri-snRNP-associated protein 2	Protein metabolism	Nucleus	0,000088	1,59544169	3
Q562R1	Beta-actin-like protein 2			0,004534	1,453138889	2;3
Q5JWF2	Guanine nucleotide-binding protein G(s) subunit alpha isoforms XLas		Cytoplasm	0,030940	1,433181469	1;3
Q6H8Q1	Actin-binding LIM protein 2	Cell growth	Cytoplasm	0,002009	1,390526647	2
Q6NXG1	Epithelial splicing regulatory protein 1		Nucleus	0,008787	0,271658095	3
Q6P587	Acylpyruvase FAHD1_ mitochondrial		Mitochondrion	0,014301	1,299265211	3
Q6PCE3	Glucose 1_6-bisphosphate synthase	Metabolism; Energy pathways	Cytoplasm	0,005755	2,132171532	3
Q6PEY2	Tubulin alpha-3E chain	Cell growth		0,029850	1,631243281	1;2;3
Q6PIW4	Fidgetin-like protein 1	Cell cycle	Nucleus	0,004196	2,158070013	3
Q6S8J3	POTE ankyrin domain family member E		Plasma membrane	0,000036	5,261387464	1;2;3
Q71UI9	Histone H2A.V	Regulation of gene expression	Nucleus	0,004956	2,007182756	1;2;3

Q86Y82	Syntaxin-12	Transport	Endosome	0,000452	1,871330097	3
Q8IYB3	Serine/arginine repetitive matrix protein 1	Regulation of nucleotide metabolism	Nucleus	0,016809	0,421057444	3
Q8IYT4	Katanin p60 ATPase-containing subunit A-like 2	Metabolism; Energy pathways		0,042661	2,078808923	3
Q8N0Y7	Probable phosphoglycerate mutase 4	Metabolism; Energy pathways		0,045956	0,571492472	2;3
Q8N1G4	Leucine-rich repeat-containing protein 47		Cytoplasm	0,010122	1,458840997	2;3
Q8N1N0	C-type lectin domain family 4 member F	Cell communication	Plasma membrane	0,000126	1,895356986	3
Q8N283	Ankyrin repeat domain-containing protein 35			0,012977	1,933920009	3
Q8N446	Zinc finger protein 843			0,024281	2,265420921	3
Q8N4C6	Ninein	Cell growth	Centrosome	0,003816	1,458044438	2
Q8N568	Serine/threonine-protein kinase DCLK2	Cell communication		0,041562	2,306858292	3
Q8N5K1	CDGSH iron-sulfur domain-containing protein 2		Plasma membrane	0,000148	2,480130777	3
Q8N6D5	Ankyrin repeat domain-containing protein 29			0,001532	2,279329882	3
Q8NB46	Serine/threonine-protein phosphatase 6 regulatory ankyrin repeat subunit C			0,004422	9,057306503	3
Q8NFI4	Putative protein FAM10A5			0,008676	2,136001501	1;2;3
Q8WXF1	Paraspeckle component 1	Regulation of nucleotide metabolism	Nucleus	0,006365	1,855020049	2;3
Q8WZA9	Immunity-related GTPase family Q protein			0,000798	3,349862763	1;2;3
Q92688	Acidic leucine-rich nuclear phosphoprotein 32 family member B		Nucleus	0,001681	1,826826651	2;3
Q92734	Protein TFG			0,000041	1,623976204	2
Q92804	TATA-binding protein-associated factor 2N	Signal transduction	Cytoplasm	0,014965	4,179453218	1;2;3
Q92841	Probable ATP-dependent RNA helicase DDX17	Regulation of nucleotide metabolism	Nucleus	0,033428	1,583202872	1;2;3
Q92878	DNA repair protein RAD50	Regulation of nucleotide metabolism	Nucleus	0,000316	2,789032089	3
Q93045	Stathmin-2	Cell communication	Golgi apparatus	0,001125	3,36085983	1;2
Q96JE9	Microtubule-associated protein 6	Cell growth	Cytoskeleton	0,007744	3,79347076	1;2;3
Q96M83	Coiled-coil domain-containing protein 7			0,007578	1,667058536	2
Q96P16	Regulation of nuclear pre-mRNA domain-containing protein 1A	Regulation of nucleotide	Nucleus	0,017844	0,491072812	3

		metabolism				
Q99497	Protein/nucleic acid deglycase DJ-1	Regulation of nucleotide metabolism	Cytoplasm	0,031686	2,840061794	1;2;3
Q99536	Synaptic vesicle membrane protein VAT-1 homolog	Transport	Cytoplasm	0,049415	2,294719181	1;2;3
Q99733	Nucleosome assembly protein 1-like 4	Regulation of nucleotide metabolism	Nucleus	0,000205	1,726657824	1;2;3
Q99961	Endophilin-A2	Cell communication	Cytoplasm; Nucleus	0,021414	1,30328806	2
Q9BPW8	Protein NipSnap homolog 1		Mitochondrion	0,031444	1,304884688	2;3
Q9BS26	Endoplasmic reticulum resident protein 44	Protein metabolism	Endoplasmic reticulum	0,010718	1,257953912	2
Q9BSA4	Protein tweety homolog 2		Plasma membrane	0,007477	1,44302528	2
Q9BUF5	Tubulin beta-6 chain	Cell growth		0,008748	2,082584317	1;2;3
Q9BUT1	3-hydroxybutyrate dehydrogenase type 2	Metabolism; Energy pathways		0,039248	1,759711645	1;3
Q9BVA1	Tubulin beta-2B chain	Cell growth		0,001906	1,853167562	1;2;3
Q9BYT8	Neurolysin_ mitochondrial	Protein metabolism	Cytoplasm	0,012099	2,045797909	1;2
Q9C040	Tripartite motif-containing protein 2		Cytoplasm	0,000328	3,518496209	2
Q9H0C8	Integrin-linked kinase-associated serine/threonine phosphatase 2C	Cell death	Cytoplasm	0,049368	0,279169919	3
Q9H1E3	Nuclear ubiquitous casein and cyclin-dependent kinase substrate 1	Regulation of nucleotide metabolism	Nucleus	0,000901	2,797512718	1
Q9H9B4	Sideroflexin-1	Transport	Mitochondrion	0,004657	0,772798774	2
Q9HB07	UPF0160 protein MYG1_ mitochondrial		Cytoplasm	0,001033	1,315226246	2;3
Q9HC38	Glyoxalase domain-containing protein 4		Mitochondrion	0,023117	2,22854275	2;3
Q9NQP4	Prefoldin subunit 4	Protein metabolism	Cytoplasm	0,018024	2,413012791	1
Q9NR31	GTP-binding protein SAR1a	Cell communication	Endoplasmic reticulum	0,001929	0,042692402	3
Q9NRR5	Ubiquilin-4	Protein metabolism	Nucleus	0,019276	0,512314356	3
Q9NUD5	Zinc finger CCHC domain-containing protein 3	Regulation of nucleotide metabolism		0,007861	0,336560004	3
Q9NVA2	Septin-11	Cell cycle	Cytoplasm	0,000693	4,199053245	1;2;3
Q9NYF8	Bcl-2-associated transcription factor 1	Regulation of nucleotide metabolism	Nucleus	0,047403	0,226310547	1;3
Q9NZI8	Insulin-like growth factor 2 mRNA-binding protein 1	Regulation of nucleotide	Cytoplasm	0,044945	1,601448506	1;2;3

		metabolism				
Q9P258	Protein RCC2	Cell growth	Nucleus	0,021411	0,15633396	1;3
Q9P2K5	Myelin expression factor 2	Regulation of nucleotide metabolism	Nucleus	0,024166	1,772039706	1;3
Q9P2M7	Cingulin	Cell growth	Nucleus	0,000639	2,652951999	3
Q9UEE9	Craniofacial development protein 1	Cell growth	Cytoplasm	0,000366	5,036446775	3
Q9UHD8	Septin-9	Cell proliferation	Cytoskeleton	0,008033	0,172771629	3
Q9UHD9	Ubiquilin-2	Protein metabolism	Cytoplasm	0,002383	3,152110424	1;3
Q9UHV9	Prefoldin subunit 2	Protein metabolism		0,000001	3,845595515	3
Q9UI15	Transgelin-3		Cytoplasm	0,000331	3,063017519	1;2;3
Q9UK76	Jupiter microtubule associated homolog 1	Cell communication		0,001224	2,367420024	2;3
Q9UMX0	Ubiquilin-1	Protein metabolism	Cytoplasm	0,005438	2,957739768	3
Q9UNZ2	NSFL1 cofactor p47	Cell growth	Nucleus	0,003702	1,944052929	1;2;3
Q9Y230	RuvB-like 2	Regulation of nucleotide metabolism	Nucleus	0,002725	1,329116946	2;3
Q9Y265	RuvB-like 1	Regulation of nucleotide metabolism	Nucleus	0,042735	1,604672961	1;2;3
Q9Y277	Voltage-dependent anion-selective channel protein 3	Transport	Mitochondrion	0,040515	2,303247957	3
Q9Y281	Cofilin-2	Cytoskeleton organization	Cytoplasm	0,000202	1,691703183	1;2;3
Q9Y3E1	Hepatoma-derived growth factor-related protein 3	Cell growth	Nucleus	0,010543	1,494147481	1;2
Q9Y536	Peptidyl-prolyl cis-trans isomerase A-like 4A			0,000958	2,183576372	1;3

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Em observância ao **§5º do Artigo 1º da Informação CCPG-UNICAMP/001/15**, referente a Bioética e Biossegurança, declaro que o conteúdo de minha Dissertação de Mestrado, intitulada "***Caracterização do proteoma mitocondrial e nuclear de células neurais derivadas de iPSCs de pacientes com esquizofrenia***", desenvolvida no Programa de Pós-Graduação em Biologia Funcional e Molecular do Instituto de Biologia da Unicamp, não versa sobre pesquisa envolvendo seres humanos, animais ou temas afetos a Biossegurança.

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Declaração

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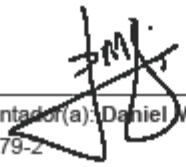
Assinatura : 
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