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# Genetic variants associated with ectopic calcifications

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#### ABSTRACT

Diffuse idiopathic skeletal hyperostosis (DISH) is a common skeletal disorder characterized by the presence of new bone formation in ligaments and entheses. DISH can co-exist with Chondrocalcinosis (CC) and it has been suggested that both diseases share the same pathogenic mechanism. To date, two genes, COL6A1 and FGF2, have been shown to have a weak positive association with DISH susceptibility. The main objective of this thesis was to investigate the genetic basis of the DISH/CC disease, making use of Next Generation Sequencing technology, association and expression studies, in a group of DISH/CC samples from the Azores biobank. Two regulatory variants in the RSPO4 gene were significantly more frequent in controls than in DISH/CC patients. These may protect against the DISH/CC phenotype, possibly by altering gene expression of the RSPO4 gene. Using whole exome sequencing we identified a significant association between the DISH/CC disease and a genetic variant in BMP4 (rs17563), a gene involved in endochondral bone formation. Another of the candidate genes associated with DISH/CC was ABCC6 that is of relevance in ectopic calcification disorders. Although inconclusive, the expression studies performed in human cartilage tissue indicated overexpression of ABCC6 in DISH and CC patients relative to the controls, raising the hypothesis that this gene may be involved in calcium pyrophosphate formation in DISH and CC. A comparative approach using teleosts revealed that the abcc6 gene is expressed in skin but was not associated with ectopic calcification of the scales. Furthermore, comparative genomics revealed the *abcc6* has only been retained in the genome of bony vertebrates. In summary, I identify for the first time potential gene variants that protect (RSPO4) or predispose (BMP4) to DISH/CC. The relevance of the ABCC6 gene in this phenotype remains to be proven. It is unlikely that one major gene is responsible for DISH/CC and instead it appears to be a polygenic disease.

Keywords: Chondrocalcinosis, DISH, WES, BMP4, ABCC6, RSPO4.

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#### **RESUMO**

A hiperostose idiopática difusa do esqueleto (DISH) é uma doença musculoesquelética comum caracterizada pela formação óssea de novo em ligamentos e enteses. A DISH pode coexistir com a condrocalcinose e por isso tem sido sugerido que ambas partilham o mesmo mecanismo patogénico. *COL6A1* e *FGF2* são os dois genes de suscetibilidade conhecidos com uma ligação genética fraca à DISH.

O objetivo principal desta tese foi investigar a genética da DISH/CC, utilizando a sequenciação de nova geração e estudos de associação e expressão, num grupo de amostras de doentes com DISH/CC do AZORBIO.

Duas variantes na região reguladora do gene *RSPO4* são significativamente mais frequentes nos controlos do que nos doentes DISH/CC. Estas variantes podem afetar a expressão do gene, conferindo proteção à doença. Utilizando a sequenciação exómica identificamos uma associação significativa entre a DISH/CC e a variante genética rs17563 no gene *BMP4*, um gene diretamente envolvido na formação óssea endocondral.

Outro gene candidato estudado foi o *ABCC6*, que parece ser relevante em doenças caracterizadas por calcificações ectópicas. Embora inconclusivos, os estudos de expressão em tecidos de cartilagem humana mostraram que o gene *ABCC6* apresenta expressão superior nos doentes DISH e CC em relação a um doente controlo, levantando a hipótese de que este aumento de expressão poderá estar envolvido com a deposição de cristais de pirofosfato de cálcio nestes doentes. Uma abordagem comparativa utilizando teleósteos revelou que o gene *abcc6* está expresso na pele dos peixes, mas não está associado com a calcificação ectópica das escamas. Além disso, nos resultados da genómica comparativa o gene *abcc6* só foi encontrado no genoma de vertebrados ósseos, indicando que este gene poderá estar envolvido em inovações específicas dos vertebrados.

Concluindo, foi identificado pela primeira vez potenciais variantes genéticas que protegem (*RSPO4*) ou predispõem (*BMP4*) à DISH/CC. A relevância do gene *ABCC6* neste fenótipo necessita de ser provada. É pouco provável que um único gene esteja envolvido no aparecimento de DISH/CC, e por isso a doença parece ser poligénica.

Palavras-chave: Condrocalcinose, DISH, WES, BMP4, ABCC6, RSPO4.

#### **RESUMO ALARGADO**

A hiperostose idiopática difusa do esqueleto (DISH, MIM 106400) é uma doença musculoesquelética comum caracterizada pela calcificação progressiva e ossificação de tecidos moles, em particular ligamentos e enteses [1, 2]. Em alguns casos a deposição óssea pode levar a alterações biomecânicas do sistema músculo-esquelético e/ou a formação de massas cervicais obstrutivas [3, 4]. Desconhece-se a prevalência e a incidência exata da DISH, porém sabe-se que é mais frequente no sexo masculino e que a sua prevalência aumenta com a idade, afetando principalmente os indivíduos com mais de 40 anos [5]. Várias evidências sugerem que fatores genéticos estão envolvidos na etiologia da DISH, como a existência de casos familiares com início precoce (na terceira ou quarta década de vida) [29], e a maior frequência da DISH em uma raça específica de cães, a raça boxer [30, 31]. Variantes de suscetibilidade para a DISH foram encontradas nos genes COL6A1 e FGF2, no entanto estas estão localizadas em regiões não codificantes da proteína e são consideradas variantes comuns na população em geral, o que sugere um efeito menor ou não patogénico. Embora os genes COL6A1 e FGF2 pareçam estar envolvidos na suscetibilidade da DISH, a genética da DISH é ainda desconhecida.

A DISH pode coexistir com um grande número de outras doenças reumáticas, sendo exemplos destas a ossificação do ligamento lateral posterior (OPLL, MIM 602475) [6], Ossificação do ligamento flavum [8], Espondilite anquilosante (AS) (MIM 106300) [7-21] e Condrocalcinose (CC) [22, 23]. A coexistência da DISH com CC é muito comum na ilha Terceira (Açores) e parece ser uma manifestação endémica. Estudos anteriores, conduzidos pelo nosso grupo, levaram à identificação e caracterização de doze famílias com início precoce de DISH e/ou CC levando o grupo a sugerir que ambas as doenças, designadas como fenótipo DISH/CC, poderiam partilhar o mesmo mecanismo patogénico. Estas famílias parecem apresentar um tipo familiar precoce, autossómica dominante, com um fenótipo que inclui calcificações entesopáticas periféricas e axiais [24]. Um fenótipo similar foi relatado em outros estudos no passado [25, 26]. Estes doentes têm a sua qualidade de vida gravemente comprometida devido ao início precoce e ao fenótipo exuberante.

Este estudo foi realizado nos Açores, um arquipelago português localizado no meio do Oceano Atlântico, numa pequena ilha com apenas 56.467 habitantes, Ilha Terceira (Census, 2011). Em populações isoladas ou com mobilidade reduzida, como é o caso da Ilha Terceira, existe uma elevada taxa de casamentos consanguíneos e uma alta probabilidade de ancestralidade comum que é particularmente valiosa no mapeamento de genes envolvidos em doenças monogénicas mendelianas e, portanto, investigar o fenótipo DISH/CC nessa população aumenta a probabilidade de identificar o gene causador desta patologia. Na ilha Terceira Açores foi estabelecido um biobanco com produtos biológicos e dados associados para a população da Ilha Terceira. Os Biobancos são essenciais na investigação, por conterem coleções de amostras e dados armazenados de forma organizada. Actualmente, o biobanco dos Açores (AZORBIO) do Serviço Especializado de Epidemiologia e Biologia Molecular (SEEBMO) tem uma colecção de material biológico e dados associados de doentes açorianos de diferentes patologias [27].

O objetivo principal desta tese foi investigar doentes e famílias afetadas com o fenótipo DISH/CC para determinar a sua base genética. Para atingir esse objetivo, foram utilizados diferentes estudos que se encontram divididos ao longo dos capítulos desta tese.

No capítulo 2 foi realizada uma revisão da literatura sobre a genética da ossificação dos ligamentos da coluna vertebral (OSL). Com base na sua análise verifica-se que a contribuição genética para o desenvolvimento destas ossificações parece ser inegável. A existência de casos familiares com início precoce (terceira/quarta década de vida) [1], a existência de modelos animais [2, 3], e a existência de uma grande variedade de genes com associação positiva, essencialmente na OPLL, são evidências que reforçam ainda mais esta predisposição genética. É provável que esta contribuição genética não seja causada por um único gene com grande efeito (padrão de herança mendeliana), mas sim por uma variedade de variantes em diversos genes. Para além disso existem também múltiplos fatores exógenos que podem estar envolvidos na patogénese da doença, mas provavelmente em indivíduos suscetíveis. Portanto, a OSL parece ser genética e multifatorial. A presença de OSL tem também sido associada com inúmeros distúrbios metabólicos de diferentes etiologias. A coexistência de ossificação dos ligamentos da coluna espinhal com alguns transtornos monogénicos tem sido relatada na literatura e estes normalmente estão associados a uma perturbação na homeostasia do cálcio e fosfato, levando-nos acreditar que os genes envolvidos nestes processos são bons candidatos para a etiologia da OSL.

No **capítulo 3** são apresentados os materiais e métodos utilizados ao longo de todo o trabalho. No **capítulo 4**, encontra-se descrito um caso de CC associado à síndrome de Gitelman. A CC é caracterizada pela deposição de sais de cálcio na cartilagem articular, membranas sinoviais e, em alguns casos, nos tecidos moles periarticulares [28]. Os sais

depositados são normalmente compostos por pirofosfato de cálcio desidratado (CPP), embora outros sais de cálcio, como a hidroxiapatite, também possam ser encontrados [28]. Sabe-se que mutações no gene ANKH, em algumas famílias, são a causa monogénica de CC articular familiar (CCAL2, MIM 118600). Esse gene está relacionado com o metabolismo do pirofosfato inorgânico (PPi) sendo responsável pelo transporte deste pela membrana. A CC pode ocorrer sob 3 formas: 1) hereditária, 2) esporádica, e 3) associada a doenças metabólicas como hiperparatiroidismo, hemacromatose, doença de Wilson, Síndrome de Gitelman entre outras. A síndrome de Gitelman é uma doença genética renal autossómica recessiva, causada por uma mutação no gene SLC12A3, o qual codifica o transportador NCCT (thiazide-sensitive sodium-chloride cotransporter) expresso no túbulo contornado distal do rim. A síndrome é caracterizada por alcalose metabólica, hipocalemia, hipocalciúria e hipomagnesiémia. A hipomagnesiémia está associada a uma redução na concentração de magnésio celular e pertence à lista de causas de CC secundária associada a síndromes metabólicos. A hipomagnesiémia parece favorecer a CC através da elevação intra-articular dos níveis de PPi extracelular e/ou através da redução da solubilidade dos cristais de CPP [4]. Neste estudo foi identificado um caso de CC associada a hipomagnesiémia causada por uma mutação patogénica homozigótica no gene SLC12A3. Alguns familiares deste doente são portadores da mutação heterozigótica e apresentavam CC.

No **capítulo 5** foi realizado um estudo de sequenciação de dois genes candidatos ao fenótipo DISH/CC, o gene *LEMD3* e o gene *RSPO4* para verificar uma possível associação com o fenótipo em estudo. Foram identificadas várias variantes no gene *RSPO4*, no entanto não foram observadas diferenças estatisticamente significativas na ocorrência destas variantes genéticas no fenótipo DISH/CC relativamente ao grupo controlo. Duas variantes na região reguladora do gene *RSPO4* (rs146447064 e rs14915407) são significativamente mais frequentes em controlos do que em doentes DISH/CC, indicando que estas podem eventualmente afetar a expressão do gene, conferindo proteção à doença. A variante estudada no gene *LEMD3* é extremamente rara e parece não estar envolvida com o fenótipo em estudo.

No **capítulo 6** desta tese descreve-se o estudo de sequenciação exómica realizado em quatro indivíduos das 12 famílias anteriormente referidas com o objetivo de determinar o possivel gene envolvido no fenótipo DISH/CC, aparentemente autossómico dominante. A sequenciação completa do exoma é uma técnica capaz de identificar rapidamente todas as variantes codificantes no genoma de um individuo. Esta técnica tem sido uma ferramenta

essencial para a deteção de variantes patogénicas causadoras de doenças. Das filtragens efetuadas surgiram vinte e uma variantes genéticas relevantes, em dezassete genes que estão direta ou indiretamente relacionados com a mineralização e/ou ossificação. Identificamos uma associação significativa entre a doença DISH/CC e a variante genética rs17563 no gene *BMP4*, um gene diretamente envolvido na formação óssea endocondral (p = 0,009, OR = 2,331).

No capítulo 7 descreve-se o estudo do gene ABCC6, um gene que surgiu das filtragens da sequenciação exómica. Este gene contém 31 exões e está localizado no cromossoma 16, assim como os seus dois pequenos pseudogenes ABCC6P1 e ABCC6P2. O gene codifica o transportador MRP6 que pertence à família de transportadores da membrana dependentes de ATP. Pensa-se que está envolvido no transporte de adenosinas trifosfato. O MRP6 é composto por 1503 aminoácidos, três segmentos membranares, consistindo em 17 hélices hidrofóbicas e dois domínios de ligação a nucleótidos. A proteína apresenta expressão ubiquitária no entanto é principalmente no fígado e rins que esta se expressa mais. Alterações neste gene e também no gene ENPP1, já anteriormente designado como associado à OPLL, estão associadas ao Pseudoxantoma Elasticum (PXE, MIM 264800) e à calcificação arterial generalizada da infância (GACI2, MIM 614473). A PXE é caracterizada por calcificações das fibras elásticas na pele, artérias, trato gastrointestinal e retina. A PXE é geralmente autossómica recessiva podendo ser esporádica ou dominante com penetrância variável. A GACI, doença autossómica recessiva, é caracterizada por calcificações na lâmina elástica interna das artérias musculares e estenose. O gene ABCC6 foi considerado um candidato ideal porque: 1) mutações genéticas neste gene são a maior causa da PXE, e em alguns casos podem causar GACI, doenças que tal como a DISH/CC causam calcificações ectópicas; 2) a maioria dos casos de GACI são devidos a mutações no gene ENPP1, levando-nos a pensar que os dois genes podem ter processos fisiológicos comuns e, para além disso, o gene ENPP1 foi anteriormente estudado por nós e por outros grupos por poder estar associado à CC; 3) recentemente foi estudado a associação de um transportador de adenosinas - ENT1- com a DISH; como o gene ABCC6 pode também ser um transportador de adenosinas, leva-nos também a pensar que pode haver algum mecanismo fisiológico comum entre os dois transportadores. A variante rara não sinónima rs41278174 no gene ABCC6 foi encontrada num doente. A variante é altamente conservada entre mamíferos, e de acordo com os algoritmos utilizados (SIFT e PolyPhen) pode afetar a proteína. Verificámos que esta variante é frequente na ilha Terceira- Açores nomeadamente em controlos masculinos quando comparados com doentes do sexo masculino (DISH/CC e AS). Esta variante está localizada no domínio transmembranar da proteína MRP6, um domínio essencial na especificidade do substrato de transportadores ABC [25]. Mutações no domínio transmembranar também podem afetar a integração da proteína na membrana celular levando a uma perda de função [26]. A variante rs41278174 poderá alterar a especificidade do transportador MRP6 nos homens, conferindo um efeito protetor através de um mecanismo desconhecido. Foram encontradas outras variantes neste gene mas de acordo com o estudo de associação não apresentam associação positiva com a DISH/CC. Os estudos de expressão por qPCR mostraram que os transcritos de *ABCC6* são pouco expressos em tecidos de cartilagem humana, no entanto verificou-se que nos doentes DISH e CC o gene apresentava expressão superior em relação a um doente controlo. Este aumento de expressão poderá estar envolvido com a formação de cristais de CPP em doentes DISH e CC.

No **capítulo 8** foi realizado uma abordagem comparativa utilizando teleósteos, que revelou que o gene *abcc6* está expresso na pele mas não está associado com a calcificação ectópica das escamas. Além disso, na genómica comparativa o gene *abcc6* só foi encontrado no genoma de vertebrados ósseos, indicando que este gene poderá estar envolvido com inovações específicas dos vertebrados.

Os resultados deste trabalho sugerem que vários genes parecem estar envolvidos na etiologia do fenótipo DISH/CC. A associação positiva encontrada para o gene *BMP4* deverá ser reproduzida com um maior número de doentes para verificar a sua veracidade. A expressão aumentada do gene *ABCC6* encontrada nos doentes DISH e CC deverá também ser confirmada com mais amostras de cartilagem a fim de esclarecer e confirmar se este gene está mesmo envolvido na formação de deposição de CPP nos doentes com DISH e CC.

Palavras-chave: Condrocalcinose, DISH, WES, *BMP4*, *ABCC6*, *RSPO4*, calcificações ectópicas, variantes genéticas, genes, Açores, PPi, CPP.

#### LIST OF ABBREVIATURES

## A

A-Affected A1-allele1 A2- allele 2 AA- Amino acids A-Allelic test ABC- ATP binding cassete ABCC6,1,3 - ATP-binding cassete subfamily C, member 6, 1,3 ABCC6P1- ATP-binding cassette subfamily C, member 6 pseudogene 1 ABCC6P2- ATP-binding cassette subfamily C, member 6 pseudogene 2 ABCG2- ATP Binding Cassette Subfamily G Member 2 **ABI-SOLiD-** Applied Biosystems Sequencing by Oligonucleotide Ligation and Detection Aca-Anolis carolinensis ACE- Angiotensin I Converting Enzyme ACVR1- Activin A receptor, type I AD-Autosomal dominant Aga-Anopheles gambiae AHSG: Alpha 2-Heremans-Schmid glycoprotein AIP- Aryl hydrocarbon receptor-interacting protein Ala- alanine ALPL- Alkaline Phosphatase, Liver/Bone/Kidney AMDH- Acromesomelic dysplasia, Hunter-Thompson Ame-Astyanax mexicanus Amel-Apis mellifera

AMER3- APC Membrane Recruitment Protein 3 AMP- Adenosine monophosphate ANKH- progressive ankyloses protein homolog ANO6- Anoctamin 6 ANTXR2- Anthrax Toxin-receptor 2 AOMS1,2- Abdominal obesity-metabolic syndrome 1,2 AP2S1- Adaptor Related Protein Complex 2 Sigma 1 Subunit **AR-** Autosomal recessive ARL6IP1- ADP ribosylation factor like protein 6 interacting protein 1 AS- Ankylosing spondylitis as- altered splicing ASARM- Acidic serine- and aspartate- rich MEPE- associated motif ASPN-Asporin At- Annealing temperature ATP- Adenosine triphosphate AVH- Ankylosing Vertebral Hyperostosis AZORBIO- AZOresBIObank

#### B

BC- Breast cancer
Bfl- Branchiostoma floridae
BID- BH3 Interacting Domain Death Agonist
BMP- Bone Morphogenetic Proteins
BMP2- Bone morphogenetic protein 2
BMP4- Bone morphogenetic protein 4
BMP9- Bone morphogenetic protein 9
BMPR1B- Bone morphogenetic protein
receptor type 1B
BOS- Buschke ollendorff syndrome
BSA- Bovine Serum Albumin

Bta-Bos taurus

#### C

C2H2- Cys2His2-like CASR- calcium-sensing receptor **CC-** Chondrocalcinosis CCAL1- Chondrocalcinosis 1 CCAL2- Chondrocalcinosis 2 CCDC91- Coiled-coil domain containing 91 CCMAR- Centro de Ciências do Mar CD4 cells- cluster of differentiation 4 cells CDKN1<sub>β</sub>- Cyclin-dependent kinase inhibitor 1β cDNA- Complementary DNA Cel- Caenorhabditis elegans CFTR- Cystic Fibrosis transmembrane **Conductance Regulator** CHISQ- Chi- squared CHISQ- Chi-squared Chr- chromosome CLCN5- Chloride voltage-gated channel 5 CLCNKB- Chloride channel clc-kb Cluf- Canis lupus familiaris CMDD- Craniometaphyseal dysplasia cMGP- carboxylated Matrix Gla Protein Cmi- Callorhinchus milii COL11A2- Collagen Type XI Alpha 2 Chain COL17A1- Collagen Type XVII Alpha 1 Chain COL1A1- Collagen Type I Alpha 1 Chain COL2A1- Collagen Type II Alpha 1 Chain COL6A1- Collagen Type VI Alpha 1 Chain COL6A4P1- collagen Type VI, alpha-4, pseudogene 1 COQ7- Coenzyme Q7 CPP- calcium pyrophosphate CPPD- Calcium pyrophosphate deposition disease

Csa- *Ciona intestinalis* C-Spine- Cervical spine Ct- cycle threshold Ct- Cycle threshold CTD- Citoplasmatic domain Cys- cystein

#### D

Dgg- dragon fish DISH- Diffuse idiopathic skeletal hyperostosis DKK1- Dickkopf WNT Signaling Pathway Inhibitor 1 Dla- Dicentrarchus labrax **DM-** Diabetes mellitus Dme-Drosophila melanogaster DMP- Deborah Mary Power DMP1- Dentin matrix acidic phosphoprotein 1 DMSO- Dimethyl sulfoxide DNA- Deoxyribonucleic acid DNase- Deoxyribonuclease DNase- Deoxyribonuclease Dno- Dasypus novemcinctus Dpu- Daphnia pulex DR- Diabetic retinopathy DRD2- Dopamine receptor Dre- Danio rerio DYRK1B- Dual specificity Tyrosine Phosphorylation regulated kinase 1<sup>β</sup>

## E

E- Exon EDIL3- EGF Like Repeats And Discoidin Domains 3 EDTA- Ethylenediamine tetraacetic acid *ENPP1 /NPPS/PC1*- ectonucleotide pyrophosphatase/phosphodiesterase 1 *ENT1*- Equilibrative Nucleoside Transporter 1 ER- Endoplasmic reticulum *ERAP1*- endoplasmic reticulum aminopeptidase 1 *ESR1*- Estrogen Receptor 1 EST- Expressed sequence tag EtOH- Ethanol ExoSAP-IT- Exonuclease I and Shrimp Alkaline Phosphatase Ext- extracellular

#### F

F- Female FAM- Fluorescein amidite FGF2- Fibroblast growth factor 2 FGF23- Fibroblast growth factor 23 FGFR1- Fibroblast Growth Factor Receptor 1 FHH- Familial Hypocalciuric hypercalcemia FLNC- Filamin C FOPNL- FOP related protein FRZB- Frizzled-related protein 1 FZD5- Frizzled Class Receptor 5

# G

Gac- Gasterosteus aculeatus GACI- Generalized arterial calcification of infancy GCM2- Glial cells missing Homolog 2 GDF5- Growth/differentiation factor 5 GERP- Genomic Evolutionary Rate Profiling Gga- Gallus gallus GH- Growth hormone Gln- Glutamine GLUT9- Glucose transporter 9 Gmo- Gadus morhua GNA11- G Protein Subunit Alpha 11 GNAS1- Guanine nucleotide binding protein, alpha stimulating GPR10- G protein-coupled receptor 101 GS- Gitelman syndrome

# Η

HAPLN1- Hyaluronan And Proteoglycan Link Protein 1 HDL- High density lipoprotein HGD-Homogentisate 1,2-Dioxygenase HGMD- Human genetic mutation database HiDi formamide- highly deionized formamide His- histidine HLA- Human Leukocyte antigen HLA-B- Human Leukocyte antigen B HLA-DQA2- major histocompatibility complex, class II, DQ alpha 1 HOA1- Hydroxyacid oxidase 1 Hro-Helobdella robusta Hsa-Homo sapiens HSEIT- Hospital de Santo Espirito da Ilha Terceira HWE- Hardy – Weinberg equilibrium

# I

i- intron IBD- Identity by descent IBSP- Integrin binding sialoprotein *IFNG*-Interferon, Gamma *IGF1*- Insulin-like growth factor 1 IL-1- Interleukin-1 *IL-15RA*- Interleukin-15 Receptor Alpha IL-17- Interleukin-17 *IL-1β*- Interleukin-17 *IL-23*- Interleukin-23 IL-23R- Interleukin-23 receptor *IL-6*- Interleukin-6 IL-8- Interleukin-8 IPD-IMGT/HLA- Immuno Polymorphism Database- ImMunoGenetics information system for Human Leucocyte Antigene

### J

JAG1- Jagged 1 JBA- Jácome Bruges-Armas

### K

K- Potassium Kb- Kilobases

## L

LaTaq- Long and accurate taq LBP- Low back pain Lch- *Latimeria chalumnae LEMD3*- LEM domain containing 3 *LEP*- Leptin *LEPR*- Leptin receptor Lji- *Lottia gigantea* Loc- *Lepisosteus oculatus* LRP6- LDL Receptor Related Protein 6 LRP6- Low density lipoprotein receptor related protein 6 L-Spine- Lumbar spine

## Μ

M- Males MAF- Minor allele frequency *MATN3*- Matrilin-3 MCP- Metacarpophalangeal Mdo- *Monodelphis domestica* MEN1- Menin 1 MGP- Matrix Gla Protein MHC- Major Histocampatibility Complex MIF- Macrophage inhibitory factor MIM- Mendelian Inheritance in Man min- minutes miRNA- micro ribonucleic acid miRNA SNP- micro ribonucleic acid related single nucleotide database mRNA- messenger ribonucleic acid Mmu- *Mus musculus* MODY- Maturity-Onset Diabetes of the young MRNA- Messenger ribonucleic acid MRP1- Multidrug resistance protein 1 MRP3- Multidrug resistance protein 3 MRP6- Multidrug resistance protein 6 *MTP*- Microsomal triglyceride transfer protein *MYH11*- Myosin heavy chain 11

### Ν

NA- Not applicable NCBI-National Center for Biotechnology Information NCCT- sodium chloride cotransporter NCX1- Sodium/calcium exchanger NDE1- Neurodevelopment protein 1 NDNC4- Nonsyndromic congenital nail disorder-4 NFB1- Nucleotide Binding Fold 1 NFB2- Nucleotide Binding Fold 2 ng- nanograms NGS-Next generation sequencing Nm: nanometers NOMO3- Nodal modulator 3 NPT3- Sodium phosphate transporter protein 3 NSAIDS- Nonsteroidal anti-inflammatory drugs NSCL/P- Nonsyndromic cleft lip with or without palate NTC- No template control

# 0

LF- Ligament flavum

OA- Osteoarthritis Oan- Ornithorhynchus anatinus Ola- Oryzias latipes OLF- Ossification of the ligament flavum OMIM- Online Mendelian Inheritance in man Oni- Oreochromis niloticus OPG- Osteoprotegerin OPLL- Ossification of the Posterior longitudinal ligament OR – Odds ratio ORF- Open reading frame OSL- Ossification of Spinal Ligaments

#### P

P-Proband PCR- Polymerase chain reaction PCSK1- Proprotein convertase subtilisin/kexin 1 PD-Paget disease PDB4- Paget disease of bone 4 PHEX- Phosphate regulating endopeptidase homolog, X-linked Pi- inorganic phosphate PLCG2- Phospholipase C Gamma 2 Pm- p value maternal Pma-Petromyzon marinus POH: Progressive osseous heteroplasia PolyPhen-Polymorphism Phenotyping v2 POMC: Pro-opiomelanocortin Pp- pvalue paternal PPi- inorganic pyrophosphate *PPP2R2D*- Protein Phosphatase 2 Regulatory Subunit B delta PRKAR1A- Protein Kinase CAMP-Dependent Type I Regulatory Subunit Alpha **Pro-**Proline PTCH1- Patched 1

PTH- Parathyroid hormone
PTHR2- Parathyroid Hormone 2 Receptor
Ptr- Pan troglodytes
PXE- Pseudoxanthoma elasticum

# Q

qPCR- Quantitative Polymerase chain reaction

#### R

r.p.m.- rotations per minute **RA-** Rheumatoid arthritis RANKL- receptor activator of nuclear factorkappaB ligand RDD- RNase-free DNase set **Ref- References RIN- RNA Integrity Number** RLT- RNeasy lysis buffer **RNA-**Ribonucleic acid RNA- Ribonucleic acid **RPS18-** GRibosomal Protein S18 **RR-** Regulatory regions **RRM- RNA recognition motif** RSPH9- radial spoke head 9 homolog RSPO2- R-spontin 2 RSPO4- R-spontin 4 RSPS15A- Ribosomal protein S15A RT-PCR- Reverse transcription polymerase chain reaction RUNX2- Runt-related transcription factor 2 RXRB- Retinoid X Receptor Beta

## S

SEEBMO- Specialized Service of Epidemiology and Molecular Biology SETS- Sequencing by oligonucleotide ligation and detection Experimental Tracking Systems SIFT- Sorting Intolerant From Tolerant *SLC12A3*- Solute carrier family 12 member 3 SLC17A3- Solute carrier family 17 member 3 SLC29A1- Solute carrier family 29 member 1 SLC2A9- Solute carrier family 2 member 9 SLC34A3- Solute carrier family 34 member 3 SNP- Single nucleotide polymorphism SNV- Single Nucleotide Variant SPDA1,2,3- Spondyloarthropathy, Susceptibility To, 1,2,3 SPL- Splicing Spu- Strongylocentrotus purpuratus SQSTM1- Sequestosome-1 STK38L: serine/threonine kinase 38 like

## Т

T- Trend test T1D-Type 1 Diabetes T2D-Type 2 Diabetes Tca-Tribolium castaneum TDT- transmission disequilibrium test TGFBR2- Transforming Growth Factor, Beta Receptor II TGF $\beta$ - Transforming Growth Factor, Beta  $TGF\beta I$ - Transforming Growth factor Beta 1 *TGF\beta3*- Transforming Growth factor Beta 3 Th17-T helper 17 THR- Tip hip replacement THR- Total hip replacement TMD- transmenbrane domain TNAP- Tissue-nonspecific alkaline phosphatase TNF- tumor necrosis factor *TNFRSF11A*- TNF Receptor Superfamily Member 11a *TNFRSF11B*- TNF Receptor Superfamily Member 11b Tni- Tetraodon nigroviridis **T-Spine-** Thoracic spine

Twy-Tiptoe Walking Yoshimura

### U

ucMGP- un-carboxylated matrix Gla Protein UHM- U2Af homology motif kinase 1 UN- Unaffected UTR- Untranslated region

#### V

VDR- Vitamin D Receptor VKORC1- Vitamin K epoxide reductase complex subunit 1 vs- versus

## W

WES- Whole exome sequencing WNT- Wingless Wt- Wild type

# X

XLD- X-linked dominant XLR- X-linked recessive Xma- *Xiphophorus maculatus* Xtr- *Xenopus tropicalis XYLT1*- Xylosyltransferase 1

# Y

*YWHAZ*- Tyrosine 3-Monooxygenase/Tryptophan 5-Monooxygenase Activation Protein Zeta

# Z

ZFR- Zucker fatty rat ZNF687- Zinc Finger Protein 68

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## **CHAPTER I: INTRODUCTION**

## 1. INTRODUCTION

## 1.1 Background of the study

The starting point of this thesis was the identification of many families, from Terceira Island, Azores, that may represent an early onset, autosomal dominant, familial type of pyrophosphate arthropathy, with a phenotype that includes peripheral and axial enthesopathic calcifications. A detailed radiological analysis of these families showed a high level of ectopic calcification especially in elbows (82.9%) and spine (81.4%). The concurrence of spinal ossifications, resembling Diffuse Idiopathic Skeletal Hyperostosis (DISH), and CPPD Chondrocalcinosis (CC), in many of those patients, suggested a shared pathogenic mechanism [24]. For a number of years the possible major gene involved in the aethiopathogenesis, of the then designated DISH/CC phenotype, has been investigated using different strategies, including whole exome linkage and an Identity-bystate study, and two zones, in chromosomes 12 and 20, seemed relevant for further investigation [29]. For this purpose a biobank with biological products and associated data was established for the population from the Terceira Island in the Azores. Biobanks are essential in research, by having collections of samples and data stored in an organized manner. At the moment the biobank Azores (AZORBIO) of the Specialized Service of Epidemiology and Molecular Biology (SEEBMO) has a collection of biological material and associated data of Azorean patients with different pathologies [27]. The Azores archipelago (Portugal) is located in the middle of the Atlantic Ocean, 1500 km from the European mainland and is formed by nine islands of volcanic origin. The islands are grouped according to their geographic positions: Eastern (São Miguel and Santa Maria), Central (Terceira, Faial, Pico, Graciosa and São Jorge) and Western (Flores and Corvo) [24, 30] (Figure 1-1). The Azores were officially populated in 1439 and have approximately 246,746 inhabitants distributed in a very asymmetric way among islands. Terceira is a relatively small island with only 56.467 inhabitants (Census, 2011). Isolated populations or populations with reduced mobility, as is the case of Terceira Island, have proven particularly valuable for the purposes of mapping genes involved in Mendelian monogenic disorders and thus, investigating this phenotype in this population it was reasoned would increase the likelihood of identifying the causative gene mutation.



Figure 1-1. Geographic location of the Azores. The islands are grouped according to their geographic positions in Eastern, Central and Western. Taken from Santos et al, 2009 [30].

## **1.2** Objectives of the thesis

The main objective of this thesis was to proceed with the investigation of the genetic basis of the DISH/CC phenotype making use of Next Generation Sequencing technology, together with association and expression studies.

The studies presented in this thesis were guided by the following objectives:

- Investigate the association of CC with the metabolic disorder- Gitelman Syndrome;
- Investigate the candidate genes *RSPO4* and *LEMD3* genes, derived from a previous analysis of identity-by-descent sharing across four families with CC;
- Select the best candidate genes in WES results from 4 unrelated DISH/CC patients;
- Perform case/control and expression studies on the best candidate genes;
- Characterize the candidate gene in terms of origin and evolution.

On completion of this thesis I expect to contribute to the identification of genetic factors involved in the DISH/CC phenotype.

Chapter I

## **1.3 Thesis outline**

The **Chapter 2** introduces the basic knowledge of what is known about the genetics of ossification of spinal ligaments- DISH, OPLL and OLF, and focusses on the main disorder investigated in this thesis: DISH. **Chapter 3** provides a detailed presentation of the material and methods used in the thesis. The association of CC with Gitelman Syndrome through the genetic analysis of the *SLC12A3* gene is presented in **chapter 4**. **Chapter 5** covers the possible role of *RSPO4* and *LEMD3* genetic variants in the aetiology of DISH/CC. The whole exome sequencing study performed in order to detect genetic variants that are expected to have a potentially damaging effect on proteins with functions related to calcification and/or ossification is reported in **chapter 6**. In **chapter 7** the candidate gene *ABCC6* is investigated using case/control and expression studies to verify the association with the phenotype under study. Finally, the characterization and comparison of the *ABCC6* gene in metazoans including humans using "in silico" methodologies is presented in **chapter 8**. The **chapter 9** presents the general discussion and conclusions of this thesis. The final chapter contains the bibliography, followed by appendix with an article publication.

# **CHAPTER II: LITERATURE REVIEW**

## 2. LITERATURE REVIEW

## **2.1 Introduction**

The spine is a columnar structure in the center of the body composed by spinal bones (vertebrae) and inter-vertebral discs. It is supported by spinal ligaments (flexible bandlike structures), which include the anterior and posterior longitudinal ligaments, ligament nuchae and the yellow ligament (ligamentum flavum) of the spine [31]. There is a group of diseases characterized by the ossification of spinal ligaments (OSL); the anterolateral spinal ligament [Diffuse Idiopathic Skeletal Hyperostosis (DISH; MIM 106400)], the posterior longitudinal ligament [Ossification of the Posterior Longitudinal Ligament (OPLL; MIM 602475)] and the ligament flavum [Ossification of Ligamentum Flavum (OLF)]. In some cases OPLL, DISH and OLF co-occur in the same patient [32] suggesting possible common aetiopathogenic factors. Genetic links in OPLL, DISH and OLF have been investigated and several papers cite or allude to genetic factors as playing a role in the aetiology of this diseases [33-35]. There are reports in the literature that describe familial cases of DISH and OPLL which further strengthen this genetic association. Although the evidence of a genetic predisposition in all the three diseases have been described, very few studies in DISH and OLF appear in the literature, only OPLL has been extensively investigated. However, the studies that have looked at the possible genetic links are still inconclusive and the aetiology of these diseases remains unknown. The main objective of this study is to investigate genetic variants associated with DISH susceptibility. Therefore, in this thesis, the genetic mechanisms already involved in OPLL and OLF actiology will be explored in detail since they can give insights into the pathogenesis of DISH.

## **2.2 Diagnosis**

DISH (DISH; MIM 106400) is the current terminology for a systemic non inflammatory disorder reported in 1925 by Knaggs [36] and later described by Forestier and Routes-Querol in 1950 [37]. This disorder has had a variety of denominations in the literature throughout the years, due to the diverse phenotypes encountered. It is a common condition amongst the elderly characterized by calcification and ossification of the anterior longitudinal ligament affecting, in particular, the right side of the spine with preservation of the intervertebral disc space. Whilst spinal involvement in DISH is nearly

Chapter II

universal, extraspinal sites, such as the elbow, shoulder, hip, knee and heel are very common [1, 5, 22, 23, 38]. The diagnosis of DISH is established using radiographies. There are two main diagnostic criteria sets to identify definite, probable or possible DISH (Table 2-1). Resnick [39] defined the first set of criteria that were, some years later, revised by Utsinger [5] for epidemiological purposes. Criteria are indicated in the following table:

Table 2-1. DISH d	liagnostic criteria.
-------------------	----------------------

			Resnick Criteria [39]	Utsinger Criteria [5]
Definite	Definite		Presence of flowing calcification and ossification along the anterolateral aspect of at least four contiguous vertebral bodies with or without associated localized pointed excrescences at the intervening vertebral body- intervertebral disc junctions.	Continuous ossification along the anterolateral aspect of at least four contiguous vertebral bodies, primarily in the thoracolumbar spine. Ossification begins as a fine ribbon-like wave of bone but commonly develops into a broad, bumpy, buttress-like band of bone.
bable	Possible	2	The presence of relative preservation of intervertebral disc height in the involved vertebral segment and the absence of extensive radiographic changes of "degenerative" disc disease, including vacuum phenomena and vertebral body marginal sclerosis.	Continuous ossification along the anterolateral aspect of at least two contiguous vertebral bodies.
Prob	Possible	3	The absence of apophyseal joint bony ankylosis and sacroiliac joint erosion, sclerosis or intraarticular osseous fusion.	Symmetrical and peripheral enthesopathy involving the posterior heel, superior patella or olecranon, with the entheseal new bone having a well-defined cortical margin.

According to the criteria, the probability of DISH is as follows: 'definite' if criterion 1 is present, 'probable' if criteria 2 and 3 are present and 'possible' if criterion 2 or 3 is present; particularly if calcaneal spurs occur together with olecranon or patellar spurs. Exclusion criteria include: abnormal disc space height in the involved areas and/or apophyseal joint ankylosis. Resnick criteria number 3 has an exclusion factor based on the erosions, sclerosis or fusion of sacroiliac joints. This helps to exclude patients with Ankylosing Spondylitis (AS), a disease that can be confused with DISH. The third factor for exclusion of DISH diagnosis was withdrawn by Utsinger because differentiation of these two disorders should be possible with lateral and antero posterior axial x-rays. Recently efforts have been made to revise the definition of DISH in order to incorporate the current knowledge about DISH, however a new definition of DISH is still under debate [40]. Despite the need for a new definition of DISH, the criteria proposed by Utsinger are still universally accepted and widely used in the literature and will be used in this thesis. OPLL (OPLL; MIM 602475) is characterized by ectopic hyperostosis and calcification of the posterior longitudinal ligament at the cervical, thoracic and lumbar spine [41]. In OPLL patients, the cervical spine (70%) is the most commonly affected, followed by the thoracic (15%) and lumbar (15%) spine [42, 43]. Some patients present myelopathy and/or radiculopathy due to chronic compression of the spinal cord and nerve roots. Symptoms of myelopathy are more severe in thoracic OPLL than in cervical OPLL due to the narrow canal, rigidity of the thoracic spine, tenuous blood supply, and inability of the spinal cord to resist much compression [42]. OPLL is diagnosed on lateral plain radiographs as an abnormal radiopacity along the posterior of the vertebral bodies [44], however because of overlying osseous structures, it is important to obtain magnetic resonance images to successfully diagnose OPLL [45]. OPLL is classified in four ossification types: continuous, segmental, mixed and localized or other [44, 46, 47]. The segmental is the most common and involves the ossification behind each vertebral body; the continuous type is an ossified mass that spans several vertebral bodies; the mixed type is a mixture of both continuous and segmental types and the localized or other type the ossification is localized to the intervertebral disk space without involvement of the vertebral body [44].

OLF, also known as ossification of the yellow ligament, is associated with serious neurologic symptoms including thoracic myelopathy and spinal stenosis [48]. The calcification is confined to the ligamentum flavum (LF) and does not extend to the closed spinal bony arch [49]. CPP and hydroxyapatite have been positively identified and are the main players in the calcification of LF [50, 51]. According to Mwaka and collaborators [52] CPP in the cervical LF seems to progress with reduction in elastic fibers, increase in collagen fibrils in the matrix, and migration of metaplastic hypertrophic chondrocytes. The lower thoracic spine is the most affected region, however several cases of cervical, upper thoracic, and lumbar areas have been reported [53, 54]. Cervical radiography, tomography, and computed tomography are useful for diagnosis, however histological examination of the calcified mass using light microscopy, scanning electron microscopy, and x-ray diffraction analysis are essential for the definitive diagnosis [49].

## 2.3 Epidemiology

The reported epidemiology of DISH differs in the literature. Cassin et al [55] assessed 1000 African blacks aged older than 40 years and reported that the DISH prevalence was

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3.8% in males and 4.2% in females. Another study analysed the data from two large American Midwest metropolitan hospital populations with 1363 individuals and reported a prevalence of DISH of 25% in males and 15% in females over 50 years of age and 35% in males and 26% in females over 70 years of age [56]. Holton et al [57] postulated that the prevalence of DISH was 42% in a group of 298 males aged over 65 from the general population. A recent study of 558 Japanese found that the prevalence of DISH was 17.6% using x-ray and 27,2% using computed tomography [58]. The exact prevalence and incidence of DISH is actually unknown, and a reliable estimate of the prevalence of the disease in the general population is difficult due to the benign nature of the condition. The affected individuals do not seek medical care and normally are diagnosed during the examination of other medical conditions [57]. However, it is well known that DISH is more frequent in males and its prevalence increases with age, affecting mainly subjects over the age of 40 [5]. Furthermore DISH seems to have a higher prevalence in developed countries [59], although this predominance might be due to the more frequent use of advanced radiological examinations in developed countries than in undeveloped countries.

OPLL can be found in any population however it is more common in Asian populations, in particular amongst Japanese with a prevalence of 2 to 4% as compared with 0.01 to 2% in non-Asian populations [60]. Men are 2.5 times more likely to develop OPLL than women [41] and the age of onset may be in the fifth decade of life [61], although in some studies no association between age and the presence of OPLL was found [41]. This lack of consensus can be explained by the fact that the study which didn't find any association probably used a group of patients with asymptomatic OPLL, while the other study only involved patients with symptomatic OPLL, already diagnosed.

OLF affects populations worldwide but there is a higher prevalence in east Asian ethnic groups, especially the Japanese, with the incidence of 12% in thoracic OLF (15% in men and 7.7% in women) [62]. OLF is common in the 6<sup>th</sup> to 7<sup>th</sup> decades [46].

## 2.4 Evidences for a genetic aetiology

Genetic links in OPLL, DISH and OLF have been investigated and several papers cite or allude to genetic factors as playing a role in the aetiology of these diseases [33-35]. The

reports in the literature that describe familial cases of DISH and OPLL and the existence of animal models further strengthen this genetic association.

#### 2.4.1 Familial cases

The genetic predisposition to OPLL and DISH is supported by several reports of familial incidence of DISH, and by studies relating a relative recurrence risk of up to 26.1% in parents of OPLL patients and 28.9% in siblings [63].

Reports of familial DISH are uncommon in the literature. One report, dating from 1969, describes a family of Greek Cypriot ancestry with eight individuals showing signs of Ankylosing Vertebral Hyperostosis (AVH) by the third decade. Only three of them had backache as symptoms. All the individuals affected with AVH also shown tylosis (punctuate hyperkeratosis) and the mean age of individuals affected was 31 years old. Six members of this family were affected only with tylosis. Axial skeleton X-ray examination of the eight affected family members showed ossification of paraspinal ligaments, especially in lower thoracic region. There were also large osteophytes with preservation of disk space and marginal sclerosis of the sacroiliac joint. Laboratory results were all normal, the authors mention normal calcium and carbohydrate metabolism and glucose tolerance tests. Obesity was present in most individuals. Weight, in the opinion of the authors, could not account for all the x-ray changes since there was one affected individual with normal build. There was one other case of an individual with tylosis, normal spine and gross obesity. Beardwell et al suggested that the co-existence of tylosis with AVH could indicate a possible genetic link between these two disorders [64]. This link was never confirmed being this association an occasional finding. Another report of familial DISH was published in 1985 by Abiteboul et al [65], where the authors describe two families, one of French Canadian origin and another of Italian origin. French Canadian family is composed of 3 brothers and one sister definitely affected by AVH developing radiological changes by the 4<sup>th</sup> decade of age. Two other are probably affected with AVH. None of the individuals had diabetes. Italian family was first identified after a coxofemoral surgery of a 71 years old woman. Her sister was submitted to the same surgery when she was 82 years old. Former patient had five daughters, all of them observed by the authors of this study. Two of them showed radiological manifestations of the AVH. Other 2 sisters had more modest phenotypes being classified as probable AVH. None of these individuals was HLA-B\*27, was obese or had diabetes. There is another report relating a family with striking cervical disease without extensive dorsal

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involvement and normal sacroiliac joints. Inflammatory markers were all normal and none of the individuals of this family was HLA-B\*27 positive. The authors denote the unusual phenotype and refer to the difficulty of classifying this condition as DISH [66]. In 2006, Bruges-Armas et al [23] reported twelve familial cases identified on the island of Terceira (Azores, Portugal), multiply affected with DISH and/or chondrocalcinosis (CC). These families may represent a familial type of pyrophosphate arthropathy with a phenotype that includes peripheral and axial enthesopathic calcifications. These findings, according to the authors' suggestion, support the hypothesis that both disorders may share common aetiopathogenic factors. One hundred and three individuals from the twelve unrelated families were assessed. Radiographs were taken of all the individuals including x-rays of the dorsolumbar, pelvis, knees, elbows and wrists, and all cases were screened for known associations of CC. Ectopic calcifications were identified in seventy patients. Axial, elbow, knee and metacarpophalangeal (MCP) pain and/or swelling, deformity and radiographic enthesopathic changes were the most frequent findings/symptoms. Elbow and MCP periarticular calcifications were observed in 35 and 5 patients respectively, and CC was identified in 12 patients. Fifteen patients had sacroiliac disease on computed tomography - ankylosis or sclerosis. 52 patients could be classified as definite (17%), probable (26%), or possible (31%) DISH. Concomitant DISH and CC was diagnosed in 12 patients. Pyrophosphate crystals were identified from knee effusions in 13 patients. The pattern of disease transmission was compatible with an autosomal dominant monogenic disease and the mean age for to develop the disease was 38 years. A recent paleopathological study mentions the co-existence of gout and DISH in the medici Grand Dukes Cosimo I and Ferdinand I [67]. Studies on these families would be very useful and would surely sum up important information related to DISH aetiopathogenesis.

Reports of familial OPLL are scarce but they also occur in the literature. The prevalence of OPLL is much greater among family members of patients with OPLL than in the general population [63, 68], which indicates a strong familial predisposition to OPLL. Familial aggregation of OPLL was first demonstrated by Terayama et al in 1989 [63] in a study assessing 1030 relatives of probands with cervical OPLL in 347 families. The authors found that OPLL was observed in 26.15% of the parents and 28.89% of the siblings of the probands. In this study, the relative risk of first degree relatives developing OPLL are greater than five times that of the expected incidence in the general population. Another study looking to 100 patients and family members with OPLL found a

prevalence of 27% with a relative risk seven times that of the general population [69]. Because the segregation rate in the siblings is higher and the higher prevalence of OPLL in the parents, both authors suggested that OPLL is possibly controlled by autosomal dominant inheritance. In contrast, Hamanishi et al [68] reported one OPLL family with a suspected autosomal recessive trait, but indicated that it was not possible to exclude that it was a dominant trait.

Altogether, familial studies suggest there is a genetic predisposition, however the mode of inheritance for OPLL is not well defined, since the segregation analysis in families support both autosomal dominant and autosomal recessive patterns of inheritance. According to Koga et al [70] the mode of inheritance is obscured by a lack of large families, the late onset of the disease, a sex difference, and environmental effects. Other OPLL familial cases exist in the literature, although they do not indicate the mode of inheritance. Tanabe et al [71] in 2002 report a case of familial thoracic OPLL in Caucasian siblings and Kim et al [72] used OPLL families to find genetic association between *BMP-2* and *COL6A1* polymorphisms.

As far as we known, there are no reports in the literature that describe familial cases of OLF.

## 2.4.2 Animal models

Several genes have been associated in the regulation of the biomineralization process. In this section genes involved in the pathological mineralization of the axial skeleton in animal models are presented. In recent years, the use of animal models has permitted specific genes to be manipulated and is a powerful tool for the identification of genetic determinants in ectopic calcification disorders. The improvement of strategies to study genetic mutations affecting the skeleton have made it possible the precisely evaluate the role of many different genes and proteins.

#### 2.4.2.1 Animal models for DISH

#### 1) Natural cases

Some naturally cases of DISH disease have been observed in some animals [73-76]. Spinal hyperostosis similar to DISH has been described in canine cases [77, 78] and are more frequent in boxer breed. As in human cases, the disease is more common in older male animals [73]. Similar cases of DISH were reported by Ghazanfar et al [79] in a

fighting Bulldog and by Kornmayer et al [80] in a Weimaraner breed. However, DISH can also occur in smaller breed dogs, and was identified in a 5 year-old, female Shihtzu [81]. The high prevalence of a specific disease in a certain dog breed and its absence in other breeds, is suggestive of a genetic mechanism [82], and thus these breeds may serve as an animal model for DISH. A recent study identified DISH in a nine years old cat which shows contiguous smooth new bone formation ventral and lateral to the vertebral extending from the cranial thoracic area to the lumbosacral junction, and appearing similar to canine DISH [75].

## 2) ENT1<sup>-/-</sup> mice

Warraich et al [83] reported that mice ENT1<sup>-/-</sup>, lacking ENT1 exhibit progressive ectopic mineralization of the upper thoracic and cervical spinal cord resembling human DISH. Furthermore these mice had a significant reduction in the expression of *Enpp1*, *Ank* and *Alpl* genes in intervertebral discs. Another study [84] using ENT1<sup>-/-</sup> mice focused on the lower portion of the spine and femur, demonstrated that these mice exhibited reduced bone density in the lower half of the spinal column as well as in the midshaft of the femur. Furthermore these authors confirmed the previous findings of Warraich et al [83] that ENT1<sup>-/-</sup> mice have osteoid formations in the upper portion of the spinal column (thoracic and cervical spinal cord).

In humans *ENT1* gene, also known as solute carrier family 29 member 1 (*SLC29A1*), is one of the four members of equilibrative nucleoside transporters that maps on chromosome 6 (6p21.1). The gene encodes a transmembrane glycoprotein, which transfers hydrophilic nucleosides, such as adenosine, across the plasma membrane (equilibrative transport) [85]. The protein is ubiquitously expressed and involved in purine metabolism transporting the majority of adenosine transport across the plasma membrane. Recently adenosine signaling has been shown to regulate bone remodeling [86]. A search in Ensembl database (<u>http://www.ensembl.org/index.html</u>) reveals that several genetic variants in this gene exist, although none are associated with a human phenotype or disease, with the exception of a mutation (T647C) described by Kim et al [87] that is involved in the development of alcoholism with increased risk of alcohol withdrawal-induced seizures.

#### 2.4.2.2 Animal models for OPLL

#### 1) tiptoe-walking-Yoshimura (twy) mouse

The spinal hyperostotic twy mouse is a naturally occurring mutant that exhibits OSL similar to human OPLL [88], which served as a model for human OPLL disease [89]. Ossification occurs not only in the spinal ligaments but also in various soft tissues such as joint capsules, tendon enthesis, chondral tissues, and peripheral ligaments [89]. The accelerated bone formation characteristic of *ttw* mice is caused by a nonsense mutation in the *Enpp1* gene that causes deficiency in its expression and protein activity. It was thought that the dysfunction of Npps, which has a predicted truncation of the gene product, resulting in the loss of more than one-third of the native protein [89]. The *Enpp1*-<sup>*t*</sup> knock-out mouse has diminished bone density with calcification of joints and vertebrae [90].

ENPP1 (also known as NPPS or PC-1) is one of the seven members of the ectonucleotide pyrophosphate\phosphodiesterase family that maps to chromosome 6 (6q22-q23) [91]. The gene encodes a membrane bound glycoprotein (NPP1) [92], that regulates bone mineralization by hydrolyzing extracellular nucleotide triphosphates (ATP) to produce pyrophosphate [93]. Since NPP1 generates pyrophosphate it serves at least in part as a physiological inhibitor of calcification. The protein occurs in a large variety of tissues, including bone and cartilage, where it occurs in osteoblasts and chondrocytes respectively [94, 95]. In humans, mutations in the ENPP1 gene are responsible for Generalized arterial calcification of infancy (GACI; MIM #208000), a severe disease characterized by progressive calcification of the internal elastic lamina of muscular arteries and stenosis due to myointimal proliferation [96]. More recently GACI disease has been related to pseudoxanthoma elasticum (PXE; MIM #264800), since in some GACI cases, mutations in ENPP1 can also cause typical pseudoxanthomatous skin lesions and angioid streaks of the retina [97]. A mouse model for GACI disease, the spontaneous asj-2J mutant mouse with the V246D missense mutation in the Enpp1 gene, has some similarities with ttw mouse. In the asj-2J mutant mouse the mutant Enpp1 protein is absent from the liver, and this causes reduced PPi levels in the plasma, and consequently extensive mineralization of a number of tissues, including blood vessels [98]. Mutations in the ENPP1 gene also causes hypophosphatemic rickets [99] and Cole disease [100].

## 2) ZFR mouse

The ZFR (Zucker fatty rat) is a murine model originally used for studies of obesity, hyperinsulinemia, hypercholesterolemia and hyperlipidemia. This mice had ossified spinal ligaments, mainly in the thoracic spine and the ossification is histopathologically similar to human OPLL [101]. A molecular variant in the leptin receptor (*LEPR*) gene is the genetic cause in ZFR rats [102].

*LEP* gene maps on chromosome 7 (7q32.1) and is closely related to bone metabolism, since leptin is a powerful inhibitor of bone turnover *in vivo* [103]. According to Elefteriou et al, leptin is an adipocyte product both necessary and sufficient to control bone mass, since increasing serum leptin levels, reduced bone mass. Conversely, reducing serum-free leptin levels by overexpressing the soluble receptor for leptin increased bone mass [103]. According to Liu et al [104] leptin promoted differentiation of vascular smooth muscle cells from female mice into osteoblasts by increasing RANKL expression. In humans, mutations in this gene cause severe obesity, and morbid obesity with hypogonadism [105].

#### 2.4.2.3 Other animal models with OSL

The *ank* mice shows generalized arthritis associated with extensive hydroxyapatite deposition in articular cartilage and synovial fluid; they also present spinal, peripheral joint, and ligament bony ankylosis and calcification of arteries [106, 107]. The *ANKH* gene maps on chromosome 5 (5p15.1) and encodes a multipass transmembrane protein ANK (492 aminoacids) that transports intracellular inorganic pyrophosphate (PPi) to the extracellular milieu [106], where it acts as a potent inhibitor of mineralization [108]. The Expression Atlas (https://www.ebi.ac.uk/gxa/home) reveals that this protein is expressed in more than 30 different tissues and cells including the eye, brain, lung, kidney, skin and cartilage.

In humans, mutations in this gene have been associated with autossomal dominant craniometaphyseal dysplasia (CMD; MIM#123000) [109] and chondrocalcinosis (CCAL2; MIM #118600) [110].

Zebrafish have been used to study vertebrate mineralization since they share many of the basic features of chondrogenesis and osteogenesis with higher vertebrates [111-118]. In common with humans and mouse, the *enpp1* mutant zebrafish (dragonfish) develops ectopic calcifications in a variety of soft tissues including skin, eye, cartilaginous

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elements, the heart, intracranial space and the notochord sheet [114]. Two other zebrafish mutants that display defective skeletal biomineralization, caused by changes in phosphate/pyrophosphate homeostasis in the embryos include *nob* (no bone, mineralization fails) and *dragonfish* (*dgf*), that has ectopic mineralization of the axial skeleton with apparent fusion of the mineralized vertebral centra and bone nodules at characteristic positions of the cleithrum [119]. The *nob* phenotype is caused by a mutation in the ectonucleotidase *entpd5* gene, which has a crucial role in providing sufficient levels of phosphate through hydrolyzing nucleoside triphosphates and diphosphates [119], *Dgf*, in turn, encodes Enpp1 [120]. According to Huitema et all [119], a stringently controlled balance between Entpd5 and Enpp1 activities determines the level of mineralization through controlling the ratio of inorganic phosphate (Pi) to pyrophosphate in the microenviroment of osteoblasts.

Mutations in the zebrafish orthologue *abcc6a* (ATP binding cassete subfamily C, member 6a) gene results in extensive hypermineralisation of the axial skeleton [113]. The ablation of *abcc6a* gene interfered with normal fish development with pericardial edema and a curled tail and was associated with fish death [111]. Another zebrafish mutant, gräte (grt; abcc6ahu4958) had a mutation in abcc6a gene, which has been associated with the regulation of tissue calcification [113]. The gräte mutant has excessive mineralisation in the craniofacial and axial skeleton [113]. In zebrafish the *abcc6a* gene is strongly expressed at the site of mineralisation and secretes ATP from cells increasing PPi locally, in contrast with the hepatically derived PPi in mammals. The authors suggested that zebrafish Abcc6a is one of several sources of nucleotides for ENPP1. In humans, the ABCC6 gene maps on chromosome 16 (16p13.1) and encodes multidrug resistance protein-6 (MRP-6), a transmembrane protein involved in transport of molecules between the extra-cellular space and the inside of the cell. The physiological role of MRP6 and its substrate specificity is unclear, although recently multiple sources of evidence indicate involvement in the regulation of human tissue calcification [121, 122]. MRP6 has a widespread tissue distribution but is highly expressed in the basolateral membrane of hepatocytes and proximal kidney tubules [123, 124]. In humans, mutations in ABCC6 gene cause PXE [125-127] and in some cases, mutations in ABCC6 were also associated with GACI, a disorder associated with *ENPP1* mutations [96]. The abcc6<sup>-/-</sup> mouse model was negative for expression of Mrp6 in the liver and has profound mineralization of several tissues including skin, arterial blood vessels and retina [128], which resembles the human PXE phenotype. Furthermore these mice display a 40% reduction in plasma PPi

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levels [129]. According to Jansen and collaborators [129], PXE is not caused by a lack of functional MRP6 in the affected tissues, but rather by the absence of PPi that is normally provided to the circulation by an MRP6 mechanism. Recently it has been proposed [130] that polymorphisms in genes known to regulate cellular pyrophosphate metabolism, such as *ALPL*, *ENPP1* and *ANKH*, are genetic risk factors contributing to PXE.

## 2.4.3 Genetic variants associated

#### 2.4.3.1 Genetic studies on DISH

The variation in the prevalence of DISH throughout the world [2], the existence of familial cases with early onset (in the third decade of life) [64] and the higher frequency of DISH in specific dog breeds [77, 78] suggests that genetic factors might play a part in its aetiology. So far, however, no single gene has been conclusively associated with the disease and very few genetic studies on DISH have been published to date. Some of the first genetic studies in DISH were performed on Major Histocompatibility Complex (MHC) genes (Human Leukocyte Antigens, HLA), due to the similarity of radiographic patterns shared with AS, a spondyloarthropathy with a well-known association with the HLA-B\*27 allele [131, 132]. The first study, performed by Shapiro et al [133], reported a positive association between HLA-B27 and DISH, since 16 out of the 47 studied patients were HLA-B27 positive (34%). The authors hypothesized that this gene could be involved in new bone formation due to the association with two disorders such as AS and DISH, where bone proliferation is an essential feature [134]. This study was followed by many more that rejected the hypothesis and the association of HLA alleles and DISH was discarded [135]. Conflicting results were reported in relation to HLA alleles [136-141] and associations of HLA-B8 [142] and HLA-B5 [143] to DISH were proposed but has never been proven. In a relatively small study, 65 individuals affected with DISH and 2352 controls, Vitamin D Receptor (VDR), collagen Type  $I_{\alpha 1}$  (COL1A1) polymorphisms were investigated. These genes are involved in bone density; COLIA1 is involved in determination of bone density and the interaction of both COL1A1 and VDR with calcium intake regulate changes of bone density over time [144]. Despite the importance of VDR and COL1A1 in bone homeostasis, the authors conclude that neither of these genes seem to contribute to DISH aetiology [145].

Another study investigated the influence of polymorphisms in collagen 6A1 gene (*COL6A1*) in 97 Japanese DISH patients (298 Japanese controls) and 96 Czech DISH

patients (96 Czech controls). One polymorphism (Intron 32; -23) was associated with DISH in Japanese patients but was not associated with DISH in Czech patients. Even so, the authors suggested that *COL6A1* could be responsible for the hyperostotic state leading to ectopic bone formation in spinal ligaments [34]. *COL6A1* encodes an extracellular matrix protein that may serve as a scaffold for osteoblast or pre-osteoblast cells or chondrocytes that subsequently contribute to membranous or endochondral ossification [34]. The *COL6A1* gene is also strongly associated to OPLL [33, 146], and polymorphisms in this gene are considered helpful markers of OPLL disease [6].

A whole genome linkage analysis followed by an "identity-by-state/descent" was performed in DISH/CC Azorean families to clarify the genetic basis of these pathologies in these families, and two zones in chromosome 12 and 20 were found [29]. Another attempt to find genetic associations was undertaken by Jun et all [147], who found that two SNPs (rs1476217 and rs3747676) in the *FGF2* gene were associated with DISH and, one of these (rs1476217), was also associated with OLF. The *FGF2* gene is involved in FGF signalling, which controls bone formation by regulating the expression of various genes involved in osteoblast differentiation and apoptosis [148].

Only two genes have been shown to have a positive association with DISH susceptibility; *COL6A1* [34] and *FGF2* [147] (Table 2-2). However, all the gene variants that showed significant association were located in non-coding regions and were common variants within the general population, which suggests that these variants have a minor effect on DISH susceptibility. In conclusion, the genetic aetiology of DISH is still unknown since the studies that have looked at the possible genetic association with DISH are still inconclusive since none of the studied genes have been shown to be pathogenetically relevant for DISH patients.

Table 2-2.	Genetic	variants	associated	with	DISH.
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Gene	Chr	Physiological function	Study type No Subjects [case/control]	SNP- significantly associated	Ref
COL6A1	21	Involved in membranous or endochondral ossification.	Association study [97/298] (Japanese) and [96/96] (Czech) (Assessed 7 SNPs in <i>COL6A1</i> gene).	Intron 32 (-29) (only in Japanese) (chi2 = 9.33; $\mathbf{p}$ = 0.0022), but not with the Czech DISH patients.	[34]
FGF2	4	Involved in bone formation by regulating the expression of various genes involved in osteoblast differentiation and apoptosis.	Association study with 154 OPLL, 3 OPLL with DISH and 222 controls.	rs1476217 ( <b>p</b> =0.03) rs3747676 ( <b>p</b> =0.01)	[147]

Abbreviations: SNP- Single nucleotide polymorphism, Chr: chromosome, p: p-value, Ref: References.

## 2.4.3.2 Genetic studies on OPLL

As in many other diseases, the genetic basis of OPLL is now being uncovered with the help of rapidly advancing genome science and technology. The aetiology of OPLL has been extensively investigated from many perspectives and despite the existence of conflicting results, a great number of genetic variants have been associated with susceptibility and severity of OPLL along the years (Table 2-3).

As with DISH, some of the first genetic studies in OPLL were performed on HLA, and this putative association has been extensively discussed in the literature. Koga et al [70] in 1998 provided a genetic linkage study of 91 affected sib pairs and they identified a predisposition locus for OPLL on 6p, close to the HLA complex. Based on this study several other studies were performed in this region [149-151], however the association between HLA alleles and OPLL have not been clarified and this association does not appear to imply causation [152].

Gene	Chr	Physiological function	Study type No Subjects [case/control]	SNP- significantly associated	Ref
IL-1β	2	Stimulates thymocyte proliferation by inducing IL-2 release, B-cell maturation and proliferation and fibroblast growth factor activity.	Case-control association study [120 (43F) /306 (140F)] (Japanese)	IL1B AbaI polymorphism (gender specific – female) (p=0.001)	[153]
		Essential for sexual development and reproductive function, but also play a role in tissues such as (Assessed 5 candidate genes; 5 SNPs)		ER (XbaI) gender specific (female) (p=0.007)	
ESR1	6	bone.		rs9340799 (p=0.017) no correction	
AHSG	3	Promotes endocytosis, possesses opsonic properties and influences the mineral phase of bone. Shows affinity for calcium and barium ions.	Large Scale Case-control study [711/896] (Japanese) (Assessed 35 candidate genes: 109 SNPs)	rs2077119 (p=0.0011)	[154]
TGFB3	14	Involved in embryogenesis and cell differentiation.		rs2268624 (p=0.00040 / p=0.044 after Bonferoni Correction)	
ACE	17	Plays a key role in the renin-angiotensin system.	Case control association study [95/274] (Korean) (Assessed I/D polymorphism in ACE)	rs2284/92 (p=0.037) no correction rs4646994 (genotype DD p<0.001; D allele p=0.009)	[155]
			Case control study [192/304] (Assessed 2 SNPs in Exon 3 of <i>BMP2</i> )	rs3178250 (p=0.003 gender specific – males)	[156]
BMP2	20	Induce bone and cartilage formation; member of TGF $\beta$ superfamily.	Case control study [57/135] (Assessed 2 SNPs in exon 2 of <i>BMP2</i> )	rs2273073 (p<0.001) susceptibility to OPLL rs1049007 (p=<0.001) severity of OPLL	[157]
			Case control study [420/506] (Assessed all coding sequencing of <i>BMP2</i> )	rs2273073( p<0.001) rs235768 (p=0.005)	[158]
			Nonparametric linkage study with 126 affected sib-pairs using microsatellite markers in 88 candidate genes	Only <i>BMP4</i> gene reached criteria of suggestive evidence of linkage (NPL=2.23; p=0.035)	[159]
<i>BMP4</i> 14	Induce bone and cartilage formation.	Case control association study [179/298] (Chinese). (Assessed 2 polymorphisms in <i>BMP4</i> )	rs17563 (genotype: p=0.039; Allele: p=0.014)	[160]	
			Case control association study (450/550) (Chinese) (Assessed complete genomic <i>BMP4</i> coding)	rs17563 rs76335800	[161]
BMP9	10	Could be involved in bone formation.	Case control association study [450/550] (Chinese) (Assessed complete genomic <i>BMP9</i> coding)	rs75024165 (p<0.001) rs34379100 (p<0.001)	[162]
COL11A2	6	Plays an important role in fibrillogenesis. May contribute to the formation of ectopic bone by	Genetic Linkage, association and haplotype analysis study of 91 affected sib pairs from 53 Japanese families	Promoter (-182) (p=0.02); rs1799907 (p=0.0004); rs1799910 (p=0.02); rs1799911 (p=0.03) Haplotypes	[70]
		ennancing endocriondral ossification.	Haplotype association [161/163]	rs1799907 (p=0.0003) (haplotype with 4 SNPs) male association	[61]
COL17A1	10	Plays a role in the integrity of hemidesmosome and the attachment of basal keratinocytes to the underlying basement membrane.	WES and association studies [28/100] (Chinese)	rs805698 (p=0.00023) rs4918079 (p=0.003)	[163]
PTCH1	9	Functions as a tumor supressor.		p.P1232L; p.T265S	[163]
COL6A1	21	A cell binding protein and may lead to increased bone mass.	Genomewide linkage study followed by fine mapping and haplotype analysis of 142 affected sib pairs	intron 32 (-29) (p=0.000003) rs2236485 (p=0.0002)(MAF 0.13) rs2236486 (P=0.00005)(MAF 0.39) rs2236487 (p=0.00006) (MAF 0.37)	[33, 146]
			Case control association study [90/155] (Chinese)	Promoter (-572) (p=0.000215) Intron 32 (-29) rs2236486 (p=0.00483)	[33]
			ttw mouse studies	Gly568stop	[89]
			Association study [323/332] (Assessed all coding sequencing of <i>ENPP1</i> gene)	IVS20-11delT (p=0.0029)	[164]
ENPPI	6	Functions in bone mineralization and soft tissue calcification by regulating pyrophosphate levels.	Case-control association study [180/265]	IVS15-14T> C (p<0.0001)	[165]
			Association study [95/90] (Chinese) (Assessed 4 SNPs in <i>ENPP1</i> )	C973T (p<0.001) IVS15-14T-C (p=0.026)	[166]

## Table 2-3. Genetic variants associated with OPLL. The physiological functions of proteins are also indicated (obtained from GeneCards).

Gene	Chr	Physiological function	Study type No Subjects [case/control]	SNP - significantly associated	Ref
НІА	6	Involved in the presentation of foreign antigens to the immune system	Family based association study with 33 families of patients with OPLL		[151]
IILA	0	involved in the presentation of foreign anugens to the minute system.	Family based association study with families of 24 patients with OPLL		[150]
II_15RA	10	Enhance cell proliferation and expression of opentosis inhibitor	A case control study [235/250] (Chinese)	rs2228059	[167]
IL-IJKA	10	Emilance cen promeration and expression of opoptosis minoritor.	Association study [166/230] (Korean)	rs2228059	[168]
RUNX2	6	Involved in osteoblastic differentiation and skeletal morphogenesis.	Case control study (Sequenom system) [82/118] (Chinese) (Assessed 19 SNPs in 4 candidate genes)	rs1321075 (p=0.043) rs12333172 (p=0.034)	[35]
RXRB	6	A member of retinoid receptor family regulating a wide variety of biological processes including development, differentiation, and cellular metabolism.	Association study and haplotype analysis [134/158] (Japanese)	3'UTR (+140) (p=0.0028) 3'UTR (+561) (p=0.034)	[169]
TGFB1	19	Mediates bone development and metabolism.	A case control [46/273]	T869>C	[170]
VDR	12	Plays a central role in calcium homeostasis.	Case-control study [63/126]	VDR FF genotype	[171]
RSPH9	6	Play a role in the membranous ossification process.		rs927485 (p=9.4x10 -9)	
STK38L	12	Play a role in the membranous ossification process.	Genome Wide association study	rs11045000 (p=2.95x10 <sup>-11</sup> )	
RSPO2	8	Implicated in the endochondral ossification process.	followed by an Association study (for replication)	rs374810 (p=1.88x10 <sup>-13</sup> ) rs13279799 (p=1.28x10 <sup>-10</sup> )	[172]
CCDC91	12		[548/6469] (Japanese)	rs1979679 (p=4.34x10 <sup>-12</sup> )	
HOA1	20	Implicated in the endochondral ossification process.		rs2423294 (p=1.10x10 <sup>-13</sup> )	
FGFR1	8	Plays an essential role in the regulation of embryonic development, cell proliferation, differentiation and migration.	Association study [157/222] (Assessed 9 SNPs in 3 genes)	rs13317 (p=0.02)	[147]
BID	22	Has a role in opoptosis signaling.	Association study [157/209] (Korean) (Assessed 2 coding SNPs in <i>BID</i> )	rs8190315 (p=0.0052) rs2072392 (p=0.0052)	[173]
TGFBR2	3	Regulate the transcription of a subset of genes related to cell proliferation.	Association study [21/42]	rs11466512 (p=0.007) rs56105708 (p=0.024)	[174]
VKORC1	16	Involved in vitamin K metabolism.	Association study [98/200] (Korean)	rs9923231 (p=0.004) (female)	[175]
IFNG	12	It is a potent activator of macrophages.	Association study [135/222]	rs2430561 rs3138557	[176]

Abbreviations: SNP- Single nucleotide polymorphism, NA: Not applicable, Ref: References, *ACE*: Angiotensin I Converting Enzyme; *BMP2*: Bone Morphogenetic Protein 2; *BMP4*: Bone Morphogenetic Protein 4; *BMP9*: Bone Morphogenetic Protein 9; *COL11A2*: Collagen Type XI Alpha 2; *COL17A1*: Collagen Type XVII Alpha 1; *COL6A1*: Collagen Type VI Alpha 1; *ENPP1*: Ectonucleotide Pyrophosphatase/Phosphodiesterase 1; *ESR1*: Estrogen Receptor 1; *HLA*: Human Leukocyte antigen; *IL-15RA*: Interleukin 15 Receptor Alpha; *IL-1β*: Interleukin 1 Beta; *PTCH1*: Patched 1; *RUNX2*: Run-Related Transcription Factor 2; *RXRB*: Retinoid X Receptor Beta; *TGFβ1*: Transforming Growth factor Beta 1; *TGFβ3*: Transforming Growth factor Beta 3; *AHSG*: Alpha 2-Heremans-Schmid glycoprotein; *VDR*: Vitamin D Receptor; *RSPH9*: radial spoke head 9 homolog; *STK38L*: serine/threonine kinase 38 like; *RSPO2*: R-spontin 2; *CCDC91*: Coiled-coil domain containing 91; *HOA1*: Hydroxyacid oxidase 1; *FGFR1*: Fibroblast Growth Factor Receptor 1; *BID*: BH3 Interacting Domain Death Agonist. *TGFBR2*: Transforming Growth Factor, Beta Receptor II. *VKORC1*: Vitamin K epoxide reductase complex subunit 1; *IFNG*: Interferon, Gamma.

Along the years several other genes located on chromosome 6 have been investigated. *COL11A2*, located at 6p21.3 was analyzed by Koga et al [70] for the presence of molecular variants associated with OPLL and 4 variants (promoter -182, rs1799907, rs1799910 and rs1799911) showed strong statistical association with OPLL (Table 2-3). On the other hand, according to Maeda [177] the rs1799907 polymorphism, previously associated with OPLL [70], might act as a protective allele in the development of OPLL, since the polymorphism is more frequently observed in controls than in OPLL patients. Interestingly, the authors found that rs1799907 resulted in altered splicing in the region containing exons 6 through 8 with preservation of exon 7. The protective effect is proposed to be due to the higher frequency of the rs1799907 allele in white populations, in whom a low frequency of OPLL has been reported. Maeda et al [61] in another study found a male-specific association of a *COL11A2* haplotype with OPLL. Other genes located in chromosome 6 such as RXR $\beta$  [169], *ESR1*, *RSPH9* and *RUNX2* were also investigated and in all of them SNPs associated with OPLL were identified (Table 2-3).

Based on the initial findings, that a nonsense mutation in the Npps gene (ENPP1; MIM\*173335) in the naturally occurring mutant ttw mouse causes ectopic ossification of the spinal ligaments that resembles OPLL [89], several studies have tried to associate this gene to OPLL. ENPP1 is the main enzyme that generates PPi (a known inhibitor of calcification), in osteoblasts and chondrocytes, regulating bone mineralization by decreasing hydroxyapatite crystal deposition [178]. Nakamura et al [164] in an association study found that ENPP1 is involved in OPLL by revealing an allelic association with an intron 20 polymorphism (denoted as IVS20-11delT). This polymorphism was significantly higher in OPLL patients than in controls, indicating that individuals with this variation may be more susceptible to abnormal ossification of the spinal ligaments. This variant is considered a risk factor for diabetes mellitus type 2 and obesity [179]. In another study the same variant - IVS20-11delT- in ENPP1 and the A861G variant of the leptin receptor gene were more frequent in patients with OPLL in the thoracic spine relative to those with OPLL restricted to the cervical spine, leading the authors to suggest that both variants are associated with more extensive OPLL, but not with the frequency with which it occurs [180]. Other studies, however, reported that IVS20-11delT was unassociated with OPLL [154, 165] and other associated variants such as IVS15-14T [165] was associated with susceptibility and severity of OPLL. Other authors showed that the polymorphism TT genotype of C973T and IVS15-14T in the same gene were associated with more severe disease [166].

In addition, *COL11A2*, *COL6A1* that map to chromosome 21 and *COL17A1* that maps to chromosome 10 have also been studied in OPLL susceptibility. The *COL6A1* gene [33, 146, 181], is strongly associated with OPLL and polymorphisms of this gene are considered helpful markers of OPLL disease. However, this association has not been confirmed by some authors [35, 72, 159]. Polymorphisms of this gene are also related to DISH in a Japanese population [34] and this suggests that *COL6A1* may not only play a role in OPLL, but in pathological ectopic ossification in general. A whole exome sequencing study revealed that *COL17A1* was associated with OPLL and two SNPs in this gene rs805698 and rs4918079 were significantly associated with OPLL [163].

Bone morphogenic proteins (BMP2, BMP4 and BMP9) and TGF $\beta$  superfamily proteins also play a role in OPLL pathogenesis. A positive association to OPLL was found with the following SNPs: rs3178250 [156], rs2273073 [157, 158] and rs1949007 [157] in the BMP2 gene. Furthermore Yan in 2013 [158], showed that the rs2273073 variant in the BMP2 gene was positively associated with the level of Smad4 protein expression and the activity of alkaline phosphatase. Activation of Smads causes their translocation from the cell cytoplasm to the nucleus where they control gene expression [182], and alkaline phosphatase is the first functional gene expressed in the process of calcification and is secreted by osteoblasts in the process of osteogenic differentiation [183]. On the other hand, Kim et al [72] showed that SNPs rs2273073 and rs1949007 in BMP2 gene may not influence the OPLL in Korean patients. Other study elaborated by Liu et al [35] also failed to show the association of BMP2 gene to OPLL in the Chinese Han population. The BMP4 protein is another candidate gene for OPLL and two SNPs rs17563 [160, 161], rs76335800 and a specific haplotype, TGGGCTT [161], were demonstrated to contribute to the risk of developing OPLL in a Chinese population. The association of BMP-4 with OPLL was also confirmed by Furushima et al [159] in a large scale screening study for candidate genes in OPLL, in which only the BMP-4 gene reached the criteria for suggestive evidence of linkage. In the BMP9 gene two SNPs have been associated with OPLL: rs75024165 and rs34379100 [162].

Another interesting gene with conflicting results is  $TGF\beta 1$ , that, according to Kamiya et al [170], is genetically determinant in predisposition for the condition (869T>C; rs1982073). However Han et al [184] showed that the SNP previously associated with OPLL (869T>C; rs1982073) and the promoter (-509C>T; rs1800469) were not

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associated with OPLL in a Korean population. Similarly, in one study that assessed 109 polymorphisms of 35 candidate genes in 711 patients with OPLL and 896 controls failed to confirm the positive association of OPLL with  $TGF\beta 1$  gene. Interestingly, in the ossified matrix and chondrocytes of adjacent cartilaginous areas of OPLL, TGF-beta1 is overexpressed, and one study examined if there is an association between the SNP 869T>C; rs1982073 and the radiological appearance of OPLL. Although a T-C transition in TGF-beta1 did not predict a difference in the radiographic appearance of the ossified segment of posterior longitudinal ligament, it was associated with the location of OPLL within the spinal column. According to the authors  $TGF\beta 1$  polymorphisms are not related to the onset of OPLL, but rather to the area of the ossified lesion. The "C" allele might be a risk factor for patients with OPLL in other areas in addition to the cervical lesion [185]. Association of  $TGF\beta 3$ , which plays an important role in regulating chondrogenic differentiation of mesenchymal stem cells in humans [186] has also been described [154] and an intronic SNP rs2268624 has a significant association with OPLL.

Other genes from large scale studies have recently emerged as promising targets for future investigation, including *AHSG*, *STK38L*, *RSPO2*, *CCDC91* and *HOA1*. In a Genome wide linkage study [187] with 214 affected sib-pairs the D20S894 marker on chromosome 20p12 was associated with OPLL. The linkage region contained 25 known genes and two genes located in this linkage region may be good candidate genes for OPLL, one example is Jagged 1 (*JAG1*) because of its potential involvement in the endochondral bone formation [188] and *BMP2* already studied and an already established important regulator of bone metabolism. Very recently 8 potentially pathogenic missense variants in 4 genes, including 3 in *COL6A1*, 2 in *COL11A2*, 2 in *FGFR1* and 1 in *BMP-2* were identified in a target exome sequencing study with 11 OPLL candidate genes using 55 Chinese patients with OPLL [181]. Although the authors suggested that these missense variants were involved in pathogenicity of OPLL, further confirmation is required.

A large number of genes have already been associated with OPLL, nonetheless it is probable that many other potential genes are involved in inheritance of the disease. OPLL does not appear to follow a simple, single gene Mendelian inheritance pattern and it is most likely multifactorial and develops in individuals with a genetic predisposition due to a variety of different mutations in various genes on various chromosomes.

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## 2.4.4 Genetic studies on OLF

As far as we known, there are few studies in the literature that investigate a disease causing gene in OLF. Kong and collaborators [33] investigated the frequency of 4 SNPs in *COL6A1* gene, a well-known OPLL susceptibility gene for OLF and OPLL, in 183 patients (61 with OLF) and 155 controls and suggest that *COL6A1* may be a common susceptibility gene for OLF in Chinese population (Table 2-4). Another study [35] investigates the possible association of four genes, that may be related to ossification of spinal ligaments (*RUNX2*; *BMP2*; *COL6A1* and *VDR*), and the authors found that *RUNX2* (rs1321075 and rs12333172 polymorphisms) could be responsible for ectopic bone formation in the spinal ligament in a Chinese population. Jun et all [147] investigated the association between *FGF2* (Fibroblast Growth Factor), *FGFR1* (Fibroblast Growth Factor Receptor 1) and *FGFR2* (Fibroblast Growth Factor Receptor 2) polymorphisms with OLF and OPLL and found a positive association of the SNP rs1476217 in *FGF2* gene (Table 2-4).

Gene	Chr	Physiological function	Study type No Subjects [case/control]	SNP- significantly associated	Ref
COL6A1	21	Collagen VI is a major structural component of microfibrils. Mutations in the genes that code for the collagen VI subunits result in the autosomal dominant disorder, Bethlem myopathy.	Case control association study with 61 OLF patients and 155 Chinese controls. Assessed 4 SNPs in <i>COL6A1</i>	rs17551710 (p=0.0005)	[33]
RUNX2	6	<i>RUNX2</i> is a transcription factor that encodes a nuclear protein with a Runt DNA-binding domain. This protein is essential for osteoblastic differentiation and skeletal morphogenesis and acts as a scaffold for nucleic acids and regulatory factors involved in skeletal gene expression. Mutations in this gene have been associated with the bone development disorder cleidocranial dysplasia.	Case control association study with 36 Chinese patients (12 with OLF and 22 with OLF and OPLL) and 118 controls	rs1321075 (p=0.034) rs12333172 (p=0.043)	[35]
FGF2	4	The protein encoded by this gene is a member of the FGF family. This protein has been implicated in diverse biological processes, including limb and nervous system development.	Case control association study of 157 OPLL patients (29 with OLF) and 222 controls	rs1476217 (p=0.01)	[147]

Table 2-4.	Genetic	variants	associated	with	OLF.
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**Abbreviations:** SNP: Single nucleotide polymorphism, Chr: chromosome, p: p-value, Ref: references, *COL6A1*: Collagen Type VI Alpha 1 Chain, *FGF2*: fibroblast growth factor 2, *RUNX2*: Runt-related transcription factor 2.

## 2.5 Association with other diseases

The presence of OSL has been reported in association with numerous disorders of different etiologies.

## 2.5.1 Monogenic disorders

Case reports of patients with monogenic metabolic disorders with co-occurrence of both DISH and OPLL have been reported in literature (Table 2-5). All of the disorders presented in table 2-5 are directly involved in calcium and phosphate homeostasis, with the exception of alkaptonuria, a disorder of tyrosine metabolism characterized by the accumulation of homogentisic acid, ochronosis, and destruction of connective tissue resulting in degenerative spondylosis and arthritis [189]. In ochronosis, calcification of intervertebral disks due to calcium hydroxyapatite and marked sclerosis including sacroiliac joint can also be observed. Genes involved in Hypophosphatemic rickets and Hypophosphatasia are, as expected, directly involved in phosphate homeostasis. Analysing the genes present in table 2-5 the FGF23 gene inhibits phosphate uptake and mineralization in vivo by suppressing expression of type IIc (SLC34A1) sodium/phosphate cotransporters in the brush border membranes of proximal tubes [190]. SLC34A1 contributes to the maintenance of inorganic phosphate concentration in the kidney [191]. DMP1 gene encodes the Dentin matrix acidic phosphoprotein 1, which plays a role in controlling osteocyte formation and phosphate homeostasis [192]. Proteolytic degradation of DMP1 leads to the release of the "Acidic serine- and aspartaterich MEPE-associated motif' (ASARM) peptides, which are potent inhibitors of mineralization (minhibins) [193]. The ASARM peptide inhibits mineralization directly by binding to hydroxyapatite crystals and decreasing expression of PHEX, whereas phosphaturic effects are mediated by renal accumulation of ASARM peptides and inhibition of Pi reabsorption. PHEX, a Type II, zinc dependent, transmembrane endopeptidase is involved in bone and dentin mineralization as well as in renal phosphate reabsorption [14]. CLCN5 is a renal chloride channel gene highly expressed in proximal tubules of the kidney that play an important role in renal tubular function [194].

Disorder	Inheritance	OMIM	Gene/Locus Involved	Ref	
	AD	193100	FGF23		
	AR	241520	DMP1	[195]	
Hypophosphatemic rickets/osteomalacia	AR	613312	ENPP1		
	AR	241530	SLC34A3		
	XLD	307800	PHEX		
	XLR	300554	CLCN5		
	AR	241500			
Hypophosphatasia	AR	241510	ALPL	[196]	
	AR, AD	146300			
Pseudohypoparathyroidism	AD	103580	GNAS1	[197]	
Hypoparathyroidism	AD	146200	GCM2	[198-200]	
Typoparatiyrotasii	AD/AR	146200	РТН		
Alkaptonuria	AR	203500	HGD	[201]	
	Somatic /AD	102200	AIP		
		102200	GNAS1		
	X linked	300943	GPR101		
Acromegaly	AD	610755	CDKN1B	[202]	
	AD	131100	MENI		
	Somatic	174800	GNAS		
	AD	160980	PRKAR1A		
	AD	145980	CASR		
Familial Hypocalciuric Hypercalcemia	AD	145981	GNA11	[203]	
	AD	600740	AP2S1		

Table 2-5. Monogenic disorders previously associated with OSL, type of inheritance, number of Mendelian Inheritance in Man database (MIM) and gene involved. Lack of inheritance means that it is unknown.

Abbreviations: AD - Autosomal Dominant, AR - Autosomal Recessive, XLD - X-linked Dominant and XLR X-linked Recessive, Ref: References, *ALPL*: Alkaline Phosphatase, Liver/Bone/Kidney, *FGF23*: Fibroblast growth factor 23, *DMP1*: Dentin matrix acidic phosphoprotein 1, *ENPP1*: ectonucleotide pyrophosphatase/phosphodiesterase 1, *SLC34A3*: Solute carrier family 34 member 3, *PHEX*: Phosphate regulating endopeptidase homolog, X-linked, *CLCN5*: Chloride voltage-gated channel 5, *GNAS1*: Guanine nucleotide binding protein, alpha stimulating, *GCM2*: Glial cells missing Homolog 2, *PTH*: Parathyroid hormone, *HGD*: Homogentisate 1,2-Dioxygenase, *AIP*: Aryl hydrocarbon receptor-interacting protein, *GPR101*: G protein-coupled receptor 101, *CDKN1* $\beta$ : Cyclin-dependent kinase inhibitor 1 $\beta$ , *MEN1*: Menin 1, *PRKAR1A*: Protein Kinase CAMP-Dependent Type I Regulatory Subunit Alpha, *CASR*: calcium-sensing receptor, *GNA11*: G Protein Subunit Alpha 11, *AP2S1*: Adaptor Related Protein Complex 2 Sigma 1 Subunit.

Alkaline phosphatase (*ALPL*) is present in matrix vesicles and has the ability to hydrolyze PPi, playing a role in bone mineralization. In hypophosphatasia the *ALPL* mutations leading to deficient activity of the tissue-non-specific alkaline phosphatase isozyme (*TNAP*), an enzyme which converts the inhibitor (PPi) into a promoter of mineralization

(Pi) [183]. Lastly, but not least is *ENPP1* gene, which has been already mentioned previously. It is particularly interesting to see that the only report of an OPLL patient with hypophosphatemic rickets is caused by a novel homozygous mutation in the *ENPP1* gene [195]. However, not all patient cases of Hypophosphatemic Rickets caused by mutations in *ENPP1* present OPLL.

Hypoparathyroidism cases associated with changes resembling DISH are reported in the literature [198-200]. The genes involved in Hypoparathyroidism *GNAS*, *GCM2* and *PTH* are also involved in both calcium and phosphate metabolism. *GNAS* (GNAS Complex Locus) play a role in signaling pathways that regulate osteogenesis, normally preventing ectopic ossification in tissues where bone should not form [204]. *GNAS* mutations have been associated with several other disorders, including Progressive Osseous Heteroplasia (POH; MIM#166350). *GCM2* (Glial Cells Missing Homolog 2) gene encodes a protein that possibly is involved in a backup endocrine mechanism for the regulation of calcium homeostasis in the absence of parathyroid glands [205]. The *PTH* gene encodes parathyroid hormone that is secreted when calcium levels drop and causes increased calcium absorption through the gut, and kidney and provokes an increase in bone resorption through direct and indirect processes. It is an essential hormone in bone homeostasis [206].

Acromegaly is a rare condition characterized by excess growth hormone (GH) production by the pituitary gland and its principle mediator insulin-like growth factor 1 (*IGF-1*) [207]. Familial syndromes associated with GH hypersecretion can be seen in table 2-5. Excess GH and IGF-1 cause proliferation of articular chondrocytes and increased matrix production [208]. It is known that GH levels may act as a bone promoting factor in DISH [209].

There is only one case report of a patient with Familial Hypocalciuric Hypercalcemia (FHH), a rare and benign cause of lifelong hypercalcemia, and DISH. This particular case, a 45-year-old diabetic woman with hypercalcemia secondary to FHH, developed dysphagia because of external esophageal compression of DISH [210]. A causal association between FHH and DISH is not yet proven.

## 2.5.2 Complex disorders

Some authors suggest that DISH, instead of a disorder by itself is only a clinical expression of metabolic disorders being angiogenesis the link leading to new bone formation [211]. The aetiology of the following associated OSL disorders is complex and

determined by the interplay of genetic and environmental factors. Environmental factors such as age, smoking, alcohol, diet, and physical inactivity may directly influence Type 2 Diabetes mellitus (T2D), metabolic syndrome and obesity. Nevertheless, although heterogeneous, there are some monogenic forms of these disorders; see table 2-6 for more details.

Disorder	Туре	Inheritance	OMIM	Gene/Locus Involved	Ref
Non-insulin-dependent	Monogenic - MODY	AD	606391	Genetically Heterogeneous – associated with mutations in 13 genes	[212, 213]
Type 2 Diabetes mellitus	Polygenic	?	125853	Many susceptibility locus identified, including in <i>ENPP1</i>	
	Monogenic	?	615812	DYRK1β	
Abdominal Obesity -		AR	200100	MTP	[214]
Metabolic Syndrome	Polygenic	?	605552	AOMS1 locus AOMS2 locus	[214]
		AR	614962	LEP	
		AR	614963	LEPR	
	Monogenic	AR	600955	PCSK1	
	Wonogenie	AR	609734	РОМС	[215]
Obesity	Polygenic	?	601665	Genetically heterogeneous but including <i>ENPP1</i> as susceptibility gene	

Table 2-6. Complex disorders previously associated with OSL. Lack of inheritance means that it is not yet known.

Abbreviations: OMIM: Online Mendelian Inheritance in man, MODY: Maturity-Onset Diabetes of the Young, AD: Autosomal Dominant, AR: Autosomal Recessive, Ref: References, *ENPP1*: ectonucleotide pyrophosphatase/phosphodiesterase 1, *DYRK1B*: Dual specificity Tyrosine Phosphorylation regulated kinase 1 $\beta$ , *MTP*: Microsomal triglyceride transfer protein, *AOMS1,2*: Abdominal obesity-metabolic syndrome 1,2, *LEP*: Leptin, *LEPR*: Leptin receptor, *PCSK1*: Proprotein convertase subtilisin/kexin 1, *POMC*: Pro-opiomelanocortin.

Diabetes mellitus is considered to be a heterogeneous group of disorders, which are characterized by persistent hyperglycemia. There are rare forms of diabetes that are monogenic, as is the case of maturity onset diabetes in the young (MODY; 606391),

however the two most common forms of diabetes are T1D, also known as insulindependent diabetes and T2D, known as non-insulin-dependent diabetes. Both T1D and T2D are polygenic, caused by a combination of genetic and environmental risk factors. Individuals with T2D usually have a tendency for having obesity and manifestations of the metabolic syndrome, which is characterized by diabetes, insulin resistance, hypertension, and hypertriglyceridemia [216]. T2D can be associated with OSL by either hyperglycemia or by the high insulin rate [217]. Studies already performed are not conclusive. Although obesity is considered to be a complex and multifactorial disease, there are some monogenic cases described as rare and severe early-onset obesity associated with endocrine disorders. The phenotype, in monogenic cases, is due to mutations in genes of the leptin/melanocortin axis involved in food uptake regulation genes of leptin (LEP) and its receptor (LEPR), Pro-opiomelanocortin (POMC) and proprotein convertase subtilisin/kexin 1 (PCSK1) [218]. Mutations in the LEPR gene, occurs in the ZFR rat model and can cause obesity, hyperinsulinemia, hypercholesterolemia and hyperlipidemia besides the ossification of spinal ligaments, resembling human OPLL [42]. It is also relevant to see ENPP1 as a susceptibility gene for both T2D [219] and obesity [220].

#### 2.5.3 Rheumatic disorders co-existing with OSL

The co-existence of DISH with rheumatic disorders has been described since its first report by Forestier and Rotes Querol, in 1950 [221] and a high percentage of DISH cases are complicated by OPLL [6] suggesting that they share common aetiopathogenic factors. Simultaneous OPLL and OLF are also very common in the literature [222, 223]. Additionally, the co-existence of the three OSL disorders – DISH; OPLL and OLF has also been reported [32].

The genetic basis of coexistent rheumatic conditions with OSL can be seen in table 2-7.

Disorder	Inheritance	OMIM	Gene/Locus Involved	Ref
Ankylosing	Multifactorial	106300	HLA-B	
Spondylitis (AS)	AD	183840	SPDA2 locus	
Spondynus (AS)		613238	SPDA3 locus	
Chondrocalcinosis	AD	118600	ANKH	[224 225]
	AD	600668	CCAL1 locus	[22 1, 223]
Rheumatoid arthritis	?	180300	6q23 (HLA)	[22, 226-228]
	?	604302	IL6/MIF	[22, 220 220]
	AD;AR	612076	SLC2A9	[22 67 229
Gout	AD	612671	SLC17A3	2301
	AD?	138900	ABCG2	230]
	Multifactorial	165720	FRZB	
	AD	140600	<i>MATN3</i> (with Heberden Nodes)	
Ostooarthritis	AD 607850 ASPN		ASPN	[22]
Osteoartinitis	?	612400	GDF5	
	AD	604864	COL2A1	
	?	2q33.3		
	?	612401	3p24.3	
	AD	602080	TNFRSF11A	
	AD	167250	SQSTM1	
Paget's Disease	AD	606263	PDB4	[224, 225]
	AR	239000	TNFRSF11B	
	AD	616833	ZNF687	

## Table 2-7. Rheumatic disorders previously seen coexisting with OSL. Lack of inheritance means that it is not yet known.

Abbreviations: AD: Autosomal Dominant, AR: Autosomal Recessive, Ref: References, ?: unknown, HLA-B: Human Leukocyte antigen B, *SPDA2,3*: Spondyloarthropathy, Susceptibility To, 2,3, *ANKH*: progressive ankyloses protein homolog, CCAL1: Chondrocalcinosis 1, *IL-6*- Interleukin-6, *MIF*: Macrophage inhibitory factor, *SLC2A9*- Solute carrier family 2 member 9, *SLC17A3*- Solute carrier family 17 member 3, *ABCG2*: ATP Binding Cassette Subfamily G Member 2, *FRZB*- Frizzled-related protein 1, *MATN3*: Matrilin-3, *ASPN*- Asporin, *GDF5*- Growth/differentiation factor 5, *COL2A1*- Collagen Type II Alpha 1 Chain, *TNFRSF11A, B*: TNF Receptor Superfamily Member 11a,b, *SQSTM1*: Sequestosome-1, *PDB4*: Paget disease of bone 4, *ZNF687*- Zinc Finger Protein 687.

The co-existence of DISH and **AS** is possible and has been thoroughly described in more recent years due to the difficulty, sometimes, to distinguish them apart [7-21]. OPLL has also been reported in patients with AS but it was determined that OPLL in AS was associated with older age [231]. AS is a chronic, multisystem inflammatory disorder characterized by inflammation and ankylosis of the sacroiliac joints and the axial

skeleton. Structural damage in AS is dominated by new bone formation that can result in spinal fusion and marked functional limitation. In Online Mendelian Inheritance in Man database (OMIM), which collects known genetic lesions responsible for human inherited diseases, the following principal loci of AS susceptibility are mentioned: HLA-B locus (SPDA1; MIM106300), 9q31-q34 (SPDA2; MIM 183840) and 2q (SPDA3; MIM 613238) (Table 2-7), however more than 100 genetic influences are reported in the literature [232] [233, 234], although many of them are pending confirmation. It is known that AS is a polygenic disorder and its heritability is estimated to be more than 90% and the MHC-1 region, particularly the HLA-B\*27, is the main contributor for this proportion [235, 236], followed by a second gene definitively associated with AS, the ERAP1. Both contribute to MHC1 antigen processing pathway, and the role played by HLA-B27 in AS pathogenesis could be explained by the association between both, and actually this association is considered the two most powerful disease risk factors to AS. ERAP1 plays a role in trimming peptides within endoplasmic reticulum (ER) into the right length binding to MHC-I molecules, and so abnormal function of ERAP1 can lead to generation of abnormal peptides of incorrect length and sequence, which subsequent to HLA-B27 binding can lead to peptide-HLA-B27 complex misfolding. These misfolded proteins could either accumulate within ER, thus contributing to the ER stress, or be transported to the cell surface as a free heavy chain. This mechanism seems to have a role in AS pathogenesis, but the degree of this contribution to the overall pathogenesis of AS remains hypothetical. The association of ERAP1 is restricted to HLA-B27 positive cases or HLA-B27 negative/HLA-B40 positive cases [232, 237, 238]. Several gain of function variants are reported as associated with AS and loss of function as protective to AS [239, 240]. In SPDA3 locus the IL-1 gene seems to be associated with AS [241]. Another genetic contribution is the involvement of interleukin IL-23/IL-17 pathway, that has been shown to have significance in the pathogenesis of AS. The *IL-23* drives the differentiation of CD4-positive Th17 cells, which produce IL-17. Il-17 in turn facilitate the production of IL-6, IL-8, TNF, chemokines, matrix metalloproteinases, and receptor activator of nuclear factor  $k\beta$  ligant from a wide range of cell types [242]. Based on genome wide association and linkage studies several risk genes involved in ectopic calcification in AS were reported in the literature. The ANTXR2 (Anthrax toxin-receptor 2), was identified as one of the risk loci for AS [243]. This gene potentially affects new bone formation as it can interact with LRP6 protein, an important surface receptor in the Wnt/ $\beta$ -catenin pathway. In Han Chinese population the ANTXR2 gene is not associated with AS [244]. Other two

risks loci that seems to be relevant to bone formation in AS were also reported in the literature, the *HAPLN1-EDIL3* at 5q14.3 and *ANO6* at 12q12.1 [244]. *HAPLN1* is involved in osteophyte formation and disc generation in Japanese women with spinal osteoarthritis [245], and *EDIL3* has an inhibitory effect on WNT/ $\beta$ .catenin signaling [246]. The *ANO6* gene controls bone mineralization by activating the calcium transporter NCX1. In mice, the lack of *Ano6* is responsible to bone mineralization defects [247]. Another relevant gene in mineralization is *ANKH* (human homolog of progressive ankyloses), a gene that is also reported as associated with AS. Curiously this association is gender specific, in other words some SNPs of the *ANKH* gene are significantly associated with AS in men and other SNPs are present in females [248]. ANKH protein regulates PPi export from the cells. It is well known that abnormal PPi levels can be associated with aberrant bone formation and in the mutant mice (ank/ank), which have a premature stop codon in the 3' end of the ank gene, severe ankylosis occurs [106].

The co-coexistence of some form of spinal ossification with chondrocalcinosis are reported in the literature [25, 26], suggesting that a genetic link exists between these diseases. The first evidence of a genetic link between OPLL and chondrocalcinosis was identified in the ttw mouse a model for OPLL which develops spinal ossification and hydroxyapatite arthropathy. Npps, also designated as PC-1, is the mutant gene that causes this mouse phenotype. In humans this gene, designated *ENPP1*, plays a role in regulating PPi levels thus regulating bone mineralization and soft tissue calcification [249]. Variants in ENPP1 are associated with GACI, diabetes (125853), obesity (601665) [250] and other diseases. The possible association of the ENPP1 gene with OPLL is not yet proven however several studies confirm a positive association (Table 2-3), the association with CC is considered a minor determinant for the disease [251, 252]. DISH and CC is very common in Terceira Island and this has led to the suggestion that both diseases share the same pathogenic mechanism [24]. The coexistence of CC and AS is also reported [253] and CC has also been associated with Gitelman syndrome (GS), a kidney disorder that causes an imbalance of potassium, magnesium and calcium ions, possibly due to their association with chronic hypomagnesaemia [254]. CC, also known as calcium pyrophosphate dehydrate (CPPD) disease, pseudogout or pyrophosphate arthropathy [255] is a disorder of ectopic calcification characterized by the deposition of calcium containing crystals in articular cartilage, synovial membranes and sometimes in periarticular soft tissues. The deposited salts are composed of CPPD although other calcium salts can also be found including hydroxyapatite [256]. In some cases, the
deposition of calcium crystals - hydroxyapatite or CPPD- can also occur in the spinal ligaments [257, 258], but it is usually difficult to distinguish from ossification [46]. The physicochemical mechanisms that cause this deposition are still unknown, but disordered PPi metabolism is suspected. The deposited crystal may be calcium hydroxyapatite (in which the local PPi concentration is presumed to be low) or CPPD (when PPi is high) [255]. In addition to the sporadic form, chondrocalcinosis a hereditary form also occurs and it may also be associated with metabolic disorders - hyperparathyroidism [259], hemochromatosis [260], and hypomagnesemia [261]. In 1963, Zitnan and Sitaj [262], reported a hereditary form of "chondrocalcinosis articularis" in seven Czechoslovakian kindreds. Since then, familial aggregation has been reported in different ethnic groups most of them showing an autosomal dominant inheritance [25, 263-265]. Genetic linkage studies have mapped the familial forms of CC to two particular chromosome regions, CCAL1 (MIM 600668) on chromosome 8 [266] and CCAL2 (MIM 118600) on chromosome 5 [267]. The later contains the human homologue (ANKH) of the murine ank gene which is expressed in cartilage and other tissues and is associated with CC and spinal and peripheral joint ankylosis in the ank/ank mouse [106]. The ANKH gene maps to chromosome 5 (5p15.1) and encodes a transmembrane inorganic pyrophosphate transporter ANK that transports intracellular pyrophosphate into the extracellular matrix, where it acts as a potent inhibitor of mineralization [108]. Analysis of this gene has identified a variety of mutations that segregate with the CC phenotype [110] [268] [29] [30] [31]. These mutations enhance ANK protein activity, thereby elevating extracellular pyrophosphate levels and promoting the formation of pyrophosphate crystals, which produce the manifestations of the disease [269]. For the moment, ANKH (CCAL2) is the only monogenic cause identified for CC. In humans, dysfunction of the ANKH gene also causes autosomal dominant craniometaphyseal dysplasia (OMIM #123000) [109]. The disease-causing gene in CCAL1 has never been identified but there is a strong possibility that this gene is primarily related to osteoarthritis (OA) and that the CPPD deposition is secondarily, enhanced by the degenerative changes in cartilage [266].

The coexistence of **Rheumatoid arthritis** (RA) with DISH, OPLL and OLF is mentioned in the literature. RA is an inflammatory disease, primarily of the joints, with autoimmune features and a complex genetic component involving many different pathways within the innate and the adaptative immune system [270]. Among the genetic components, genes in the MHC region on chromosome 6 are widely acknowledged as major players in RA. *MIF* (Macrophage migration inhibitory factor) gene also seems to play a role in RA

#### Chapter II

pathogenesis, the gene encodes a lymphokine involved in cell-mediated immunity, immunoregulation, and inflammation. Other genes that are involved in the disease is Interleukin-6 (*IL-6*) which encodes a cytokine that functions in inflammation and the maturation of B cells.

**Gout** is a form of arthritis caused by impaired urate metabolism, leading to high serum urate levels (hyperuricemia) and accumulation of sodium urate crystals in the joints.

At least three genes are associated with gout - *SLC17A3*, *SLC2A9* and *ABCG2* - all of them correspond to urate transporters located in the epithelial cells of renal proximal tubules (Table 2-7). The genes most strongly linked to gout corresponds to the solute carrier 2A9 (*SLC2A9*), also known as glucose transporter 9 (*GLUT9*). This transporter was initially identified as a glucose/fructose transporter [271], however it is also a high-affinity urate transporter and functions in renal urate reabsorption. The second locus linked to gout corresponds to the gene encoding the solute carrier 17A3 (*SLC17A3*), also known as the renal sodium phosphate transport protein 3 (*NPT3*), that excretes intracellular urate and organic anions. Mutations in the *SLC17A3* gene caused reduced urate efflux compared to the wildtype when expressed in xenopus oocytes [273]. The last gene linked to gout corresponds to *ABCG2*, a gene which encodes a multidrug resistance transporter belonging to the ATP-binding cassette (ABC) superfamily. It has recently been discovered that this transporter is also involved in renal urate elimination, and the presence of a specific polymorphism (Q141K) induces a decrease in urate efflux [274, 275].

**Osteoarthritis** (OA) is a degenerative disease of the joints characterized by loss and/or remodeling of joint synovium, cartilage, and bone. The sites most frequently affected are knee, hip, feet and hands, although involvement of lumbar and cervical spine, elbows, wrists and other joints can also occur [276, 277]. According to the OMIM database, osteoarthritis susceptibility (OS) has been associated with several regions/genes: *FRZB* (OS1; 165720), *MATN3* (OS2; 140600), *ASPN* (OS3; 607850), region 2q33 (OS4; 610839), *GDF5* (OS5; 612400) and region 3p24 (OS6; 612401). Another susceptibility gene for osteoarthritis (with chondrodysplasia) (304864) is the *COL2A1* gene (Table 2-7). Particularly, *FRZB* (Frizzled-Related protein 1) gene encodes a secreted protein antagonist of wingless (WNT) signaling involved in the regulation of bone development. It is known that functional polymorphisms within *FRZB* causes susceptibility for hip OA in females [278], implicating the WNT signaling pathway in the pathogenesis of this disease. The *MATN3* (Matrilin 3) gene encodes a protein present in the cartilage

extracellular matrix and has a role in the development and homeostasis of cartilage and bone [279]. This gene has recently been shown to bind cartilage extracellular matrix proteins, including collagen types II and IX [280], and promotes chondrogenesis through an interleukin-1 receptor antagonist-dependent mechanism [280, 281]. Variants in this gene result in hand osteoarthritis [277, 282] and other skeletal diseases, including multiple epiphyseal dysplasia, which is characterized by abnormal ossification in the growth plate and early onset OA [283]. ASPN is another osteoarthritis susceptibility gene, which encodes asporin, a cartilage extracellular protein that regulates chondrogenesis by inhibiting transforming growth factor-beta 1-induced gene expression in cartilage. In addition, this protein also binds calcium and collagen and may induce collagen mineralization. Polymorphisms in this gene are associated with knee osteoarthritis susceptibility [284, 285]. Associations between this gene and lumbar disk degeneration [286] and AS are also reported [287]. The GDF5 (Growth Differentiation Factor 5) gene is a member of the TGF- $\beta$ /BMP superfamily which is involved in bone and cartilage formation by inducing chondroblastic and osteoblastic differentiation and the formation of joints [288, 289]. Mutations in this gene seems to be involved in hip and knee OA progression [290] and other skeletal disorders, such as Acromesomelic dysplasia (AMDH; MIM #201250) [291], Chondrodysplasia (MIM; 200700) [292], among others. The other gene associated with OA is *COL2A1* (Collagen Type II Alpha 1 Chain) which encodes Type II collagen, the major collagen synthesized by chondrocytes. Besides the association of Osteoarthritis with mild chondrodysplasia (604864) [289, 293], this gene is also associated with achondrogenesis (MIM; 200610), Spondyloperipheral dysplasia (MIM; 271700), and other diseases. Lastly but not least, two candidate genes for osteoarthritis susceptibility were found in the region 2q33.3, the Parathyroid Hormone 2 Receptor (PTHR2) and Frizzled Class Receptor 5 (FZD5), however only a missense variant in the *PTHR2* gene co-segregate with the disease [294]. For the region 3p24.3, several variants in collagen Type VI, alpha-4, pseudogene 1 (COL6A4P1 or DVWA) seem to contribute strongly to knee osteoarthritis susceptibility [295] and a functional role in cartilage has been suggested despite its pseudogene status [296].

**Paget's disease (PD)** is a metabolic bone disease characterized by an imbalance between osteoclast and osteoblast activity that typically begins with excessive bone resorption followed by an increase in bone formation [297]. It has a predilection for the axial skeleton but any bone may be affected [298]. Several susceptibility genes for PD have been identified (Table 2-7). The gene most frequent linked to PD is *SQSTM1* which

encodes sequestosome 1 a multifunctional protein involved in the IL-1, TNF, and RANKL signaling pathways [297].

TNFRSF11A (TNF Receptor Superfamily Member 11a) and TNFRSF11B are genes which encodes the RANK protein and osteoprotegerin (OPG), respectively. Both RANK and OPG are involved in the RANKL/OPG/RANK signaling pathway, which is the principal regulator of osteoclastogenesis [299]. The TNFRSF11A gene is not only associated with PD, but also with familial expansile osteolysis (174810) and osteopetrosis (612301) and the TNFRSF11B gene could also be associated with bone mineral density and osteoporosis [300] and a gain of function mutation in this gene causes osteoarthritis with chondrocalcinosis [301]. The ZNF687 gene was recently found in a whole exome sequencing study as associated with PD [302]. There is not much information about this gene, however it is known that it encodes a C2H2 (Cys2His2-like) zinc finger protein involved in the transcriptional regulator complex Z3 [303]. It has been suggested that probably this zinc finger protein is involved in bone cell proliferation and differentiation since it is up-regulated during osteoblast and osteoclast differentiation and is highly expressed during the regeneration of caudal fins in zebrafish [302]. Lastly, a linkage to the 5q31 region, designated by PD bone 4 (PDB4), seems to be associated with PD, however no candidate gene has been found in this region yet.

# CHAPTER III: MATERIAL AND METHODS

# 3. MATERIAL AND METHODS

#### 3.1 Collections- patients/families and associated data

The biobank Azores (AZORBIO) of the Specialized Service of Epidemiology and Molecular Biology (SEEBMO) has a collection of biological material (DNA; RNA; cartilage; plasma; serum; cell lines and urine) and associated data (clinical; epidemiological and genetic data) of Azorean patients with different pathologies. AZORBIO was founded in 1998 and has the facilities and equipment necessary for its operation. All the samples and data are manipulated in the same way according to standard operating procedures and all the samples are tested by a quality control process. All the collections have the documentation required by Portuguese law (Lei nº 12/2005), such as informed consent of all individuals [304]. The main objective of this biobank is to store biological products and associated data for further confirmation of the disease and for research.

#### 3.1.1. Families DISH/CC

Eleven probands from ten families (AZ1-10) (Figure 2-1) were identified through a record review conducted at the Rheumatic Diseases Clinic of the Hospital of Santo Espírito da Ilha Terceira (HSEIT). The 11 probands and 71 family members (Figure 3-1 and table 3-1) were interviewed and examined for the presence of DISH and or CC by a rheumatologist (JBA). All participants gave informed consent, and standard X rays were taken from: knees, axial skeleton, wrists, hands, elbows, and pelvis. Pathological status was determined radiographically, with the diagnosis of DISH being made according to the Utsinger criteria [5], and the diagnosis of chondrocalcinosis on the classic radiological evidence of deposition of calcium in the fibrocartilage. All individuals were screened for secondary causes of chondrocalcinosis, using appropriate biochemical and genetic tests. The pedigrees and the associated data of the collaborating families were available in AZORBIO and were used in this work.



Figure 3-1. Azorean families included in the study.

Code	Sex	Age	DISH/CC	Other diseases	Code	Sex	Age	DISH/CC	Other diseases
AZ1					AZ2				
II:1	М	94	А		II:1	М	?	А	
II:2	F	90	UN		III:1	F	81	А	Lithiasis; DM
II:3	М	98	А		III:2	М	85	А	Lithiasis; polyarthritis
II:4	F	94	UN		III:3	М	94	А	1 2
II:5	М	86	А	AS; DM	IV:2	F	58	А	Obesity
II:7	F	91	А	AS	IV:3	F	61	А	
II:9	М	?	UN	AS	V:1	М	33	А	
III:1	Μ	56	А		AZ4				
III:2	М	61	Α		II:3	М	93	А	
III:3	F	57	UN		III:1	F	?	UN	
III:4	М	53	А	Obesity; AS	III:2	М	64	А	Lithiasis
III:5	М	56	UN		III:3	М	71	А	
III:6	F	71	А	AS	III:4	М	75	А	
III:7	F	76	А		III:5	F	70	А	DM; obesity; lithiasis
IV:1	М	31	?		III:6	М	68	А	Lithiasis
IV:2	F	30	?		III:7	М	81	А	
IV:3	F	34	?		III:8	F	77	UN	Kidney cramps
IV:4	F	36	?		III:9	М	90	А	
AZ3					III:11	М	87	А	
II:1	М	80	А	Sjogren	IV:1	М	53	UN	
II:4	F	89	А	Obesity	IV:2	F	48	А	
III:1	М	48	Α	AS ;LBP	IV:3	М	43	Α	
III:2	М	83	А		IV:4	F	58	А	DR
III:3	F	60	А	Periodontitis	AZ5				
AZ6					I:1	М	87	А	
I:2	F	?	А		II:1	F	62	?	
II:1	F	72	А		II:2	М	77	UN	Coxarthrosis
II:2	F	75	UN	LBP	II:3	М	58	Α	
II:3	М	66	UN		II:4	М	55	Α	
AZ7					II:5	М	52	UN	Crohn disease
I:1	М	93	А		AZ8				
II:1	М	61	А	AS	II:1	М	57	А	Lung cancer
II:2	М	67	?	LBP; AS	II:2	М	65	А	Parkinson
II:3	М	66	UN		II:3	М	62	А	AS
AZ10					II:4	F	62	UN	
III:1	F	68	UN		AZ9	1	1		
III:2	М	71	А	CC	I:1	М	86	А	Parkinson; Osteopoikilosis
III:4	М	60	А		I:2	F	82	UN	
III:5	М	76	UN		II:1	F	61	UN	
III:6	F	70	А		II:3	F	54	А	LBP
III:7	M	68	A	ļ	II:4	F	54	A	
111:8	F	77	A		11:5	M	58	A	
1V:1	M	46	UN			M	31	UN	
1V:2	F	45	UN		111:2	M	32	UN	
1V:3	F	42	<i>!</i>						
11:4	Г	33	1			L	L		

Table 3-1. Azorean families included in the study and associated data (pedigree code; sex; age and other diseases). Probands are represented in bold.

**Abbreviations:** M: male, F: female, AS: Ankylosing spondylitis. A: Affected; UN: Unaffected, CC: Chondrocalcinosis, DM: Diabetes mellitus, LBP: Low back pain, DR: Diabetic retinopathy, ?: Unknown.

# 3.1.2 DISH/CC patients not related

The 55 patients (36 males; 19 females) from this collection were identified through a record review conducted at the Rheumatic Diseases Clinic of HSEIT. Blood was obtained from all participants who gave informed consent. Standard X rays were taken from: knees, axial skeleton, wrists, hands, elbows and pelvis. All individuals were interviewed and examined for the presence of DISH and/or CC by a rheumatologist (JBA). Affected status was determined radiographically, with the diagnosis of DISH being made according to the Utsinger criteria [5], and the diagnosis of chondrocalcinosis on the classic radiological evidence of deposition of calcium in the fibrocartilage. The biological material and the associated data (Table 3-2) of these patients were available in AZORBIO.

Code	Sex	Age	Other diseases	Code	Sex	Age	Other diseases
D1	М	72	Gastric cancer	D29	F	77	Mieloproliferative disease
D2	F	61		D30	Μ	60	Osteoid osteoma
D3	F	65		D31	М	86	
D4	F	70		D32	М	73	
D5	М	64	Parkinson disease; periodontitis	D33	F	66	
D6	М	66	Colorectal cancer	D34	F	74	
D7	М	54		D35	М	87	
D8	М	63		D36	F	70	Arterial disease
D9	М	61		D37	F	62	Osteoarthritis; DR
D10	М	59		D38	М	71	
D11	М	80	Sjogren syndrome	D39	М	70	DM
D12	М	88	DR	D40	F	81	
D13	М	79		D41	F	68	BC
D14	М	79		D42	F	56	
D15	М	65	Kidney cancer	D43	F	73	DR
D16	М	80	Prostate cancer	D44	F	64	BC
D17	М	62		D45	М	85	
D18	М	67	Lung cancer	D46	F	68	
D19	М	60		D47	М	65	Arterial hypertension
D20	М	67	Colorectal cancer	D48	F	78	
D21	М	87	Colorectal cancer	D49	F	72	BC
D22	М	70		D50	М	65	
D23	М	94		D51	Μ	64	
D24	М	69		D52	Μ	78	Colorectal cancer
D25	М	98		D53	F	91	Total hip replacement
D26	М	55		D54	М	86	Parkinson disease; osteopoikilosis
D27	М	66	Psoriatic arthritis	D55	F	77	DM;DR
D28	F	73					

Table 3-2. Patients with DISH/CC and associated data.

Abbreviations: M: male, F: female, DM: Diabetes mellitus, DR: Diabetic retinopathy, BC: breast cancer.

#### 3.1.3 Gitelman syndrome family



Figure 3-2. Gitelman family. The proband with GS and chondrocalcinosis is indicated by an arrow.

A proband with bilateral knee CC, hypomagnesemia and hypokalemia, was identified in the Rheumatic Diseases Clinic, HSEIT, Azores, Portugal. Blood was obtained from all family members who gave informed consent, and standard X rays were taken from: knees, axial skeleton, wrists, hands, elbows and pelvis. Proband and 13 family members (Figure 3-2) were interviewed and examined for the presence of CC by a rheumatologist (JBA). Pathological status was determined radiographically, with the diagnosis of CC on the classic radiological evidence of deposition of calcium in the fibrocartilage and Gitelman syndrome by the presence of a hypomagnesemia and hypokalemia. The biological material and the associated data (Table 3-3) of this family were available in AZORBIO.

Ind	ividuals		Biochemical analysis Dise						
Code	Sex	Age	Magnesium	Potassium	Calcium	GS	CC		
III.2	Μ	62	1,1	3,2	9,9	X	X		
III.12	М	75	2,1	4,7	9,1				
III.13	F	67	2,2	4,1 9,5					
III.16	М	75	2	4,6	9,5		X		
III.19	F	79	1,9	4,7	9,7		X		
IV.1	М	35	2,3	3,7 ?					
IV.2	F	54	2,2	4,2 9,7					
IV.4	М	46	1,9	4	9,2				
IV.14	F	51	1,9	4	9				
IV.16	F	49	2,2	4,1	9,1				
IV.17	F	45	1,9	4,3	9				
IV.21	М	37	2,1	4,1	10				
IV.22	F	36	2	3,7	3,7 9,7				
V.1	F	25	2	4,7	9,5				

Table 3-3. Gitelman syndrome family and associated data (code, sex, age, biochemical analysis and diseases). Reference values: Magnesium (1.5-2.5 mg/Dl); Potassium (3.3-5.1 mmol/L) and calcium (8.0-10.2 mg/dL). The proband are represented in bold.

Abbreviations: M-Male, F- Female, GS- Gitelman Syndrome; CC-Chondrocalcinosis.

# 3.1.4 Ankylosing Spondylitis (AS) patients

The 25 ankylosing spondylitis patients in this collection were identified through a record review conducted at the Rheumatic Diseases Clinic of HSEIT. Blood was obtained from all participants who gave informed consent and axial skeletal radiographs and CT scans of the sacroiliac joints, as needed, were taken. The HLA–B27 typing was also performed in all patients. All individuals were interviewed and examined for the presence of AS by a rheumatologist (JBA). Affected status was determined radiographically, with the definitive diagnosis of AS being made in accordance with the modified New York criteria [305].

The biological material and the associated data (Table 3-4) of these patients were available in AZORBIO:

Code	Sex	Age	Other diseases	Code	Sex	Age	Other diseases
AS1	F	57	LBP	AS14	М	51	DISH/CC; colorectal cancer
AS2	М	58		AS15	М	58	
AS3	F	47	Polyarthritis; total hip replacement	AS16	М	73	Dementia
AS4	М	40		AS17	М	70	Psoriatic arthritis; uveitis
AS5	М	46		AS18	М	91	
AS6	F	55	Uveitis	AS19	F	74	Uveitis
AS7	М	71		AS20	М	37	
AS8	М	63		AS21	М	47	
AS9	М	58		AS22	F	65	Uveitis; vasculitis
AS10	F	81	DR	AS23	F	37	
AS11	М	82	Psoriatic arthritis	AS24	М	65	
AS12	М	57		AS25	М	90	
AS13	М	60	Psoriatic arthritis				

Table 3-4. AS population and associated data (sex; age and other diseases).

Abbreviations: M- male, F- female, LBP- Low back pain, DR- Diabetic retinopathy, CC-chondrocalcinosis, DISH- diffuse idiopathic skeletal hyperostosis.

#### **3.1.5** Control population without DISH/CC

This population cohort consists of 36 individuals (16 Males and 20 Females), older than 65 years of age, living in the Terceira Island, that were being followed by the Rheumatic Diseases Clinic and Oncology Service of HSEIT. Blood was obtained from all participants who gave informed consent, and radiographs of the axial spine, pelvis, knees, wrists, hands and elbows (assessed by a rheumatologist (JBA) to confirm the absence of calcifications and/or ossifications). The biological material and the associated data (Table 3-5) of these patients were available in AZORBIO.

Table 3-5. Population control without DISH and or CC and associated data (sex; age and other diseases).

Code	Sex	Age	Diseases	Code	Sex	Age	Diseases
C1	М	64	RA; hypothyroidism	C19	М	102	
C2	F	69	Chronic lymphoid leukemia	C20	F	57	
C3	М	76	Colorectal and lung cancer	C21	F	74	BC
C4	F	68	BC	C22	F	72	Myelofibrosis; myeloproleferative disease
C5	F	77	Non hodgkin lymphoma	C23	F	72	
C6	F	61		C24	F	63	
C7	М	67	Colorectal cancer	C25	F	72	BC
C8	F	75	BC	C26	F	66	Colorectal cancer

Code	Sex	Age	Diseases	Code	Sex	Age	Diseases
С9	F	59	Colorectal cancer	C27	М	69	Gastric cancer
C10	М	73		C28	F	68	Lymphoma
C11	М	74		C29	F	59	BC
C12	М	63	Lung cancer	C30	F	63	BC
C13	М	62	Myelodysplastic syndrome	C31	F	70	BC
C14	М	80	Lung and colorectal cancer	C32	F	68	BC
C15	М	60	Lymphoma	C33	F	67	
C16	М	63	Pancreas cancer	C34	F	60	Colorectal cancer
C17	М	82	Non hodgkin lymphoma	C35	М	69	Non hodgkin lymphoma
C18	М	63	BC	C36	М	64	Lung cancer

Abbreviations: M- male, F- female, RA- Rheumatoid arthristis, BC- breast cancer.

#### 3.1.6 Representative population of Terceira Island

Presently, Terceira island is an autonomous Portuguese region with approximately 60,000 inhabitants. The two collections used in this thesis consist of individuals living on Terceira Island.

#### 3.1.6.1 Randomized cohort

This population cohort consists of 124 individuals (46 males; 78 females; mean current age 66; range, 35-100), older than 18 years of age, living in the Terceira Island. The randomization was performed by "Serviço Regional de Estatística dos Açores" using the census carried out in 1981. All participants were interviewed about: demographic information and personal and familial diseases. Blood was obtained from all participants who gave informed consent and individuals who reported back pain (11 males; 19 females), radiographs of the axial spine was also performed. The biological material and the associated data (Table 3-6) of these patients were available in AZORBIO.

Code	Sex	Age	Diseases	Code	Sex	Age	Diseases
R1	F	60	LBP; phlebitis	R63	F	88	LBP
R2	F	53	Hyperparathyroidism	R64	F	74	DM
R3	М	61		R65	F	76	RA; hypercholesterolaemia
R4	Μ	46	Knee pain	R66	F	88	DM
R5	М	64		R67	F	54	LBP
R6	Μ	85	Colorectal cancer	R68	F	82	LBP
R7	Μ	49		R69	F	96	Cardiac disease
<b>R8</b>	Μ	63	Colorectal cancer	R70	F	96	LBP
R9	M	85	LBP	R71	F	61	Epilepsy
R10	M	53	Psoriasis; AS	R72	F	61	LBP
R11	F	100	LBP; poliomyelitis	R73	F	57	
R12	F	90	Juvenil arthritis	R74	F	70	Hand osteoarthritis
R13	F	58		R75	F	94	
R14	F	46	LBP	R76	F	77	
R15	F	60		R77	F	67	
R16	F	76		R78	F	78	LBP
R17	М	61	LBP; kidney cramps; psoriasis	R79	F	54	
R18	M	56		R80	F	90	LBP; colitis
R19	F	70		R81	F	54	BC
R20	M	76	LBP	R82	F	63	Poliomyelitis
R21	F	53		R83	F	68	Left sacroiliitis; LBP; right sciatica
R22	F	52		R84	F	73	LBP; hypercholesterolaemia; DM; BC
R23	F	89	DM; LBP	R85	F	48	Hypertension; transient schemic attack
R24	F	56	Deformities in tibias	R86	F	47	
R25	F	60	LBP; AS	R87	F	35	
R26	Μ	78	DM	R88	F	65	LBP
R27	Μ	87		R89	F	64	Kidney cramps; BC
R28	M	84		R90	F	71	
R29	M	55	LBP; leucopeny	R91	F	53	AS
R30	M	65		R92	F	61	
R31	F	53	LBP; multi brain strokes	R93	F	86	
R32	F	56	Juvenil stroke	R94	F	68	Anemia
R33	M	89		R95	F	74	
R34	M	49	LBP	R96	F	65	
R35	М	73	deformities; lung cancer	R97	F	70	Enteritis; LBP
R36	М	96	Chronic obstructive pulmonary disease	R98	F	61	
R37	М	71	LBP; CC	R99	F	83	LBP; coxofemoral fracture
R38	М	69	LBP	R100	F	93	
R39	М	66		R101	F	81	AS
R40	М	67		R102	F	79	DM; osteoarthritis; RA; LBP
R41	F	93		R103	F	62	
R42	М	67	Kidney pain	R104	F	76	
R43	F	80		R105	М	42	
R44	F	55	Colitis	R106	F	46	AS
R45	F	63		R107	F	81	BC
R46	F	64		R108	F	45	Psoriasis

Table 3-6. Individuals from the randomized population and associated data (sex, age and diseases).

Code	Sex	Age	Diseases	Code	Sex	Age	Diseases
R47	F	55		R109	М	46	
R48	Μ	63	LBP	R110	М	75	
R49	М	42		R111	М	51	
R50	Μ	81		R112	М	49	
R51	F	54		R113	М	42	
R52	F	71		R114	F	57	
R53	F	45	Scoliosis	R115	F	50	Polyarthritis
R54	Μ	78		R116	F	74	
R55	Μ	72	LBP; AS	R117	F	41	Knee swelling; LBP
R56	Μ	44	LBP	R118	М	89	
R57	Μ	84	LBP; osteoporosis	R119	М	55	Ischemic stroke
R58	М	67		R120	F	79	Psychiatric disorder
R59	Μ	77	Diabetes; two myocardial	R121	F	47	
R60	Μ	68		R122	М	42	
R61	Μ	92	Cardic disease; LBP	R123	М	42	
R62	F	51		R124	F	77	

**Abbreviations:** M- male, F- female, AS- ankylosing spondylitis; CC- chondrocalcinosis; LBP- Low back pain; BC- breast cancer; RA- Rheumatoid arthritis, DM- Diabetes mellitus.

#### 3.1.6.2 Two regions - Angra do Heroísmo and Praia da Vitória

This population cohort consists of 375 individuals (85 males; 290 females; mean current age 55; range, 25-91), older than 18 years of age, living in the Terceira Island, that were attended in clinical laboratories located in the two main municipalities of the Terceira island; Angra do Heroísmo and Praia da Vitória. All participants who gave informed consent were interviewed about breast cancer and other inherited diseases, socio and demographic information. Blood was obtained from all participants who gave informed consent. The biological material and the associated data (Table 3-7) of these patients were available in AZORBIO.

Table 3-7. Representative population of two regions of Terceira Island and associated data (sex, age and diseases).

Code	Sex	Age	Diseases	Code	Sex	Age	Diseases	Code	Sex	Age	Diseases
2R1	F	56		2R126	М	57		2R251	F	62	
2R2	F	41		2R127	М	37		2R252	F	75	
2R3	F	48		2R128	М	68		2R253	F	58	
2R4	F	47		2R129	М	84		2R254	F	56	Bilateral uveitis
2R5	F	47		2R130	М	56		2R255	F	74	
2R6	F	47		2R131	М	66		2R256	F	43	
2R7	М	56		2R132	М	46		2R257	М	34	
2R8	F	41		2R133	F	27		2R258	F	72	
2R9	F	35		2R134	М	45		2R259	F	72	
2R10	М	79		2R135	М	59		2R260	F	73	
2R11	F	84		2R136	М	59		2R261	F	59	

Code	Sex	Age	Diseases	Code	Sex	Age	Diseases	Code	Sex	Age	Diseases
2R12	М	63		2R137	М	86		2R262	F	80	
2R13	М	65		2R138	М	64		2R263	F	70	
2R14	М	78		2R139	F	78	RA	2R264	F	46	
2R15	М	51		2R140	М	72	Chronic lymphoid leukemia	2R265	F	53	
2R16	F	75		2R141	М	59		2R266	F	51	
2R17	М	73		2R142	М	82		2R267	F	70	
2R18	F	52		2R143	М	36		2R268	F	71	
2R19	М	78		2R144	F	87		2R269	F	77	
2R20	F	56		2R145	М	73		2R270	F	49	
2R21	F	60		2R146	М	86	Dementia	2R271	F	65	
2R22	F	61		2R147	F	46		2R272	F	69	
2R23	F	43		2R148	F	62		2R273	F	56	
2R24	F	55		2R149	F	43		2R274	F	32	
2R25	F	65	Polyarthritis	2R150	F	45		2R275	F	86	
2R26	F	52		2R151	М	57		2R276	F	61	RA
2R27	F	46		2R152	F	69		2R277	F	61	Lacunar stroke
2R28	F	60	DM	2R153	F	45		2R278	F	59	
2R29	F	59	AS; uveitis	2R154	М	68		2R279	F	70	
2R30	F	45		2R155	F	47		2R280	F	66	
2R31	F	66		2R156	F	56		2R281	F	49	
2R32	F	47	Dysuria	2R157	F	52		2R282	F	58	
2R33	F	74		2R158	F	58		2R283	М	40	
2R34	F	50		2R159	F	56		2R284	F	67	
2R35	F	52		2R160	F	63		2R285	F	55	
2R36	F	62		2R161	М	35		2R286	М	55	
2R37	F	46		2R162	F	50		2R287	М	47	Psoriatic arthrtis; gonarthrosis
2R38	F	45		2R163	F	53		2R288	F	69	
2R39	F	55		2R164	F	26		2R289	F	70	
2R40	F	59	AS	2R165	F	66		2R290	F	60	
2R41	F	37		2R166	F	53		2R291	М	64	
2R42	F	44		2R167	М	60		2R292	F	45	
2R43	F	36		2R168	F	55		2R293	F	65	
2R44	F	45		2R169	F	59		2R294	F	67	
2R45	F	41		2R170	F	62	AS; RA	2R295	F	34	
2R46	М	75		2R171	F	52		2R296	F	81	
2R47	F	32		2R172	F	47		2R297	F	79	
2R48	F	52		2R173	F	53		2R298	F	72	
2R49	F	39		2R174	F	56		2R299	F	65	
2R50	F	42		2R175	F	57		2R300	F	81	
2R51	М	56		2R176	F	72		2R301	F	57	BC
2R52	F	34		2R177	М	37	Bilateral uveitis	2R302	F	51	
2R53	М	34		2R178	F	52		2R303	F	27	
2R54	F	76		2R179	F	44		2R304	М	38	
2R55	F	43		2R180	F	86		2R305	F	62	

Code	Sex	Age	Diseases	Code	Sex	Age	Diseases	Code	Sex	Age	Diseases
2R56	F	41		2R181	F	57		2R306	F	39	
2R57	F	61		2R182	F	77		2R307	F	41	
2R58	F	38	polyarthralgia; acrocyanosis; ischemic feet	2R183	М	38		2R308	F	57	
2R59	F	56		2R184	F	76	Lacunar stroke	2R309	F	53	
2R60	F	38		2R185	F	58		2R310	F	34	
2R61	F	39		2R186	F	78		2R311	F	25	
2R62	М	55		2R187	F	87		2R312	М	50	
2R63	F	46		2R188	F	66		2R313	F	62	
2R64	М	35		2R189	F	76	DISH/CC; colorectal	2R314	F	53	
2R65	F	39		2R190	F	57		2R315	М	69	
2R66	F	35		2R191	F	79		2R316	М	47	
2R67	М	56		2R192	F	44		2R317	М	45	
2R68	М	46		2R193	F	65		2R318	М	41	
2R69	F	43		2R194	F	48		2R319	F	25	
2R70	F	40		2R195	F	77		2R320	F	45	
2R71	М	32		2R196	F	70		2R321	F	48	
2R72	F	59		2R197	F	52	Oligoarthritis	2R322	F	44	
2R73	F	36		2R198	F	67		2R323	F	61	
2R74	М	75	Ischaemic stroke	2R199	М	76		2R324	F	39	
2R75	F	44		2R200	F	58		2R325	М	41	
2R76	F	58	Convulsion	2R201	F	48		2R326	М	57	
2 <b>R</b> 77	F	50		2R202	F	52		2R327	М	31	
2R78	М	42		2R203	F	62		2R328	М	40	
2R79	М	67		2R204	F	65		2R329	F	38	
2R80	F	45		2R205	F	76	DR	2R330	М	44	
2R81	F	39		2R206	F	54		2R331	М	42	
2R82	М	81		2R207	М	64		2R332	М	31	
2R83	F	55	AS	2R208	F	72		2R333	М	64	
2R84	F	54		2R209	F	69	Peripheral arterial disease	2R334	F	62	
2R85	F	54		2R210	F	91		2R335	F	31	
2R86	F	34		2R211	F	48		2R336	F	83	
2R87	F	26		2R212	F	39		2R337	F	54	Colorectal
2R88	М	84	AS	2R213	F	54		2R338	М	69	Neck pain
2R89	F	47		2R214	F	29		2R339	F	55	
2R90	F	41		2R215	F	63	DISH/CC	2R340	F	36	
2R91	Μ	78		2R216	F	52		2R341	F	35	
2R92	М	65		2R217	F	68		2R342	F	62	
2R93	М	49		2R218	F	41		2R343	F	49	Cerebral venous thrombosis
2R94	F	55		2R219	F	29		2R344	М	43	
2R95	F	85		2R220	F	68		2R345	F	37	
2R96	М	73		2R221	F	71		2R346	F	32	Leukorrhoea

Code	Sex	Age	Diseases	Code	Sex	Age	Diseases	Code	Sex	Age	Diseases
2R97	F	59	Uveitis	2R222	F	54	Cerebellar infarction left	2R347	F	55	RA
2R98	F	52	BC	2R223	F	73		2R348	F	44	
2R99	F	53		2R224	F	55		2R349	F	38	DISH/CC
2R100	F	54		2R225	F	81		2R350	F	37	
2R101	F	59		2R226	F	55		2R351	F	35	
2R102	М	38		2R227	F	61		2R352	F	40	
2R103	F	66		2R228	М	81		2R353	F	33	
2R104	F	63		2R229	F	64		2R354	F	25	
2R105	F	56	AS	2R230	F	70	Betathalassemia syndrome	2R355	F	32	
2R106	F	48		2R231	F	74		2R356	F	79	
2R107	F	51		2R232	F	53		2R357	F	42	
2R108	М	35		2R233	F	57		2R358	F	44	
2R109	М	53		2R234	F	59		2R359	F	25	
2R110	М	51		2R235	F	64		2R360	М	29	
2R111	F	49	Multi brain strokes	2R236	F	58		2R361	М	68	
2R112	F	55		2R237	F	55		2R362	F	88	
2R113	F	64		2R238	F	54		2R363	F	56	
2R114	F	72		2R239	F	53		2R364	F	35	
2R115	F	48		2R240	F	70		2R365	М	34	
2R116	F	59		2R241	F	90		2R366	М	75	
2R117	F	64		2R242	F	62		2R367	F	37	Cerebral venous
2R118	F	57		2R243	F	61	DISH/CC	2R368	F	27	
2R119	F	60		2R244	F	49		2R369	F	47	
2R120	F	27		2R245	F	61		2R370	F	41	
2R121	F	61		2R246	F	67	BC	2R371	F	63	
2R122	М	64		2R247	F	34		2R372	М	39	
2R123	М	49		2R248	F	91		2R373	F	45	
2R124	F	78		2R249	F	63	Spherocytosis	2R374	F	51	
2R125	М	66		2R250	F	83	RA	2R375	F	61	

**Abbreviations:** M- male, F- female, AS- Ankylosing spondylitis; RA- Rheumatoid arthritis; DR- Diabetic retinopathy; BC- Breast cancer, CC- chondrocalcinosis, DISH- diffuse idiopathic skeletal hyperostosis.

# 3.1.7 Total hip replacement group

This collection of 53 individuals (34 male, 17 female; mean current age, 71 years; range, 47-93 years) (Table 3-8) was obtained from patients undergoing total hip replacement surgery. Informed consent was obtained from these patients for use of their rejected tissue in research. Sterile cartilage sections (of approximately 3 mm diameter) from the coxofemoral articular cartilage were prepared with a scalpel and a cutter and immediately stored at -80°C in RNA later.

Code	Sex	Age	Diseases	Code	Sex	Age	Diseases
THR1	М	81	DR	THR28	М	65	
THR2	F	79		THR29	М	47	
THR3	М	66		THR30	F	78	
THR4	F	67	DISH, BC	THR31	М	53	
THR5	М	57		THR32	М	73	
THR6	М	74		THR33	F	82	
THR7	М	56		THR34	F	65	
THR8	М			THR35	М	82	CC (knees)
THR9	М	72		THR36	F	64	CC (knees)
THR10	F	91		<b>THR37</b>	F	72	
THR11	М	59		THR38	F	71	
THR12	F	84		THR39			
THR13	М	79	DISH	THR40	F	68	
THR14	М	76		THR41	F	59	
THR15	М	79		THR42	F	89	
THR16	М	70		THR43	М	77	Osteoarthritis
<b>THR17</b>	М	77		THR44	F	53	
THR18	М	72		THR45	F	59	
THR19	М	73		THR46	F	56	
THR20	М	77	Hypertension	<b>THR47</b>	М	71	Lithiasis
THR21	М	74		THR48		50	
THR22	М	87	Prostate cancer	THR49	М	84	
THR23	М	81		THR50	М	72	
THR24	М	83		THR51	М	69	RA
THR25	М	69		THR52	М	79	
THR26	Μ	62		THR53	F	93	DISH/CC; AS
THR27	Μ	70					

Table 3-8. Total hip replacement group.

Abbreviations: M-male, F- female, AS- Ankylosing spondylitis; R- Rheumatoid arthritis, D- Diabetic retinopathy; BC- Breast cancer, DISH- diffuse idiopathic skeletal hyperostosis.

# **3.2 Methods**

#### **3.2.1 Gene sequencing**

#### **3.2.1.1 DNA extraction and quantification**

Genomic DNA was obtained from peripheral blood cells in EDTA (Ethylenediamine tetraacetic acid) anticoagulant, using a standard Salting-Out extraction method [306], and an automatic procedure (EZ1;Qiagen) according to the manufacturer's instructions. The DNA concentration and A260:A280 ratio was determined using the NanoVue spectrophotometer (GE Healthcare).

#### **3.2.1.2 Amplification of regions of interest**

PCR oligonucleotide primers were designed using the software Primer3 (<u>http://www.bioinformatics.nl/cgi-bin/primer3plus/primer3plus.cgi</u>) for intronic sequences with the objective of amplify/sequence fragments from the following genes:

*SLC12A3*, *RSPO4*, *ENPP1*, *PPP2R2D*, *PLCG2*, *AMER3*, *FLNC*, *FGF2*, *COL11A2*, *VDR*, *BMP4* and *BMP2*. The primers used to amplify the *LEMD3* gene (exon 13) were previously described by Hellemans and collaborators [307] and primers for *ABCC6* gene fragments described by Miksch et al [308] and Cai et al [309]. PCR reactions were optimized for all primer sets (Table 3-9) in order to obtain the expected single reaction product.

Table 3-9. Forward and reverse oligonucleotide primers  $(5' \rightarrow 3')$  used in PCR reactions and sequencing of *SLC12A3*, *RSPO4*, *LEMD3*, *ENPP1*, *PPP2R2D*, *PLCG2*, *AMER3*, *FLNC*, *FGF2*, *COL11A2*, *VDR*, *BMP4*, *BMP2* and *ABCC6* genes.

Gene	Exon	Forward	Reverse		
	1	CTCAGAAGAGCCACTCCAGG	GAGGTCACACAGCAGGGAAG		
	2	AGTGGGCTGGATGCAGAGA	AGAGCTGAGCCTGGATGGA		
	3	AGTGGGTGAAGAAGGGACC	AGGATTCAGGCAAGCTGG		
	4	AGATGAACGTAGGTCGCATGG	CAGGATTAGGAGCCCACGAG		
	5	CACGAGATGGCCTCAGCTATC	TGGTTCCTGATGGGTGAAGTC		
	6	ATCGTCCTAGCAGAGTGCACC	CACGTGACCACCTCCATGTC		
	7	GTGAATAATGGAGAAACGGGC	TTCCTGGGTAGAGAGTCCCTG		
	8	ACTGGGAGGATGGGATTACC	CAGGATTCTGCTCATAGCCC		
	9	GCCTAATGTCCTCCGTCCCT	TGCTCTGATCATTGCCAAGATAC		
	10	ATCATCTGCAGCACCTCGC	CAGTGTCCACCACAAGTCG		
	11	CGCAGTAGGGAATGAAGTGC	CCTATTGTGCCTCTAGCCCAG		
	12	AAACAGACACCAGGACCCAG	TGCCCACTAACTGTCAGGC		
51 ( 1242	13	CAGTCCTTGGCAGAGTTGC	CTGACCTCAAGTGATCCGC		
SLC12A3	14	CCTAGAAAGAGGCTCGACTGC	GTTTCTTGCCACATTGGGAG		
	15	AGAAGGCCGACATTACCTCTG	GTCTAGGCTTGGAAACTCCCA		
	16	CATGTAGGGTCATGCTGGTG	GGCTGGTCTCAAACTCCTGA		
	17	GTGAAGGCAGCTGGTGATGT	CAAGCCGTAAGTCCTGTAGGG		
	18	TTGAGAATCAGCACATCTGGAG	CAATGGGCCCAAATTAACAG		
	19	TGGTAGGAAGCAGAGCCAACT	AACTTTCTGGGAGTGGGTGG		
	20	CCTGTCAAGGAGGAACCCA	AGTGCCCTGAGCTCTGAGTG		
	21	TTCCTGTTCCACCTGCCA	GGCGACTTCAGCTCTTCTCTC		
	22	CACATAGTGCTCTGTCCTGAGTG	TTTGGGACAATCTCAGTGCC		
	23	GCAGAGGTTGCAGTGAATCG	GTCTCCAGGCACACAGTTGG		
	24	CCTCAACCCACTTTCTCGTC	AGCTCAAGACATGCAGGACA		
	25	AATGAGGCCATAGACGTGGT	AGCTGAGACACCTGACTCTGG		
	26	CTGAGGGACGGTAAACAGAC	AGAGGCAATCAAGTTCCAAC		
	1	CAACGCCCTCACTAGACCTG	AGCCTCAATCTCCCCATCTTA		
	2	TGACCATCTCTCTCTCCCTTTC	GAGCCCAGCACTAGCATAGAAC		
RSPO4	3	GGGGTGTCCCTGGCTCTA	GCCCCTAACATCTCTCACCA		
	4	TCTGTCTGTCTCCCCTTTCACC	CAGCCTCGTGTGCCTGTC		
	5	GCACCCTTGTCTTTCAGGACT	AAGAGTAAGAGGAGGAGGAGGAGAA		
LEMD3	13	CTTTTACCACAGTTAATTTTCTGC	GAACCTTAAGACTTCTGGAACG		
ENPP1	4	CATGGTAGTGGCAGATTCTG	TTCAGCTAATATAGTTGGCC		
PPP2R2D	7	GCCTGAAGATCCCAGCAGTA	CCTATGAGCGTCCTCCTCTG		

Gene	Exon	Forward	Reverse			
	19	CCCACTGACAGCCTGGAG	CTGAAGTTCCCCCTTGTCTCT			
PLCG2	21	TGAGGTTTCAACTCCTCTATCAAA	AACAGAGTCAGGGTGGGAAT			
	33	CCACTGCTGATGGTGAAATC	TCTTACATTTCCAGCTCATCCTC			
AMER3	3	GAGGGCTACTATGATTCCTTCTCG	AAGCTGCATATGGACAGTGG			
FLNC	26	TGTCATCGGCTTCTGGGAAC	ATCCCCATTGTCCCGGATGT			
FGF2	3´UTR	GCTTTAGGCGGCAGATGATA	ACACAGCGGTTCGAGAAGTT			
COL11A2	6	ACCTTCCAATTACCCCATCC	TGGGAGAAAGGGAAGAAATG			
VDR	5	CTGGCACTGACTCTGGCTCT	TGCAGCCTTCACAGGTCATA			
BMP4	7	GGGACCAGTGAAAACTCTGC	GGGGGCTTCATAACCTCATAA			
BMP2	3	TTCCGAGAACAGATGCAAGA	TCAAAACTTTCCCACCTGCT			
	5'UTR- LR	TCCTGGAAATTGCTGGGTCCAAAGTGT TTAGGAAGTCT	CAGCTCACCTGCCCAGGGGGGCCAG GCAACT			
	1	CCGAGCAGTCTGCCCAGAGACTT	GGGGGTCTCTCCTCTCCCCAGTAT			
	2	TGGCCCCTGGGCAGGTGAG	GTCCCCTGCCTCCCCGAACA			
	3-4-LR	CCGGGGCTACCTCCGGATGTC	GGCCTGTAAGACAGGAAATTGTGTTG ATAAGA			
	3	CCGCCTACCAGTTTGCTGTGAC	GGAGCCTCTTCTCTCCCCTTGT			
	4	CTGCTGCTTTGCCTGCCACAGT	GTGCGGGAGTGGATTTTGTGTCTCT			
	5	GTCCCCAGAGTGGGCACTGAC	CTTTTGGTCACCTGGGGGGAGAC			
	6	TCCTGTCTTCCTACCCTTGCCACAT	GGCCATGGCTGGGAATCAGAG			
	7	GCCAGGATCCTGCAGGGGTGAA	CGCACCCGGCCAATGATGAG			
	8-9 LR	AGGCTAGATCCACACCCACCCATCTCCACTGT	CGTCCACGGACACCAGATTGACCACATCAC			
	8	CCGCTGGCGGCTGAGAGTAT	GGCCCTGGAAGGATGCCACTA			
	9	TTGGGCAAAGGCAACACCCTTAG	ACTGCTTTTCCTGGCTGGGAAGAC			
	10-LR	GAGCCCTGAGAGGTTGGCCTAAGAGA CTTTACTC	TTCCCCCTAAAATGTTCTCCTCTTGTGTT TTGTG			
	10	CCACCTGGGGCATCCCTCTG	GGGGAAGGACGAGGGGGGAGAA			
	11	TGCTCTGGTTCACGTGCCTCTG	TCAGCTCTCCCCTCCCCATCTC			
	12	GGTGAGATGAATGGGATTTGCTGAAG	GGGGGGCTCCACCTACCTCAC			
ABCC6	13	GCTTGCCCAGGCTGCCCTATC	GGTAGGGAAGCTGGAGCCAGGTGTA			
	14	GCCACACATCTTGAGACACCGACAC	CCAGTACTGATGCTGGCTTGCCATTA			
	15	ATGGTGCCTGGGGGGCCTCTC	GCAGGAGCCCCATGCATCTTCT			
	16	TCAGCTCCGTCTGGGGGCTCATC	GTGGGAAGGCAGCGAGGAAGTG			
	17	CAGCTCCCACTGCTCCTCAAAAC	TCCATCATACTGCCCATGATGAGTC			
	18	AGCCTGGGCACCCCAGTTTC	AAACTTGGGTTAGGACTGGATGCTAAGT			
	19	CCACATGCTTTGGCTTCCCAAAGTGT	AGGGTGTGGCCAGAGCACTCCATTC			
	20	AAGGCCACATAGTCAGTGGGTGTCA	GCGGGTGGTCCCTTCAGCTACT			
	21	TGGCTGTCAGTGGGCCTGAG	GGTGAGTATCACTGCCAAGTGCTACA			
	22	TCCCATCTGCCATGGGCATGTTTT	TTTGCACACTGTTCCAGGGGGGACAG			
	23	CACCATGGGGTAGCGGGAGAGAC	GGGAATTCTAGGAACAGCCCCTAGATGTC			
	24	GGCTCTCTGTGCTTCTGGAAACTA	GGATATGGATGAATTGCAAGGTCTT			
	25	TCCTTGTGCCCAGAGAAGCATCTC	CCACTAGCAGGGGTCCGACAGTC			
	26	GGCTGTTGCAAGCCCTCAAGTG	AAACTCCAAAGCCTGTAGCAGATGTCA			
	27	GAAGCTGATAGAGGTGGGCCATCTTG	GGTTTAGGGCCTTGTCCCTGGAGTC			
	28	GAGGGATGGATAGACAGATCTCGGGTACA	ATCCGCAGAGAGCCAGGGAACAG			
	29	GGTGGAGGGGGGGGGGGGGAAAGA	GGCATGGCCATCCCCTCTCTC			
	30	CTGTTTCTGGGCACACCCACACATC	CCAGGACTGCCTCCGCCTCCT			
	31	CGCAGACACACTGGGCTCTCACA	GATGACCACGGGTCACTTCCATCTC			

Abbreviations: LR- Long range.

PCR amplification for each gene fragment were performed using the PCR System 9700 (Applied Biosystems) using the conditions described in table 3-10. Long range PCR reaction for E08-E09-LR in *ABCC6* gene were performed using Long and Accurate (LA-Taq) polymerase (TAKARA) and a PCR cycle protocol according to the manufacturer's instructions. PCR products were subjected to electrophoreses on a 1.7% agarose gel (Seakem), at 125V for 25 minutes and stained with GelRed (Olerup) to verify the presence of specific PCR products of the expected size (Table 3-10).

Table 3-10. PCR conditions, annealing temperature and PCR product size for *SLC12A3*, *RSPO4*, *LEMD3*, *ENPP1*, *PPP2R2D*, *PLCG2*, *AMER3*, *FLNC*, *FGF2*, *COL11A2*, *VDR*, *BMP4*, *BMP2* and *ABCC6* genes. To amplify the exon 18 of *SLC12A3* and exon 26 of *ABCC6*, 2 and 2.5 µl of DMSO were added.

	Exon	PCR conditions								
Gene		Buffer	MgCl2 (mM)	dNTPs (mM)	Primers (F+R) pmol	BSA (mg/ml)	GoTaq (U)	DNA (ng)	At (°C)	bp
	1	1X	2	0.15	0.2	0.3	0.04	50	65-55*	579
	2	1X	2	0.15	0.2	0.3	0.04	50	65-55*	292
	3	1X	2	0.15	0.2	0.3	0.04	50	65-55*	279
	4	1X	2	0.15	0.2	0.3	0.04	50	65-55*	240
	5	1X	2	0.15	0.16	0.3	0.02	50	55°	388
	6	1X	2	0.15	0.2	0.3	0.04	50	65-55*	263
	7	1X	1	0.15	0.2	0.3	0.04	50	50°	275
	8	1X	2	0.15	0.2	0.3	0.04	50	65-55*	309
	9	1X	1	0.2	0.8	-	0.01	30	56°	358
	10	1X	2	0.15	0.32	0.3	0.02	50	55°	429
	11	1X	2	0.15	0.32	0.3	0.02	50	55°	254
	12	1X	2	0.15	0.2	0.3	0.04	50	65-55*	378
SI C1243	13	1X	0,8	0.16	0.64	-	0.01	50	58°	395
SLC12A5	14	1X	1	0.15	0.2	0.3	0.04	50	50°	370
	15	1X	2	0.15	0.2	0.3	0.04	50	65-55*	272
	16	1X	2	0.15	0.2	0.3	0.04	50	65-55*	476
	17	1X	2	0.15	0.2	0.3	0.04	50	65-55*	224
	18	1X	2	0.15	0.2	0.3	0.04	50	50°	266
	19	1X	2	0.15	0.2	0.3	0.04	50	65-55*	221
	20	1X	2	0.15	0.2	0.3	0.04	50	65-55*	181
	21	1X	2	0.15	0.16	0.3	0.02	50	55°	435
	22	1X	2	0.15	0.2	0.3	0.04	50	65-55*	297
	23	1X	0,8	0.16	0.64	-	0.01	50	58°	252
	24	1X	2	0.15	0.32	0.3	0.02	50	55°	549
	25	1.25X	2.5	0.19	0.25	0.4	0.05	50	65-55*	203
	26	1.25X	2.5	0.19	0.25	0.4	0.05	50	65-55*	315
	1	1X	1	0.2	1	-	0.01	20	54°	407
	2	1X	1	0.2	0.5	-	0.01	50	50°	201
RSPO4	3	1X	1	0.2	0.5	-	0.01	50	50°	243
	4	1X	1	0.2	0.5	-	0.01	50	50°	243
	5	1X	1	0.2	0.5	-	0.01	50	50°	282
LEMD3	13	1X	3	0.15	0.4	0.3	0.05	25	65-55*	400
ENPP1	4	1X	3	0.15	0.2	0.14	0.05	50	60°	396
PPP2R2D	7	1X	1	02	0.5	-	0.01	50	60	363

	Exon	PCR conditions								
Gene		Buffer	MgCl2 (mM)	dNTPs (mM)	Primers (F+R) pmol	BSA (mg/ml)	GoTaq (U)	DNA (ng)	At (°C)	bp
PLCG2	19	1X	1	0.16	1	-	0.01	30	55°	257
	21	1X	1	0.16	1	-	0.01	30	55°	584
	33	1X	1	0.16	1	-	0.01	30	55°	494
AMER3	3	1X	1	0.2	1	0.4	0.01	30	65-55*	233
FLNC	26	1X	1.25	0.2	1	-	0.03	25	65-55*	434
FGF2	3´UTR	1X	1.5	0.2	0.5	-	0.01	50	52	135
COL11A2	6	1X	1.25	0.2	0.5	-	0.01	50	60	170
VDR	5	1X	1	0.2	0.5	-	0.01	50	60	133
BMP4	7	1X	1	0.2	1	-	0.01	50	60	170
BMP2	3	1X	1.5	0.2	0.5	-	0.01	50	52	167
	5'UTR-LR	1X	1.5	0.2	0.5	-	0.03	50	68	1929
	2	1X	1.25	0.2	0.5	-	0.03	20	66	311
1.D.G.G.C	3-4-LR	1X	1.25	0.2	0.5	-	0.03	20	68	2356
ABCC6	5	1X	1.25	0.2	0.5	-	0.03	20	62	295
	6	1X	1.25	0.2	0.5	-	0.03	20	62	194
	7	1X	1.25	0.2	0.5	-	0.03	20	62	259
	8-9-LR	1x		0.4	1	-	0.04*	40	68	5626
	10-LR	1X	1.25	0.2	0.5	-	0.03	20	64	1193
	11	1X	1.25	0.2	0.5	-	0.03	20	64	253
	12	1X	1.25	0.2	0.5	-	0.03	20	64	387
	13	1X	1.25	0.2	0.5	-	0.03	20	64	286
	14	1X	1.25	0.2	0.5	-	0.03	20	64	262
	15	1X	1.25	0.2	0.5	-	0.03	20	64	219
	16	1X	1.25	0.2	0.5	-	0.03	20	66	282
	17	1X	1.25	0.2	0.5	-	0.03	20	62	343
	18	1X	1.25	0.2	0.5	-	0.03	20	64	318
	19	1X	1.25	0.2	0.5	-	0.03	20	66	374
ABCC6	20	1X	1.25	0.2	0.5	-	0.03	20	64	221
	21	1X	1.25	0.2	0.5	-	0.03	20	63	305
	22	1X	1.25	0.2	0.5	-	0.03	20	66	431
	23	1X	1.25	0.2	0.5	-	0.03	25	68	533
	24	1X	1.25	0.2	0.5	-	0.03	20	62	322
	25	1X	1.25	0.2	0.5	-	0.03	20	62	270
	26	1.25X	1.25	0.12	1	-	0.03	50	62	258
	27	1X	1.25	0.2	0.5	-	0.03	20	65	297
	28	1X	1.25	0.2	0.5	-	0.03	20	66	371
	29	1X	1.25	0.2	0.5	-	0.03	20	66	296
	30	1X	1.25	0.2	0.5	-	0.03	20	66	344
	31	1X	1.25	0.2	0.5	-	0.03	20	66	270

**Abbreviations:** DMSO: Dimethyl sulfoxide, BSA: Bovine Serum Albumin, At: Annealing temperature, F: forward, R: reverse, bp: base-pair. \* Long and accurate (LA) taq (TAKARA).

#### 3.2.1.3 Sequencing

The PCR products with a positive band were then purified using ExoSAP-IT<sup>TM</sup> (Exonuclease I and Shrimp Alkaline Phosphatase) according to manufactures instructions. Sequencing reaction with BigDye<sup>®</sup> Terminator v3.1 and v1.1 was performed in a 10  $\mu$ l volume containing 2  $\mu$ l template, 2  $\mu$ l 5X Sequencing Buffer, 1  $\mu$ l Sequencing Premix (Big Dye v3.1 or v1.1), 0.16  $\mu$ l primer (10pmol) (Table 3-9) and ddH<sub>2</sub>O to achieve final

volume. Reaction conditions included an initial denaturation step at 96°C for 1 minute followed by 25 cycles of: denaturing at 96°C for 10 seconds, annealing at 50°C for 5 seconds, and elongation at 60°C for 4 minutes. Purification of the products for sequencing was performed by precipitating with 0.5 M EDTA and 3 M sodium acetate, and a final precipitation with 70% and absolute EtOH. Templates were ressuspended in 15  $\mu$ l highly deionized formamide (HiDi formamide) and sequenced using the ABI 3130xl (Applied Biosystems<sup>®</sup>).

#### **3.2.1.4 Sequence analysis**

Genetic variants of exons and intron-exon boundaries of the genes were screened with Sequencing Analysis and SeqScape software (Applied Biosystems<sup>®</sup>) using as reference the sequences present in NCBI (Table 3-11).

Gene	NCBI reference
SLC12A3	NG_009386.1
RSPO4	NG_013043.1
LEMD3	NG_016210.1
ENPP1	NG_008206
PPP2R2D	NM_018461.4
PLCG2	NG_032019.2
AMER3	NM_152698.2
FLNC	NG_011807.1
BMP4	NG_009215.1
FGF2	NG_029067.1
BMP2	NG_023233.1
VDR	NG_008731.1
COL11A2	NG_011589.1
ABCC6	NG_007558.2

#### Table 3-11. NCBI references for the genes studied.

#### **3.2.2 Tissue expression**

#### 3.2.2.1 Cartilage homogenization

Cartilage sections preserved in RNA later were reduced to a powder using a mortar and pestle and liquid nitrogen. The cartilage powder was placed in 1 ml TRIzol reagent and stored at -80°C for 24 hours.

#### 3.2.2.2 RNA isolation

The RNA was obtained using a TRIzol RNA isolation protocol. Trizol reagent (Invitrogen) is a ready to use reagent for the isolation of total RNA from cells and tissues. The reagent, a mono-phasic solution of phenol and guanidine isothiocyanate is an improvement of the single-step RNA isolation method development by Chomezynski and Sacchi [310]. During sample homogenization or lysis, TRIzol reagent maintains the integrity of the RNA, while disrupting cells and dissolving cell components. Addition of chloroform followed by centrifugation was used to separate the aqueous phase containing RNA and the organic phase containing DNA and other material.

#### • Separation phase

- The samples were thawed by placing them at room temperature for 10 minutes;
- Placed into the Thermo Mixer at 37°C for 10 minutes and 1400 rotations per minute (r.p.m);
- 0.2 ml of chloroform was added and the tubes vortexed for 15 minutes at the highest velocity;
- Samples were then centrifuged for 10 minutes at 8°C at 10600 r.p.m..

**Note:** Following centrifugation, the mixture separates into different phases: a lower red, phenol-chloroform phase, an interface, and a colourless aqueous phase. RNA remains exclusively in the aqueous phase.

#### • RNA precipitation

- The aqueous phase was transferred to a new RNase free tube (approximately 0.5 ml);
- The washing was repeated with chloroform, but it was vortex only 15 seconds, centrifuged for 10 minutes at 8°C at 10600 r.p.m and the aqueous phase was transferred to a new RNase free tube;
- The RNA was precipitated from the aqueous phase by mixing with 0.5 ml of cold (4°C) 100% EtOH. The tube was inverted 5 times to mix;
- The samples were incubated at -20°C for 30 minutes and were centrifuged at 10 minutes at 10600 r.p.m.

Note: The RNA precipitate forms a gel-like pellet on the side and bottom of the tube.

# • RNA wash

- The supernatant was removed by inverting the tube and the RNA pellet washed with 1 ml of 75% EtOH;
- The samples were mixed by inverting the tube. The samples were centrifuged at no more than 8400 r.p.m for 5 minutes at 8°C;
- The supernatant was taken off carefully with a 1000 µl pipet (always at the opposite side of the pellet).

# • Redissolving the RNA

- The RNA pellet was dried in a Thermo Mixer at 37°C for 2-5 minutes; it is important not to let the RNA pellet dry completely as this will significantly decrease its solubility;
- The RNA was dissolved immediately in 24 µl RNase-free water.

# **3.2.2.3 RNA purification**

#### 3.2.2.3.1 RNA clean-up

The clean-up of the RNA samples was performed using the RNeasy MinElute Cleanup kit (Qiagen) according to the manufacturer's instructions. This clean-up protocol is important for RNA to be used for enzymatic reactions, for desalting, and for concentrating the RNA.

#### 3.2.2.3.2 DNase digestion

All the samples were digested with DNase (Deoxyribonuclease I). We added to the RNA samples 10  $\mu$ l of the DNA digestion buffer RDD (RNase-Free DNase Set) and 2,5  $\mu$ l of DNase solution and the volume was completed with water up to 100  $\mu$ l. The samples were placed into the Thermo Mixer at 23°C for 10 minutes. Subsequently the samples were cleaned using RNeasy MinElute Cleanup kit (Qiagen) adding  $\beta$ -mercaptoethanol to RLT buffer (RNeasy Lysis Buffer) to obtain better results.

### 3.2.2.3.3 Ethanol precipitation of RNA

For the samples with poor quality we used 3 EtOH wash. We added to the RNA sample 1/10 volume of Sodium Acetate (3 M, pH 5.2) and 3 x volume of 100% EtOH. The samples were incubated on ice 15 minutes and centrifuged at 14,500xg for 30 minutes at room temperature. The supernatant was discarded and the pellet washed with 70% EtOH. The samples were centrifuged again for 15 minutes at the same speed. The supernatant was discarded and the pellet washed with 70% EtOH. The pellet was discarded in 14µl RNase free water.

#### 3.2.2.4. RNA quality assessment

#### 3.2.2.4.1 Concentration and integrity

For detection of RNA quality, RNA yield, A260:A280 ratio (good ratios between 1.8 and 2.0) and concentration were determined using a NanoVue spectrophotometer (GE Healthcare). RNA integrity was determined by measuring 28S/18S rRNA ratios and calculating the RNA integrity number (RIN) using an Agilent 2100 Bioanalyser and RNA 6000 Nano LabChip (Agilent Technologies).

#### 3.2.2.4.2 Reverse transcription polymerase chain reaction (RT-PCR) and β-Actin test

The RNA samples with RIN numbers above 4 were used for cDNA synthesis using 100 ng of total RNA and a High Capacity cDNA Reverse Transcription kit and following the manufactures instructions.

PCR amplification of a fragment of  $\beta$ -actin gene, the reference gene, was performed in a 20 µl final reaction volume using the following conditions: 1X GoTaq Flexi Buffer; 0.125 mM of each dNTP; 0.8 mM of MgCl; 5 pmol of each primer and 0.25 U of GoTaq (Promega). 100 ng of cDNA was used in each reaction and deionized water was used to attain the final volume. Primer sequences and optimal annealing temperatures applied are given in table 3-12.

Table 3-12. Forward and reverse oligonucleotide primers  $(5' \rightarrow 3')$  used in PCR reactions of  $\beta$ -Actin gene.

Forward	Reverse	At (°C)	PCR band size (bp)	
TGGTGGGCATGGGTCAGA	GTACATGGCTGGGGGTGTTGA	54	249	

Abbreviations: At- Annealing temperature, bp- base-pair.

#### **3.2.2.5 Gene Expression**

The Real-Time PCR reactions were performed with TaqMan chemistry using an Applied Biosystems 7500 Fast Real-Time PCR System. For each sample duplicate reactions were used and the TaqMan Gene Expression Assays: Hs00184566\_m1 for the target gene (*ABCC6* gene) and the Hs00237047\_m1 for the endogenous control gene *YWHAZ* (Tyrosine 3-Monooxygenase/Tryptophan 5-Monooxygenase Activation Protein Zeta). The reactions were made using 200 ng of cDNA in the control assay plate and 400ng in the target gene plate. The PCR conditions were performed according to the manufacturer's instructions. For each assay we used Standard run and the comparative  $\Delta$ Ct method ( $\Delta$ Ct).

# CHAPTER IV: CHONDROCALCINOSIS ASSOCIATED WITH GITELMAN SYNDROME

# 4. CHONDROCALCINOSIS ASSOCIATED WITH GITELMAN SYNDROME

# 4.1 Abstract

Gitelman Syndrome (GS) is a rare autossomal recessive inherited tubulopathy caused by mutations in the *SLC12A3* gene. The association of GS with chondrocalcinosis (CC) has been described in the literature as a typical example of hypomagnesemia-induced crystal deposition disease but its role in CC development is not fully understood. We aimed to investigate the association between GS and CC, by analysing one Azorean kindred, with an index-case presenting CC, hypomagnesemia and hypokalemia.

*SLC12A3* gene was screened in the proband and the variant detected was procured in family members. The proband was homozygous for the S615L mutation and presented chondrocalcinosis. Seven of the tested individuals in the probands family were heterozygous for the mutation and one presented CC. The presence of CC in two other individuals of the family was most likely sporadic, and associated with their advanced age.

The genetic cause for GS in a proband with secondary early onset CC was associated with S615L mutation of the *SLC12A3* gene.

Keywords: SLC12A3, Gitelman syndrome, Chondrocalcinosis, hypomagnesemia.

### **4.2 Introduction**

Gitelman Syndrome (GS, OMIM #263800) is a rare autossomal recessive tubulopathy with a prevalence of approximately 1:40.000 in the Caucasian population [311]. Onset usually occurs in adult life, but cases of childhood onset are also known [311]. The condition is characterized by hypomagnesemia, hypokalemia, metabolic alkalosis, hypocalciuria and hyperreninemic hyperaldosteronism [312]. The clinical spectrum is wide and includes: cramps, myalgies, muscle weakness, tetany, and paralysis [313]. GS is caused by inactivating mutations in member 3 of the solute carrier family 12 gene (SLC12A3), which consists of 26 exons and is located on the long arm of chromosome 16 [311]. This gene encodes a thiazide-sensitive sodium-chloride cotransporter (NCCT) expressed in the distal convoluted tubule of the kidney. NCCT is a polypeptide which consists of 1021 amino acids. Its 2-D structure is predicted to contain 12 transmembrane domains and intracellular amino- and carboxyterminal regions [313, 314]. To date, according to the Human Gene Mutation Database (http://www.hgmd.cf.ac.uk/), more than 300 different mutations have been identified in patients with GS. Detected mutations include missense, non-sense, frame-shift, and splice-site mutations and are scattered throughout the transporter protein with a possible clustering of mutations in the carboxyterminal tail [315, 316]. Genetic heterogeneity exist, and a minority of patients with GS phenotype, who do not have mutations in the SLC12A3 gene, has been shown to have mutations in the *CLCNKB* gene [317, 318]. This gene encodes the renal chloride channel ClC-Kb, located in the basolateral membrane of cells of the thick ascending limb of Henle's loop and the distal tubules. Mutations in CLCNKB gene have also been associated with classic Bartter syndrome, the most important genetic disorder to consider in the differential diagnosis of GS. Both loss-of-function mutations in NCCT and in CLC-Kb lead to disruption of NaCl reabsorption in the distal convoluted tubule. Therefore, it is important to screen the *CLCNKB* gene in patients with GS who do not have mutations in the SLC12A3 gene [319].

The association of GS with CC has been described in the literature as a typical example of hypomagnesemia-induced crystal deposition disease [312]. CC is characterized by deposition of crystals of calcium pyrophosphate dihydrate (CPPD) in articular hyaline and fibro-cartilage [312]. Several cases of GS associated with CC have been published in the literature [261, 312, 320-331]. The role of hypomagnesaemia in the development of CC, however, is not fully understood. A cross-sectional study demonstrated that CC was

significantly higher in patients with lower serum magnesium levels (OR 13.5, 95% CI 2.76-127.3, P<0.0001) [332]. Magnesium is an important cofactor for alkaline pyrophosphatase, an enzyme that plays a key role by converting inorganic pyrophosphate (PPi) to orthophosphate (Pi). A reduction in the activity of this enzyme due to hypomagnesaemia could induce CPPD by raising extracellular levels of PPi that with calcium is a crucial precursor for CCPD crystal nucleation [333]. CPPD may be found in other conditions associated with hypomagnesaemia, such as short bowel syndrome or tacrolimus therapy in liver transplantation patients [333].

The aim of this study was to investigate the association between GS and CC, by analysing one Azorean kindred, with an index-case presenting CC, hypomagnesemia and hypokalemia. The *SLC12A3* gene was screened in the proband and the variant detected was procured in family members and they were also clinically evaluated to determine if they presented CC.

#### 4.3 Material and methods

The proband, a 60 years-old Caucasian male, was first observed in the Rheumatic Diseases Clinic, Hospital de Santo Espírito da Ilha Terceira (HSEIT), Azores, Portugal when he was 48 years old. The proband and his parents were born in Terceira island. Symptoms started when the proband was 33 years old, mainly affecting knees, ankles, wrists, elbows and achilles tendons. In the proband, pyrophosphate crystals were identified in the synovial fluid aspirated from a right knee effusion. From that time he was treated with colchicine, NSAIDS (Nonsteroidal anti-inflammatory drugs), and oral potassium and magnesium. Laboratory tests revealed normal leukocyte, erythrocyte and platelet count. Blood urea was 33 mg/dl, creatinine 0.9 mg/dl and glucose 177 mg/dl. Serum electrolyte concentrations were as follows: sodium 139 mEq/L, potassium 3.2 mEq/L, calcium 9.8 mg/dl, and magnesium 1.1 mg/dl. In spite of the treatment with colchicine, patient remained hypokalemic and hypomagnesemic, however he showed some improvements. Using the diagnostic criteria of Bettinelli et al [334] a clinical diagnosis of GS was suspected, and a diagnosis of knee CC was made after the identification of bilateral knee cartilage calcification (Figure 4-1). The family members of the proband were investigated and a blood sample and x-rays were taken from all of them.



Figure 4-1. X-rays of proband showing classical CC in knees (image A) and his son without CC (image B). The presence of CC is indicated by arrows.

Genomic DNA was extracted from peripheral blood cells using the salting out procedure and used as the template for PCR amplification of individual exons of the *SLC12A3* gene. Twenty-six pairs of oligonucleotide primers were generated to amplify all 26 exons (primer sequences and PCR conditions available in chapter 2 of this thesis).

PCR products were purified using ExoSAP-IT<sup>TM</sup> and following the manufactures instruction and then sequenced using BigDye<sup>®</sup> Terminator v3.1. In brief, PCR amplicons were ressuspended in 15  $\mu$ l formamide and directly sequenced using the ABI 3130xl sequencer (Applied Biosystems<sup>®</sup>). Genetic variants of all the 26 exons and intron-exon boundaries of the *SLC12A3* gene were screened with SeqScape (Applied Biosystems<sup>®</sup>) using as reference the NCBI sequence NG\_009386.1. *SLC12A3* gene was screened in the proband and the variant detected was then screened in family members. This study was approved by the HSEIT Ethics Committee and all participants provided informed consent.

# 4.4 Results

Through *SLC12A3* direct sequence analysis in the proband a silent variant, A to G transition at position c.366 (rs2304479) in exon 2 and a missense substitution in exon 15 (rs779160677) previously described as associated to GS were detected [335]. This mutation (rs779160677), a C to T transition at position c.1869, changed the small size and polar amino acid serine to a medium size and hydrophobic leucine at position 615 (S615L), and had a SIFT score of 0 and a PolyPhen value of 0.996, both values suggestive of a deleterious variation.

The presence of the mutation in thirteen family members was investigated (5 men, 8 women; 25-79 years; mean age 51 years) and blood tests and x-rays were obtained from
each family member (data not shown). The pedigree with investigated individuals is shown in figure 4-2.



Figure 4-2. Heredogram with investigated individuals; Proband with GS and CC is indicated by the arrow.

Biochemical data in these patients revealed they had normal levels of serum magnesium ranging from 1.9 to 2.3 mg/dL and normal levels of potassium ranging from 3.7 to 4.7 mmol/L. Taking in consideration the ratio K/Mg, we found that all the individuals with CC (III.2, III.16 and III.19) had a racio >2.3. The only individual with a K/Mg ratio > 2.3 that did not present any signs of CC, is a Human leukocyte antigen (HLA) B27+ young female of only 25 years of age (Table 4-1).

Table 4-1. Characteristics and SLC12A3 gene variants and blood chemistry levels in the
proband and the thirteen selected individuals from their family pedigree. The proband is
indicated by bold. a Normal serum magnesium 1.5 - 2.5 mg/Dl : b Normal serum potassium
3.3 - 5.1 mmol/L.

					Racio		SLC12A3	variants
Individuals	Sex	Age	<b>Mg</b> <sup>a</sup> mg/dL	<b>K</b> <sup>b</sup> mmol/L	(K/Mg)	CC	A122A	S615L
III.2	М	62	1.1	3.2	2.9	+	A122A/A122A	S615L/S615L
III.12	М	75	2.1	4.7	2.23	-	A122A/WT	S615L/WT
III.13	F	67	2.2	4.1	1.86	-	WT/WT	WT/WT
III.16	М	75	2.0	4.6	2.3	+	WT/WT	WT/WT
III.19	F	79	1.9	4.7	2.47	+	A122A/WT	S615L/WT
IV.1	М	35	2.3	3.7	1.6	-	A122A/WT	S615L/WT
IV.2	F	54	2.2	4.2	1.9	-	A122A/WT	S615L/WT
IV.4	М	46	1.9	4.0	2.1	-	A122A/WT	S615L/WT
IV.14	F	51	1.9	4.0	2.1	-	WT/WT	WT/WT
IV.16	F	49	2.2	4.1	1.86	-	WT/WT	WT/WT
IV.17	F	45	1.9	4.3	2.26	-	WT/WT	WT/WT
IV.21	М	37	2.1	4.1	1.95	-	A122A/WT	S615L/WT
IV.22	F	36	2.0	3.7	1.85	-	A122A/WT	S615L/WT
V.1	F	25	2.0	4.7	2.35	-	WT/WT	WT/WT

Abbreviations: M- male, F- female, CC- Chondrocalcinosis, WT- wild type, Mg- Magnesium, K- potassium.

Seven of the 13 family members analysed were found to be heterozygous for the S615L mutation, but only one, a female of 79 years of age, presented CC. Furthermore, six individuals of the 13 were wild-type homozygous at position 615 in the gene, nonetheless, one of them, a male of 75 years of age (III.16) presented CC (Figure 4-2 and table 4-1).

#### **4.5 Discussion**

The GS patient described in this study has the S615L variation in homozygosity, while all of the other cases of GS with this variation were reported in compound heterozygote's (2, 10). In our study, seven individuals heterozygous for the S615L mutation did not have either hypokalemia or hypomagnesemia, indicating that they were asymptomatic carriers of this mutation. Hypomagnesemia and hypocalciuria are found in most cases of GS, however, some cases with mutations in the NCCT do not show these conditions [336]. It is believed that hypomagnesaemia causes CC by increasing the formation and at the same time reducing the solubility of CCP crystals [333]. It is known that an excess of PPi is the main precursor for CPP crystal nucleation. Because magnesium is a necessary cofactor

for numerous enzymes, such as pyrophosphatases, and considering the fact that it increases the solubility of CPP crystals, it has been proposed that low levels of magnesium could induce CPP deposition disease by raising PPi and/or reducing the saturation product of CPP crystals [329]. As far as we know the ratio Mg/K was never considered in CC development. In this study, this ratio seems relevant since all the patients with CC show a ratio >2.3. Individual V.1, presenting a K/Mg ratio of 2.35 does not show any signs of CC yet, however she is HLA-B27+ (B\*2705;49). HLA-B\*27 belongs to the MHC complex on chromosome 6 that is strongly associated with ankylosing spondylitis, a disease characterized by the presence of calcifications on the axial skeleton [131, 132].

The prevalence of CC increases with age (10-15% for people between 65 and 75 years) and is hence called sporadic in patients older than 60 years, whereas in younger individuals there are several putative underlying disorders causing CPPD deposition disease, such as hemochromatosis, hyperparathyroidism, hypomagnesemia or hypophosphatemia [337]. The assumption that GS is caused by a defect in the NCCT cotransporter in the renal distal tubule has been demonstrated by the association of a number of different mutations in the *SLC12A3* gene in patients with GS [311, 315, 336, 338]. In spite of the growing number of causative mutations identified in GS patients, more than 40% of patients carry only a single mutation in *SLC12A3*, instead of being compound heterozygous or homozygous, suggesting mutations may predispose to the disease and in the presence of other factors, yet to be identified, the disease develops or not [3].

In the present study, the specific involvement of this cotransporter in the aetiology of this disorder is further substantiated by the finding that the proband is homozygous for the S615L variation. The S615L identified in this study has previously been described by Cruz and co-workers [335] in a study involved 36 kindreds from the United States, Canada and England and later reported in a study by Syrén *et al* [339] in which 21 patients from 19 unrelated families were investigated and fifteen new mutations were identified. Although the *SLC12A3* variations reported in previous studies are distributed throughout the whole protein [315, 340], the study of Lemmink et al [315] indicates that the carboxy-terminal end represents a hot spot for variations. S615L is located at the intracellular C-terminal end of the NCCT protein. It is conceivable that structural alterations due to *SLC12A3* variations in the C-terminal domain interfere with

phosphorylation of the NCCT protein and as such with its regulation and that this creates physiological conditions that favour CCP crystal formation [315]. Evidence for an association between CC and GS mainly comes from uncontrolled case reports, case series and only one cross-sectional study. As a result, its epidemiology remains unknown [333]. There have been few cases described with a definite diagnosis of CC due to GS. In some patients with CPPD deposition disease secondary to hypomagnesemia, the stabilization of magnesium and potassium levels can reduce the deposition of CPP crystals in the synovium and synovial fluid, reducing the frequency of attacks of articular pain [329]. We are facing a case of a pedigree where the genetic cause for GS has been identified. The presence of CC in two individuals of this family is probably sporadic since they are both older than 65 years old. In this study, the number of patients included was small (one family); however our results suggest that our proband had an early onset of CC because it was secondary to GS. Further studies are needed in order to gain insight into the pathophysiology and prevalence of CC in patients with GS.

#### 4.6 Conclusion

GS is a hereditary disease characterized by defective tubular reabsorption of magnesium and potassium, mostly caused by mutations in the *SLC12A3* gene. Sometimes GS patients, as in our study, might come with a CC diagnosis. We identified the genetic cause for GS in a proband with secondary early onset CC. Further studies are needed in order to shed light on the pathophysiology and prevalence of CC in patients with GS.

#### 4.7 Future work

- Typing the HLA-B-allele of all family members to verify from where derives the B27<sup>+</sup>
- Verify the relevance of Mg/K ratio in one cohort of CC patients comparing with a control group.

## CHAPTER V: INVESTIGATING THE ROLE OF THE *RSPO4* AND *LEMD3* GENES WITH DISH/CC PHENOTYPE

# 5. INVESTIGATING THE ROLE OF THE *RSPO4* AND *LEMD3* GENES WITH DISH/CC PHENOTYPE

#### **5.1 Abstract**

DISH/CC is a poorly understood phenotype characterised by peripheral and axial enthesopathic calcifications, frequently fulfilling the radiological criteria for DISH, and in some cases associated with CPPD Chondrocalcinosis (CC). The concurrence of DISH and CC suggests a shared pathogenic mechanism. To date, the *ANKH* gene is the only monogenic cause identified for CC and *COL6A1* and *FGF2* are two susceptibility genes with a weak genetic link to DISH. Two genes; *RSPO4* and *LEMD3* were identified in a previous analysis of shared chromosomal segments across 4 DISH/CC families from Terceira Island. The current study aims to investigate the possible link between *RSPO4* and *LEMD3* genetic variants in the aetiology of DISH/CC.

DNA from 55 patients with DISH/CC and 36 controls without DISH/CC were obtained for a case control association study. To verify the segregation within families, 74 family members from 9 families harbouring one or more genetic variant in *RSPO4* or *LEMD3* genes were investigated. The entire DNA coding region of the candidate gene *RSPO4* and exon 13 of the *LEMD3* gene were amplified by PCR and Sanger sequencing and statistical analysis was performed using Plink V1.9.

Nine genetic variants were identified in the *RSPO4* gene; 3 regulatory region variants (rs146447064, rs149154047 and rs6056520), 1 splice site variant (rs775644973), 2 synonymous (rs150446609 and rs41275604) and 3 missense mutation variants (rs6140807, rs201485021 and rs61740632). No statistically significant difference in the occurrence of these genetic variants was observed in DISH/CC phenotype relative to the control. However, two regulatory variants (rs146447064 and rs14915407) are significantly more frequent in controls than in DISH/CC patients. The 10 genetic variants in *RSPO4* and in *LEMD3*, did not segregate within the families studied.

The results of the present study revealed that the *RSPO4* gene regulatory variants: rs146447064 rs149154047, may protect against the DISH/CC phenotype in Terceira Island, possibly by altering gene expression of the *RSPO4* gene. Variant rs201930700 in *LEMD3* is extremely rare thus, its effect is difficult to ascertain at this point.

Keywords: RSPO4, LEMD3, Chondrocalcinosis, DISH, sequencing, variants.

#### **5.2 Introduction**

Diffuse Idiopathic Skeletal Hyperostosis (DISH, MIM 106400) and Chondrocalcinosis (CC; MIM #118600) are diseases characterized by ectopic calcifications. DISH is characterized by the ossification of enthesis in the axial and peripheral skeleton, affecting the anterior longitudinal ligament, in particular the right side of the spine, with preservation of the intervertebral disc space [1]. CC is characterized by the deposition of calcium containing crystals in articular cartilage, synovial membranes and, less often, in periarticular soft tissues [341, 342]. ANKH mutations are the only known cause for a very small number of cases of monogenic CC (CC; MIM #118600) [110, 343-345] as well as craniometaphyseal dysplasia (CMDD; MIM #123000) [346-348]. The ANKH gene maps on chromosome 5 (5p15.1) and encodes a multipass transmembrane protein ANK that transports intracellular PPi to the extracellular milieu [106], where it acts as a potent inhibitor of mineralization [108]. The aetiology of DISH is still unknown, but several lines of evidence suggest that genetic factors might be involved in its aetiology [64, 77, 78]. Very few genetic studies on DISH have been published and up until now only two genes - COL6A1 [33, 146] and FGF2 [147] - have been shown to have a positive association with DISH susceptibility. Nonetheless, variants that showed significant association, in both genes, are located in non-coding regions and are very common variants within the general population, which suggests that these variants have only a minor effect on DISH susceptibility. DISH is very similar to, and can coexist with Ossification of the Posterior Longitudinal Ligament (OPLL; MIM 602475), a disease in which the genetic background is considered relevant in its aetiology. Unlike DISH, OPLL has been extensively investigated and despite some conflicting studies, a great number of susceptibility genes have been reported along the years. These included genes for Collagen 6A1 and 11A2 (COL6A1 and COL11A2) [33, 177], Bone morphogenetic protein 2 and 4 (BMP2 and BMP4) [158, 161], Ectonucleotide Pyrophosphatase/Phosphodiesterase 1 (ENPP1) [166], Transforming growth factor 1 and 3 receptor (TGF\$1 and TGF\$3) [154, 170], Estrogen receptor 1 (ESR1) [154], R-Spondin 2 (RSPO2) [172, 349] among others. However, as in DISH, genetic variants with a positive association with OPLL seem to have a minor effect on susceptibility to the disease.

The coexistence of DISH with CC is very common on Terceira Island-Azores leading our group to hypothesise that both diseases, hereafter designated as DISH/CC phenotype,

share the same pathogenic mechanism [23]. A similar phenotype has been reported in several studies in the past [25, 26]. In a previous study, our group, try to determine the genetic cause for this phenotype using a whole genome linkage analysis followed by an "Identity-by-state/descent" mapping in 10 affected individuals from 4 different families. Identity by descent (IBD) mapping is a statistical method for detection of genetic loci that share an ancestral segment among "unrelated" affected pairs of individuals. IBD mapping is more robust to allelic heterogeneity and can be used as a complementary method to genome-wide linkage studies, to identify rare inherited variants when combined with sequence data. The chromosome zones considered of interest were selected taking into consideration the maximum pairs sharing. Two zones, in chromosome 12 (65667554 -68670915) and 20 (821749-1266214 and 5157217-6074302) had the maximum number of pairs and thus the genes within this region were investigated. Two candidate genes were further investigated: RSPO4 in chromosome 20 (Chr 20:958452 - 1002284) and LEMD3 located very near the chromosome 12 (65169571-652483279). RSPO4 encodes a member of the R-spondin family, a group of four proteins which positively regulate canonical Wnt signaling by reducing Wnt receptor turnover and thereby increasing betacatenin stabilization. R-spondins may contribute to the maintenance of adult bone mass by regulating osteoblastogenesis and bone formation [350]. Loss of function mutations in the RSPO4 gene cause congenital anonychia (NDNC4; MIM #206800) or the absence of nails [351]. LEMD3 (LEM Domain Containing 3) encodes the Inner nuclear membrane protein Man1, which helps to control two important signaling pathways namely the Transforming Growth Factor- $\beta$ eta (TGF- $\beta$ ) and the Bone Morphogenetic Protein (BMP) signaling. Man1 can interact directly with the TGF- $\beta$  superfamily ligands, including bone morphogenic proteins (BMPs) and activin, or via its C-terminal domain, directly with Smad, which bind to specific areas of DNA to activate specific genes [352]. Genetic variants of LEMD3 have been associated with Osteopoikilosis and Buschke-Ollendorff Syndrome (BOS; MIM #166700) [353]. The present study targets genetic variants of the RSPO4 and LEMD3 genes located in chromosomal segments identified in a previous study as being associated with DISH/CC.

#### 5.3 Material & methods

#### 5.3.1 Subjects

This study involved nine DISH/CC families and studied 74 members (44 males; 30 females). Blood was obtained from all members who gave informed consent. Genomic DNA was extracted from peripheral blood cells using a standard Salting-out procedure. Standard X- rays were taken from: knees, axial skeleton, wrists, hands, elbows and pelvis. Amongst the 74 members, 46 were affected with DISH/CC, 20 had no signs of the disease and 8 were too young (< 25 years old) to establish likely disease status. A group of 55 unrelated Azorean patients with a diagnosis of DISH/CC (36 male, 19 female; age of onset around 40 years) and 36 unrelated controls (with no signs of DISH/CC) with a similar ethnic background (16 male, 20 female; mean current age, 68 years; range, 57-102) were also included.

The *LEMD3* rs201930700 frequency was evaluated on a randomized population of 124 individuals from Terceira Island (45 males, 79 females; mean age, 66 years; range, 35-100). This study was conducted with the approval of the HSEIT Ethics Committee.

#### 5.3.2 RSPO4 & LEMD3 sequencing

*RSPO4* gene primer pairs were designed using the software Primer3 (http://www.bioinformatics.nl/cgi-bin/primer3plus/primer3plus.cgi) to amplify/sequence regulatory, coding regions and intron exon boundaries, from 55 patients with DISH/CC disease and from 36 unaffected controls subjects. The *LEMD3* variant (rs201930700) was typed using primers previously described by Hellemans and collaborators [307].

All primers, amplification conditions and codes for reference sequences are available in the materials and methods section of this thesis. PCR fragments were purified with ExoSAP-IT<sup>TM</sup> and sequenced using ABI Big Dye chemistry (unidirectional, or when necessary, bidirectional) followed by purification with EDTA/Sodium Acetate and ethanol precipitation. Sequencing products were run on an automated DNA sequencer ABI 3130XL (Applied Biosystems<sup>®</sup>) and genetic variants were screened by sequence analysis and SeqScape (Applied Biosystems<sup>®</sup>). Base calling for heterozygous positions was made if the lower peak of the two co-incident peaks was higher than 25% of the highest peak. The genetic variants found in the *RSPO4* gene were screened within the families, where they occurred, whenever possible. The *LEMD3* rs201930700 variant was typed in a representative randomized group of 124 individuals from Terceira Island.

#### 5.3.3 Statistical analysis

All SNPs were checked for Hardy-Weinberg equilibrium (HWE). For all DISH/CC families, a transmission disequilibrium test (TDT) was used to assess the difference of the allele frequencies between the affected patients with DISH/CC and unaffected individuals. The TDT test was calculated for CHISQ, odds ratios (OR) (95% confidence interval) and corresponding p-values. To assess the difference in allele frequencies between the 55 patients with DISH/CC and the 36 control individuals and between males and females a Fisher exact test was used. The Fisher exact test was calculated for odds ratios (OR) (95% confidence interval) and corresponding p-values.

To perform an association between the DISH/CC disease and an allele variant other tests were employed: Cohran-Armitage trend, dominant and recessive gene action tests with 1 degree of freedom and genotypic test with 2 degree of freedom. For all statistical tests used a p-value of  $\leq 0.05$  was considered statistically significant. All statistical analysis were performed using PLINK software [354].

#### **5.4 Results**

#### 5.4.1 RSPO4 sequencing

Nine genetic variants were identified in the *RSPO4* gene; 3 missense variants (rs6140807 and rs61740632), 1 splice site variant (rs775644973), 2 synonymous (rs150446609 and rs41275604) and 3 regulatory region variants (rs146447064, rs149154047 and rs6056520) (Table 5-1). All of them were in HWE. Two of the variants located on the regulatory region of the *RSPO4* gene (rs146447064 and rs149154047) were located in a fully conserved region and were rare, with a MAF value of 0.01 (Table 5-1). The same was observed for the synonymous variant rs150446609 which was very rare (<0.01) and was located in a fully conserved region. The missense variant rs201485021 was located in exon 3 and the SIFT score of 0 and PolyPhen value of 1 indicates that this variant has a deleterious and a damaging effect on the protein, respectively. In addition, this variant was located in a fully conserved region and was extremely rare (MAF <0.01); in the

"1000 genomes" (genomes from 26 different populations) the variant was identified in only 2 males from an Iberian population in Spain.

Table 5-1. Genetic variants identified in the *RSPO4* gene and functional significance information. Nucleotide conservation was obtained using an alignment of: Human, Chimpanzee, Mouse lemur, Pig, Hedgehog and Elephant available in the Ensembl database database (http://www.ensembl.org/index.html) (Accessed on January 2017).

Exon/ Intron	Variant	SNP	Type of variant	MAF	SIFT	PolyPhen	Nucleotide Conservation
Upstream gene	c131C>T	rs146447064	Regulatory region	0.01	NA	NA	Fully conserved
Upstream gene	c115G>A	rs149154047	Regulatory region	0.01	NA	NA	Fully conserved
5'prime	c85 G>A	rs6056520	Regulatory region	0.35	NA	NA	1 species non conserved (Mouse lemur)
Exon 1	c. 12 A>C	rs150446609	Synonymous p.Pro4=	<0.01	NA	NA	Fully conserved
Intron 1	c.79+1G>A	rs775644973	Splice donor (HGMD mutation)	<0.01	NA	NA	Fully conserved
Exon 3	c.317G>A	rs6140807	Missense p.Arg106Gln	0.03	0.21	0.072	2 species non conserved (Pig and Hedgehog)
Exon 5	c.367 C>G	rs201485021	Missense p.Pro123Ala	<0.01	0	1	Fully conserved
Exon 4	c.471C>T	rs41275604	Synonymous p.Cys157=	0.01	NA	NA	1 species non conserved (Hedgehog)
Exon 4	c.524A>T	rs61740632	Missense p.His175Pro	0.01	0.3	0	4 species non conserved (Mouse lemur, Pig, Hedgehog and Elephant)

Abbreviations: SNP- Single nucleotide polymorphism, MAF- Minor allele frequency, SIFT- Sorting Intolerant From Tolerant, PolyPhen- Polymorphism Phenotyping, HGMD- Human gene mutation database, Pro- Proline, Arg- Arginine, Gln- glutamine, Ala- alanine, Cys- Cysteine, His- histidine, NA- not applicable.

In our study, this variant was found in only one female in our control group (n=36). The other two missense variants (rs6140807 and rs61740632), despite presenting SIFT and PolyPhen values indicatives of a minor effect on the protein (tolerated and benign, respectively), were both relatively rare. We found an extremely rare HGMD mutation (rs775644973 or CS065613), that has been associated with congenital anonychia [355]. The variant was found in only one female in our group of 55 DISH/CC patients, which is unaffected by congenital anonychia.

In order to perform a segregation analysis we tracked back the variants within 7 DISH/CC families, available in the AZORBIO biobank, where the variants were found. We investigated 7 variants: rs146447064 in AZ2, rs149154047 in AZ4, rs6056520 in AZ1, AZ2, AZ4 and AZ9, rs150446609 in AZ5, rs6140807 in AZ7 and AZ8, rs41275604 in AZ1 and AZ5 and rs61740632 in AZ1 and AZ7 families (Figure 5-1).



Figure 5-1. Typing results for RSPO4 gene in DISH/CC families.

In AZ2 family we studied three individuals and we found the regulatory region variant **rs146447064** in heterozygosity in two of them (III:1 and IV:2) (Figure 5-1). In this family, all the individuals studied were affected and so the results from this family were not used for statistical tests.

The other regulatory region variant - **rs149154047** - was found in heterozygosity in 9 individuals; 7 DISH/CC affected and in 2 unaffected. According to the statistical analysis shown in table 5-2, the variant rs149154047 was not associated with DISH/CC phenotype in AZ4 family. However, an important consideration in relation to this family was that of the 15 individuals studied, 12 of them are affected and only 3 were unaffected (individual III-1; III-8 and IV-1, with unknown age, 77 and 53 years, respectively).

CNID	E	Alleles	TDT					
SNP	Family	M/m	TR:UT	OR	CHISQ	Р		
rs146447064	AZ2	C/T	1:0	NA	1	0.317		
rs149154047	AZ4	G/A	1:1	1	0	1		
	AZ1	T/C	0:2	0	2	0.157		
ma 6 0 5 6 5 2 0	AZ2	C/T	0:1	0	1	0.317		
rs6056520	AZ4	C/T	1:1	1	0	1		
	AZ9	C/T	2:1	2	0.333	0.564		
rs61740632	AZ1	A/C	0:1	0	1	0.317		

Table 5-2. Family based association test (TDT test) results for variants of RSPO4 gene.

The variant **rs6056520** was heterozygous in several families in a great number of individuals. However it was homozygous only in DISH/CC affected males of the families AZ1 and AZ4 (Figure 5-1).

The synonymous variant **rs150446609** in the AZ5 family was present in all DISH/CC affected individuals, however the variant was also found in one unaffected individual (II:5 individual) (Figure 5-1). In the AZ5 family few individuals were studied (6 individuals; 3 affected, 2 unaffected and 1 unknown), so it is not possible to draw great conclusions.

The missense variant **rs6140807** was present in all the individuals studied in AZ7 and AZ8 families, except the affected individual (proband) in AZ8 family (individual II:1) which was the wild type for this variant (Figure 5-1).

The synonymous variant **rs41275604** was found in AZ1 and AZ5 families. In the AZ5 family the 3 DISH/CC affected individuals were carriers of the rs41275604 variant, which contrasts with the AZ1 family in which none of the 9 DISH/CC affected individuals presented the variant. In this family the **rs41275604** variant was only found in

**Abbreviations:** SNP- Single nucleotide polymorphism, M/m – major allele/minor allele, TDT-Transmission disequilibrium test, TR:NT-Transmitted/Untransmitted minor allele account, OR- odds ratio, P- pvalue, p value, NA- not applicable.

one unaffected female (III:3). No relationship was found between this variant and the DISH / CC phenotype.

The variant **rs61740632** in the AZ1 family was only found in one unaffected woman (II: 4), however segregation with the DISH/CC phenotype seemed to occur in the AZ4 family; the variant was present in all DISH/CC affected individuals and absent in the unaffected individuals. No association was verified maybe because the number of individuals studied was too small to reach statistical significance.

The *RSPO4* gene was further sequenced in 36 unrelated control individuals without DISH/CC in order to perform a case/control association study. The results are shown in table 5-3.

Table 5-3. Association study results of genetic variants found in *RSPO4* gene in Azorean patients with DISH/CC and controls without DISH/CC disease. The minor allele is represented in bold.

				Μ	AF				F	isher e	xact te	st	
SND	eles	]	DISH/CO	2		Controls		DISH/CC vs Controls					
5141	III	All	F	М	All	F	М	All		F		М	
		N=55	N=19	N=36	N=36	N=22	N=14	OR	Р	OR	Р	OR	Р
rs146447064	C/T	0.05	0.03	0.06	0.14	0.18	0.07	0.30	0.03	0.12	0.03	0.76	0.67
rs149154047	G/A	0.05	0.07	0.03	0.10	0.07	0.14	0.44	0.22	1.17	1	0.17	0.05
rs6056520	C/T	0.28	0.18	0.33	0.19	0.18	0.21	1.63	0.22	1.02	1	1.83	0.33
rs150446609	A/C	0.05	0.05	0.04	0.01	0.02	0	3.38	0.41	2.39	0.59	NA	0.56
rs775644973	G/A	0.01	0.03	0	0	0	0	NA	1	NA	0.46	NA	1
rs6140807	G/A	0.18	0	0.03	0	0	0	NA	0.52	NA	1	NA	1
rs201485021	C/G	0	0	0	0.01	0.02	0	0	0.40	0	1	NA	1
rs41275604	C/T	0.04	0.05	0.03	0.03	0.05	0	1.32	1	1.17	1	NA	1
rs61740632	A/C	0.04	0	0.06	0.01	0.02	0	2.68	0.65	0	1	NA	0.57

**Abbreviations:** SNP- Single nucleotide polymorphism, MAF- Minor allele frequency, OR- odds ratio, P-pvalue, N- number of individuals, NA- not applicable, F- Female, M-Male.

The regulatory region variant **rs146447064** in heterozygosity was found in 9% of the DISH/CC patients and in 11% of the controls (Supplementary table 5-1). In homozygosity the variant was only found in the controls, particularly in 3 females

(Supplementary table 5-1). There was a significant statistical difference in frequencies between DISH/CC patients and controls (p=0.03) and when adjusted for gender it was statistically different in females (p=0.03), but not in males (Table 5-3). Similar results for significance were obtained using the Cochran-Armitage trend and allelic tests (Table 5-4).

	DISH/CC (A1/A2) Controls (A1/A2)					DIS	H/CC	vs Cont	rols				
~~~~								A	11	N	Л	]	7
SNP (A1/A2)	All N=110	M N=72	F N=38	All N=72	M N=28	F N=44	Test	CHISQ	Ρ	CHISQ	Ρ	CHISQ	Ρ
rs146447064	5/105	4/68	1/37	10/62	2/26	8/36	Т	3.73	0.05	0.10	0.76	3.10	0.08
(1/C)							A	5.02	0.03	0.09	0.76	5.05	0.02
rs149154047	5/105	2/70	3/35	7/65	1/24	3//1	Т	2.04	0.15	5.06	0.02	0.04	0.85
(A/G)	5/105	2/70	5/55	7705	4/24	.4 3/41	А	1.89	0.17	4.73	0.03	0.03	0.85
rs6056520	21/70	04/40	7/01	14/50	<i>c 1</i> 22	0/26	Т	1.41	0.23	0.95	0.33	0	0.89
(T/C)	31/79	24/48	//31	14/58	6/22	/22 8/36	Т	1.79	0.18	1.36	0.24	0	0.98
rs150446609	5/105	2/60	2/26	1 /7 1	0/29		А	0.82	0.36	0.73	0.39	0.31	0.58
(C/A)	5/105	3/69	2/36	1//1	0/28	1/43	Т	1.36	0.24	1.20	0.27	0.52	0.47
rs775644973	1/100	0/72	1/27	0/72	0/29	0/44	Α	0.66	0.42	NA	NA	1.19	0.28
(A/G)	1/109	0/72	1/37	0/72	0/28	0/44	Т	0.66	0.42	NA	NA	1.17	0.28
rs6140807	2/108	2/70	0/29	0/72	0/28	0/44	Т	1.34	0.25	0.81	0.37	NA	NA
(A/G)	2/108	2/70	0/38	0/72	0/20	0/44	Α	1.32	0.25	0.79	0.37	NA	NA
rs201485021	0/110	0/72	0/29	1/71	0/29	1/42	Т	1.55	0.21	NA	NA	0.89	0.35
(T/C)	0/110	0/72	0/38	1//1	0/28	1/43	А	1.54	0.22	NA	NA	0.87	0.35
rs41275604	4/106	2/70	2/26	2/70	0/29	2/42	Т	0.08	0.78	0.81	0.37	0.02	0.90
(G/C)	4/100	2/70	2/30	2/70	0/28	28 2/42	Т	0.10	0.75	0.79	0.37	0.02	0.88
rs61740632	4/100	1/69	0/29	1/71	0/28	1/42	Т	0.85	0.36	1.69	0.16	0.89	0.35
(C/A)	4/106	4/68	0/38	1//1	0/28	1/43	А	0.82	0.36	1.62	0.20	0.87	0.35

Table 5-4. Statistical results using the Cochran-Armitage trend and allelic tests of genetic variants found in *RSPO4* gene in Azorean patients with DISH/CC and controls without DISH/CC disease.

Abbreviations: SNP- Single nucleotide polymorphism, M-Males, F-females, T-trend, A- allelic, OR- odds ratio, P- p-value, N- number of individuals, A1- allele 1, A2- allele 2, M- males, F- females, NA- Not applicable.

The other regulatory region variant **rs149154047** in heterozygosity was found in 9% of DISH/CC patients and in 19% of the controls (Supplementary Table 5-1). There was a significant statistical difference in frequencies between DISH/CC male and control males; the frequency of the "G/A" genotype in male DISH/CC was significantly lower than in males of the control group (p=0.05) (Table 5-3). But, significant statistical differences were not found in female DISH/CC patients relative to control females (Table 5-3). Similar results, but with a more significant p-value were obtain using the Cochran-

Armitage trend test (p=0.02, CHISQ=5.06, Df=1) and allelic test (p=0.03, CHISQ=4.73, Df=1) (Table 5-4).

#### 5.4.2 *LEMD3* sequencing

All the coding region of *LEMD3* gene had previously been sequenced in probands from the 4 IBD/IBS families. Three intronic (rs11175678, rs11610822 and rs10534559) and 1 missense mutation (rs201930700) were found (Table 5-5). In this study only the missense variant rs201930700 was investigated.

Table 5-5. Genetic variants identified in *LEMD3* gene in the four probands, previously investigated, and functional significance information.

Exon/Intron	Variant	SNP	Type of variant	MAF	SIFT	PolyPhen	Family/Proband
Intron 1	C.1523 -12 C>T	rs11175678	Intronic	0.04	NA	NA	AZ1/ II:1 (Ht)
Introp 5	a 1605 ± 100 C> A	ra11610822	Intronio	0.25	NA	NA	AZ1/ II:1 (Ht)
Intron 5	c. 1093 +100 G>A	1811010822	intronic	0.25	INA	INA	AZ4/ III:5 (Ht)
							AZ1/ II:1 (Ht)
Intron 7	c.2024 -34_2024 - 31 del GATT	rs10534559	Intronic (deletion)	?	NA	NA	AZ3/II:1 (Hm)
	51 461 67111		(deletion)				AZ4/ III:5 (Ht)
Exon 13	c.2701 C>T	rs201930700	Missense	?	0	0.995	AZ3/II:1 (ht)

Abbreviations: SNP- Single nucleotide polymorphism, MAF- Minor allele frequency, SIFT- Sorting Intolerant From Tolerant, PolyPhen- Polymorphism Phenotyping, Ht- heterozygous, Hm- homozygous, NA- not applicable.

Variant rs201930700 was located in exon 13 of the *LEMD3* gene and the SIFT score of 0 and PolyPhen value of 0.995 indicates that this variant has a deleterious and a damaging effect on the protein, respectively. The variant was extremely rare, the MAF was unknown due to insufficient data to establish population frequency, it was identified in only 5 of 121412 alleles (ExAc\_Aggregated\_Populations), indicating that it was unquestionably very rare (MAF 0.00004). A cohort of 124 individuals, all from Terceira Island, was typed for this mutation and one other individual carrying the variant was identified. This individual and his family were examined (interviewed for clinical purposes, x-rayed and typed). The two families that presented the rs201930700 variant were further investigated (Figure 5-2).



Figure 5-2. Typing results for *LEMD3* gene in DISH/CC families.

The rs201930700 variant was in HWE. Of the 5 individuals studied in the AZ3 family, 4 individuals (2 males and 2 females) were DISH/CC affected and carriers of the rs201930700 variant and 1 individual (male) was DISH/CC affected however, he was a non-carrier of the variant (Figure 5-2). In the AZ3 family it was impossible to verify segregation since all the individuals studied were DISH/CC affected, so the association test was not performed in this family.

Interestingly, the male individual from the AZ10 family found in the randomized population of 124 individuals that were tested for the rs201930700 variant, had DISH/CC disease, as did some of their relatives. Of the 11 individuals studied in the AZ10 family, 5 individuals (3 males and 2 females) were DISH/CC affected, in which one individual was a carrier of the rs201930700 variant and the other 4 were wild type. The variant was also found in 1 male of the 4 unaffected individuals (2 males and 2 females) and in 2 younger females (Figure 5-2). As can be seen in figure 5-2, the majority of individuals in the AZ10 family were DISH/CC affected and apparently no segregation occurs in this family

#### **5.5 Discussion**

DISH/CC is a poorly understood phenotype characterised by peripheral and axial enthesopathic calcifications, fulfilling the radiological criteria for DISH, and in some cases associated with CC [26, 356, 357]. The concurrence of DISH and CC suggest a shared pathogenic mechanism [24]. The aetiology of DISH/CC is unknown, however, since it is a bone forming disease it is expected that genes related to the calcification and ossification process are implicated in its aetiology. The two genes investigated in the present study, RSPO4 and LEMD3, fulfil the expectations of good candidate genes. In the present study we have found two interesting variants in RSPO4 gene (rs146447064 and rs14915407) which are significantly more frequent in controls than in DISH/CC patients indicating a possible protective role for these variants in the DISH/CC phenotype. According to what we know the variants rs146447064 and rs14915407 were not associated with Nail disorder or Anonychia (MIM #206800), an autosomal recessive disorder caused by a homozygous or compound heterozygous mutation in the RSPO4 gene [355]. The rs146447064 variant is a regulatory region variant located in the promoter region, which indicates that this variant could affect the expression of RSPO4. It is an extremely rare variant with a MAF value of 0.01 in all populations and 2% in European populations. Interestingly this variant, that in our study gave a protective effect against the disease, does not exist in Asian populations, where the prevalence of OPLL is higher, a disorder very similar to DISH. In addition, the variant is significantly more frequent in control females (p=0.02) than in control males, which could be explained by the fact that 3 control females were homozygous for this rare variant. The variant was also found in heterozygosity in four controls (2 females and 2 males) and in 5 DISH/CC patients (1 female and 4 males).

The rs149154047 variant is also a regulatory region variant located in the promoter region (20: 1002275-1002283). It is also an extremely rare variant with a MAF value of 0.01 in all populations and 3% in European populations. The variant rs149154047 was not associated with the occurrence of the DISH/CC phenotype, however when adjusted for gender, the analysis revealed a significant association between the A allele of the rs149154047 variant and the occurrence of the DISH/CC phenotype in control males (p=0.02) but not in control females. The variant was also found in heterozygosity in 7 controls (3 females and 4 males) and in 5 DISH/CC patients (3 female and 2 males). As far as we known no phenotype was associated with this variant.

The R-spondin proteins activate Wnt/beta-catenin signaling pathways [358] through LRP6 (low density lipoprotein receptor related protein 6) by antagonizing Dickkopf (DKK1) function, which is an inhibitor of osteoblastogenesis and its lower levels are linked to new bone formation [359]. A recent study show, that DISH patients have the levels of total serum DKK1 significantly lower than in healthy controls [360]. It is known that the induction of the Wnt signaling pathway by R-spondin proteins may be a direct consequence of DKK1 inhibition [359, 361]. Based on this knowledge we hypothesise that rs146447064 and rs14915407 are variants associated with the reduction in *RSPO4* gene expression, thus reducing Wnt activation and consequently enhanced the DKK1 which protects against bone formation. However, further studies are needed to ascertain this theory.

In the LEMD3 gene the missense variant, c.2701 C>T (rs201930700) was found in two families. This variant has been identified very few times previously and both families in which it was typed present the phenotype DISH/CC. This variant causes the substitution of amino acid 901 from a large and basic arginine to a large and aromatic tryptophan. According to the Ensembl database the modified nucleotide is highly conserved in all vertebrates and is located in the carboxyl-terminal nucleoplasmic region of the Man1 protein. This region (amino acids 782-911) is predicted to be an RNA recognition motiflike (RRM-like) protein interaction domain named the U2AF homology motif [362, 363]. This conserved region that contains the UHM domain (U2AF homology motif kinase 1) is exclusive to Man1 proteins and is essential for smad2 and smad3 binding [364]. It is known that interaction between Man1 and Smad1 or Smad2 and Smad3 inhibits bone morphogenic protein (BMP) and TGF-β signaling, respectively [352, 365]. It is reported that heterozygous loss-of-function mutations in *LEMD3* enhance TGF- $\beta$  signaling leading to sclerosing bone dysplasia osteopoikilosis, and Buschke-Ollendorff syndrome [307]. As this variant (rs201930700) is not a loss-of-function mutation, the carriers of this variant do not present any signs of Osteopoikilosis or Buschke-Ollendorff Syndrome. The effect that the rs201930700 variant produces in the investigated phenotype is difficult to ascertain at this point. We postulate that the rs201930700 variant may lead to enhanced TGF- $\beta$  signaling, leading to increased bone formation. Our hypothesis was not confirmed by the segregation analysis which might be explained by the characteristics of the sample, in which almost all individuals were DISH/CC affected, making it very difficult to verify segregation. Other studies are necessary to verify the importance of this rare variant on the phenotype under study in order to establish a possible association.

In conclusion, our results suggest a protective role for two *RSPO4* gene regulatory variants, probably by altering gene expression of the *RSPO4* gene. The relevance of the extremely rare variant of *LEMD3* (rs201930700) in the phenotype DISH/CC is difficult to ascertain at this point. To our knowledge, this study is the first to investigate the relationship between *RSPO4* and *LEMD3* genes and DISH and or CC diseases.

#### 5.6. Supplementary material

			DISU/CC			CONTROL	c	
			Alle p=55					
		Т	AII: II-35		Ecomolo: n=22			
SND	Genotype	<b>Г</b>	Moles n=19					
5141		A 11	Male: II=30	M-1.	A 11	France: II=14	N. 1.	
		$\frac{AII}{P(0)}$	Female $\mathbf{r}(\mathbf{q}(\mathbf{r}))$	$\mathbf{Male}$	$\frac{AII}{P(0(1))}$	$\mathbf{F}$ emale	$\mathbf{Male}$	
	CIC	II(70)	18 (05)	11 (70)	II(70)	17 (77)	12 (96)	
146445064		50 (91)	18 (95)	32 (89)	29 (81)	1/(//)	12 (80)	
rs146447064		5 (9)	1 (5)	4(11)	4(11)	2 (9)	2 (14)	
	1/1	0(0)	0(0)	0(0)	3 (8)	3 (14)	0(0)	
	G/G	50 (91)	16 (84)	34 (94)	29 (81)	19 (86)	10 (71)	
rs149154047	G/A	5 (9)	3 (15)	2 (6)	7 (19)	3 (14)	4 (29)	
	A/A	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	
	C/C	31 (56)	12 (63)	2 (6)	25 (69)	15 (68)	10 (71)	
rs6056520	C/T	17 (31)	7 (37)	10 (28)	8 (22)	6 (27)	2 (14)	
	T/T	7 (13)	0 (0)	7 (19)	3 (8)	1 (5)	2 (14)	
	A/A	52 (95)	18 (95)	34 (94)	35 (97)	21 (95)	14 (100)	
rs150446609	A/C	1 (2)	0 (0)	1 (3)	1 (3)	1 (4)	0 (0)	
	C/C	2 (4)	1 (5)	1 (3)	0 (0)	0 (0)	0 (0)	
	G/G	54 (98)	18 (95)	0 (0)	36 (100)	22 (100)	14 (100)	
rs775644973	G/A	1 (2)	1 (5)	0 (0)	0 (0)	0 (0)	0 (0)	
	A/A	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	
	G/G	53 (96)	19 (100)	34 (94)	36 (100)	22 (100)	14 (100)	
rs6140807	G/A	2 (4)	0 (0)	2 (6)	0 (0)	0 (0)	0 (0)	
	A/A	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	
	C/C	55 (100)	19 (100)	36 (100)	35 (97)	21 (95)	14 (100)	
rs201485021	C/G	0 (0)	0 (0)	0 (0)	1 (3)	1 (5)	0 (0)	
	G/G	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	
	C/C	53 (96)	18 (95)	34 (94)	34 (94)	20 (91)	14 (100)	
rs41275604	C/T	2 (4)	0 (0)	2 (6)	2 (6)	2 (9)	0 (0)	
	T/T	1 (2)	1 (5)	0 (0)	0 (0)	0 (0)	0 (0)	
	A/A	51 (93)	19 (100)	32 (89)	35 (97)	21 (95)	14 (100)	
rs61740632	A/C	4(7)	0 (0)	4 (11)	1 (3)	1 (5)	0 (0)	
	C/C	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	

Supplementary table 5-1. Results of genetic variants found in the *RSPO4* gene in Azorean patients with DISH/CC compared to the controls.

**Abbreviations:** SNP- Single nucleotide polymorphism, n- number of invividuals, %- percentage, MAF-Minor allele frequency, SIFT- Sorting Intolerant From Tolerant, PolyPhen- Polymorphism Phenotyping, Ht- heterozygous, Hm- homozygous, NA- not applicable.

## CHAPTER VI: WHOLE EXOME SEQUENCING

### 6. WHOLE EXOME SEQUENCING OF PATIENTS SHOWING EXUBERANT ECTOPIC CALCIFICATIONS IN THE AXIAL AND APPENDICULAR SKELETON

#### 6.1. Abstract

Diffuse idiopathic skeletal hyperostosis (DISH) is a common skeletal disorder characterized by the presence of new bone formation in ligaments and entheses. To date, only two susceptibility genes (*COL6A1* and *FGF2*) have a weak genetic link to DISH. In order to identify genetic variants associated with DISH we performed whole exome sequencing in four patients with ectopic calcifications that displayed the rare coexistence of two different rheumatic entities: Diffuse Idiopathic Skeletal Hyperostosis (DISH, MIM 106400) and chondrocalcinosis (CC).

DNA was extracted by a standard salting out procedure. Four DISH/CC patients from different affected families were selected (two females and two males). Sequencing of all coding regions and intron-exon boundaries was performed using an ABI-SOLiD platform. Exome data were filtered in order to find a variant or a group of variants that could be associated with the DISH/CC phenotype. The variants of interest were subsequently confirmed by Sanger sequencing. Selected variants were screened in different pedigrees and in a cohort of DISH/CC patient's vs controls. The statistical analysis was performed using PLINK V1.9.

We successfully identified 21 relevant genetic variants in 17 genes that were directly or indirectly related to mineralization. The commonly used algorithms; SIFT and PolyPhen revealed that several of the gene variants were predicted to be deleterious and damaging to the coded proteins. We identified a significant association between DISH/CC disease and a genetic variant in *BMP4* (rs17563), a gene involved in endochondral bone formation (p=0,009; OR=2.331).

The results of the present study revealed that the variant rs17563 in *BMP4* gene was significantly associated with DISH/CC phenotype. Further studies with an enlarged number of samples will be needed to clarify this association with the phenotype under study.

Keywords: WES, BMP4, ABCC6, DISH, CC, variants.

#### **6.2 Introduction**

Whole exome sequencing is a technique that makes use of the massive parallel sequencing capabilities of next-generation platforms to rapidly identify rare variants in the  $\sim 1\%$  of the genome that codes for proteins. The power of exome sequencing comes from the fact that the majority of monogenic diseases arise from mutations within this protein-coding portion of the genome. Furthermore, whole-exome sequencing is now a realistic strategy for detecting pathogenic variants in families in which linkage analysis was not conclusive. Most exome sequencing studies are based on a small number of samples for identification of the causal variants for disease and PCR and Sanger sequencing is then used to extend and reinforce the identified causal variants in a greater number of individuals [366, 367].

Previous studies, undertaken by our group, led to the identification and characterization of twelve families multiply affected with DISH and/or Chondrocalcinosis (CC). A common pathogenic mechanism, was suggested to be shared by the two conditions [24]. Diffuse idiopathic skeletal hyperostosis (DISH, MIM 106400) is a common skeletal disorder characterized by progressive calcification and ossification of ligaments and entheses [1, 2]. The exact prevalence and incidence of DISH is unknown, however it is well known that DISH is more frequent in males and its prevalence rapidly increases with age, affecting mainly subjects over the age of 40 [5]. Weinfeld and colleagues found the prevalence of DISH in patients over 50 years of age to be 25% in males and 15% in females [368], and this disease is becoming a serious problem in aging societies. DISH can co-exist with a great number of other similar rheumatic diseases, and examples of these are the ossification of the posterior lateral ligament (OPLL, MIM 602475) [6], Ossification of the ligamentum flavum [32], Ankylosing spondylitis (MIM 106300) [7-21] and CC [22, 23]. CC is characterized by the deposition of crystals of calcium pyrophosphate (CPP) in articular hyaline and fibro-cartilage [312]. For the moment ANKH (CCAL2; #118600) is the only monogenic cause identified for chondrocalcinosis [269], and one study shows that the gene TNFRSF11B, encoding osteoprotegerin, is involved in the development of osteoarthritis with chondrocalcinosis [301]. Several lines of evidence suggest that genetic factors may play a part in the aetiology of DISH, such as the existence of familial cases with early onset (in the third decade of life) [64] and the higher frequency of DISH in a specific dog breed, the boxer [77, 78]. So far, however, no single gene has been conclusively associated with the disease. Molecular genetic studies,

therefore, are important to the understanding of the genetic aetiology of DISH. Several linkage and association studies have identified candidate genes/loci that could be linked to DISH susceptibility, including Human Leukocyte Antigens (HLA), Collagen 6A1 gene (*COL6A1*) [34], Fibroblast Growth factor 2 (*FGF2*), [147], Vitamin D (1,25-Dihydroxyvitamin D3) Receptor (*VDR*) and Collagen Type  $I_{\alpha 1}$  (*COL1A1*) [145]. However, none of the preceding genes have been demonstrated to be pathogenetically relevant for DISH patients.

DISH is considered a bone forming disease and so genes related to the calcification and ossification process are considered good candidate genes for this disease. In the present study, we performed targeted exome sequencing on four DISH/CC patients, with an apparently autosomal dominant DISH/CC phenotype. The aim was to capture rare and pathogenic variants that are expected to have potentially damaging effects on protein function that leads to modified calcification and/or ossification. To our knowledge this study represents the first report of exome sequencing analysis in DISH disease.

#### 6.3 Material & methods

#### 6.3.1. Subjects

This study involved four patients from four distinct DISH/CC families (AZ1-AZ4) which were selected for whole exome sequencing (2 males and 2 females; age of onset around 40 years). The four families (AZ1-4) contain 35 members (20 males and 15 females; mean age of onset, 36 years; range, 20-50) in which 33 were affected with DISH/CC and 8 had no signs of the disease (see material and methods of this thesis). Standard X rays were taken from: knees, axial skeleton, wrists, hands, elbows, and pelvis. The 4 patients were radiologically characterized (Table 6-1). A group of 55 unrelated Azorean patients with a diagnosis of DISH/CC (36 male, 19 female; age of onset around 40 years) and 36 unrelated healthy controls with a similar ethnic background (16 males and 20 females; mean current age, 68 years; range, 57-102) were also included. This study was approved by the HSEIT Ethics Committee and all participants provided informed consent.

itient	Sex			Age at	Other			
$\mathbf{P}_{\mathbf{a}}$	•1	C-Spine	T-Spine	L-Spine	Knees	Elbow	onset	uiseases
AZ1	М	Normal	Normal	Sindesmophytosis Inc DISH	?	Enthesopathy ; calcifications	<40	Obesity
AZ2	F	DISH inc C5- C6	DISH	DISH	Arthrosis, enthesopathy	Enthesopathy, osteophytosis, calcifications	30	Lithiasis, Diabetes mellitus
AZ3	F	N/A	DISH inc	DISH inc	Enthesopathy, osteophytosis, arthrosis	Calcifications, enthesopathy	?	Obesity
AZ4	М	Normal	Sindesmophytosis	Syndesmophytosis, anterior osteophytosis	Osteophytosis , calcifications in capsule, arthrosis	Calcifications, enthesopathy osteophytosis	<40	Lithiasis, cardiac arrythmia

Table 6-1. R	Radiology	results f	from fo	our selecte	ed patients	for	WES.
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**Definition of Radiological terminology 1) DISH:** continuous ossification along the anterolateral aspect of four contiguous vertebral bodies. **DISH/CC inc:** Continuous ossification along the anterolateral aspect of two or three contiguous vertebral bodies. **2) Sindesmophytosis:** Vertical and symmetrical calcification of the lateral margins of the intervertebral disc space. **3) Osteophytosis:** presence of spurs, which are outgrowths of bone tissue. **4) Enthesopathy:** calcification/ossification process at the site of the insertion of ligaments, tendons, fascia or articular capsule into bone. **5) Arthrosis:** presence of joint space narrowing, sclerosis and osteophytosis.

**Abbreviations:** M- male, F- female, DISH- diffuse idiopathic skeletal hyperostosis, C-Spine- Cervical spine, T- Spine- Thoracic spine, L-Spine- Lumbar spine, ?- unknown, N/A- not available.

#### 6.3.2. Exome capture

The selection of patients was made after ruling out mutations in ANKH, the only monogenic disease causing gene yet known for CC. All secondary causes for CC were also ruled out by appropriate biochemical testing. DNA was extracted using a standard salting out procedure. Samples were resequenced, using an Applied Byosystems -Sequencing by Oligonucleotide Ligation and Detection platform (ABI-SOLiD) and Agilent's SureSelect Target Enrichment System for 38 Mb, by "Sistemas Genómicos, S.L." in Valencia, Spain. The quality and quantity of extracted DNA was evaluated by agarose gel electrophoresis, measurement of absorbance at 260 nm was established using a NanoDrop 1000 and Qubit fluorescence quantification. SOLiD Fragment libraries were prepared and enriched with SureSelect All Human Enrichment Target Exon. The quality and quantity of the libraries were assessed by analysis with Agilent 2100 Bioanalyzer and Qubit. Each library went through a process of emulsion PCR for clonal amplification of the fragments, followed by an enrichment process and chemical modification to allow loading in the reaction chamber. The quality and quantity of the beads obtained for each library were estimated taking into account the parameters given by Work Flow Analysis. Then, ligation sequencing was done to obtain sequences of 50 nucleotides +35 nucleotides

(Paired-end) in SOLiD4. The data quality was estimated using the parameters provided by the software SETS (SOLiD Experimental Tracking System). Single Nucleotide Variants (SNVs) were classified using Ensembl's nomenclature and grouped using the following the scheme: Known and Novel (Coding, Splicing, Others). The coding variants were divided into Non-synonymous and Synonymous. The `Others' included intronic, untranslated (UTR), regulatory region, intergenic, downstream and upstream variants.

#### 6.3.3. WES filtering

Three filtering strategies were applied in order to find a variant or a group of variants that could be associated with the DISH/CC disease.

#### 6.3.3.1. Filtering candidate genes provided by WES results

Two different models (dominant and recessive) were used to identify candidate genes. The most probable model for inheritance of the disorder under study is an autosomal dominant model. Taking into consideration that the majority of the families used for the study come from a restricted area of the Terceira Island, a genetic founder effect was expected. A recessive model cannot be ruled out, due to the high consanguinity present on the island, but it is less likely due to the distribution pattern of the disease in pedigrees.

A list of 815, 917, 872 and 593 genes, was generated to include the candidate genes under a dominant model (Table 6-2). These genes were then filtered based on sharing between the four investigated DISH/CC patients. A group of 52 genes were common to the four patients (Table 6-3), and from this group the candidate genes for testing were selected taking into consideration their function. For this reason priority was given to candidate genes involved in the calcification and/or ossification process or related conditions that could be associated with DISH/CC disease.

Samples	Number of candidate genes							
Samples	Dominant model	Recessive Model						
AZ1	815	48						
AZ2	917	58						
AZ3	872	47						
AZ4	593	25						

Table 6-2. Number of candidate genes per sample.

There was only one gene that came out as a good candidate gene for a recessive model: HLA-*DQA2* (Table 6-3), which was also present in the list of candidate genes when using

a dominant model of inheritance. There is not much information available about the HLA-DQA2 gene and the IPD-IMGT/HLA Database does not have typing results for this gene. The study of this gene was not therefore carried out in the present study, due to time constraints.

Patients	Number of candid	late genes shared:
	Dominant model	Recessive Model
AZ1+AZ2+AZ3+AZ4	<u>52</u>	<u>1</u>
AZ1+AZ2+AZ3	118	2
AZ1+AZ2+AZ4	65	1
AZ2+AZ3+AZ4	78	2
AZ1+AZ3+AZ4	77	1
AZ1+AZ2	220	6
AZ1+AZ3	212	4
AZ1+AZ4	139	4
AZ2+AZ3	249	6
AZ2+AZ4	149	4
AZ3+AZ4	162	3

Table 6-3. Number of candidate genes shared by the investigated DISH/CC patients.

We then procured all the variants in the shared genes and focused on nonsynonymous, splice sites, stop loss/gain and frameshift variants, anticipating that synonymous and intronic variants would be far less likely than functional variants to be relevant in the pathogenicity.

#### 6.3.3.2. Filtering within candidate genes

A group of 20 candidate genes was selected through a literature search, and included genes that are possibly involved in bone metabolism and/or related conditions. These genes are Alkaline Phosphatase (*ALPL/TNAP*), the Calcium Sensing Receptor (*CASR*), Bone morphogenetic protein receptor type 1B (*BMPR1B*), Osteopontin (*OPN/SPP1*), Integrin binding sialoprotein (*IBSP*), Fibroblast Growth factor 2 (*FGF2*), Inorganic Pyrophosphate Transport Regulator (*ANKH*), Collagen type XI, alpha 2 (*COL11A2*), Nucleotide pyrophosphatase 1 (*ENPP1*), Runt-related transcription factor (*RUNX2*), Dickkopf WNT signaling pathway (*DKK-1*), Insulin like growth factor 1 (*IGF1*), Matrix Gla protein (*MGP*); Vitamin D (*VDR*), Bone morphogenetic protein 4 (*BMP4*), Collagen type 1 alpha 1 (*COL1A1*), Transforming growth factor beta 1 (*TGFβ*1), Solute carrier family 29 member 1 (*SLC29A1*), Bone morphogenetic protein 2 (*BMP2*) and Collagen type VI, alpha 1 (*COL6A1*). The genes selected were screened against the WES results

and the variants were annotated in an excel file. Subsequently we focused only on nonsynonymous, splice sites, loss or gain of a stop and frameshift variants.

#### 6.3.3.3. Filtering pathogenic variants

In this filtering strategy we used two levels; variant and knowledge level (Figure 6-1). In the variant level we first filtered according to variant type and focused on variants with functional significance (splice sites, frameshift coding, nonsynonymous coding, lost or gained stop variants. Only the SIFT prediction with Damaging and Unknown and GERP values equal or higher than 3 were included. We excluded variants with MAF values higher than 0.05 by filtering the SNP\_IDs (rs number or by chromosome position) against public Ensembl Variant Effect Predictor a tool. (http://www.ensembl.org/info/docs/tools/vep/index.html). Then at the "knowledge level" we focused only on genes associated with calcification and/or ossification processes or related conditions. Lastly we evaluated the functional significance and pathogenic potential of each variant found in the selected genes.



Figure 6-1. The two-level filtration approach used to analyze the WES results from 4 patients with DISH/CC disease. WES: Whole exome sequencing, SIFT: Sorting Intolerant From Tolerant, GERP: Genomic Evolutionary Rate Profiling score and MAF: Minor Allele Frequency.

#### 6.3.4. Validation and Evaluation of Genes/Variants

PCR primers designed using the software Primer3 were (http://www.bioinformatics.nl/cgi-bin/primer3plus/primer3plus.cgi) to amplify and validate variants detected by Exome Sequencing (primers sequences and PCR conditions are indicated in the materials and methods of this thesis). PCR products were purified using ExoSAP-IT<sup>TM</sup> following the manufacturer's instructions. After purification with ExoSAP-IT, sequencing reactions with BigDye<sup>®</sup> Terminator were performed unidirectionally, or when necessary, bidirectionally. Sequencing reactions were purified with acetic acid and EDTA followed by ethanol precipitation. The templates were ressuspended in Hi-Di formamide and analysed using an automated DNA sequencer ABI 3130xl (Applied Biosystems<sup>®</sup>). Genetic variants were screened using Sequencing analysis and SeqScape software's (Applied Biosystems®) and using as a reference NCBI sequences (see the material and methods section of this thesis for more detail).

The information about each gene was obtained from several databases, including Ensembl (<u>http://www.ensembl.org/index</u>), National Center for Biotechnology Information (NCBI) (<u>http://www.ncbi.nih.gov</u>) and Pubmed (<u>https://www.ncbi.nlm.nih.gov/pubmedwe</u>), GeneCards (<u>http://www.genecards.org/</u>), Online Mendelian Inheritance in Man (OMIM) (<u>http://www.omim.org/</u>) and MalaCards (<u>http://www.malacards.org/</u>).

The functional significance and the potential deleterious effect of each variant was explored in the following databases: Ensembl (<u>http://www.ensembl.org/index</u>), Human Gene Mutation Database (HGMD) (<u>http://www.hgmd.cf.ac.uk/ac/index.php</u>) and dbSNP (<u>https://www.ncbi.nlm.nih.gov/projects/SNP/</u>), making use of algorithms, such as PolyPhen-2 (Polymorphism Phenotyping v2) (<u>http://genetics.bwh.harvard.edu/pph2/</u>) that defines severity as, benign, [0-0.2], possibly damaging (0.2-0.85), and probably damaging [0.85-1]) and for SIFT, damaging if less than 0.05 and for GERP, this ranges from -12.3 to 6.17, with 6.17 being the most conserved [369]). The MAF values of each variant were also analyzed. Protein conservation analysis was performed using ClustalW (<u>http://www.genome.jp/tools/clustalw/</u>) to compare homologous amino acid sequences among multiple vertebrates at the sites where the variations occur. The accession numbers of the transcript are available in supplementary table 6-1.

#### **6.3.5.** Association studies

In order to verify a possible association with DISH/CC phenotype selected variants were screened in family members (affected with DISH/CC and unaffected), and the more conserved variants, those that were present in three or four WES patients, were selected for screening in a group of DISH/CC patients and controls.

#### **6.3.6. Statistical analysis**

All SNPs were checked to assess their compliance with the Hardy-Weinberg equilibrium (HWE). For all DISH/CC families, a basic family based association test (transmission disequilibrium test -TDT) was used to assess the allele transmission. The TDT test was calculated for CHISQ, odds ratios (OR) (95% confidence interval) and corresponding p-values. To assess the difference in allele frequencies between the 55 patients with DISH/CC and the 36 control individuals a Fisher exact test was used. The Fisher exact test was calculated for odds ratios (OR) (95% confidence interval) and corresponding p-values. For all statistical tests used a p-value of  $\leq 0.01$  was considered statistically significant. All statistical analysis were performed using PLINK software [354].

#### 6.4 Results

#### 6.4.1. Exome capture - variants detected

An average of approximately 3.8 billion bases of sequence per patient were generated and the capture specificity and sensibility in all samples was about 55% and 94%, respectively. The average sensibility for all four samples was over 94%. Table 6-4 summarizes the results after the SNV calling and indel identification steps for each sample.

Table 6-4. Known, novel and total number of SNVs and Indels for the	four samples analysed
(AZ1-4).	

Sample		SNVs			Indels		Tatal				
	Known	Novel	Total	Known	Novel	Complex	Total	TOTAL/sample			
AZ1	17281	1619	18900	457	405	51	913	19813			
AZ2	18086	1759	19845	440	496	66	1002	20847			
AZ3	18327	1650	19977	524	505	73	1102	21079			
AZ4	17575	1223	18798	475	424	72	971	19769			

Abbreviations: SNVs: Single nucleotide variants

#### 6.4.2. Filtering Results

From the three filtering strategies deployed we obtained 21 missense, deletion and splice site variants in 17 genes: *PLCG2*, obtained in the first filtering strategy that was based on candidate genes in a dominant model; *ALPL, CASR, FGF2, COL11A2, ENPP1, MGP, VDR, BMP4, COL1A1, TGF\beta1, BMP2 and COL6A1, were obtained from the second filtering based on candidate genes and <i>FLNC, AMER3, PPP2R2D* and *ABCC6*, were obtained from the third filter based on predicted pathogenic variants (Table 6-5).

After analysis of the functional significance of the variants we found several with a possible effect on protein function and/or low MAF values, which are indicative of a deleterious variant. The variants **c.**2054+7G>A and c.3786G>C (K1262N) in *PLCG2* gene are both extremely rare. The c.2054+7G>A is a splice site variation located seven bases after exon 19 and the c.3786G>C (K1262N) is a missense variant which causes substitution of lysine with asparagine at amino acid 1262. The amino acid lysine is basic and polar and asparagine is neutral and polar. The logarithm SIFT (0) in c.3786G>C (K1262N) suggests the variation has a deleterious effect on the PLCG2 protein. The splice site variant c.2054+7G>A was present in patients AZ3 and AZ4 and the missense variant c.3786G>C (N1260K) was present in AZ2 and all were heterozygous (Table 6-5).

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#### Table 6-5. List of variants found by WES and confirmed by Sanger Sequencing.

Gene	Gene function	Chr	r SNP	Variant	AA	MAF	SIFT	PolyPhen		Patie	ent	
							<u> </u>		AZ1	AZ2	AZ3	AZ4
PLCG2	A calcium dependent phosphatidylinositol-specific phospholipase C, which is crucial in transmembrane signalling. Involved in the Wnt receptor signaling pathway.			c.2054+7G>A	NA	0,01	NA	NA			ht	ht
	This gene regulates osteoclastogenesis, and in a mice model, a deletion of this gene leads to an osteopetrotic phenotype [3/0].		rs374430619	c.3786G>C	K1262N	?	0	0,008		ht		
ALPL	Play a role in bone mineralization. Hypophosphatasia in adult (#146300), Infantil (#241500) and Childhood (#241510) are caused by mutations in this gene.	1	rs149344982	c.455G>A	R152H	0,01	0,56	0,077		ht		
			rs3200254	c.787T>C	Y263H	0,27	1	0	ht		ht	
CASR Pl in	Plays a pivotal role in systemic calcium metabolism. Loss of function mutations cause hyperparathyroidism neonatal (#239200) [371], whereas gain of function result in hypocalcemia with Bartter syndrome (#601198) [371].	3	rs1801725	c.2956G>T	A986S	0,09	0,22	0,01		ht		ht
			rs1801726	c.3031G>C	E1021Q	0,08	1	0		hm	hm	hm
FGF2	Osteoblast gene expression and differentiation [148]. Diseases associated with FGF2 include Corneal Neovascularization and Crouzon Syndrome. One study associated this gene with DISH susceptibility [147].	4	rs1048201	c.*757C>T	NA	?	NA	NA	ht	ht		ht
6011142	Involvement in the ossification process. Mutations in this gene cause Otospondylomegaepiphyseal dysplasia (#215150), Weissenbacher-Zweymuller syndrome	6	rs9277934	c.826G>A	E276K	0,32	0.45	0.557	hm	ht	hm	ht
COLITA2	(#21/610), Fibrochondrogenesis 2 (#614524), Stickler syndrome, type III (#184840) and Deatness (#601868 and #609/06). Mutations in this gene may also be associated with OPLL disease (%602475).		rs2229792	c.5165C>T	P1722L	0,01	0.01	0.088				ht
ENPP1	Regulates soft-tissue calcification and bone mineralization by producing PPi [89]. Mutations in this gene are associated with Cole disease (#615522), Hypophosphatemic Rickets (#613312) and Arterial calcification generalized of infancy 1(#208000). Mutations in this gene have been also associated with OPLL [165].	6	rs1044498	c.517A>C	K173Q	0,34	0,19	0,014	ht	ht	ht	
MGP	Physiological inhibitor of ectopic calcification. Diseases associated with this gene include Keutel Syndrome (#245150) and Vitamin K deficiency Hemorrhagic Disease.	12	rs4236	c.304A>G	T102A	0,39	1	0	ht		ht	ht
VDR	Involved in mineral metabolism; control the absorption of calcium and phosphate. Diseases associated with this gene include Rickets, vitamin D-resistant (#277440) and osteoporosis (#166710).	12	rs2228570	c.2T>C	M1T	0.35	0	0.995	hm	hm	ht	ht
BMP4	Involved in endochondral bone formation. Diseases associated with BMP4 include Microphthalmia Syndromic 6 (#607932) and Orafacial Cleft 11 (#600625).	14	rs17563	c.455T>C	V152A	0,37	0,57	0,005	hm		hm	ht
COLIAI	Involved in bone maturation, development and mineralization [372]. Mutations in this gene cause Caffey Disease (#114000) and Osteogenesis Imperfecta Type I-IV (#166200, #166210, #259420 and #166220, respectively).	17	rs372029024	c.3247G>T	A1083T	?	0.08	0	hm			
TGFβ1	Bone remodeling; potent stimulator of osteoblastic bone formation. Diseases associated with this gene include Camurati-Engelmann Disease (#131300) and Cystic Fibrosis (#219700).	19	rs55659002	c.713-8delC	NA	?	NA	NA			ht	
BMP2	Induce bone and cartilage formation. Diseases associated are Brachydactyly, Type A2 (#112600) and Hemochromatosis (#235200).	20	rs235768	c.570A>T	R190S	0,24	0	0,977	ht		ht	ht
COL6A1	Play a role in maintaining the integrity of various tissues. Mutations in this gene could cause ectopic bone formation in OPLL and DISH [34, 146].	21	rs1053312	c.2549G>A	R850H	0.27	0,11	0,018		hm		
FLNC	Involved in reshaping of the cytoskeleton. Mutations in this gene cause Myofibrillar myopathy-5 (MFM5 #601419) [373] and distal myopathy-4 (MPD4; MIM 614065), which shows a different pattern of muscle involvement [374].	7	rs2291569	c.4700G>A	R1567Q	0.06	0,01	0.999		ht		
AMER3	Is a positive regulator of Wnt-β-catenin signaling pathway.	2	rs72854996	c.1300C>G	L434V	0.05	1	0	ht			
PPP2R2D	Catalyze the removal of phosphate groups from serine and/or threonine residues by the hydrolysis of phosphoric acid monoesters. The protein belongs to the TGF- $\beta$ pathway.	10	rs34473884	c.1072G>A	G358S	0,18	0.03	0.173	hm	ht	ht	ht
ABCC6	Unknown function however during the last few years has been extensively related to ectopic calcification. Cause Pseudoxanthoma elasticum (PXE; MIM#264800), a disorder with calcification of the elastic fibres and in some cases can cause arterial calcification generalized of infancy type 2 (GACI2; MIM#614473).	16	rs41278174	c.3190C>T	R1064W	0.01	0	0.932			ht	

Abbreviations: Chr- chromosome, SNP-Single nucleotide polymorphism, AA- Amino acid, MAF- Minor allele frequency, SIFT- Sorting Intolerant From Tolerant, PolyPhen- Polymorphism Phenotyping v2, ht-heterozygous, hm-homozygous, NA- Not Applicable, *PLCG2*- Phospholipase C Gamma 2, *ALPL*- Alkaline Phosphatase, Liver/Bone/Kidney, *CASR*- calcium-sensing receptor, *FGF2*- Fibroblast growth factor 2, *COL11A2*- Collagen Type XI Alpha 2 Chain, *ENPP1*- ectonucleotide pyrophosphatase/phosphodiesterase 1, MGP- Matrix Gla Protein, VDR- Vitamin D Receptor, *BMP4*- Bone morphogenetic protein 4, *COL1A1*- Collagen Type I Alpha 1 Chain, *TGFβ1*- Transforming Growth factor Beta 1, *BMP2*- Bone morphogenetic protein 3, *PPP2R2D*- Protein Phosphatase 2 Regulatory Subunit B delta, *ABCC6* – ATP-binding cassete subfamily C, member 6.

*COL11A2* gene variants c.826G>A (E276K) and c.5165C>T (P1722L) are both missense; the c.826G>A (E276K) causes a glutamate substitution for a lysine at amino acid position 276. The amino acid glutamate is acidic and lysine is basic. The c.5165C>T (P1722L) variant is extremely rare (MAF of 0.01) and causes a proline substitution for a leucine in 1722 protein position. Both amino acids are non-polar. The logarithm PolyPhen (0.557; possibly damaging) in c.826G>A (E276K) and the SIFT (0.01; deleterious) in c.5165C>T (P1722L) suggests a damaging and deleterious effect, respectively on the COL11A2 protein. The c.826G>A (E276K) was identified in homozygosity in AZ1 and AZ3; and in heterozygosity in AZ2 and AZ4. The c.5165C>T (P1722L) was identified in heterozygosity in AZ4 patient (Table 6-5).

The variant c.2T>C (M1T) in the *VDR* gene is a missense mutation which causes a methionine substitution for a threonine in amino acid 1 of the protein. The amino acid change is from non-polar (methionine) to polar (threonine). According to the conservation analysis this amino acid position is totally conserved between all mammals analyzed (Supplementary figure 6-1), and the logarithms SIFT (0; deleterious) and PolyPhen (0.995; probably damaging) suggest a strong effect on the VDR protein. The variant was homozygous in AZ1 and AZ2; and heterozygous in AZ3 and AZ4 (Table 6-5).

The variant c.570A>T (R190S) in the *BMP2* gene is a missense which causes an arginine substitution for a serine in amino acid 190 of the protein. The amino acid change is from basic (arginine) to polar (serine). The amino acid position is totally conserved between all the vertebrates studied so far (Supplementary figure 6-1). In addition, the logarithms SIFT (0; deleterious) and PolyPhen (0.977; probably damaging) suggest a strong effect on the BMP2 protein. The variant was found in AZ1, AZ3 and AZ4 in heterozygosity (Table 6-5).

In the *FLNC* gene we found the missense variant c.4700G>A (R1567Q) which causes an arginine substitution for a glutamine at amino acid 1567 of the protein. The amino acid change is from a large, basic amino acid (arginine) to a medium and polar amino acid (glutamine). According to the conservation analysis this amino acid position is highly conserved in vertebrates (Supplementary figure 6-1), furthermore the logarithms SIFT score (0.01; deleterious) and PolyPhen (0.999; probably damaging) indicates that this variant has a damaging effect on the protein. The frequency of this variant is relatively low in Europe with a MAF of 0.06. The variant was heterozygous in AZ2 (Table 6-5).

The variant c.1072G>A (G327S) found in *PPP2R2D* gene is a missense variant which causes substitution of glycine for serine at amino acid 327 in the protein. These two amino acids are hydrophilic but glycine is non-polar and serine is polar. The amino acid position is totally
conserved in all vertebrates studied (Supplementary figure 6-1), and the variant has a low, deleterious, SIFT score (0.03) but the Polyphen score (0,173) does not corroborate its harmful effect. The frequency of this variant is high in Europe with a MAF of 0.18 and this variant was identified in all four DISH/CC patients used for WES; AZ1 was homozygous and AZ2, 3 and 4 were heterozygous (Table 6-5). The variant c.3190C>T (R1064W) in the *ABCC6* gene is a conserved missense variant that seems to be of fundamental importance since the algorithms SIFT score (0; deleterious) and PolyPhen (0.932; probably damaging) indicates that this mutation has a deleterious effect on the protein and is a rare variant (MAF of 0.01). The variant was heterozygous in AZ3 (Table 6-5). We found eight genetic variants, in heterozygous and/or homozygous states, in conserved positions in proteins associated with mineralization; four variants were in regions that are normally highly conserved across the vertebrates (*CASR* ((rs1801725), *BMP2* (rs235768), *FLNC* (rs2291569) and *PPP2R2D* (rs34473884)), and four other variants were in positions normally conserved in mammals (*VDR* (rs2228570), *BMP4* (rs17563), *COL1A1* (rs372029024) and *ABCC6* (rs41278174)) (Table 6-6).

Table 6-6. Conservation analysis of the variants identified in this study. In **bold** are represented the conserved variants found in at least 3 patients.

Patient		Mutational spectr	um
(sex)	Highly conserved	Conserved between mammals	Relaxed regions
AZ1 (M)	<i>BMP2</i> (rs235768/ht) <i>PPP2R2D</i> (rs34473884/hm)	<i>VDR</i> (rs2228570/hm) <i>BMP4</i> (rs17563/hm) <i>COL1A1</i> (rs372029024/hm)	<i>ALPL</i> (rs3200254), <i>ENPP1</i> (rs1044498), <i>MGP</i> (rs4236), <i>AMER3</i> (rs72854996), <i>COL11A2</i> (rs9277934).
AZ2 (F)	CASR (rs1801725/ht) FLNC (rs2291569/ht) PPP2R2D (rs34473884/ht)	<i>VDR</i> (rs2228570/hm)	CASR (rs1801726), COL6A1 (rs1053312), PLCG2 (rs374430619), ALPL (rs149344982), COL11A2 (rs9277934), ENPP1 (rs1044498).
AZ3 (F)	<i>BMP2</i> (rs235768/ht), <i>PPP2R2D</i> (rs34473884/ht)	<i>BMP4</i> (rs17563/hm) <i>ABCC6</i> (rs41278174/ht)	<i>PLCG2</i> (rs138158454), <i>ALPL</i> (rs3200254), <i>ENPP1</i> (rs1044498), <i>MGP</i> (rs4236), <i>VDR</i> (rs2228570), <i>TGFB</i> (rs55659002), <i>CASR</i> (rs1801726), <i>COL11A2</i> (rs9277934).
AZ4 (M)	CASR (rs1801725/ht) BMP2 (rs235768/ht), PPP2R2D (rs34473884/ht)	VDR (rs2228570/ht) BMP4 (rs17563/ht)	<i>PLCG2</i> (rs138158454), <i>COL11A2</i> (rs2229792), <i>MGP</i> (rs4236), <i>CASR</i> (rs1801726).

**Abbreviations:** M- male, F-female, ht-heterozygous, hm-homozygous, *PLCG2*- Phospholipase C Gamma 2, *ALPL*- Alkaline Phosphatase, Liver/Bone/Kidney, *CASR*- calcium-sensing receptor, *COL11A2*- Collagen Type XI Alpha 2 Chain, *ENPP1*- ectonucleotide pyrophosphatase/phosphodiesterase 1, MGP- Matrix Gla Protein, VDR- Vitamin D Receptor, *BMP4*- Bone morphogenetic protein 4, *COL1A1*- Collagen Type I Alpha 1 Chain, *BMP2*- Bone morphogenetic protein 2, *COL6A1*- Collagen Type VI Alpha 1 Chain, *FLNC*- Filamin C, *AMER3*- APC Membrane Recruitment Protein 3, *PPP2R2D*- Protein Phosphatase 2 Regulatory Subunit B delta, *ABCC6* – ATP-binding cassete subfamily C, member 6.

As can be seen in table 6-6, all patients have at least 2 highly conserved genetic variants in combination with other variants that are normally conserved in mammals.

#### 6.4.3. Association between variants and DISH/CC phenotype

#### 6.4.3.1. Segregation of variants

We selected 6 variants in genes *PLCG2* (c.2054+7G>A and c.3786G>C (K1260N)), *FLNC* (c.4700G>A (R1567Q)), *AMER3* (c.1300C>G (L434V)), *PPP2R2D* (c.1072G>A (G327S)) and *ABCC6* (c.3190C>T/R1064W) to verify the segregation within families of the investigated patients (Figure 6-2).



Figure 6-2. Segregation results with DISH/CC phenotype in families AZ1-4. WES sequencing patients: III:4 (AZ1), III-2 (AZ2), II:4 (AZ3) and III:6 (AZ4).

Most of the individuals were affected by DISH/CC disease and this made it difficult to verify segregation in these families. The selected variants, individually studied, did not segregate within families mainly because these families were uninformative and lacked unaffected individuals, and therefore the segregation analysis was not performed for all the candidate genes presented in table 6-5. Although not statistically significant, it was possible to evaluate the variants in *AMER3* and *FLNC* genes (Table 6-7).

Table 6-7. Family based association test (TDT test) results for variants of *AMER3* gene in AZ1 family and *FLNC* gene in AZ2 family.

Como	CND	Alleles		]	ГDT	
Gelle	SINF	M/m	TR:UT	OR	CHISQ	Р
AMER3	rs72854996	C/G	1:2	0.5	0.3333	0.5637
FLNC	rs2291569	G/A	2:0	NA	2	0.1573

**Abbreviations:** SNP- Single nucleotide polymorphism, M/m – major allele/minor allele, TDT- Transmission disequilibrium test, TR:NT-Transmitted/Untransmitted minor allele account, OR- odds ratio, P- pvalue, NA- not applicable.

#### 6.4.3.2. Case/control studies

The variants rs34473884, rs9277934 and rs2228570 in *PPP2R2D*, *COL11A2* and *VDR* genes, respectively, were present in all 4 WES patients. The variants rs1048201, rs235768, rs1044498 and rs17563 in *FGF2*, *BMP2*, *ENPP1* and *BMP4* genes, respectively were present in three of the four WES patients. All these variants had a high degree of conservation. The variants rs4236 in *MGP* gene and rs1801726 in *CASR* gene were present in three of the four WES patients however they were not conserved and therefore the case/control study of these genes was not performed. Seven variants were screened in a group of 55 DISH/CC patients and 36 controls and the results are indicated in table 6-8. The variant rs17563 in *BMP4* gene was found to be more frequent in DISH/CC group than in controls (p=0.009; OR=2.331) (Table 6.8).

Chr	Cono	CNID	Allele	MA	AF	OP	n voluo
Cm	Gene	5141	M/m	DISH/CC (N=55)	Controls (N=36)	UK	p-value
4	FGF2	rs1048201	C/T	0,155	0,139	1,133	0,771
6	COL11A2	rs9277934	G/A	0,373	0,389	0,934	0,826
6	ENPP1	rs1044498	A/C	0,191	0,208	0,897	0,773
10	PPP2R2D	rs34473884	G/A	0,255	0,181	1,550	0,243
12	VDR	rs2228570	T/C	0,382	0,389	0,971	0,924
14	BMP4	rs17563	T/C	0,473	0,278	2,331	0,009
20	BMP2	rs235768	A/T	0,264	0,250	1,074	0,837

 Table 6-8. Association study between seven variants from seven genes and DISH/CC phenotype.

 The risk allele are in bold.

**Abbreviations:** SNP- Single nucleotide polymorphism, M/m – major allele/minor allele, MAF- Minor allele frequency, OR- odds ratio, Chr- chromosome.

# 6.5. Discussion

Many human diseases appear to have a strong hereditary component. A large number of studies, using the WES technique, have reported variants and genes responsible for several monogenic diseases of unknown causes [163, 366, 375]. In this study, we used WES as a method to identify candidate genes for DISH/CC aetiology, and association studies to investigate specific variants. As expected, thousands of protein coding variants per patient were identified across each exome, which meant a huge number of variants had to be filtered and identification of the causative variant is like "finding a needle in a haystack". Consequently, different filtering strategies were used to find potential high risk variants in genes that could be associated with the DISH/CC phenotype. It is not easy to draw conclusions from segregation study since most of the individuals studied were DISH/CC affected making these families uninformative, however the association study performed in this study indicated that the SNP rs17563 in BMP4 gene was significantly associated with the DISH/CC phenotype. Bone morphogenetic proteins (BMPs) are multi-functional growth factors that belong to the transforming growth factor beta (TGFB) superfamily. BMP4 has the same origin as BMP2 and they are similar in structure and function. BMP2 and BMP4 are genes mapping to chromosomes 20 and 14, respectively that encode important regulators of bone formation [376]. In one study, Ono et al [377] found that BMP2 and TGF- $\beta$  played an important role in ossification in the conditions OPLL, a disorder that is very similar to, and can coexist with DISH [6], and ligamentum flavum, by acting on the progenitor cells in the ligament, causing them to proliferate, form cartilage and then ossify. BMP4 also seems to play a crucial role in the pathogenesis of OPLL, as demonstrated in a large scale study by Furushima and collaborators that found evidence of linkage with this gene [159]. Despite the association of BMP2 and BMP4 with ectopic bone formation, their association with OPLL is controversial, and there is both evidence in favor [160, 161] and against this idea [72]. Interestingly, Kan et al [378] produced a mice overexpressing BMP4 and observed the development of progressive postnatal heterotopic endochondral ossification, a phenotype similar to human Fibrodysplasia ossificans progressive (FOP). In rabbits, recombinant human BMP4 enhances posterior spinal fusion [379]. In the present study we identified two variants in BMP genes. The variant (R190S) in the BMP2 gene had a low SIFT score and a higher, PolyPhen, which predicted a deleterious and a damaging effect on the protein and this variant has previously been associated with the occurrence of OPLL [158] and with Immunoglobulin A nephropathy [380]. The missense variant c.455T>C (V152A) in the *BMP4* gene, which in this study was significantly more frequent in the DISH/CC group relative to the control group, was located in the translated region of BMP4 exon 5 and caused the substitution of a valine by an alanine at amino acid position 152, a position conserved between species (Supplementary figure 6-1). The structure and function of the protein was apparently not significantly affected by the substitution due to physicochemical similarities of the involved amino acids. Furthermore, the algorithms SIFT (0.57; tolerated) and PolyPhen (0.005; benign) did not suggest a strong effect on the protein. However, according to Capasso et al [381] the variant rs17563 affected BMP4 gene expression; this variant promotes a change in the structure of the mRNA, and the levels of BMP4 mRNA were significantly higher in carriers of this variant relative to non-carriers. Tanno et al [382] found that the mRNA and expression of BMP4 protein were significantly increased in OPLL cells derived from ossified spinal ligament when compared to non OPLL cells. This variant was associated with the occurrence and severity of OPLL in Chinese males [160] and has been reported to affect hip bone density in postmenopausal women [383].

Polymorphisms in other genes such as *COL6A1* [33, 146] and *FGF2* [147] have been r associated with DISH susceptibility, however these associations do not fully explain the disease. The *COL6A1* gene encodes an extracellular matrix protein that might serve as a scaffold for osteoblast or pre-osteoblast cells or chondrocytes that subsequently proceed to membranous or endochondral ossification [34]. According to several authors, this gene is strongly associated with OPLL and certain polymorphisms are considered helpful markers of OPLL [33, 146]. One of these polymorphisms, intron 32 (-29), associated with OPLL was also significantly associated with DISH Japanese patients but not with DISH Czech

patients[34]. In our study, we identified the variant rs1053312 in COL6A1 and it was homozygous in one WES patient, however no differences were found between DISH/CC patients and controls groups. This variant was already studied in OPLL disease but, as in our study, no association was found [146]. The other gene with a positive association with DISH is FGF2 which encodes a member of the fibroblast growth factor family and is involved in FGF signalling, which controls bone formation by regulating the expression of various genes involved in osteoblast differentiation and apoptosis [148], and thus abnormalities in this gene are closely related to ectopic ossification diseases. Disruption of the FGF2 gene results in decreased bone mass and bone formation [384]. Jun and colleagues [147] found association between 2 polymorphisms in FGF2 (rs1476217 and rs3747676) and DISH, however no other studies have confirmed this association. In our study we identified the 3'UTR variant rs1048201, which was heterozygous in three patients, however no differences were found between DISH/CC patients and controls. This variant (rs1048201) seems to contribute to osteoporosis susceptibility, most likely through their effects on altered binding affinity for specific miRNAs [385]. The 3'UTR region often contains regulatory elements that influence post transcriptional gene expression by MicroRNAs (miRNAs) [385, 386]. According to the miRNA related **SNP** database (miRNASNP v2.0, http://www.bioguo.org/miRNASNP2/online.php), this variant causes the loss of a binding site for hsa-miR-196a-3p miRNA. Probably in absence of the rs1048201 variant the has-miR-196a-3bp would bind optimally to FGF2 mRNA transcripts and negatively regulate protein expression by repressing mRNA translation and/or promoting mRNA degradation. On the other hand, the presence of rs1048201 variant may contribute to reduce binding efficacy between has-miR-196a-3bp and FGF2 and therefore would allow higher levels of FGF2 expression, which would be expected to stimulate osteoblastogenesis through osteoblasts formation and therefore bone formation. A recent study showed that the variant rs1048201 has also been reported to be associated with the risk of cleft palate [387], a disease which the etiopathogenesis is mostly unknown.

Normally, variants in the human genome with a deleterious effect on proteins are the basis for the development of diseases. However, all the *COL6A1* and *FGF2* variants reported in the literature with a significant association with DISH have a non-functional effect on protein and are common variants within the general population, which suggests that the gene variants found so far have a minor effect on the development of the disease. The findings of our study lead us to suggest, as described in OPLL [181], that DISH can also be influenced by the interaction of multiple gene variants in which *BMP4* gene could be one of them.

# 6.6. Conclusion

The variant rs17563 in *BMP4* gene was significantly associated with DISH/CC phenotype and may contribute to the development of DISH/CC phenotype. Further studies with a larger number of samples will be needed to clarify this association with the phenotype under study.

# 6.7. Future work

- 1) Explore how rs17563 in *BMP4* gene affects *BMP4* signaling in appropriate model systems.
- 2) Perform case/control studies in all the conserved genetic variants;
- 3) Investigate the role of HLA-DQA2 in this disorder by sequencing (typing) this gene in families and cohorts of patients/controls if necessary;
- 4) Design a customized panel (NGS) and by means of NGS sequence a cluster of genes involved in mineralization (including the genes identified in this study) in a cohort of patients and controls.

# **6.8. Supplementary material**

Supplementary table 6-1. List of genes and their accession transcript numbers, used for conservation analysis. Data was retrieved from the Ensembl genome database; accessed on November 2016).

Comos		Specie	
Genes	Human	Chimp	Dog
PLCG2	ENST00000564138.5	ENSPTRT00000015479.3	ENSCAFT00000031815.3
ALPL	ENST00000374840.7	ENSPTRT0000000592.2	ENSCAFT00000023578.3
CASR	ENST00000498619.3	ENSPTRT00000043996.4	ENSCAFT00000018760.3
COL11A2	ENST00000341947.6	ENSPTRT00000048564.4	ENSCAFT00000001409.4
ENPP1	ENST00000360971.6	ENSPTRT00000034356.3	ENSCAFT0000000001.3
MGP	ENST00000539261.5	ENSPTRT0000008732.4	ENSFCAT00000031714.1
VDR	ENST00000229022.7	Ni	ENSCAFT00000043473.2
BMP4	ENST00000245451.8	ENSPTRT00000011643.4	ENSCAFT00000023624.3
COL1A1	ENST00000225964.9	ENSPTRT00000017231.4	ENSCAFT00000026953.3
BMP2	ENST00000378827.4	ENSPTRT00000024606.3	ENSCAFT00000049690.1
COL6A1	ENST00000361866.7	ENSPTRT00000026156.3	ENSCAFT00000018918.3
FLNC	ENST00000325888.12	ENSPTRT00000036444.5	ENSCAFT0000002504.3
AMER3	ENST00000423981.1	ENSPTRT00000023124.3	ENSCAFT0000006747.2
PPP2R2D	ENST00000455566.5	ENSPTRT00000005829.4	ENSCAFT00000044416.1
ABCC6	ENST00000205557.11	ENSPTRT00000014398.4	ENSCAFT00000028908.3
Conos		Specie	
Genes	Mouse	Specie Chicken	Zebrafish
Genes PLCG2	Mouse ENSMUST0000081232.8	Specie Chicken ENSGALT0000050238.1	Zebrafish ENSDART0000021399.7
Genes PLCG2 ALPL	Mouse ENSMUST00000081232.8 ENSMUST00000030551.10	Specie Chicken ENSGALT00000050238.1 ENSGALT00000068960.1	Zebrafish ENSDART00000021399.7 ENSDART00000131101.2
Genes PLCG2 ALPL CASR	Mouse           ENSMUST00000081232.8           ENSMUST00000030551.10           ENSMUST00000063597.13	Specie           Chicken           ENSGALT00000050238.1           ENSGALT00000068960.1           XM_416491.5.1	Zebrafish ENSDART0000021399.7 ENSDART00000131101.2 ENSDART0000010934.8
Genes PLCG2 ALPL CASR COL11A2	Mouse           ENSMUST00000081232.8           ENSMUST00000030551.10           ENSMUST00000063597.13           ENSMUST00000087497.10	Specie           Chicken           ENSGALT00000050238.1           ENSGALT00000068960.1           XM_416491.5.1           Ni	Zebrafish ENSDART00000021399.7 ENSDART00000131101.2 ENSDART00000010934.8 ENSDART00000105754.4
Genes PLCG2 ALPL CASR COL11A2 ENPP1	Mouse           ENSMUST0000081232.8           ENSMUST00000030551.10           ENSMUST00000063597.13           ENSMUST00000087497.10           ENSMUST00000105520.7	Specie           Chicken           ENSGALT00000050238.1           ENSGALT00000068960.1           XM_416491.5.1           Ni           ENSGALT00000066498.1	Zebrafish           ENSDART0000021399.7           ENSDART00000131101.2           ENSDART0000010934.8           ENSDART00000105754.4           ENSDART00000127350.3
Genes PLCG2 ALPL CASR COL11A2 ENPP1 MGP	Mouse           ENSMUST0000081232.8           ENSMUST0000030551.10           ENSMUST0000063597.13           ENSMUST00000087497.10           ENSMUST00000105520.7           ENSMUST0000032342.2	Specie           Chicken           ENSGALT00000050238.1           ENSGALT00000068960.1           XM_416491.5.1           Ni           ENSGALT0000066498.1           ENSGALT00000019173.4	Zebrafish ENSDART0000021399.7 ENSDART00000131101.2 ENSDART0000010934.8 ENSDART00000105754.4 ENSDART00000127350.3 ENSDART00000149622.2
Genes PLCG2 ALPL CASR COL11A2 ENPP1 MGP VDR	Mouse           ENSMUST0000081232.8           ENSMUST0000030551.10           ENSMUST0000063597.13           ENSMUST00000087497.10           ENSMUST00000105520.7           ENSMUST0000032342.2           ENSMUST000000323119.14	Specie           Chicken           ENSGALT0000050238.1           ENSGALT0000068960.1           XM_416491.5.1           Ni           ENSGALT0000066498.1           ENSGALT00000066498.1           ENSGALT00000019173.4           ENSGALT00000071682.1	Zebrafish           ENSDART0000021399.7           ENSDART00000131101.2           ENSDART0000010934.8           ENSDART00000105754.4           ENSDART00000127350.3           ENSDART00000149622.2           ENSDART00000161892.1
Genes PLCG2 ALPL CASR COL11A2 ENPP1 MGP VDR BMP4	Mouse           ENSMUST0000081232.8           ENSMUST0000030551.10           ENSMUST0000063597.13           ENSMUST00000087497.10           ENSMUST00000105520.7           ENSMUST0000032342.2           ENSMUST000000323119.14           ENSMUST00000074077.11	Specie           Chicken           ENSGALT0000050238.1           ENSGALT0000068960.1           XM_416491.5.1           Ni           ENSGALT0000066498.1           ENSGALT00000019173.4           ENSGALT00000071682.1           ENSGALT00000020316.5	Zebrafish           ENSDART0000021399.7           ENSDART00000131101.2           ENSDART0000010934.8           ENSDART00000105754.4           ENSDART00000127350.3           ENSDART00000149622.2           ENSDART00000161892.1           ENSDART0000075150.4
Genes PLCG2 ALPL CASR COL11A2 ENPP1 MGP VDR BMP4 COL1A1	Mouse           ENSMUST0000081232.8           ENSMUST0000030551.10           ENSMUST0000063597.13           ENSMUST0000087497.10           ENSMUST00000105520.7           ENSMUST0000032342.2           ENSMUST00000023119.14           ENSMUST0000074077.11           ENSMUST0000001547.7	Specie           Chicken           ENSGALT00000050238.1           ENSGALT00000068960.1           XM_416491.5.1           Ni           ENSGALT0000066498.1           ENSGALT00000066498.1           ENSGALT00000019173.4           ENSGALT00000071682.1           ENSGALT00000071682.1           ENSGALT00000020316.5           XM_015273228.1.1	Zebrafish           ENSDART0000021399.7           ENSDART00000131101.2           ENSDART0000010934.8           ENSDART00000105754.4           ENSDART00000127350.3           ENSDART00000149622.2           ENSDART00000161892.1           ENSDART0000075150.4           ENSDART000009393.7
Genes PLCG2 ALPL CASR COL11A2 ENPP1 MGP VDR BMP4 COL1A1 BMP2	Mouse           ENSMUST0000081232.8           ENSMUST0000030551.10           ENSMUST0000063597.13           ENSMUST0000087497.10           ENSMUST00000105520.7           ENSMUST0000032342.2           ENSMUST00000032342.2	Specie           Chicken           ENSGALT0000050238.1           ENSGALT0000068960.1           XM_416491.5.1           XM_416491.5.1           ENSGALT0000066498.1           ENSGALT00000066498.1           ENSGALT00000019173.4           ENSGALT00000019173.4           ENSGALT00000020316.5           XM_015273228.1.1           ENSGALT00000065435.1	Zebrafish           ENSDART0000021399.7           ENSDART00000131101.2           ENSDART0000010934.8           ENSDART00000105754.4           ENSDART00000127350.3           ENSDART00000149622.2           ENSDART00000161892.1           ENSDART0000075150.4           ENSDART0000075150.4           ENSDART00000161892.1           ENSDART00000075150.4           ENSDART00000066657.1
Genes PLCG2 ALPL CASR COL11A2 ENPP1 MGP VDR BMP4 COL1A1 BMP2 COL6A1	Mouse           ENSMUST0000081232.8           ENSMUST0000030551.10           ENSMUST0000063597.13           ENSMUST0000087497.10           ENSMUST00000105520.7           ENSMUST0000032342.2           ENSMUST00000032342.2           ENSMUST000000147.7.11           ENSMUST0000001547.7           ENSMUST0000001547.7           ENSMUST0000001447.4	Specie           Chicken           ENSGALT0000050238.1           ENSGALT0000068960.1           XM_416491.5.1           XM_416491.5.1           Ni           ENSGALT0000066498.1           ENSGALT00000019173.4           ENSGALT00000019173.4           ENSGALT00000019173.4           ENSGALT00000019173.4           ENSGALT00000019173.4           ENSGALT00000019173.4           ENSGALT00000019173.4           ENSGALT00000019173.4           ENSGALT00000019173.4	Zebrafish           ENSDART0000021399.7           ENSDART00000131101.2           ENSDART0000010934.8           ENSDART00000105754.4           ENSDART00000127350.3           ENSDART00000149622.2           ENSDART00000161892.1           ENSDART00000075150.4           ENSDART00000161892.1           ENSDART00000161892.1           ENSDART00000161892.1           ENSDART00000075150.4           ENSDART00000161892.1           ENSDART00000161892.1           ENSDART00000161892.1
Genes PLCG2 ALPL CASR COL11A2 ENPP1 MGP VDR BMP4 COL1A1 BMP2 COL6A1 FLNC	Mouse           ENSMUST0000081232.8           ENSMUST0000030551.10           ENSMUST0000063597.13           ENSMUST0000087497.10           ENSMUST00000105520.7           ENSMUST0000032342.2           ENSMUST00000023119.14           ENSMUST00000023119.14           ENSMUST0000001547.7           ENSMUST0000001547.7           ENSMUST00000028836.6           ENSMUST0000001147.4           ENSMUST00000065090.7	Specie           Chicken           ENSGALT00000050238.1           ENSGALT00000068960.1           XM_416491.5.1           XM_416491.5.1           Ni           ENSGALT00000066498.1           ENSGALT00000066498.1           ENSGALT00000019173.4           ENSGALT0000001682.1           ENSGALT0000001682.1           ENSGALT0000005431.5           XM_015273228.1.1           ENSGALT0000005435.1           ENSGALT00000039669.3           NM_204573.1.1	Zebrafish           ENSDART0000021399.7           ENSDART00000131101.2           ENSDART0000010934.8           ENSDART00000105754.4           ENSDART00000127350.3           ENSDART00000149622.2           ENSDART00000161892.1           ENSDART0000015150.4           ENSDART00000075150.4           ENSDART00000166657.1           ENSDART00000166657.1           ENSDART00000110608.3           Ni
Genes PLCG2 ALPL CASR COL11A2 ENPP1 MGP VDR BMP4 COL1A1 BMP2 COL6A1 FLNC AMER3	Mouse           ENSMUST0000081232.8           ENSMUST0000030551.10           ENSMUST0000063597.13           ENSMUST0000087497.10           ENSMUST0000087497.10           ENSMUST0000032342.2           ENSMUST0000032342.2           ENSMUST00000023119.14           ENSMUST00000074077.11           ENSMUST0000001547.7           ENSMUST0000001547.7           ENSMUST0000001147.4           ENSMUST0000001147.4           ENSMUST00000052836.6           ENSMUST00000052836.7           ENSMUST0000001147.4	Specie           Chicken           ENSGALT0000050238.1           ENSGALT0000068960.1           XM_416491.5.1           XM_416491.5.1           Ni           ENSGALT0000066498.1           ENSGALT00000019173.4           ENSGALT00000019173.4           ENSGALT00000019173.4           ENSGALT00000019173.4           ENSGALT00000019173.4           ENSGALT0000000316.5           XM_015273228.1.1           ENSGALT00000039669.3           NM_204573.1.1           ENSGALT00000055960.1	Zebrafish           ENSDART0000021399.7           ENSDART00000131101.2           ENSDART0000010934.8           ENSDART00000105754.4           ENSDART00000127350.3           ENSDART00000149622.2           ENSDART00000161892.1           ENSDART00000075150.4           ENSDART00000161892.1           ENSDART00000161892.1           ENSDART00000161892.1           ENSDART00000161892.1           ENSDART00000161892.1           ENSDART00000161892.1           ENSDART00000161892.1           ENSDART00000166657.1           ENSDART00000110608.3           Ni           ENSDART00000149992.2
Genes PLCG2 ALPL CASR COL11A2 ENPP1 MGP VDR BMP4 COL1A1 BMP2 COL6A1 FLNC AMER3 PPP2R2D	Mouse           ENSMUST0000081232.8           ENSMUST0000030551.10           ENSMUST0000063597.13           ENSMUST0000087497.10           ENSMUST0000087497.10           ENSMUST0000032342.2           ENSMUST0000023119.14           ENSMUST00000023119.14           ENSMUST0000001547.7           ENSMUST0000001547.7           ENSMUST0000001417.4           ENSMUST0000001147.4           ENSMUST00000052670.10           ENSMUST00000052670.10	Specie           Chicken           ENSGALT0000050238.1           ENSGALT0000068960.1           XM_416491.5.1           XM_416491.5.1           Ni           ENSGALT0000066498.1           ENSGALT00000019173.4           ENSGALT00000019173.4           ENSGALT00000019173.4           ENSGALT00000019173.4           ENSGALT00000019173.4           ENSGALT0000003165.1           ENSGALT00000039669.3           NM_204573.1.1           ENSGALT00000055960.1           ENSGALT00000055960.1	Zebrafish           ENSDART0000021399.7           ENSDART00000131101.2           ENSDART0000010934.8           ENSDART00000105754.4           ENSDART00000127350.3           ENSDART00000149622.2           ENSDART00000161892.1           ENSDART00000161892.1           ENSDART0000016657.1           ENSDART00000166657.1           ENSDART00000166657.1           ENSDART00000149992.2           ENSDART00000149992.2           ENSDART00000149992.2

**Abbreviations:** Ni: note identified, *PLCG2*- Phospholipase C Gamma 2, *ALPL*- Alkaline Phosphatase, Liver/Bone/Kidney, *CASR*- calcium-sensing receptor, *COL11A2*- Collagen Type XI Alpha 2 Chain, *ENPP1*- ectonucleotide pyrophosphatase/phosphodiesterase 1, MGP- Matrix Gla Protein, VDR- Vitamin D Receptor, *BMP4*- Bone morphogenetic protein 4, *COL1A1*- Collagen Type I Alpha 1 Chain, *BMP2*- Bone morphogenetic protein 2, *COL6A1*- Collagen Type VI Alpha 1 Chain, *FLNC*- Filamin C, *AMER3*- APC Membrane Recruitment Protein 3, *PPP2R2D*- Protein Phosphatase 2 Regulatory Subunit B delta, *ABCC6* – ATP-binding cassete subfamily C, member 6.

c.3786G>C p.K1262N	ALPL	c.455G>A p.R152H	c.787T>C p.Y263H	CASR	c.2986G>T p.A986S	c.3061G>C p.E1021Q
VSNSKFYS VSNSKFYS VSNSKFYS VSNSKFYS INNSKFYS	Human (H. sapiens) Chimp (P.troglodyte Dog (C. I. familiaris) Mouse (M. musculu Chicken (G. gallus) Zebrafish (D. rerio)	TSILEWAKD. TSILEWAKD. S) TSILEWAKD. S) TSILEWAKD. TSILEWAKD. TSILEWAKD.	FKPRYKHSH FKPRYKHSH FKPRYKHSH FKPRYKHSH TKPASKVAK RVKEK-RGF	Human (H. sapien Chimp (P.troglody Dog (C. l. familiari Mouse (M. muscu Chicken (G. gallus, Zebrafish (D. rerio	s) PQKNAMAHR ( tes)PQKNAMAHR ( s) PQKSAAAPR ( lus)PQKNAMAHR ( ) PQKNAMANR ( ) ARNS	TRHEPLLP: TRHOPLLP: ARPCALLP NRHCALLP: MRHRALLA:
c.826G>A p.E276K	c.5165C>T E	NPP1	c.517A>C p.K173Q	MGP	.304A>G p.T102A	
YYDYD PPYY YYDYD PPYH  KPTPAPKTA	LGAPERRGG' Hui LGAPERRGG' Chi LGAPERRGG' Dog LGAPERRGG' Mo FGEDNOKFG: Chi Zeb	man (H. sapiens) mp (P.troglodyte: 5 (C. I. familiaris) use (M. musculus cken (G. gallus) rafish (D. rerio)	DCKDRGDCC H b) DCKDGGDCC Cl DCRDRGDCC Ca b) DCKTHNDCC M DCVENNDCC Cl DCVENNDCC Cl DCVKVGDCC Ze	uman (H. sapiens) K himp (P.troglodytes) K at (F. catus) Q louse (M. musculus) Q hicken (G. gallus) R ebrafish (D. rerio) P	RRGHK RRGAK RRGAKY RRNK QQLRANQQ	
c.2T>C	RMPA	c.455T>C	01141	c.3247G>T	RMP2	c.570A>T
P.MIT NEAMA; NEATA; DADMDTVAA;	Human (H. sapiens) Chimp (P. troglodytes, Dog (C. I. familiaris) Mouse (M. musculus) Chicken (G. gallus) Zebrafish (D. rerio)	PENEVISSA PENEVISSA PENEVISSA PENEVISSA PDNEVISSA PEDELISTA	Human (H. sapier Chimp (P.troglod) Dog (C. I. familiari Mouse (M. muscu Chicken (G. gallus Zebrafish (D. reric	p.A10831 (GPVGARGPA) (tes) GPVGARGPA (is) GPVGARGPA (lus) GPAGARGPA (Jus) GPAGARGPA (S) VPLVUVVLL (GPSG <mark>B</mark> RGPS)	Human (H. sapiens) Chimp (P.troglodyte Dog (C. I. familiaris) Mouse (M. musculu Chicken (G. gallus) Zebrafish (D. rerio)	FPVTRLLDT SFPVTRLLDT FPVTRLLDT SFPVTRLLDT DPVTRLLDT EPITRLLDT
c.2549G>A	FLNC	c.4700G>A	AMER3	c.1300C>G	PPP2R2D	c.1072G>A p.G358S
DTTKRFAKR DTTKRFAKR DTTKRFAKR ETTKVFAKR DTTKNFVKR EMTKDFSRM	Human (H. sapiens) Chimp (P.troglodytes Dog (C. l. familiaris) Mouse (M. musculus) Chicken (G. gallus)	TIDARDAGE TIDARDAGE TIDARDAGE TIDARDAGE	Human (H. sapien: Chimp (P.troglody Dog (C. I. familiari: Mouse (M. muscul Chicken (G. gallus)	s) SEGPTGPSP tes) SEGPUGPSP s) SEGPUGPSL lus) SEAPUGP-I NEVKINPVM	Human (H. sapiens) Chimp (P.troglodytes Dog (C. I. familiaris) Mouse (M. musculus, Chicken (G. gallus) Zebrafish (D. rerio)	CCWNCSDSA CCWNCSDSA CCWSCSDSA CCWNCSDSA CCWNCSDSA CCWNCSDGA CCWNCSD
c.3190C>T p.R1064W PDKLRSLLM PDKLRSLLM PDKLRSLLI PDKLRSLLT PDKLRSLLG PDCKLRSLLG						
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Supplementary figure 6-1. Analysis of sequence conservation among six vertebrates (some genes are not available in all species) of variants identified in candidate genes possibly associated with DISH/CC phenotype. The variant for FGF2 gene is not presented since it is a 3'prime region variant.

# CHAPTER VII: INVESTIGATING THE ROLE OF *ABCC6* GENE IN ECTOPIC CALCIFICATION

# 7. INVESTIGATING THE ROLE OF *ABCC6* GENE IN ECTOPIC CALCIFICATION

#### 7.1 Abstract

Ectopic calcification is a pathological process caused by deposition of calcium salts or inappropriate biomineralization in soft tissues such as the eyes, skin, arteries, entheses, and cartilage. Both DISH/CC and Ankylosing Spondylitis (AS) are bone forming conditions that share many common features and often coexist, and therefore it has been proposed that their susceptibility genes may overlap. The *ABCC6* gene has been extensively related to dermal ectopic calcification and has recently become a new member of the calcification regulators in mammals. *ABCC6* deficiency causes an imbalance in the homeostasis of multiple organs leading to BMP activation and consequently bone formation in these sites. The present study investigates the role of the *ABCC6* gene in the aetiology of the following axial and peripheral ectopic calcification disorders: DISH, CC and AS. We test the hypothesis that if *ABCC6* is involved in DISH, CC and AS it's mutated in affected individuals. A preliminary expression study of the *ABCC6* gene was performed to verify gene expression and abundance in cartilage tissues.

DNA from 55 patients with DISH/CC, 25 with AS and 36 controls without DISH/CC and or AS were obtained for a case control association study. All 31 *ABCC6* exons and the proximal *ABCC6* gene promoter were amplified by PCR and Sanger sequencing of the products and statistical analysis was performed using Plink V1.9. *ABCC6* gene expression was performed using a quantitative RT-PCR (qPCR) in 13 cartilage samples obtained from the femoral head during hip replacements. The data analysis was performed using the comparative Ct method ( $\Delta$ Ct).

We identified 31 sequence variants of the *ABCC6* gene that were classified according to character into: regulatory (n = 3), missense (n = 6), splice site (n = 3), synonymous (n = 5), intronic (n = 13) and 1 variant located in the 3'UTR region. Using Cochran-Armitage trend adjusted for gender, the variant rs12931472 located in exon 14 of *ABCC6* gene was statistically more frequent in AS than in controls, but only in females. Furthermore, a gender-specific protective association of the rare variant rs41278174 located on exon 23 of the *ABCC6* gene was detected in both DISH/CC and AS males. When comparing DISH/CC with AS we observed that the regulatory variant rs778876717 was statistically more frequent in AS than in DISH/CC. The expression studies by qPCR showed that *ABCC6* transcripts was very

low abundance in in cartilage tissues, and in the patients with DISH and CC the gene was upregulated in relation to a control patient.

Our findings support the hypothesis that the *ABCC6* gene plays a role in the axial ectopic calcification process and possibly reveals a gender specific interaction, however the statistical significance of our results is limited due to the relatively small cohort size, and larger cohort studies are required to further test this association. The gene expression studies on cartilage, although preliminary and not yielding statistically significant support reveals that differential expression could play a role in the disease process. To our knowledge, this is the first study to investigate the relationship between the *ABCC6* gene and diseases characterized by ossification of the axial skeleton, such as DISH and AS.

Keywords: ABCC6, DISH, CC, sequencing, qPCR.

## 7.2. Introduction

Ectopic calcification is caused by the inappropriate mineralization of soft tissues and is responsible for a significant number of disorders characterized by extraskeletal deposition of calcium and phosphate crystals [388]. Diffuse Idiopathic Skeletal Hyperostosis (DISH, MIM 106400), Chondrocalcinosis (CC, MIM 118600) and Ankylosing Spondylitis (AS, MIM 106300) are common rheumatic disorders characterized by ectopic calcification. DISH is characterized by the ossification of enthesis in the axial and peripheral skeleton, affecting the anterior longitudinal ligament [1] and CC by the deposition of calcium containing crystals in articular cartilage, synovial membranes and, less often, in periarticular soft tissues [341, 342]. AS is a chronic, multisystem inflammatory disorder characterized by inflammation and ankylosis of the sacroiliac joints and the axial skeleton. It is known that AS is strongly associated with HLA-B27 [235, 236], but other genes, including ERAP1 and IL23R, have also been associated with the disease [243]. Studies of HLA association with DISH were performed due to the similarity of the radiographic images with AS. The association between DISH and the HLA locus is unclear and some studies have refuted the results [136-141], while others have demonstrated association [142, 143]. The discrepancy between the results obtained by different studies may be explained by the coincidence of DISH and AS, or by difficulties in differentiating between these two disorders. The association of HLA antigens with DISH has never been proven and this association has now been shelved. The aetiology of DISH is still unknown, but several lines of evidence suggest that genetic factors might be involved in its aetiology [64, 77, 78]. A small number of cases of monogenic CC (CC MIM 118600) are caused by mutations in the *ANKH* gene [110, 343-345], which encodes a multipass transmembrane protein ANK that transports intracellular inorganic pyrophosphate (PPi) to the extracellular milieu [106]. The coexistence of DISH with CC is very common on Terceira Island, Azores and it was hypothesized that both diseases share common pathogenic mechanisms [23].

Little is known about the reasons why calcification or ossification occurs outside the skeleton and considerable efforts have been made to understand why such events occur. Three proteins have been identified as central regulators of extracellular PPi and Pi levels, tissue-nonspecific alkaline phosphatase (TNAP) which converts the inhibitor (PPi) into a promoter of mineralization (Pi) [183], ectonucleotide pyrophosphatase 1 protein (ENPP1), which generates PPi from nucleoside triphosphates (ATP) [93] and the Inorganic Pyrophosphate Transport Regulator (ANK) which mediates intracellular to extracellular channelling of PPi [106]. Several other genes have been associated with the regulation of the biomineralization process, such as the ABCC6 gene (ATP Binding Cassete Subfamily C Member 6), which maps to chromosome region 16p13.11 and encodes the transmembrane transporter MRP6 (Multidrug Resistance Protein 6) [389]. Inactivating mutations in this gene are the cause of most cases of Pseudoxanthoma elasticum (PXE; MIM#264800) and some cases of arterial calcification generalized of infancy type 2 (GACI2; MIM#614473)[390]. GACI is characterized by the calcification of the internal elastic lamina of muscular arteries and stenosis due to myointimal proliferation. Mutations in the ENPP1 gene are the main cause for the GACI cases [96], and can also cause PXE [390]. In GACI the ectopic tissue mineralization occurs as a result of reduced ENPP1 activity and consequently an increase in the Pi to PPi ratio. PPi is hydrolyzed by TNAP to generate P<sub>i</sub>, which is a component of hydroxyapatite crystal deposition and plays a role in the regulation of osteoblast differentiation [391]. PXE, in turn is characterized by aberrant mineralization of soft connective tissue with degeneration of the elastic fibers, involving primarily the eyes, the cardiovascular system, and the skin [392]. There have also been some studies associating polymorphisms in the *ENPP1* gene to a higher risk of developing ossification of the posterior longitudinal ligament (OPLL) [180].

There is a consensus that the *ABCC6* gene is mainly expressed in the liver and kidneys [393, 394], although two studies have reported its ubiquitous tissue expression [124, 395]. The majority of PXE causing mutations in *ABCC6* gene normally lead to an altered folding and/or protein stability leading to intracellular retention and reduced trafficking [112]. However, PXE is not caused by a lack of the functional MRP6 protein in the affected tissues but rather

by the absence of an unknown factor provided to the central circulation by an MRP6 dependent mechanism [396]. It is known that PPi is the central regulatory metabolite preventing matrix calcification in PXE, however the underlying molecular mechanism leading to reduction of PPi in PXE is unknown since the substrate(s) of this transporter remains to be elucidated. One theory suggested [129, 397] that MRP6 mediates the release of ATP directly from the liver into the circulation; ATP is converted into AMP and PPi and represents the main source of the mineralization inhibitor PPi in plasma. This explain why patients with PXE [397] and *Abcc6-/-* mice [129] have reduced PPi plasma levels compared to healthy individuals and wild type control mice, respectively. In the *Enpp1<sup>-/-</sup>* mouse model for GACI ectopic calcification also depends on plasma PPi levels and not on local PPi production [398]. The zebrafish mutant, *gräte* (*grt; abcc6ahu4958*) that carries a *abcc6a* mutated gene, shows signs of excessive hypermineralisation in the craniofacial and axial skeleton. In the zebrafish model the *abcc6a* gene is strongly expressed at the site of mineralisation and secretes ATP from cells increasing PPi locally, and this is unlike the mammalian model in which PPi is hepatically derived [113].

Although the PXE and GACI are considered two distinct diseases linked to *ABCC6* and *ENPP1* genes, respectively, the overlap of genotype and phenotype of both diseases suggests that the pathophysiology of both may derive from the same physiological mechanism or pathway [97, 390], probably involving reduced PPi [399]. Under physiological conditions PPi serves as a powerful anti-mineralization factor, preventing ectopic mineralization and dysregulated cellular production, degradation, and transport [400]. For instance, mutations in genes encoding known PPi-regulating enzymes like *ENPP1*, progressive ankylosis protein homolog (*ANKH*) and tissue-nonspecific alkaline phosphatase (*TNAP*) causes OPLL [195], CC [110] and Hypophosphatasia [401], respectively. Furthermore, a recent study showed that polymorphisms in *ENPP1*, *TNAP* and *ANKH* are important genetic risk factors contributing to PXE [130].

The *ABCC6* gene has recently joined the list of calcification regulators as a new member playing a role in pyrophosphate metabolism. The present investigation is a follow-up study of the chapter 6 of this thesis, which includes the genetic analysis of all *ABCC6* gene (exons, the adjacent introns and the proximal promoter region). We test the hypothesis that if *ABCC6* is involved in DISH, CC and AS its expression will be modified in affected individuals. A preliminary expression study of the *ABCC6* gene was performed to verify gene expression and abundance in cartilage.

#### 7.3. Material & methods

#### 7.3.1. Subjects

This study involved a group of 12 probands (patients who are the initial members of a family to come under study) with a diagnosis of DISH/CC (8 male, 4 female; age of onset around 40 years), a cohort of 55 unrelated Azorean patients with a diagnosis of DISH/CC (36 male, 19 female; age of onset around 40 years), a cohort of 25 unrelated Azorean patients with a diagnosis of Ankylosing Spondylitis (18 male, 7 female; mean current age, 61 years; range, 37-91) and 36 unrelated healthy controls with a similar ethnic background (16 male, 20 female; mean current age, 68 years; range, 57-102). Standard X rays, to evaluate the severity status of the disease, were taken from: knees, axial skeleton, wrists, hands, elbows, and pelvis from selected DISH/CC patients.

In order to evaluate variant frequency two representative populations of Terceira Island, one with 124 individuals (45 male, 79 female; mean age, 66 years; range, 35-100) (population 1) and the other with 375 individuals (85 male, 29 female; mean age, 55 years; range, 25-90) (population 2) were used. This study was approved by the HSEIT Ethics Committee and all participants provided informed consent.

From 2008 to 2013 a collection of samples from the coxofemoral articular cartilage was obtained from 53 patients undergoing total hip replacement surgery (34 male, 17 female; mean current age, 71 years; range, 47-93 years). Sterile cartilage sections (of approximately 3 mm diameter) were prepared with a scalpel and a cutter and flash-frozen in RNA later at - 80°C. Informed consent was obtained from these patients for use of their rejected tissue in research.

#### 7.3.2. Gene sequencing

#### 7.3.2.1. Mutation screening

Mutation screening was performed by Sanger sequencing of the 31 exons of *ABCC6*, including the exon–intron boundaries after polymerase chain reaction (PCR) amplification using previously described primers [308, 309], excluding the amplification of the two *ABCC6*-pseudogenes *ABCC6P1* and *ABCC6P2*, previously described [402] (primers sequences and PCR conditions available in the material and methods of this thesis). DNA from 12 DISH/CC probands was first sequenced followed by a group of 55 DISH/CC patients, 25 AS patients and 36 controls without DISH/CC disease.

Sequencing was carried out using ABI Big Dye chemistry on an ABI 3130xl automated sequencer (Applied Biosystems<sup>®</sup>) and genetic variants were screened with sequencing analysis and SeqScape (Applied Biosystems<sup>®</sup>) using as reference the NC\_000016.10 sequence (see the material and methods section of this thesis for more detail).

The functional significance and the potential effect of each variant on the protein was subsequently explored in following databases: dbSNP the (https://www.ncbi.nlm.nih.gov/projects/SNP/, Human Gene Mutation Database (HGMD) (http://www.hgmd.cf.ac.uk/ac/index.php), Human Splicing Finder (http://www.umd.be/HSF3/HSF.html), Ensembl (http://www.ensembl.org/index), making use PolyPhen-2 Phenotyping of various algorithms, such as (Polymorphism v2) (http://genetics.bwh.harvard.edu/pph2/) (benign, [0-0.2], possibly damaging (0.2-0.85), and probably damaging [0.85-1]) and SIFT (Sorting Intolerant From Tolerant) (damaging if less than 0.05). The Minor Allele Frequencies (MAF) of each variant were also analyzed.

Protein conservation analysis was performed using ClustalW (<u>http://www.genome.jp/tools/clustalw/</u>) to compare homologous amino acid sequences among multiple vertebrates at the sites where the variations occur. The accession numbers of each transcript are available in table 7-1.

Species	Accession numbers
Human	ENST00000205557.11
Chimpanzee	ENSPTRT00000014398.4
Mouse	ENSMUST0000002850.7
Cow	ENSBTAT00000050284.3
Dog	ENSCAFT00000028908.3
Chicken	ENSGALT00000048627.1
Xenopus	ENSXETT00000042610.2
Spotted gar	ENSLOCT0000008702.1

 Table 7-1. List accession transcript numbers for ABCC6 gene, used for conservation analysis.

 Data was retrieved from the Ensembl genome database; accessed on Jully 2015.

#### 7.3.2.2. Statistical analysis

To assess the difference in allele frequencies between the 55 patients with DISH/CC and the 36 control individuals and between males and females a Fisher exact test was used. The same test was also used to assess the difference in the AS patients and controls. The Fisher exact test was calculated for odds ratios (OR) (95% confidence interval) and corresponding p-values.

To determine the association between the DISH/CC disease and allele variants other tests were employed: Cochran-Armitage trend, dominant and recessive gene action tests with 1 degree of freedom and genotypic test with 2 degrees of freedom. For all the statistical tests used a p-value of  $\leq 0.05$  was considered statistically significant. All statistical analysis were performed using PLINK software [354].

To compare the two groups of patients (DISH/CC and AS) a contingency table analysis for calculation of Fisher's exact probability test was performed using the VassarStats: Website for Statistical Computation (<u>http://vassarstats.net/tab2x2.html</u>).

#### 7.3.3. Gene expression

#### 7.3.3.1.RNA isolation and quality control

Cartilage samples were prepared using a combination of physical, chemical and enzymatic treatments. In brief, coxofemoral articular cartilage sections were minced, frozen, and pulverized in liquid nitrogen with a mortar and pestle. The tissue powder was placed in Trizol and total RNA was isolated using the Trizol RNA isolation protocol, developed by Chomezynski and Sacchi [310].

Purification of RNA samples was performed an RNeasy MinElute Cleanup kit (Qiagen) according to the manufacturer's instructions, a DNase (Deoxyribonuclease I) digestion and ethanol wash were subsequently performed. RNA integrity was assessed using a NanoVue spectrophotometer (GE Healthcare) and an Agilent 2100 Bioanalyser and RNA 6000 Nano LabChip (Agilent Technologies).

#### 7.3.3.2 Reverse transcription- RT-PCR

RNA (100 ng) samples with RNA Integrity Number (RIN) above 4 were reverse-transcribed using High Capacity cDNA Reverse Transcription kit (Thermofisher) following the manufacturer's instructions. To verify the efficiency of RT-PCR the cDNA from human cartilage was used as a template for PCR amplification of the  $\beta$ -actin gene using a PCR System 9700 (Applied Biosystems). The  $\beta$ -actin amplicon of 249 bp was visualized on 1.7% agarose gel (sequence primers and PCR conditions available in material and methods of this thesis).

#### 7.3.3.3.Quantitative RT-PCR (qRT-PCR)

Gene expression evaluation was performed using quantitative RT-PCR (qRT-PCR) with TaqMan chemistry. FAM-labeled TaqMan Gene Expression Assays (Applied Biosystems)

were used for the target gene *ABCC6* (*ABCC6*, Hs00184566\_m1) and the primers include the 17-18 exon junction of this gene. The housekeeping gene *YWHAZ* (Tyrosine 3-Monnoxygenase/Tryptophan 5-Monooxygenase Activation Protein Zeta) is one of the most stable genes in cartilage tissues and is considered the best normalizer [403, 404] for use in this type of tissues. FAM-labeled TaqMan Gene Expression Assays (Applied Biosystems) were used for the internal control (*YWHAZ*, Hs00237047\_m1), and the primers include the 1-2 exon junction of this gene.

The qPCR was performed for 20  $\mu$ l final reactions using 20X TaqMan Gene Expression Master mix and 20X TaqMan Gene Expression assay for *ABCC6* and *YWHAZ* genes. Reactions were performed using the Applied Biosystems 7500 Fast Real-Time PCR System following the program: 2 min at 50°C, 10 min at 95°C, and 40 cycles repeating denaturation 15 s at 95°C, and annealing for 1 min at 60°C. Duplicate reactions were used for each sample and 400ng of synthesized cDNA was used to amplify the target gene and 200 ng to amplify the control gene.

Threshold cycle (Ct) values were determined using 7500 System Software V2.0.6 (Applied Biosystems) and data were further analyzed with Microsoft Office Excel 2013 (Microsoft Corporation). The data analysis was performed using the comparative Ct method ( $\Delta$ Ct) [405].  $\Delta$ Ct values were used to measure gene expression, which was normalized using *YWHAZ* expression levels. The expression study was preliminary and because of low sample number it was not be possible to carry out statistical analysis.

#### 7.3.3.4. Typing ABCC6 gene variants

Functionally relevant variants were considered to be those that were located in regulatory regions such as; splice sites and missense variants in the promoter region, exons 10, 14,15, 22, 23, 25 and 27. The presence and location of mutations in the *ABCC6* gene were procured in the DNA of all patients selected for the expression studies (13 individuals; 9 males, 4 females; mean age of surgery, 66 years; range, 47-76 years).

## 7.4. Results

#### 7.4.1. Sequencing

#### 7.4.1.1. ABCC6 variants

The coding region of the *ABCC6* gene was sequenced in a group of 12 DISH/CC probands and the variants identified are indicated in table 7-2. Thirty-one genetic variants were identified in the *ABCC6* gene; 3 located in regulatory regions, 3 in splice sites, 6 missense variants, 5 synonymous, 13 intronic and 1 variant located in the 3'UTR (Table 7-2).

Overall, three variants were found in the *ABCC6* promoter region variant rs28529549, and rs565625561 were present in P8 and rs778876717 were present in P1 and P9. The MAF values for the variants were not available in Ensembl. In the Human Gene Mutation Database the rs28529549 variant is associated with PXE and has a protective effect [406]. The splice site variants rs55778939 in P1, rs9940089 in P1-9 and P11 and rs41278172 in P8 probably have no impact on splicing. Splice variant rs41278172 is rare (MAF 0.01), rs55778939 is relatively rare (MAF 0.02) and rs9940089 is a frequent variant (MAF 0.18) (Table 7-2). Of the 6 missense variants, three of them are rare, with a MAF of 0.01. Variants rs41278174 in P1 and P9 and rs613450537 and rs2606921 in P8 were extremely rare and had an unknown MAF as there was insufficient data to establish population frequency since it was identified in only 3 of 114594 alleles (ExAc\_Aggregated\_Populations), indicating that it was unquestionably very rare (MAF 0.00003023). The variant rs41278174 (R1064W, P1 and P8) causes the substitution of arginine by tryptophan at amino acid 1064 in the protein and causes a shift from large and basic arginine to large and aromatic tryptophan.

Exon/ Intron modification	Variant	SNP	Type of variant	SPL	MAF	SIFT	PolyPhen	P1	P2	P3	P4	P5	P6	P7	P8	Р9	P10	P11	P12
Promoter	c219A>C	rs28529549	RR	?	?	NA	NA								ht				
Promoter	c132C>T	rs565625561	RR	?	?	NA	NA								ht				
Promoter	c127C>T	rs778876717	RR	?	?	NA	NA	ht								hm			
intron3	c.345+26C>T	rs56019914	Intronic		0.03	NA	NA								ht				
i3	c.346-6G>A	rs55778939	Splicing		0.02	NA	NA	ht											
E4	c.473C>T (A158V)	rs2606921	Missense	as	?	0.22	0.003								ht				
i4	c.474+13G>A	rs111339199	Intronic		0.01	NA	NA	ht								ht			
i8	c.998+99G>A	rs150203830	Intronic		0.16	NA	NA	ht		ht	ht			?	ht		hm	ht	ht
i9	c.1176+243C>T	rs2283503	Intronic		0.36	NA	NA	ht	hm	ht	?					hm		ht	ht
i9	c.1177-94T>C	rs12935658	Intronic		0.32	NA	NA				ht	hm	hm	hm	ht				
i9	c.1177-89G>A	rs12935089	Intronic		0.32	NA	NA				ht	hm	hm	hm	ht				
E10	c.1233T>C (N411N)	rs9930886	Synonymous	as	0.28	NA	NA				ht	ht	ht	hm	ht				
E10	c.1245G>A (V415V)	rs9940825	Synonymous	as	0.23	NA	NA				ht	ht	ht	hm	ht				
i10	c.1338+7C>G	rs9940089	Splicing		0.18	NA	NA	ht	hm	ht	ht	hm	hm	hm	ht	ht		ht	
i10	c.1338+20C>T	rs12929920	Intronic		0.27	NA	NA	ht	hm	ht	ht	hm	ht	hm	ht	ht		ht	
i10	c.1338+62C>G	rs58394656	Intronic		0.17	NA	NA	ht		ht	ht	ht			ht	ht	hm	ht	hm
i11	c.1432-41A>G	rs2239322	Intronic		0.32	NA	NA	ht	ht	hm						hm		ht	
i12	c.1635+48C>T	rs55707615	Intronic		0.32	NA	NA	ht	ht	hm						hm		ht	
E14	c.1841T>C (V614A)	rs12931472	Missense		0.37	0.77	0	ht	ht		ht	ht	ht	hm	ht			ht	
i14	c.1868-57G>A	rs41278182	Intronic		0.30	NA	NA	ht	ht	hm						hm		ht	
E15	c.1890C>G T630T	rs8058696	Synonymous	as	0.33	NA	NA	ht	ht		ht	ht	hm	hm	ht			ht	
E15	c.1896C>A (H632Q)	rs8058694	Missense	as	0.36	0.59	0.001	ht	ht		ht	ht	hm	hm	ht			ht	
E19	c.2490C>T (A830A)	rs9924755	Synonymous	as	0.15	NA	NA	ht				ht	hm					ht	
E22	c.2835C>T (P945P)	rs2856585	Synonymous	as	0.12	NA	NA				ht								ht
E22	c.2836C>A (L946I)	rs61340537	Missense	as	0.01	0.42	0.013								ht				
E23	c.3190C>T (R1064W)	rs41278174	Missense	as	0.01	0	0.932	ht								ht			
i24	c.3507-3C>T	rs41278172	Splicing		0.01	NA	NA								ht				
E27	c.3803G>A (R1268Q)	rs2238472	Missense	as	0.19	0.19	0.004	ht	hm		hm			ht	ht	ht			ht
i28	c.4042-30C>T	rs2066738	Intronic		0.18	NA	NA		hm	ht						ht			
i30	c.4404-31A>G	rs212097	Intronic	as	0.28	NA	NA	ht	ht		hm	ht		ht	hm	ht	hm		hm
3'UTR	c.*17G>A	rs3902401	3'UTR	?	0.07	NA	NA								ht				ht

Table 7-2. *ABCC6* variants identified in a group of 12 DISH/CC probands (P1-12) and information about their functional significance (assessed on December 2016). The effect on splicing is indicated in Column SPL and absence of information stands for 'no affect splicing'.

Abbreviations: SNP - Single nucleotide polymorphism, SPL- splicing, MAF - Minor Allele frequency, SIFT - Sorting Intolerant From Tolerant, P-proband, E-exon, iintron, RR-Regulatory region, as - altered splicing NA - not applicable, ht - heterozygous, h - homozygous and ? - unknown genotype, as- altered splicing

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According to the ensemble database this nucleotide position is totally conserved in mammals (Figure 7-1). This variant seems to have a fundamental relevance since its localization indicates a potential alteration of splicing and the algorithms SIFT score (0; deleterious) and PolyPhen (0.932; probably damaging) indicates a deleterious and a damaging effect on the protein (Table 7-2).

The positions of variants in the topology model of MRP6 protein and the conservation of the related amino acids are shown in figure 7-1. One variant occurs in extracellular domain (p.A158V), three variants in the transmembrane domain (P945P, L946I and R1064W), while seven were located in the cytoplasmic region (N411N, V415V, V614A, T630T, H632Q, A830A and R1268Q).



Protein region	Ext			СТ	D				TMD	i	CTD
AA change in human	A158V	N411N	V415V	V614A	T630T	H632Q	A830A	P945P	L946I	R1064W	R1268Q
Human	A	N	v	v	Т	н	Α	Р	L	R	R
Chimpanzee	-	N	v	А	т	н	А	Ρ	L	R	R
Mouse	G	N	v	G	S	н	Т	Ρ	L	R	R
Cow	G	N	v	А	S	Q	А	Ρ	L	R	R
Dog	G	N	v	А	R	н	А	Ρ	L	R	R
Chicken	R	N	v	-	1	R	Т	Ρ	L	К	R
Xenopus	-	Ν	Т	S	т	R	R	W	Υ	Μ	Q
Spotted gar	E	N	А	Ν	V	E	Е	А	L	К	R

Figure 7-1. Predicted transmembrane protein topology of MRP6 (Protter) with locations of human variants and comparison with the amino acid in the equivalent position in other vertebrate species. In the protein structure the amino acids positions affected by a missense variant are highlighted in red and the synonymous variants are indicated in green. Ext: extracellular, CTD: cytoplasmatic domain and TMD: Transmembrane domain.

#### 7.4.1.2. Case/control study

In order to perform a case/control study we selected functionally relevant variants, namely those that were located in regulatory regions including splice sites and missense variants and assessed their distribution in two groups of patients with DISH/CC and AS and in a group of unaffected controls. The 12 SNPs identified were in HWE and the results are shown in table 7-3. The missense variant rs12931472 in exon 14 was found in all AS females; 3 were heterozygous and 4 were homozygous (Supplementary table 7-1), however a fisher exact test did not give statistically significant p-value between AS females and controls females (Table 7-3). However, a significant difference was found between AS and control females when a Cochran-Armitage trend test (p=0.03, CHISQ=4.62) and allelic test (p=0.04, CHISQ=4.09) was used (Table 7-4). The missense variant rs41278174 in exon 23 was not found in the AS group (Supplementary table 7-1). Using the Cochran-Armitage trend and allelic tests the rs41278174 variant was significantly less frequent in both DISH/CC and AS males relative to the control males, where it was more frequent (Table 7-4).

						MAF					FISHER EXACT TEST											
CND	eles	D	ISH/CO		C	ONTRO	LS		AS			DIS	SH/CC	vs Cont	rols				AS vs (	Control	s	
SNr	АПс	All	F	М	All	F	М	All	All F M		A	.11	]	F	N	1	All		]	7	М	
		N=55	N=19	N=36	N=36	N=22	N=14	N=25	N=7	N=18	OR	Р	OR	Р	OR	Р	OR	Р	OR	Р	OR	Р
rs28529549	A/C	0.06	0.05	0.07	0.03	0	0.07	0.02	0	0.03	2.38	0.49	NA	0.21	0.97	1	0.71	1	NA	1	0.37	0.58
rs565625561	C/T	0.03	0	0.04	0.01	0	0.04	0.02	0	0.03	1.99	1	NA	1	1.17	1	1.45	1	NA	1	0.77	1
rs778876717	C/T	0.06	0.11	0.04	0.11	0.09	0.14	0.14	0.07	0.17	0.54	0.28	1.18	1	0.26	0.09	1.30	0.78	0.77	1	1.20	1
rs55778939	G/A	0.08	0.05	0.10	0.06	0.05	0.07	0.04	0.07	0.03	1.52	0.57	1.17	1	1.40	1	0.71	1	1.62	1	0.37	0.58
rs2606921	C/T	0.02	0	0.03	0.01	0	0.04	0.06	0	0.08	1.32	1	NA	1	0.77	1	4.53	0.30	NA	1	2.46	0.63
rs9940089	C/G	0.29	0.29	0.29	0.32	0.32	0.32	0.22	0.29	0.19	0.87	0.74	0.87	0.81	0.87	0.81	0.60	0.31	0.86	1	0.51	0.26
rs12931472	T/C	0.51	0.47	0.50	0.46	0.52	0.43	0.54	0.21	0.44	1.23	0.55	0.82	0.82	1.33	0.66	1.39	0.46	0.25	0.06	1.07	1
rs8058694	C/A	0.48	0.50	0.47	0.40	0.43	0.36	0.48	0.64	0.42	1.38	0.36	1.32	0.66	1.61	0.37	1.37	0.46	2.37	0.22	1.29	0.80
rs61340537	C/A	0.01	0	0.01	0.01	0.02	0	0.04	0	0.06	0.65	1	0	1	NA	1	2.96	0.57	0	1	NA	0.50
rs41278174	C/T	0.04	0.08	0.01	0.06	0.02	0.11	0	0	0	0.64	0.71	3.69	0.33	0.12	0.07	0	0.14	0	1	0	0.08
rs41278172	C/T	0.01	0	0.01	0.01	0.02	0	0.04	0	0.06	0.65	1	0	1	NA	1	2.96	0.57	0	2.92	NA	0.50
rs2238472	G/A	0.22	0.24	0.21	0.21	0.20	0.21	0.24	0.43	0.17	1.06	1	1.21	0.79	0.96	1	1.20	0.82	2.92	0.16	0.73	0.75

Table 7-3. The results of the association study of genetic variants found in the *ABCC6* gene in Azorean patients with DISH/CC and AS compared to the controls. The minor allele is represented in **bold**.

Abbreviations: SNP- Single nucleotide polymorphism, AS- Ankylosing Spondylitis, MAF- Minor allele frequency, OR- odds ratio, P- pvalue, N- number of individuals, NA- not applicable, vs: versus, F- Female, M- Male.

Table 7-4. Association study of the genetic variants in the *ABCC6* gene in DISH/CC and AS patients compared to the controls.

	$\hat{\mathbf{C}}$	(	DISH/	/CC (A2	1/A2)	Cont	Controls (A1/A2)		A2) AS (A1/A2) DISH/CC vs Controls						AS vs Co	ontrols								
(D)D	( <b>A</b> ]	(A2			-			-			-	$\mathbf{ST}$	All		Μ		F		All		Μ		F	
SNP	Allele	Allele	All N=110	M N=72	F N=38	All N=72	M N=28	F N=44	All N=50	M N=36	F N=14	ΞL	CHISQ	Р	CHISQ	Р	CHISQ	Р	CHISQ	Р	CHISQ	Р	CHISQ	Р
rs28520540	C	Δ	7/103	5/67	2/36	2/70	2/26	0/44	1//0	1/35	0/14	Т	1.26	0.26	0	0.97	2.44	0.12	0.08	0.78	0.71	0.40	NA	NA
1820327347	C	Л	//105	5/07	2/30	2/70	2/20	0/44	1/4/	1/55	0/14	А	1.19	0.28	0	0.97	2.37	0.12	0.07	0.79	0.67	0.41	NA	NA
rs565625561	т	С	3/107	3/69	0/38	1/71	1/27	0/44	1/49	1/35	0/14	Т	0.37	0.54	0.02	0.89	NA	NA	0.07	0.79	0.03	0.85	NA	NA
10000020001	-	0	0/10/	0,07	0,20	1, , 1		0, 11	17.12	1,00	0/1.	А	0.36	0.55	0.02	0.89	NA	NA	0.07	0.79	0.03	0.86	NA	NA
rs778876717	Т	С	7/103	3/69	4/34	8/64	4/24	4/40	7/43	6/30	1/13	Т	1.43	0.23	3.43	0.06	0.05	0.82	0.27	0.61	0.08	0.77	0.06	0.81
												А	1.30	0.25	3.17	0.07	0.05	0.83	0.23	0.63	0.07	0.79	0.05	0.82
rs55778939	А	G	9/101	7/65	2/36	4/68	2/26	2/42	2/48	1/35	1/13	Т	0.42	0.52	0.14	0.71	0.02	0.88	0.16	0.69	0.71	0.40	0.15	0.69
												А	0.45	0.50	0.16	0.69	0.02	0.88	0.15	0.70	0.67	0.41	0.15	0.70
rs2606921	Т	С	2/108	2/70	0/38	1/71	1/27	0/44	3/47	3/33	0/14	Т	0.05	0.82	0.05	0.83	NA	NA	2.05	0.15	0.65	0.42	NA	NA
												Α	0.05	0.82	0.04	0.86	NA	NA	1.98	0.16	0.61	0.44	NA	NA
rs9940089	С	G	32/78	21/51	11/27	23/49	9/19	14/30	11/39	7/29	4/10	Т	0.15	0.70	0.08	0.78	0.06	0.80	1.23	0.27	1.35	0.24	0.04	0.84
												А	0.17	0.68	0.09	0.77	0.08	0.78	1.45	0.23	1.35	0.24	0.05	0.82
rs12931472	Т	С	56/54	36/36	18/20	33/39	12/16	23/21	27/23	16/20	3/11	T	0.46	0.50	0.40	0.53	0.22	0.64	0.89	0.35	0.02	0.89	4.62	0.03
												A	0.45	0.50	0.41	0.52	0.20	0.66	0.79	0.37	0.02	0.90	4.09	0.04
rs8058694	А	С	53/57	34/38	19/19	29/43	10/18	19/25	24/26	15/21	9/5	1	1.07	0.30	1.06	0.30	0.37	0.54	0.74	0.39	0.27	0.61	1.83	0.18
												А	1.10	0.29	0.40	0.50	0.38	0.54	0.72	0.40	0.23	0.03	0.22	0.17
rs61340537	А	С	1/109	1/71	0/38	1/71	0/28	1/43	2/48	2/34	0/14	1	0.09	0.76	0.40	0.53	0.89	0.35	0.80	0.55	1.00	0.20	0.33	0.57
												Т	0.09	0.70	4 76	0.33	1.46	0.33	2.97	0.30	4.26	0.21	0.32	0.57
rs41278174	Т	С	4/106	1/71	3/35	4/68	3/25	1/43	0/50	0/36	0/14	A	0.38	0.54	4.57	0.03	1.39	0.23	2.97	0.09	4.05	0.04	0.32	0.57
	_	~										Т	0.09	0.76	0.40	0.53	0.89	0.35	0.86	0.35	4.66	0.20	0.33	0.57
rs41278172	Т	С	1/109	1/71	0/38	1/71	0/28	1/43	2/48	2/34	0/14	A	0.09	0.76	0.39	0.53	0.87	0.35	0.84	0.36	1.61	0.21	0.321	0.57
		~			0.005			0.1 <b>0</b> F	10/0-		<i>c.</i> (0)	Т	0.02	0.88	0	0.95	0.12	0.73	0.17	0.69	0.24	0.62	2.75	0.10
rs2238472	А	G	24/86	15/57	9/29	15/57	6/22	9/35	12/38	6/30	6/8	А	0.03	0.87	0	0.95	0.12	0.72	0.17	0.68	0.23	0.63	2.78	0.10

Abbreviations: SNP- Single nucleotide polymorphism, AS- Ankylosing Spondylitis, M-Males, F-females, T-trend, A- allelic, P- p-value, N- number of individuals.

To compare the variant frequency between DISH/CC and AS we used a Fisher Exact Probability test (Table 7-5).

	Allele	Allele	e DISH/CC (A1/A2)				AS (A1/A	.2)	p-value one tailed/two tailed			
SNP	(A1)	(A2)	All N=110	M N=72	F N=38	All N=50	M N=36	F N=14	All	М	F	
rs28529549	С	А	7/103	5/67	2/36	1/49	1/35	0/14	0.22/0.44	0.34/0.66	0.53/1	
rs565625561	Т	С	3/107	3/69	0/38	1/49	1/35	0/14	0.62/1	0.59/1	1/1	
rs778876717	Т	С	7/103	3/69	4/34	7/43	6/30	1/13	0.10/0.13	0.03/0.05	0.59/1	
rs55778939	А	G	9/101	7/65	2/36	2/48	1/35	1/13	0.27/0.50	0.18/0.26	0.61/1	
rs2606921	Т	С	2/108	2/70	0/38	3/47	3/33	0/14	0.18/0.33	1/1	0.21/0.33	
rs9940089	С	G	32/78	21/51	11/27	11/39	7/29	4/10	0.23/0.44	0.20/0.35	0.63/1	
rs12931472	Т	С	56/54	36/36	18/20	27/23	16/20	3/11	0.42/0.74	0.37/0.68	0.08/0.11	
rs8058694	А	С	53/57	34/38	19/19	24/26	15/21	9/5	0.56/1	0.37/0.68	0.27/0.53	
rs61340537	А	С	1/109	1/71	0/38	2/48	2/34	0/14	0.23/0.23	0.67/1	1/1	
rs41278174	Т	С	4/106	1/71	3/35	0/50	0/36	0/14	0.22/0.31	0.66/1	0.21/0.31	
rs41278172	Т	С	1/109	1/71	0/38	2/48	2/34	0/14	0.23/0.23	0.26/0.55	1/1	
rs2238472	А	G	24/86	15/57	9/29	12/38	6/30	6/8	0.45/0.84	0.41/0.80	0.16/0.30	

Table 7-5. Frequency comparison of the genetic variants found in the coding exons of the *ABCC6* gene between the DISH/CC and AS groups.

**Abbreviations:** SNP- Single nucleotide polymorphism, AS- Ankylosing Spondylitis, M-Males, F-females, T-trend, A- allelic, OR- odds ratio, P- pvalue, N- number of individuals.

The frequency of the variant rs778876717 was significantly different between the DISH/CC and AS cohorts, particularly in males and it was more frequent in AS males than in DISH/CC males (Table 7-5). The rs778876717variant is located in the promotor region and no frequency or population information exists for this variant.

#### 7.4.1.3 SNP frequencies

The variant rs41278174 (R1064W) was found in ten individuals (in two probands, 4 DISH/CC patients and 4 healthy controls). Since rs41278174 is extremely rare (Table 7-2) we procured for this variant in two representative populations of Terceira Island that contained 124 and 385 individuals to verify if the frequency is also higher in these groups (Table 7-6).

Variant	SND		Population 1			Population	2
variant	SINE	All (N=124)	F (N=77)	M (N=45)	All (N=385)	F (N=299)	M (N=86)
c.3190C>T R1064W	rs41278174	14 11%	11 14%	3 7%	19 5%	16 5%	3 3%

Table 7-6. Frequency in population 1 and population 2 of Terceira Island of the *ABCC6* gene variant (c.3190C>T/R1064W) in exon 23.

Abbreviations: SNP- Single nucleotide polymorphism, F-females, M-Males, N- number of individuals.

The c.3190C>T/R1064W variant was found in 14 individuals in population 1 and in 19 individuals in population 2, all of them were heterozygous. In addition, a further rare variant (rs60707953) was found in exon 23, which have a MAF of 0.01 in two individuals, one female and one male from the population 1. The male suffers from lower back pain and the female is healthy. The variant causes a substitution of a leucine by isoleucine at amino acid 1097 in the protein. Both amino acids have similar physico-chemical properties and both residues are medium size and hydrophobic.

# 7.4.2. Expression

It was only possible to assess the expression of the *ABCC6* gene in 13 (9 males and 4 females; mean age 72 years; range 53-84) (Table 7-7 and supplementary figure 7.1) out of 53 RNA cartilage samples due to the poor quality of the RNA (Supplementary table 7-2).

Table 7-7. Details of the 13 patients undergoing hip replacement from whom femoral head cartilage where obtained. The sample used as a control is highlighted in bold (THR-40). \* Age (yr-years) at time of operation. The pathological anatomy of the affected tissue is also indicated.

Samples	Sex	Age (yr)*	Diagnosis	Affected tissue			
THR-4	F	61(?)	DISH (thoracic)	Cartilaginous tissue			
THR-6	М	67	Coxoarthrosis (right)	Cartilaginous tissue with degenerative alterations			
THR-13	Μ	76	DISH (cervical, lumbar and throracic), Coxoarthrosis	Cartilaginous tissue			
THR-20	М	70	Coxoarthrosis (bilateral), hypertension	Cartilaginous tissue with superficial fibrosis with papilliform contours			
THR-31	М	47	Coxoarthrosis (right)	Fragment of cartilaginous tissue with focal fibrous cap			
THR-34	F	58	Coxoarthrosis (left)	Synovial and cartilaginous fibrous tissue			
THR-35	М	75	Chondrocalcinosis (knees), Coxoarthrosis (bilateral)	Cartilaginous tissue			
THR-36	F	59	Chondrocalcinosis (knees), Coxoarthrosis	Cartilaginous tissue with degenerative aspects			
THR-40	F	64	Left femoral fracture	No pathology			
THR-43	М	73	Osteoarthritis	Cartilaginous tissue			
THR-47	М	64	Coxoarthrosis (left), lithiasis	Cartilaginous tissue with superficial fibrosis forming papillary projections			
THR-49	М	76	Coxoarthrosis (right)	Fragments of cartilaginous tissue with calcifications			
THR-51	М	63	Coxoarthrosis (right), Rheumatoid arthritis	Cartilaginous tissue			

Abbreviations: F-females, M-Males, THR: Total hip replacement.

Of the 13 samples selected for expression studies (9 males, 4 females; mean age at surgery, 66 years; range, 47-76 years) there were two patients with DISH (confirmed with radiology), two patients with Knee chondrocalcinosis, 1 with lithiasis, 1 with osteoarthritis and 1 with rheumatoid arthritis (Table 7-7). These 5 groups of patients were compared with the control sample THR-40, since this individual did not present any disease pathology characterized by ectopic calcifications and the medical intervention was only due to a femoral fracture. Gene transcripts of the *ABCC6* gene were detected in cartilage tissues. The *ABCC6* gene was up regulated in all samples from diseased tissue relative to the control sample THR-40. The only exception was THR-6 patient in which *ABCC6* transcript abundance was lower than the control sample (Figure 7-2). The samples with higher *ABCC6* transcripts were THR-4, THR-13, THR-35, THR-47 and THR-51.



Figure 7-2. Relative expression of *ABCC6* gene in cartilage tissue samples. The expression of the *ABCC6* gene was determined in cDNA synthesized from cartilage tissues. The values were normalized in relation to the expression of the reference gene *YWHAZ*. The dashed line in the graph represents the value 1 of the control sample TRH40.

Analyzing the samples by grouping them according to pathology revealed that the groups with coxoarthrosis, chondrocalcinosis and DISH, seemed to have a higher expression of the *ABCC6* gene in relation to the normal control THR-40, but the DISH group is the group with more expression (Figure 7-3).



Figure 7-3. Relative expression of the *ABCC6* gene in normal (n = 1), coxoarthrosis (n = 8), DISH (n = 2) and CC (n = 2) individuals. Coxoarthrosis group include all the THR cohort with the exception of the normal individual THR-40 and the CC (THR-35, 36) and DISH patients (THR-4, 13).

#### 7.5. Discussion

Both, DISH and AS are bone forming diseases that involve the axial skeleton and the peripheral entheses, resulting in bone proliferation in the spine and at the extraspinal entheseal sites in the later phases of their course. Since these conditions can coexist it has been suggested that their susceptibility genes may overlap. We performed a mutational analysis of the ABCC6 gene in a group of DISH/CC and AS patients in order to find a possible association between the gene and these diseases. In this study we identified 31 different variants along the 31 exons of ABCC6 gene. Analysis of the topology of these variants in the MRP6 protein (Figure 7-1) shows that the vast majority lie within the cytoplasmic domains. In PXE diseases the majority of disease causing variants are also located in the cytoplasmic region, particularly in the eighth intracellular loop encoded by exon 24, and the two nucleotide binding folds (NFB1 and NFB2) of MRP6, encoded by the exons 16-18 and 28-30, respectively [407]. As expected, in our group of patients that did not present PXE lesions, we did not find variants in these particular cytoplasmic regions. However in general it is thought that missense variants within the cytosolic domain of proteins, may affect their function by changing their substrate specificity or by disrupting the correct folding of the protein necessary for its function [308]. The variant rs12931472 of the ABCC6 gene is located in the sixth intracellular loop of the deduced protein, and is encoded by exon 14 and causes the substitution of amino acid 614 from a medium size and hydrophobic valine (V) to a small size and hydrophobic alanine (A). As shown in figure 7-1 this amino acid position is variable in other species, furthermore the altered amino acid (A) in the human variant is the normal amino acid in other vertebrates, such as chimpanzee, cow and dog. This variant is frequent in the human ABCC6 gene and it has a MAF value of 0.34(G) in all populations and in Peruvian population the presence of this variant can reach to 52%. In the present study the rs12931472 variant was not associated with the occurrence of the DISH/CC or AS phenotypes; however a Cochran-Armitage trend and allelic tests adjusted for gender indicated that this variant is statistically more frequent in AS females than in control females. Despite the limited number of AS females (n=14) in the present study all of them had the rs12931472 variation in a heterozygous or homozygous state. The sexual divergence in ABCC6 variants ties in with the notion that gender specific differences occur between males and females with AS. AS females are more prone to cervical spine involvement, and males frequently complain about lumbar pain [408]. It is observed that female AS patients present higher fatigue scores, higher disease activity and more frequent peripheral involvement [409, 410]. Different haplotype

combinations in the *ANKH* gene have also been reported in males and females with AS. The authors found that in families with affected individuals of both sexes, two *ANKH* SNPs (rs28006 and rs25957) were associated with AS but only in affected women [248]. It is unlikely that the major genetic factors that account for these differences are X-linked because there is no linkage of AS susceptibility with X-chromosome markers [411]. The underlying pathogenic mechanism that result in gender-associated differences in terms of the manifestations of AS, is currently unknown.

The missense variant rs41278174 identified in this study is rare (MAF 0.01) and is located on transmembrane domain; comparative analysis revealed that the modified amino acid is normally highly conserved between mammals (Figure 7-1) and although SIFT and PolyPhen indicate the mutation is deleterious it has never been linked to PXE or other disorder. The variant was found in two PXE families, however it was considered non disease causing since it did not segregate with the disease phenotype [308]. We also evaluated the allele frequency of this rare variant in two groups of Azorean Terceira island individuals with 124 and 385 individuals. The variant was detected in 33 individuals, indicating that this variant is not as rare in the island as in the general population from 1000 genomes project. The higher frequency of this variant in Terceira island (11% in population 1) can be explained by the consanguinity which tends to occur on small islands. Besides, this variant was not found in the AS group and it was significantly more frequent in male controls than in DISH/CC and AS males, which may suggest it has a protective effect against both diseases, but only in males. The protective effect of this variant on both diseases is difficult to explain and may suggest it affects pathological features shared by DISH and AS, such as the ossification of the axial skeleton. It is known that the transmembrane domain of MRP6 determines the substrate specificity of ABC transporters, and therefore it is likely that missense variants in this region change the substrate specificity of MRP6 causing substrate accumulation [412]. Mutations in the transmembrane domain can also affect the integration of the protein into the cell membrane and lead to a loss of function [308]. Probably the variant rs41278174 in males changes the specificity of MRP6 transporter, conferring a protective effect via an unknown mechanism.

In the *ABCC6* promoter we found the polymorphisms rs28529549, rs565625561 and rs778876717. Interestingly the rs28529549 (c.-219A>C) variant, according to Schulz et al [406], has a protective effect for PXE disease and is located in a transcriptional activator sequence of the *ABCC6* promoter and occurs in the binding site of a transcriptional repressor, predominantly found in genes that participate in lipid metabolism. In fact, several studies

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have described genetic mutations in the *ABCC6* gene associated with variations in quantitative plasma lipoproteins [413], low High density lipoprotein (HDL) and/or coronary heart disease risk [414]. Alterations in lipoprotein composition with lowered plasma HDL cholesterol levels and hypertriglyceridemia were also found in plasma samples of PXE patients [406]. Furthermore, the *Abcc6* knockout mice have HDL cholesterol plasma levels reduced by 25% [415], confirming the potential role of *ABCC6* in lipid homeostasis [416]. The association between the polymorphism rs2238472 (p.R1268Q) in the exon 27 of the *ABCC6* gene, found in our study in a great number of individuals (7 probands, 10 AS; 14 controls and 14 DISH/CC individuals), with plasma lipoprotein levels has previously been reported [413]. The variant is pathogenic (HGMD mutation) for PXE disease only in compound heterozygous (associated with R1141X) and is harmless in homozygotes [417].

Coxoarthrosis is characterized by focal areas of damage to the hip articular cartilage, associated with increased activity in the subchondral bone and marginal osteophyte formation [418], leading to hip replacement surgery in majority of cases. The most common reason for hip replacement is osteoarthritis, but other diseases such as rheumatoid arthritis [419], DISH [420] and CC [421, 422] can also be responsible for this outcome. In the present study in general the *ABCC6* gene had expression in cartilage tissues and its expression was much higher in DISH/CC patients. As already mentioned, it is believed that the MRP6 mediates ectopic calcification via the circulation since *ABCC6* is absent or minimally expressed in the calcified tissue resulting from the deficiency [423].

Previous studies on *ABCC6* associate BMP signaling with *ABCC6* deficiency and it is this that promotes the osteochondrogenic transitions in susceptible cells [423]. One study revealed BMP2/SMADS/RUNX2 were up-regulated as were the Tgfb2/smad2/3 pathways at the mineralization sites in *ABCC6* deficiency mice [424]. The *ABCC6* deficient mice develops ectopic calcification similar to both the human PXE and mouse dystrophic cardiac calcification phenotypes, and in mice this *ABCC6* deficiency stimulates BMP signaling by acting on the expression of multiple BMPs. The same authors verified an enhanced BMP signaling in liver, kidney and aortic tissues in the absence of *ABCC6*, leading the authors to hypothesize that deficiency of ABCC6, which is mainly expressed in liver, affects BMP signaling in other organs [423]. It is believed that the change in BMP signaling involves matrix Gla protein (MGP), an extracellular glycoprotein that inhibits tissue mineralization by chelating calcium [425] and regulating local BMP signaling [426]. However, to be a calcification inhibitor, MGP has to be activated by  $\gamma$ -glutamyl carboxylation, a vitamin k dependent reaction. This protein is active in its carboxylated form (cMGP) and inactive in the

un-carboxylated form (ucMGP) [121]. In one study MGP was isolated from the liver of Abcc6-/- mice and was largely present as ucMGP and was inactive, and it was demonstrated that there is an association between ucMGP forms of MGP and ectopic mineralization [427]. Low levels of serum MGP have been reported in MRP6 deficiency and PXE patients have also lower serum concentration of MGP compared to controls, MGP is present within elastic fibers and is associated with calcification of dermal elastic fibers [428, 429]. MGP is expressed in various tissues and up regulated in bone and cartilage [430], it is believed that MGPs actions include the inhibition of mineralization by suppression of BMP2, which is a potent osteogenic factor [431]. Sarzi-Puttini et al reported higher serum MGP levels in DISH males and females, and the group suggested that MGP may be a marker of hyperostosis because it is produced in larger amounts by this patients [432]. It is possible that the higher concentration of ucMGP reported in DISH patient is most likely a consequence of the failure of the method to distinguish between the noncarboxylated and the  $\gamma$ - carboxylated forms of MGP. Other investigations have shown that BMP2 can regulate phosphate uptake [433], and that phosphate levels can regulate BMP2 expression [434], however it is not clear how pyrophosphate mediates other MRP6 actions. Although the physiological function of MRP6 towards calcification is likely exerted via the systemic circulation of its substrate(s), the exact mechanism by which this protein affects the susceptibility to mineralization in distal tissues has yet to be defined.

Our results suggest that *ABCC6* gene plays a role in the ectopic calcification process in patients from the Azores and identifies possible alleles and reveals probable gender specificity in this interaction. The expression study of *ABCC6* in cartilage suggests that differential expression of *ABCC6* transcripts could play a role in the disease process. However, a much bigger sample size will be required to give robust statistical support to this hypothesis.

# 7.6. Supplementary material

Supplementary table 7-1. Results of genetic variants found in the *ABCC6* gene in Azorean patients with DISH/CC and AS compared to the controls.

	Genotype		DISH/CC			SPA			Controls	
		All: N=55 Female: N=19		All: N=25 Female: N=7		All: N=36 Female: N=22				
SNP		Male: N=36			Male: N=18		Male: N=14			
		All	Female	Male	All	Female	Male	All	Female	Male
		N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
rs28529549	AA	48 (87)	17 (89)	31 (86)	24 (96)	7 (100)	17 (94)	34 (94)	22 (100)	12 (86)
	AC	7 (13)	2 (10)	5 (14)	1 (4)	0 (0)	1 (6)	2 (6)	0 (0)	2 (14)
	CC	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
rs565625561	CC	52 (95)	19 (100)	33 (92)	24 (96)	7 (100)	17 (94)	35 (97)	22 (100)	13 (93)
	СТ	3 (5)	0 (0)	3 (8)	1 (4)	0 (0)	1 (6)	1 (3)	0 (0)	1 (7)
	TT	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
rs778876717	CC	48 (87)	15 (79)	33 (92)	18 (72)	6 (86)	12 (67)	28 (78)	18 (82)	10(71)
	СТ	7 (13)	4 (21)	3 (8)	7 (28)	1 (14)	6 (33)	8 (22)	4 (18)	4 (29)
	TT	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
rs55778939	GG	47 (85)	17 (89)	30 (83)	23 (92)	6 (85)	17 (94)	32 (89)	20 (91)	12 (86)
	GA	7 (13)	2 (11)	5 (14)	2 (8)	1 (14)	1 (6)	4 (11)	2 (9)	2 (14)
	AA	1 (2)	0 (0)	1 (3)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
	CC	53 (96)	19 (100)	34 (94)	22 (88)	7 (100)	15 (83)	35 (97)	22 (100)	13 (93)
rs2606921	СТ	2 (4)	0 (0)	2 (6)	3 (12)	0 (0)	3 (17)	1 (3)	0 (0)	1 (7)
	TT	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
	CC	5 (9)	10 (52)	18 (50)	1 (4)	4 (57)	11 (61)	6 (17)	12 (55)	7 (50)
rs9940089	CA	22 (40)	7 (37)	15 (42)	9 (36)	2 (29)	7 (39)	11 (31)	6 (27)	5 (36)
	AA	28 (51)	2 (11)	3 (8)	15 (60)	1 (14)	0 (0)	19 (53)	4 (18)	2 (14)
rs12931472	TT	13 (24)	4 (21)	9 (25)	4 (16)	0 (0)	4 (22)	10 (28)	5 (23)	5 (36)
	TC	28 (51)	10 (53)	18 (50)	15 (60)	3 (43)	12 (67)	19 (53)	13 (59)	6 (43)
	CC	14 (25)	5 (26)	9 (25)	6 (24)	4 (57)	2 (11)	7 (19)	4 (18)	3 (21)
	CC	15 (27)	5 (26)	10 (28)	6 (24)	1 (14)	5 (28)	13 (36)	7 (32)	6 (43)
rs8058694	CA	27 (49)	9 (47)	18 (50)	14 (56)	3 (43)	11 (61)	17 (47)	11 (50)	6 (43)
	AA	13 (24)	5 (26)	8 (22)	5 (20)	3 (43)	2 (11)	6 (17)	4 (18)	2 (14)
rs61340537	CC	54 (98)	19 (100)	35 (97)	23 (92)	7 (100)	16 (89)	35 (97)	22 (100)	13 (93)
	CA	1 (2)	0 (0)	1 (3)	2 (8)	0 (0)	2 (11)	1 (3)	0 (0)	1 (7)
	AA	0 (0)	0 (0)	0 (0)	2 (8)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
	CC	51 (93)	16 (84)	35 (97)	25 (100)	7 (100)	18 (100)	32 (89)	21 (95)	11 (79)
rs41278174	СТ	4 (7)	3 (16)	1 (3)	0 (0)	0 (0)	0 (0)	4 (11)	1 (4)	3 (21)
	TT	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
rs41278172	CC	54 (98)	19 (100)	35 (97)	23 (92)	7 (100)	16 (89)	35 (97)	21 (95)	14 (100)
	СТ	1 (2)	0 (0)	1 (3)	2 (8)	0 (0)	2 (11)	1 (3)	1 (4)	0 (0)
	TT	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
rs2238472	GG	35 (64)	12 (63)	23 (64)	15 (60)	3 (43)	12 (67)	22 (61)	13 (59)	9 (64)
	GA	16 (29)	5 (26)	11 (31)	8 (32)	2 (29)	6 (33)	13 (36)	9 (41)	4 (29)
	AA	4 (7)	2 (11)	2 (6)	2 (8)	2 (29)	0 (0)	1 (3)	0 (0)	1 (7)

**Abbreviations:** SNP- Single nucleotide polymorphism, N= number of individuals, A- adenine, C- cytosine, T-Thymine, G- guanine.
Sample         Ing/µl         Ratio         RIN         Ratio 28/18s         In           THR-1         1580         1,838         2         0.0         11           THR-2         37         2,028         Too low         11           THR-3         112         1,488         Too low         11           THR-4         38         1,597         7.6         1.5         1           THR-5         164         1,89         2.4         0.0         1           THR-6         196         1,976         7.3         1.2         2           THR-7         150         1,698         Too low         1         1           THR-8         162         1,851         4.1         0.0         1           THR-9         51         2,084         N/A         0.0         1           THR-10         61         1,733         1.1         0.0         1           THR-11         32         1,281         N/A         0.0         1           THR-13         55         1,816         4,2         1.5         1           THR-14         38         1,809         N/A         0.0         1 <t< th=""><th>ng/µl 005 25 92 279 97 7 12 3 3 47 5 52 50</th></t<>	ng/µl 005 25 92 279 97 7 12 3 3 47 5 52 50
THR-1       1580       1,838       2       0.0       1         THR-2       37       2,028       Too low       Too low         THR-3       112       1,488       Too low       Too low         THR-4       38       1,597       7.6       1.5       1         THR-5       164       1,89       2.4       0.0       1         THR-6       196       1,976       7.3       1.2       2         THR-7       150       1,698       Too low       1         THR-8       162       1,851       4.1       0.0       1         THR-9       51       2,084       N/A       0.0       1         THR-10       61       1,733       1.1       0.0       1         THR-11       32       1,281       N/A       0.0       1         THR-12       52       1,874       Too low       1       1         THR-13       55       1,816       4,2       1.5       6         THR-14       38       1,809       N/A       0.0       1         THR-15       188       1,72       2.1       0.0       1         THR-16       162<	005 25 92 279 97 7 12 3 47 5 52 50
THR-2       37       2,028       Too low         THR-3       112       1,488       Too low         THR-4       38       1,597       7.6       1.5         THR-5       164       1,89       2.4       0.0         THR-6       196       1,976       7.3       1.2       2         THR-7       150       1,698       Too low       7         THR-8       162       1,851       4.1       0.0       9         THR-9       51       2,084       N/A       0.0       9         THR-10       61       1,733       1.1       0.0       9         THR-11       32       1,281       N/A       0.0       9         THR-12       52       1,874       Too low       9         THR-13       55       1,816       4,2       1.5       9         THR-14       38       1,809       N/A       0.0       9         THR-15       188       1,72       2.1       0.0       3         THR-16       162       2,283       3       0.0       3         THR-18       38       1,646       7       0.0       3	<b>25</b> 92 <b>279</b> 97 7 12 3 <b>47</b> 5 52 50
THR-3       112       1,488       Too low         THR-4       38       1,597       7.6       1.5         THR-5       164       1,89       2.4       0.0         THR-6       196       1,976       7.3       1.2       2         THR-7       150       1,698       Too low         THR-8       162       1,851       4.1       0.0       9         THR-9       51       2,084       N/A       0.0       9         THR-10       61       1,733       1.1       0.0       9         THR-11       32       1,281       N/A       0.0       9         THR-12       52       1,874       Too low       7         THR-13       55       1,816       4,2       1.5       6         THR-14       38       1,809       N/A       0.0       9         THR-15       188       1,72       2.1       0.0       3         THR-16       162       2,283       3       0.0       3         THR-17       87       2,871       N/A       0.0       3         THR-18       38       1,646       7       0.0       3	<b>25</b> 92 <b>279</b> 97 7 12 3 <b>47</b> 5 52 50
THR-4         38         1,597         7.6         1.5         1           THR-5         164         1,89         2.4         0.0         9           THR-6         196         1,976         7.3         1.2         2           THR-7         150         1,698         Too low         7           THR-8         162         1,851         4.1         0.0         9           THR-9         51         2,084         N/A         0.0         9           THR-9         51         2,084         N/A         0.0         9           THR-10         61         1,733         1.1         0.0         9           THR-11         32         1,281         N/A         0.0         9           THR-12         52         1,874         Too low         9         9           THR-13         55         1,816         4,2         1.5         9           THR-14         38         1,809         N/A         0.0         9           THR-15         188         1,72         2.1         0.0         9           THR-16         162         2,283         3         0.0         9 <t< td=""><td><b>25</b> 92 <b>279</b> 97 7 12 3 <b>47</b> 5 52 50</td></t<>	<b>25</b> 92 <b>279</b> 97 7 12 3 <b>47</b> 5 52 50
THR-5       164       1,89       2.4       0.0       9         THR-6       196       1,976       7.3       1.2       2         THR-7       150       1,698       Too low         THR-8       162       1,851       4.1       0.0       9         THR-9       51       2,084       N/A       0.0       9         THR-10       61       1,733       1.1       0.0       9         THR-11       32       1,281       N/A       0.0       9         THR-13       55       1,816       4,2       1.5       9         THR-14       38       1,809       N/A       0.0       9         THR-15       188       1,72       2.1       0.0       9         THR-16       162       2,283       3       0.0       9         THR-17       87       2,871       N/A       0.0       9         THR-18       38       1,646       7       0.0       3         THR-19       8.3       1,829       N/A       0.0       9         THR-20       45       1,654       7.4       1.0       9         THR-21       18 </td <td>92 279 97 7 12 3 47 5 52 50</td>	92 279 97 7 12 3 47 5 52 50
THR-6         196         1,976         7.3         1.2         2           THR-7         150         1,698         Too low         Too low           THR-8         162         1,851         4.1         0.0         9           THR-9         51         2,084         N/A         0.0         9           THR-10         61         1,733         1.1         0.0         9           THR-11         32         1,281         N/A         0.0         9           THR-12         52         1,874         Too low         9           THR-13         55         1,816         4,2         1.5         9           THR-14         38         1,809         N/A         0.0         9           THR-15         188         1,72         2.1         0.0         9           THR-16         162         2,283         3         0.0         9           THR-17         87         2,871         N/A         0.0         9           THR-18         38         1,646         7         0.0         3           THR-20         45         1,654         7.4         1.0         9           <	<b>279</b> 97 7 12 3 <b>47</b> 5 52 50
THR-7         150         1,698         Too low           THR-8         162         1,851         4.1         0.0         9           THR-9         51         2,084         N/A         0.0         9           THR-9         51         2,084         N/A         0.0         9           THR-10         61         1,733         1.1         0.0         1           THR-11         32         1,281         N/A         0.0         1           THR-13         55         1,816         4,2         1.5         6           THR-13         55         1,816         4,2         1.5         6           THR-14         38         1,809         N/A         0.0         1           THR-15         188         1,72         2.1         0.0         2           THR-16         162         2,283         3         0.0         2           THR-17         87         2,871         N/A         0.0         3           THR-18         38         1,646         7         0.0         3           THR-20         45         1,654         7.4         1.0         6           THR-21	97 7 12 3 <b>47</b> 5 52 50
THR-8       162       1,851       4.1       0.0       9         THR-9       51       2,084       N/A       0.0       1         THR-10       61       1,733       1.1       0.0       1         THR-10       61       1,733       1.1       0.0       1         THR-11       32       1,281       N/A       0.0       1         THR-12       52       1,874       Too low       1         THR-13       55       1,816       4,2       1.5       1         THR-14       38       1,809       N/A       0.0       1       1         THR-15       188       1,72       2.1       0.0       1       1         THR-16       162       2,283       3       0.0       1       1         THR-17       87       2,871       N/A       0.0       1       1         THR-19       8.3       1,654       7.4       1.0       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1 <td>97 7 12 3 47 5 52 50</td>	97 7 12 3 47 5 52 50
THR-9         51         2,084         N/A         0.0           THR-10         61         1,733         1.1         0.0           THR-11         32         1,281         N/A         0.0           THR-12         52         1,874         Too low           THR-13         55         1,816         4,2         1.5           THR-14         38         1,809         N/A         0.0           THR-15         188         1,72         2.1         0.0         3           THR-16         162         2,283         3         0.0         3           THR-17         87         2,871         N/A         0.0         3           THR-18         38         1,646         7         0.0         3           THR-19         8.3         1,829         N/A         0.0         3           THR-20         45         1,654         7.4         1.0         4           THR-21         18         1,505         N/A         0.0         3           THR-22         42         1,957         1         0.0         3           THR-23         52         1,813         1.2         0.0	7 12 3 <b>47</b> 5 52 50
THR-10       61       1,733       1.1       0.0         THR-11       32       1,281       N/A       0.0         THR-12       52       1,874       Too low         THR-13       55       1,816       4,2       1.5         THR-14       38       1,809       N/A       0.0         THR-14       38       1,809       N/A       0.0         THR-15       188       1,72       2.1       0.0       0         THR-16       162       2,283       3       0.0       0         THR-17       87       2,871       N/A       0.0       0         THR-18       38       1,646       7       0.0       3         THR-19       8.3       1,829       N/A       0.0       0         THR-20       45       1,654       7.4       1.0       0         THR-21       18       1,505       N/A       0.0       0         THR-22       42       1,957       1       0.0       0       0         THR-23       52       1,813       1.2       0.0       0       0         THR-24       16       1,718       N/A       <	12 3 47 5 52 50
THR-11       32       1,281       N/A       0.0         THR-12       52       1,874       Too low         THR-13       55       1,816       4,2       1.5       4         THR-14       38       1,809       N/A       0.0       5         THR-15       188       1,72       2.1       0.0       5         THR-16       162       2,283       3       0.0       5         THR-17       87       2,871       N/A       0.0       5         THR-18       38       1,646       7       0.0       3         THR-19       8.3       1,829       N/A       0.0       5         THR-20       45       1,654       7.4       1.0       6         THR-21       18       1,505       N/A       0.0       5         THR-22       42       1,957       1       0.0       5         THR-23       52       1,8	3 47 5 52 50
THR-12         52         1,874         Too low           THR-13         55         1,816         4,2         1.5         4           THR-14         38         1,809         N/A         0.0         1           THR-14         38         1,809         N/A         0.0         1           THR-15         188         1,72         2.1         0.0         1           THR-16         162         2,283         3         0.0         1           THR-16         162         2,871         N/A         0.0         1           THR-17         87         2,871         N/A         0.0         3           THR-18         38         1,646         7         0.0         3           THR-19         8.3         1,829         N/A         0.0         1           THR-20         45         1,654         7.4         1.0         4           THR-21         18         1,505         N/A         0.0         1           THR-23         52         1,813         1.2         0.0         1           THR-24         16         1,718         N/A         0.0         1           TH	<b>47</b> 5 52 50
THR-13         55         1,816         4,2         1.5           THR-14         38         1,809         N/A         0.0         1           THR-15         188         1,72         2.1         0.0         1           THR-16         162         2,283         3         0.0         1           THR-16         162         2,283         3         0.0         1           THR-17         87         2,871         N/A         0.0         3           THR-18         38         1,646         7         0.0         3           THR-19         8.3         1,829         N/A         0.0         3           THR-20         45         1,654         7.4         1.0         4           THR-21         18         1,505         N/A         0.0         1           THR-23         52         1,813         1.2         0.0         1           THR-24         16         1,718         N/A         0.0         1           THR-25         53         1,456         N/A         0.0         1           THR-26         19         1,612         3         0.0         1	<b>47</b> 5 52 50
THR-14       38       1,809       N/A       0.0         THR-15       188       1,72       2.1       0.0       3         THR-16       162       2,283       3       0.0       3         THR-17       87       2,871       N/A       0.0       3         THR-18       38       1,646       7       0.0       3         THR-19       8.3       1,646       7       0.0       3         THR-19       8.3       1,654       7.4       1.0       4         THR-20       45       1,654       7.4       1.0       4         THR-21       18       1,505       N/A       0.0       3         THR-22       42       1,957       1       0.0       3         THR-23       52       1,813       1.2       0.0       3         THR-24       16       1,718       N/A       0.0       3         THR-25       53       1,456       N/A       0.0       3         THR-26       19       1,612       3       0.0       3         THR-28       57       1,789       N/A       0.0       3         THR-30	5 52 50
THR-15       188       1,72       2.1       0.0       1         THR-16       162       2,283       3       0.0       1         THR-17       87       2,871       N/A       0.0       1         THR-17       87       2,871       N/A       0.0       3         THR-18       38       1,646       7       0.0       3         THR-19       8.3       1,829       N/A       0.0       3         THR-20       45       1,654       7.4       1.0       4         THR-21       18       1,505       N/A       0.0       3         THR-22       42       1,957       1       0.0       4         THR-23       52       1,813       1.2       0.0       3         THR-24       16       1,718       N/A       0.0       3         THR-25       53       1,456       N/A       0.0       3         THR-26       19       1,612       3       0.0       3         THR-28       57       1,789       N/A       0.0       3         THR-30       99       1,724       2.4       0.0       3	52 50
THR-16       162       2,283       3       0.0       1         THR-17       87       2,871       N/A       0.0       3         THR-18       38       1,646       7       0.0       3         THR-19       8.3       1,829       N/A       0.0       3         THR-19       8.3       1,829       N/A       0.0       3         THR-20       45       1,654       7.4       1.0       4         THR-21       18       1,505       N/A       0.0       3         THR-23       52       1,813       1.2       0.0       3         THR-24       16       1,718       N/A       0.0       3         THR-25       53       1,456       N/A       0.0       3         THR-26       19       1,612       3       0.0       3         THR-27       39       1,726       N/A       0.0       3         THR-28       57       1,789       N/A       0.0       3         THR-29       13       1,307       6       0.0       3         THR-31       59       1,644       6.5       0.3       4 <td>50</td>	50
THR-17       87       2,871       N/A       0.0         THR-18       38       1,646       7       0.0       3         THR-19       8.3       1,829       N/A       0.0       3         THR-20       45       1,654       7.4       1.0       4         THR-21       18       1,505       N/A       0.0       3         THR-22       42       1,957       1       0.0       3         THR-23       52       1,813       1.2       0.0       3         THR-24       16       1,718       N/A       0.0       3         THR-25       53       1,456       N/A       0.0       3         THR-26       19       1,612       3       0.0       3         THR-28       57       1,789       N/A       0.0       3         THR-29       13       1,307       6       0.0       3         THR-30       99       1,724       2.4       0.0       3	
THR-18       38       1,646       7       0.0       3         THR-19       8.3       1,829       N/A       0.0       3         THR-20       45       1,654       7.4       1.0       6         THR-21       18       1,505       N/A       0.0       6         THR-22       42       1,957       1       0.0       6         THR-23       52       1,813       1.2       0.0       6         THR-24       16       1,718       N/A       0.0       6         THR-25       53       1,456       N/A       0.0       6         THR-26       19       1,612       3       0.0       6         THR-27       39       1,726       N/A       0.0       7         THR-28       57       1,789       N/A       0.0       7         THR-29       13       1,307       6       0.0       7         THR-30       99       1,724       2.4       0.0       7         THR-31       59       1,644       6.5       0.3       6	8
THR-19       8.3       1,829       N/A       0.0         THR-20       45       1,654       7.4       1.0       4         THR-21       18       1,505       N/A       0.0       4         THR-22       42       1,957       1       0.0       4         THR-23       52       1,813       1.2       0.0       4         THR-24       16       1,718       N/A       0.0       4         THR-25       53       1,456       N/A       0.0       4         THR-26       19       1,612       3       0.0       5         THR-27       39       1,726       N/A       0.0       5         THR-28       57       1,789       N/A       0.0       5         THR-29       13       1,307       6       0.0       5         THR-30       99       1,724       2.4       0.0       5         THR-31       59       1,644       6.5       0.3       4	37,8
THR-20451,6547.41.0THR-21181,505N/A0.0THR-22421,95710.0THR-23521,8131.20.0THR-24161,718N/A0.0THR-25531,456N/A0.0THR-26191,61230.0THR-27391,726N/A0.0THR-28571,789N/A0.0THR-29131,30760.0THR-30991,7242.40.0THR-31591,6446.50.3	1
THR-21       18       1,505       N/A       0.0         THR-22       42       1,957       1       0.0         THR-23       52       1,813       1.2       0.0       1         THR-24       16       1,718       N/A       0.0       1         THR-25       53       1,456       N/A       0.0       1         THR-26       19       1,612       3       0.0       1         THR-27       39       1,726       N/A       0.0       1         THR-28       57       1,789       N/A       0.0       1         THR-29       13       1,307       6       0.0       1         THR-30       99       1,724       2.4       0.0       1	43
THR-22       42       1,957       1       0.0         THR-23       52       1,813       1.2       0.0       1         THR-24       16       1,718       N/A       0.0       1         THR-25       53       1,456       N/A       0.0       1         THR-26       19       1,612       3       0.0       1         THR-27       39       1,726       N/A       0.0       1         THR-28       57       1,789       N/A       0.0       1         THR-29       13       1,307       6       0.0       1         THR-30       99       1,724       2.4       0.0       1	5
THR-23       52       1,813       1.2       0.0       1         THR-24       16       1,718       N/A       0.0       1         THR-25       53       1,456       N/A       0.0       1         THR-26       19       1,612       3       0.0       1         THR-27       39       1,726       N/A       0.0       1         THR-28       57       1,789       N/A       0.0       1         THR-29       13       1,307       6       0.0       1         THR-30       99       1,724       2.4       0.0       1         THR-31       59       1,644       6.5       0.3       4	14
THR-24161,718N/A0.0THR-25531,456N/A0.0THR-26191,61230.0THR-27391,726N/A0.0THR-28571,789N/A0.0THR-29131,30760.0THR-30991,7242.40.0THR-31591,6446.50.3	21
THR-25       53       1,456       N/A       0.0         THR-26       19       1,612       3       0.0       3         THR-26       19       1,612       3       0.0       3         THR-27       39       1,726       N/A       0.0       3         THR-28       57       1,789       N/A       0.0       3         THR-29       13       1,307       6       0.0       3         THR-30       99       1,724       2.4       0.0       3         THR-31       59       1,644       6.5       0.3       4	3
THR-26191,61230.01THR-27391,726N/A0.0THR-28571,789N/A0.0THR-29131,30760.0THR-30991,7242.40.0THR-31591,6446.50.3	7
THR-27391,726N/A0.0THR-28571,789N/A0.0THR-29131,30760.0THR-30991,7242.40.02THR-31591,6446.50.34	36
THR-28         57         1,789         N/A         0.0           THR-29         13         1,307         6         0.0           THR-30         99         1,724         2.4         0.0         1 <b>THR-31 59 1,644 6.5 0.3</b> 4	8
THR-29         13         1,307         6         0.0           THR-30         99         1,724         2.4         0.0         2           THR-31         59         1,644         6.5         0.3         4	5
THR-30         99         1,724         2.4         0.0         1           THR-31         59         1,644         6.5         0.3         4	6
THR-31         59         1,644         6.5         0.3	31
	47
THR-32 61 1,87 6.8 0.0	12
THR-33 28 1,992 3.5 0.0	12
THR-34 96 1,6 7.3 1.0	68
THR-35 331 1,981 7.5 1.0 4	496
THR-36 279 1,772 6.0 0.4 3	352
THR-37 114 1,728 6.8 0.2	16
THR-38 57 1,823 6.8 0.0	14
THR-39 460 1.785 2.9 0.3 2	298
THR-40 27 1,513 5.7 1.7	18
THR-41 20 2,116 Too low	
THR-42 99 1,684 1.1 0.0	21
THR-43 146 1,71 7.5 1.1	76
THR-44 73 1,547 5.5 0.0	11

Supplementary table 7-2. RNA cartilage samples and measures of NanoVue and Agilent. The samples used in gene expression are highlighted in bold.

Comula	Nanovue spectr	ophotometer	Agilent					
Sample	[] ng/µl	Ratio	RIN	RIN Ratio 28s/18s [] n				
THR-45	54	1,476		Too low				
THR-46	42	1,907	7.3	0.0	14			
<b>THR-47</b>	264	1,976	7.9	1.1	401			
THR-48	15	1,393	N/A	0.0	1			
THR-49	15	1,851	7.3	1.0	14			
THR-50	264	2,091	2.8	0.0	168			
<b>THR-51</b>	47	1,987	7	0.7	70			
THR-52	163	1,7		Too low				
THR-53	71	11,708	2.1	0.0	40			

Abbreviations: THR- Total hip replacement patient, RIN- RNA integrity number.

MM 100	THR-4	THR-6	THR-13	THR-20	THR-31	THR-34	THR-35	THR-36	THR-40	THR-43	THR-47	THR-49	THR-51	NTC

Supplementary figure 7-1. Conventional PCR amplification for  $\beta$ -actin gene (249 base pairs) on cDNA samples. Ethidium bromide stained 1.7% agarose gel. NTC- No template control, THR: Total hip replacement patient.

# CHAPTER VIII: THE ORIGIN OF *ABCC6* GENE IS POTENTIALLY LINKED WITH THE EMERGENCE OF A BONY SKELETON IN VERTEBRATES

## 8. THE ORIGIN OF *ABCC6* GENE IS POTENTIALLY LINKED WITH THE EMERGENCE OF A BONY SKELETON IN VERTEBRATES

#### 8.1 Abstract

The ATP-binding cassette transporter *ABCC6* gene encodes an ABC transporter protein (MRP6) expressed primarily in the human liver and kidneys. This gene has been shown to be involved in the regulation of tissue calcification in vertebrates. We aimed to study the evolution of the *ABCC6* gene during the vertebrate radiation and characterize its potential role during the formation of the mineralized scale in the skin.

The evolution of *ABCC6* gene was performed using in silico comparative analysis and the PXE mutations were mapped in human MRP6 protein and compared with the respective amino acids positions in other species. The mRNA expression levels of *abcc6* and *abcc1* (closely related family member) were assessed during scale formation by quantitative RT-PCR on a sea bream skin/scale regeneration model.

The *abcc6* gene was only found in bony vertebrate genomes and evidence suggest that this gene was deleted from non-bony vertebrates, since no putative *abcc6* genes were retrieved from the cartilaginous fish elephant shark and lamprey. In teleosts duplication of the *abcc6* gene occurred, but the gene duplicates only persisted in the genomes of some species, suggesting that lineage or species-specific gene deletion occurred across their radiation. Nine amino acid positions, common between the fish and the mutated human MRP6 protein were found which suggest that the amino acids that cause the disease in humans, could have an important role in the calcification process in fish. No difference in *abcc6* and *abcc1* transcript abundance was detected during skin regeneration and the formation of the mineralized scale (2-3 days).

Our results provide evidence for parallel evolution of *abcc6* gene with the acquisition of a bony skeleton and highlight its potential association with calcium regulation. However, in teleost skin *abcc6* expression does not seem to be associated with scale formation/mineralization.

Keywords: ABCC6, ABCC1, ABCC3, Fish, PXE, vertebrates, invertebrates, MRP6.

#### 8.2. Introduction

The ATP-binding cassette (ABC) proteins belong to a large and ancient family of active transporter proteins that are present in a broad spectrum of organisms from bacteria to vertebrates [435]. Members of this family play a pivotal role in cell physiology as they are involved in uni-or bidirectional transport [436] of a large variety of substrates in cells [435, 437]. These active transporter proteins have been exploited for cellular delivery of drugs, including cancer chemotherapeutics and thus are of major pharmacological interest in human medicine. ABC transporters are typically composed of two transmembrane domains (TMD) and two nucleotide binding domains (NBD), also known as the ATP-binding cassette [435]. The NBDs, are the motor domains of ABC transporters and are characterized by the presence of a phosphate binding loop (Walker A), a magnesium binding site (Walker B), a switch region that contains a histidine loop targeted for hydrolysis, a Q-motif that interacts with the gamma phosphate of ATP via a water molecule and a conserved signature motif (LSGCQ) that is specific of the ABC transporters [438, 439]. The NBDs together bind and hydrolyze ATP, producing the driving force for the transport of molecules across the cell membrane against a concentration gradient. The TMD participates in molecular recognition and translocation [440], and two ATP molecules are necessary for the transport of one substrate molecule across the cell membrane [441]. The human ABC gene family contains an estimated 49 members divided into seven subgroups (ABCA to ABCG), and deleterious mutations in these genes have been linked to several heritable human diseases . The ABCC (ABC subfamily C) subgroup (Table 8-1) are large proteins (1325-1582 amino acids in length) that include 8 members encoding multidrug resistance-associated proteins (MRP) and 3 members encoding ion channel proteins or regulators of potassium channels [435]. Evolutionary analysis has revealed that with the exception of the ABCC13 gene, two major ABCC subfamily clusters exist: one that contains ABCC1, 3, 2, 6, 8 and 9 and another that contains ABCC4, 7, 5, 11, 12 and 10 [435]. The ABCC6 gene encodes the multidrug resistance protein 6 (MRP6) which has recently been shown to be involved in the regulation of tissue calcification in vertebrates [122]. Calcification is the physiological mechanism by which calcium salts are deposited in body tissues. Bone formation in vertebrates is the most common example of a normal calcification process. However, calcification disorders can also occur when calcium is abnormally deposited in soft tissues causing ectopic calcification [442].

Table 8-1. Human *ABCC* genes and their functions, as listed in Ensembl and OMIM database (modified from Dean et al [400]). Thirteen genes are described and the chromosome location, number of exons and the corresponding protein are also indicated. The *ABCC6* gene is highlighted in bold as it is the research topic of the present study.

Gene	Chr location	Exons	AA	Protein	Function
ABCC1	16p13.1	31	1531	MRP1	drug-efflux pump
ABCC2	10q24.2	32	1545	MRP2	Organic anion transporter
ABCC3	17q21.33	31	1527	MRP3	Multidrug resistance
ABCC4	13q32.1	31	1325	MRP4	Nucleoside transport
ABCC5	3q27.1	30	1437	MRP5	Nucleoside transport
ABCC6	16q13.11	31	1503	MRP6	Unknown function
ABCC7	7q31.2	27	1480	CFTR	Chloride ion channel
ABCC8	11p15.1	39	1582	SUR1	Sulfonylurea receptor
ABCC9	12p12.1	38	1549	SUR2	Encodes the regulatory SUR2A subunit of the cardiac K+ (ATP) channel
ABCC10	6p21.1	22	1492	MRP7	Drug resistance
ABCC11	16q12.1	29	1382	MRP8	Drug resistance in breast cancer
ABCC12	16q12.1	29	1359	ABCC12	Drug resistance
ABCC13	21q11.2	Truncate	ed protein	ABCC13	Unknown function

Abbreviations: AA- amino acid; Chr- chromosome, MRP- multidrug resistance protein, ATP- adenosine triphosphate.

The *ABCC6* gene has been associated with human calcification disorders such as human Pseudoxanthoma Elasticum (PXE; OMIM 264800), a heritable disorder characterized by calcification of elastic fibers in skin, arteries and the retina [125-127] and Generalized Arterial Calcification of Infancy (GACI; OMIM 614473), characterized by the calcification of the internal elastic lamina of muscular arteries and stenosis due to myointimal proliferation [96]. In humans, MRP6 transporter has a widespread tissue distribution and the protein is mostly detected in the basolateral membrane of hepatocytes, as well as in the proximal kidney tubules [123, 124]. Albeit with low expression, it is also found in the skin, retina and vessel walls [121, 125, 443]. Little is known about the molecules transported by MRP6 but these may be involved in stopping ectopic calcification, as in affected PXE patients MRP6 protein triphosphate (ATP) from cells and the release of pyrophosphate (PPi) from the break-down of ATP, and is suggested to be involved in the control of calcium and other mineral deposition. Thus, the disease is not caused by the lack of functional MRP6 but rather by the absence of PPi provided to the circulation by an *ABCC6*- dependent mechanism [129].

In other vertebrates, homologues of the human *ABCC6* are also present but its role in tissue calcification is poorly understood. Teleost fish are the largest and most successful group of

extant vertebrates and their genomes have evolved and adapted during their radiation. Studies in fish have largely focused on the study of vertebrate mineralization as they share many of the basic features of the formation of cartilage (chondrogenesis) and bone (osteogenesis) tissue [111-118]. Fish, as well as mammals develop ectopic calcifications; the zebrafish *abcc6* mutant develops ectopic calcifications around perichondral bone in the craniofacial and axial skeleton [113], and zebrafish *enpp1* mutants develops ectopic calcification in a variety of soft tissues, including the skin, cartilage elements, the heart, intracranial space and the notochord sheet [114]. Zebrafish is the only teleost model system in which the *abcc6* gene has been isolated and found to be associated with tissue mineralization [111] [113]. Mutations of the zebrafish *abcc6* gene resulted in extensive hypermineralization of the axial skeleton, suggesting that functional conservation with the human exists and that it is also associated with tissue calcification in other vertebrates [113].

In order to better understand the potential association of *abcc6* genes with vertebrate calcification and mineralization we studied the evolution of the *abcc6* gene during the vertebrate radiation and characterized transcript expression during the process of scale regeneration in fish skin. In fish, scales are important skin appendages imbricated in the dermis that are a reservoir of minerals. When scales are lost, fish have the capacity to regenerate them and the formation of the new scale and scale pocket occurs immediately to protect the individual [444]. A sea bream skin regeneration model was available and it was observed that at 4 days after scale removal the skin had healed and a new scale had formed [444]. The potential involvement of *abcc6* and *abcc1* in the process of scale regeneration was studied by analyzing transcripts of skin and scale in the sea bream skin-scale regeneration model over 4 days of regeneration.

#### 8.3. Methods

#### **8.3.1.** Database searches and sequence retrieval

The genomes of several vertebrates and invertebrates (with publicly available data) were explored for orthologues of the human *ABCC6* gene (ENSG00000091262) and the related family members, *ABCC1* (ENSG00000103222) and *ABCC3* (ENSG00000108846). A total of 24 vertebrate genomes representative of different classes (Supplementary table 8-1), were searched using the BLAST algorithm or database annotations for orthologues of *ABCC6*, *ABCC1* and *ABCC3* genes. The majority was deposited and assembled in the Ensembl database (GRCh38.p2) (http://ensemblgenomes.org/, accessed April 2015). The retrieved

genomes included 7 mammals (Chimpanzee, Pan troglodytes; Mouse, Mus musculus; Dog, Canis lupus familiaris; Armadillo, Dasypus novemcinctus; Cow, Bos taurus; Opossum, Monodelphis domestica; Platypus, Ornithorhynchus anatinus); a bird, chicken (Gallus gallus); the reptile green anole lizard (Anolis carolinensis); the amphibian Xenopus (Xenopus tropicalis); the Sarcopterygii Coelacanth (Latimeria chalumnae); 10 teleost (Actinopterigii) and 1 Agnatha (marine lamprey, Petromyzon marinus). The teleost genomes explored were: Tilapia, Oreochromis niloticus; Platyfish, Xiphophorus maculates; Cod, Gadus morhua; Stickleback, Gasterosteus aculeatus; Medaka, Oryzias latipes; Tetraodon, Tetraodon nigroviridis; Blind cave fish, Astyanax mexicanus; Zebrafish, Danio rerio; Spotted gar, Lepisosteus oculatus) and the sea bass, Dicentrarchus labrax assessed from the sea bass genome assembly [445]. To complement the characterization of the ABCC genes the genome of the elephant shark (*Callorhinchus milii*) a cartilaginous fish which diverged prior to the emergence of bony vertebrates, (Class Chondrichthyes) (http://ensembl.fugusg.org/index.html, accessed April 2015) was studied along with the teleost European sea bass (Dicentrarchus labrax. http://seabass.mpipz.de/cgi-

bin/hgGateway?org=European+seabass&db=dicLab1).

To trace the likely evolutionary origin of the *ABCC6* genes the genomes of several invertebrates species were also analyzed by accessing the Ensembl Metazoa database (<u>http://metazoa.ensembl.org/index.html</u>, accessed April 2015). Invertebrate genomes analyzed (n = 11, supplementary table 8-2) included deuterostomes basal to the vertebrates, the tunicate Ciona (*Ciona savigny*) and the cephalochordate Amphioxus (*Branchiostoma floridae*) and the echinoderm, the Sea urchin (*Strongylocentrotus purpuratus*) and also the protostome genomes of the owl limpet (*Lottia gigantea*), the leech (*Helobdella robusta*), the fruit fly (*Drosophila melanogaster*), the Honeybee (*Apis mellifera*), the flour beetle (*Tribolium castaneum*), the malaria mosquito (*Anopheles gambiae*), the crustacean Daphnia (*Daphnia pulex*) and the nematode (*Caenorhabditis elegans*).

The amino acid sequences of putative *ABCC1*, *3* and *6* candidates were retrieved by selecting those with the lowest e-value, similarity with the query proteins and then confirming putative identity by searching against the NCBI (<u>http://blast.ncbi.nlm.nih.gov/Blast.cgi</u>, accessed April 2015) protein database using the Blastp algorithm. We also searched the sequences of the others human ABCC transporters: *ABCC2* (ENSG00000023839), *ABCC4* (ENSG00000125257), *ABCC5* (ENSG00000114770), *ABCC7* (ENSG000000124574), *ABCC9* (ENSG00000069431), *ABCC10* (ENSG00000124574),

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*ABCC11* (ENSG00000121270), *ABCC12* (ENSG00000140798) and *ABCC13* (ENSG00000243064) to better resolve the origin of the vertebrate *ABCC6*, *1* and *3* members.

#### 8.3.2. Multiple sequence alignments and sequence comparisons

The deduced amino acid sequences of *ABCC6*, *ABCC1* and *ABCC3* genes from 35 species were aligned using ClustalW (<u>http://www.genome.jp/tools/clustalw/</u>, accessed April 2015) and were manually edited using GeneDoc 2.7 software, to remove sequence gaps and regions of poor aligned sequences. This software was also used to calculate the percentage of sequence identity/similarity between the homologue genes of the different species. The deduced mature sequence of the full-length human *ABCC6* gene (ENSG00000091262) and the two pseudogenes *ABCC6P1* (ENSG00000256340) and *ABCC6P2* (ENSG00000255277) were also aligned using ClustalW (<u>http://www.genome.jp/tools/clustalw/</u>, accessed April 2015) to identify differences between the sequences.

The full-length human and vertebrate MRP6 deduced proteins were aligned using ClustalW and the amino acids that are normally changed in of the principal nucleotide mutations responsible for the manifestation of the PXE disease (<u>http://www.hgmd.cf.ac.uk/</u>; acceded May 2016) were mapped across the different species.

#### 8.3.3. Phylogenetic analysis

Phylogenic trees were constructed using the deduced amino acid sequence alignment of the retrieved sequences (Supplementary table 8-1 and 8-2). We also added the sequences of the other human ABCC transporters: ABCC2, 4,5,7,8,9,10,11,12 and 13. The sequence alignment was edited in GeneDoc 2.7 software to eliminate gaps, and the edited final alignment with average sequence lengths of 1180-1200 was submitted to ProtTest 2.4 server software to select the best model to study protein evolution using the Selection Criterion of AIC (Akaike Information Criterion) [446]. The phylogenetic tree was established using the Maximum Likelihood (ML) method implemented in PhyML 3.0 software, available from the ATGC (http://www.atgc-montpellier.fr/phyml/, accessed April 2015) platform [447], using a JTT+I+G+F substitution model and the following parameters: gamma shape- 4 rate categories (G=1,109) and proportion of invariable sites (I=0.017). Sequence branch statistical support was assessed using 100 bootstrap replicates. The consensus phylogenetic tree was displayed and annotated with the FigTree4 program and was rooted using the protostome ABCC branch.

#### **8.3.4.** Gene organization and gene synteny

Human *ABCC6* and its two pseudogenes (*ABCC6P1* and *ABCC6P2*) and the *abcc6* gene from spotted gar was deduced using the Ensembl gene annotation tool. The gene structure and exon/intron sizes were compared between both species.

To characterize the gene environment of the vertebrate ABCC6 gene we used as template the genome annotation of the Genomicus database (http://www.genomicus.biologie.ens.fr/genomicus-79.01/cgi-bin/search.pl, accessed August 2015). The human gene environment was selected, and neighboring genes were identified in the following vertebrates (Opossum (Monodelphis domestica), Platypus (Ornithorhynchus anatinus), Chicken (Gallus gallus), Xenopus (Xenopus tropicalis), Coelacanth (Latimeria chalumnae), Spotted gar (Lepisosteus oculatus), Zebrafish (Danio rerio), Tetraodon (Tetraodon nigroviridis), Stickleback (Gasterosteus aculeatus), Medaka (Oryzias latipes) and the sea bass (Dicentrarchus labrax) using genome annotations available from the genome assemblies. The neighboring genes were characterized and identified based upon Ensembl database gene annotation and complemented with sequence homology searches (http://www.ensembl.org/Multi/Tools/Blast?db=core, accessed May 2015). The Elephant shark (Callorhinchus milii) homologue genome region was also characterized using a similar strategy to that described above. The accession numbers used for linkage analysis are available in supplementary table 8-3.

#### 8.3.5 Transcriptome database searches

To increase knowledge about the physiological importance of the ABCC genes, searches on vertebrate transcriptome data were also performed. The "in silico" distribution of the nonmammalian ABCC6 was characterized and the transcriptome and EST (Expressed sequence tag) databases of the human, bird, reptile, amphibian and teleost were searched to construct a digital expression map to infer possible overlapping tissue expression of the ABCC6 gene with human. Searches were performed in lineage-specific NCBI EST databases human (taxid: 9606); birds (taxid:8782); reptiles (taxid:8504); amphibians (taxid:8292) and teleost fishes (taxid:32443) using the human, chicken, anole lizard, xenopus and zebrafish *abcc6* sequences, respectively. The identity of the sequences retrieved was confirmed by homology with the human orthologues. Searches were also performed in other databases where expression data has been deposited: Geisha (http://geisha.arizona.edu/geisha/), Xenbase (http://www.xenbase.org/entry/), Expression Atlas Database (<u>http://www.ebi.ac.uk/gxa/home</u>), GeneCards (http://www.genecards.org/), Ensembl (http://www.ensembl.org/index.html) and complemented with published data [113].

In addition, a sea bass scale and skin transcriptomes available "in house" was also searched for *abcc6* and *abcc1* transcripts (Pinto et al., unpublished).

#### 8.3.6 Polymerase chain reaction (PCR) and quantitative-PCR (qPCR)

Based on the sea bass transcriptome data we further explored the potential physiological role of the abcc transcripts in fish skin and scale formation. *abcc6* and *abcc1* genes were studied in the skin/scale of sea bream (*Sparus auratus*) using a regenerating skin model over a 4 days period as previously described [444]. The experiments were carried out following international and national guidelines for animal care and experimentation, under a "Group-I" licence from the Portuguese Government Central Veterinary service to CCMAR and conducted by a certified investigator (DMP).

Briefly, adult sea bream of the same age class (1 year) were used and at time zero scales were removed from the left flank of the body by gently stroking the skin with forceps to minimize damage of the dermis. Samples (N = 8/ time point) of intact skin (untouched right hand flank) and damaged skin (left hand flank) were collected during a time series after scale removal: 6 h (disruption of the dermis and scale pocket) and 24 h (reorganization of the epidermis to wound heal), 48h (emergence of dermal papilla that defines the localization of the new scale), 72h (scale emergence) and 96h (scale mineralization). In this way, the same fish provided control and regenerating skin samples and they could be directly compared. Specific primers for the sea bream *abcc6* and *abcc1* were designed by searching the CCMAR sea bream transcriptome database with transcripts from various tissues [448]. The primers for *abcc6* were Sb\_abcc6fwd ttagagacaagacccgcat and Sb\_abcc6rev tggcaaaggtgtggatgaag and for abcc1 were Sb\_abcc1fwd tatgagtcacctcaacaaagc and Sb\_abcc1rev tccgttcatactggattacca. Preliminary expression analysis of *abcc6* and *abcc1* by PCR on sea bream cDNA (bone, skin, larva, scale) (available in the laboratory) was carried out using the following cycle: 95°C, 3 min; (95°C 30 sec, 60°C 30 sec, 72°C 30 sec) cycled 40 times and a final extension of 72°C, 5 min. The amplified PCR products were sequenced to confirm their identity before testing for gene expression on the skin regeneration model.

To investigate the potential involvement of *abcc6* and *abcc1* in sea bream skin regeneration a preliminary qPCR experiment was run using cDNA pools composed of RNA from both intact and damaged skin in 6 individuals for each time point. The qPCR was performed for a 10 $\mu$ l final reactions volume using the 1× SsoFast-Evagreen Supermix (Biorad) and 300 nM of

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forward and reverse primers. Reactions were performed using the StepOnePlus thermocycler (Applied Biosystems, UK) following the program: 30 s at 95 °C, 45 cycles of 5 s at 95 °C and 15 s at 60 °C. A final melting curve was carried out between 60 and 95 °C and produced a single product dissociation curve for each gene. Relative expression between the damaged and intact skin samples were compared using the delta Ct values normalized with the housekeeping gene *rps18*.

#### 8.4. Results

#### 8.4.1. Members of the ABCC6 in vertebrates and invertebrates

Orthologues of the human *abcc6* gene were identified in all the teleost and tetrapod genomes analyzed with the exception of two fishes: the cartilaginous fish elephant shark (*Callorhinchus milii*) and the lamprey (*Petromyzon marinus*). In some teleost species such as the stickleback (*Gasterosteus aculeatus*), blind cave fish (*Astyanax mexicanus*) and zebrafish (*Danio rerio*) more than one *abcc6* gene was identified. In stickleback and blind cave fish two *abcc6* genes were found and in the zebrafish three seem to exist (Figure 8-1).

Multiple sequence alignment of the deduced amino acid sequence of the *ABCC6* gene sequences revealed a relatively high conservation overall and several highly conserved regions (alignment of *ABCC6* and *ABCC1* genes of vertebrates available in supplementary figure 8.1). Comparison of the deduced mature protein sequence of the full-length MRP6 transcripts in human with the orthologue in the chicken (*Gallus gallus*) indicated that the deduced proteins shared 52% amino acid identity and 69% similarity. Between the human and the lobe finned fish Coelacanth (*Latimeria chalumnae*) the MRP6 proteins shared 48% identity and 67% similarity and 42-47% identity and 61-65% similarity with the orthologues in the teleosts, stickleback (*Gasterosteus aculeatus*), *European sea bass* (*Dicentrarchus labrax*), tetraodon (*Tetraodon nigroviridis*), tilapia (*Oreochromis niloticus*), medaka (*Oryzias latipes*), platyfish, (*Xiphophorus maculates*), cod (*Gadus morhua*), *zebrafish* (*Danio rerio*), blind cave fish (*Astyanax mexicanus*) and spotted gar (*Lepisosteus oculatus*) (Supplementary table 8-4). *ABCC6*-related family members, the *ABCC1* and *ABCC3* genes, were also retrieved from the databases for evolutionary comparisons because, a) they are similar to *ABCC6* and b) *ABCC1* in the human genome is localized in proximity to the *ABCC6* locus.



Figure 8-1. Dendrogram indicating the number of *ABCC6* genes and the related *ABCC1* and *ABCC3* genes identified in the different vertebrate and invertebrate genomes. Circles with different colours represent members of the different gene families and uncoloured circles means the gene was not identified. The dendrogram was drawn having in consideration the evolutionary relationship of the different species and the two major genome duplication events (1R and 2R) that are proposed to have occurred early in the vertebrate radiation. The teleost specific genome duplication event (3R) is also indicated. Gene accession numbers are available in supplementary table 8-1 and 8-2.

Orthologues of the human *ABCC1* and *ABCC3* genes were also identified in almost all vertebrates with the exception of *abcc1* in cod (*Gadus morhua*) and lamprey (*Petromyzon marinus*) genomes, and *abcc3* in the sea bass (*Dicentrarchus labrax*) and the cartilaginous fish elephant shark (*Callorhinchus milii*) (Figure 8-1). It is unclear if the absence of the *abcc1* and *abcc3* genes in several species is the result of their elimination from these species genomes or if they are the consequence of incomplete genome assemblies. Teleost duplicate genes were also found for *abcc1* in platyfish (*Xiphophorus maculatus*) and for *abcc3* in coelacanth (*Latimeria chalumnae*) and zebrafish (*Danio rerio*) (Figure 8-1). Searches in early deuterostomes and protostome genomes were also carried out to characterize the origin of the *abcc6*, *1 and 3* genes. Queries using the human MRP6 sequence identified putative *abcc6*-like genes in several invertebrate genomes and many species seem to possess multiple gene copies (Supplementary table 8-2).

#### 8.4.2 Sequence conservation of the amino acids altered in PXE disease

A total of 139 mutation associated with PXE disease were retrieved from Human Gene Mutation database (HGMD) and the amino acids positions altered by mutation were mapped in the alignment and compared across the different vertebrate species. Mutations have been identified throughout the protein however the "hot spots" associated with PXE is more located within the cytoplasmatic region of human MRP6. Comparisons of the vertebrate homologue amino acid positions revealed that in general the mutations mapped in the alignment are well conserved across mammals (Supplementary figure 8-1). More than 50 amino acid positions are 100% conserved across vertebrates (Supplementary figure 8-1), suggesting that these positions were under high selective conservative pressure during the vertebrate radiation. Interestingly, in some species, especially within fish, there are positions in which the amino acid positions, common between the fish and the mutated human MRP6 protein, map to the cytoplasmatic region (252; 415; 881; 1049; 1226 and 1268) and the transmembrane region (594; 946 and 950) and are represented in Figure 8-2.



Protein region	стр	стр	TMD	стр	TMD		стр	c	тр
AA position	252	415	594	881	946	950	1049	1226	1268
Codon change in human	CTT-TTT	GTG-GCG	GCC-GTC	AGG-AGT	CTC-ATC	GCA-ACA; GTA	TCC-GCC	<b>CTA-ATA</b>	CGG-CAG
Human variation in PXE disease	F	A	v	s	I T,V		А	1.1	Q
Human	L	v	Α	R	L	A	S	L	R
Chimpanzee	L	v	A	R	L	A	S	L	R
Mouse	L	v	A	G	L	т	S	L	R
Cow	L	v	A	G	L	A	S	L	R
Dog	L	v	A	E	L	A	S	L	R
Amadilo	L	v	A	G	L	A	S	L	R
Opossum	L	v	A	т	1.1	v	S	L	R
Platypus	L.	v	A	ĸ	G	т	S	L	R
Chicken	А	v	А	R	L	1.1	s	1.1	R
Anolelizard	F	v	A	Q	A	1.1	s	1.1	R
Xenopus	F	т	s	P	Y	s	A	м	Q
Coelacanth	L	v	А	т	L	v	S	1.1	R
Stickleback_a	E.	A	A	s	1.1	1.00	s	v	E
Stickleback_b	L	A	A	s	1.1	1.0	S	v	Q
Robalo	L	A	A	s	1.1	1.00	A	v	Q
Tetraodon	L	A	A	E	1.1	1.00	A	v	Q
Platyfish	L	A	A	s	1.1	1.00	A	v	Q
Cod	-	A	х	s	L	1.00	A	v	Q
Zebrafish_a	L	A	A	S	L	1.00	A	v	Q
Zebrafish_b	L	A	v	S	F	1.00	S	v	Q
Zebrafish_c	L	A	A	н	L	1.00	S	v	Q
Blind cave fish_a	L	A	A	s	L	1.00	S	v	Q
Blind cave fish_b	L	A	А	s	L	1.00	A	v	Q
Medaka	L	A	А	s	1.1	1.0	v	v	Q
Spotted gar	L	A	А	S	L	1	s	v	R

TMD: Transmenbrane domain CTD: Citopiasmatic domain EXT: Extracellular

Figure 8-2. Alignment of the MRP6 amino acid positions affected by 16 selected mutations previously associated with PXE disease in human and in other vertebrates in which amino acid that cause PXE in humans is the normal in other species.

Comparisons of *ABCC6* and *ABCC1* revealed that the *ABCC6* PXE point mutation are also generally highly conserved across this related family member, suggesting that they may also play a pivotal role in the maintenance of ABCC family function.

#### 8.4.3 Phylogeny of ABCC6

Phylogenetic analysis was performed using the protein alignment of the deduced vertebrate MRP6, MRP1 and MRP3 mature proteins and their putative homologues in invertebrates (early deuterostomes and protostomes). The tree topology shows that *ABCC6* and the two

other members are in three independent branches (with strong bootstrap support) and that the family members shared common ancestry prior to the vertebrate emergence (Figure 8-3). The tree suggests that *ABCC3* members diverged earlier than *ABCC1* and *ABCC6* genes that seem to be the result of a more recent gene duplication. The invertebrate branch contains several ABCC-like genes that apparently share a common ancestor with the vertebrate genes but they form a separate clade and do not group with any of the vertebrate protein clusters. Several duplications of genes occurred in invertebrate species and also in some vertebrates, such as the teleosts. Based upon the sequence clustering in the tree, gene duplication of *abcc6* seems to be the result of the teleost specific whole genome duplication event and in the zebrafish subsequent species-specific gene duplications also occurred.

The tree topology, failed to cluster the coelacanth sequences ENSLACG00000022117 (annotated as *abcc1* in ensembl database) and ENSLACG00000001471 (annotated as *abcc6* in ensembl database) in the expected branch. According to the clustering in the phylogenetic tree the sequence ENSLACG00000022117 is an *abcc6* gene, and the sequence ENSLACG0000001471 is an *abcc1* gene. The absence of the *abcc6* gene in lamprey (*Petromyzon marinus*) and cartilaginous fish elephant shark (*Callorhinchus milli*) suggests that *abcc6* gene does not group as expected based on the consensus in relation to species evolution, suggesting that abcc6 in this specie suffered distinct selective pressures or there may be an errors in the genome or incomplete genome assemblies. The Coelacanth (*Latimeria chalumnae*) *abcc3* gene did not group as expected since the putative coelacanth *abcc3* sequence (ENSLACG0000006619) was very incomplete.

Addition of the other human ABCC transporters revealed that the early deuterostomes sequences identified shared common ancestry with vertebrate *ABCC6*, *1* and *3* members and that the protostome members retrieved from the insect and nematode genomes seem to have shared a common origin with the *ABCC2* family early in the ancestral bilaterial genome (Figure 8-3).

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Figure 8-3. Phylogenetic tree of the vertebrate and invertebrate ABCC6, 1 and 3 with the other human ABCC family members. The phylogenetic tree was built using the ML method with PhyML 3.0 software with 100 bootstrap replicates using JTT+I+G+F substitution model given by Protest and was rooted using the invertebrate ABCC-like branch. To facilitate interpretation, the three major vertebrate ABCC clades are boxed with different colours, and the detailed presentation of the invertebrates and the other human ABCC family members (ABCC2, 4, 5, 7, 8, 9, 10, 11 and 12) have been collapsed. The original tree is available in supplementary figure 8-2 and the accession numbers are given in the supplementary tables 8-1 and 8-2.

#### 8.4.4. Gene structure and gene linkage across vertebrate

The gene structure of the human *ABCC6* genes (including the two *ABCC6* pseudogenes *ABCC6P1* and *ABCC6P2*) was compared with the fish spotted gar *abcc6* gene (Figure 8-4). In human, the full *ABCC6* gene structure is composed of 31 exons and spans 74,56kb in chromosome 16. The two pseudogenes are much smaller and map in close proximity to the full-length *ABCC6* gene. *ABCC6P1* is composed of 11 exons and *ABCC6P2* is composed of 5 exons which span 27,14Kb and 3,88 Kb, respectively (Figure 8-4). Exons 2, 3, 4 and 5 of *ABCC6P2*, *ABCC6P1* and *ABCC6* have almost the same sequence and only differ at exon 1. Exon 8, 9 and 10 of *ABCC6P1* have the same coding potential as *ABCC6* and the differences in the remaining exons may be a consequence of their divergence after gene duplication.



Figure 8-4. Gene organization of the *ABCC6* gene in human and spotted gar. The two incomplete human *ABCC6* pseudogenes (*ABCC6P1* and *ABCC6P2*) are also represented. Gene sizes are indicated and exons are represented by numbered boxes and the solid black line denotes the introns.

No putative *ABCC6* pseudogenes were found in other vertebrate genomes; they seem to be characteristics of the human genome. Comparison of the predicted *in silico* gene structure of the human and spotted gar (a slow evolving teleost genome, that has not suffered tetraploidization, 3R) revealed that they share the same exon number and most exons (21 exactly) are of similar size (Supplementary table 8-5). Exon 15 and Exon 16 are the most divergent and they encode a region of low conservation within the cytoplasmic motif.

Several conserved genes flank the vertebrate *ABCC6* gene suggesting that evolution of this chromosome segment in vertebrates was under conservative pressures. The genes *ABCC1*; *COQ7*; *ARL6IP1*; *RPS15A*; *NOMO3*; *XYLT1*; *MYH11*; *FOPNL* and *NDE1* were found in the

vicinity of the *ABCC6* gene across many vertebrate genomes. Gene synteny analysis revealed that with the exception of the *abcc6* gene in the Elephant shark (*Callorhinchus milli*) and *ARL6IP1* in Platypus (*Ornithorhynchus anatinus*) and *FOPNL* in Coelacanth (*Latimeria chalumnae*) and Xenopus (*Xenopus tropicalis*) at least ten genes that are part of the human *ABCC6* gene environment have been maintained across vertebrates (Figure 8-5). In the genomes of primates a conserved gene environment with the human and other vertebrates was also identified but no putative *ABCC6* pseudogenes were found further suggesting that these were acquired during the radiation of the human.

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Figure 8-5. Gene synteny analysis of the *ABCC6* gene environment across vertebrates. The Human, Opossum, Platypus, Chicken, Xenopus, Coelacanth, Zebrafish, Stickleback, Spotted gar and Elephant shark homologue genome regions are represented. Arrowheads represent gene orientation in the genome. Members of the same family are indicated by the same color. The position of the genes in the genome fragments is indicated.

#### 8.4.5 Expression analysis in non-mammals

Searches on ESTs and several other databases for non-mammalian vertebrates revealed the tissue distribution of the *ABCC6* transcripts (Table 8-2). A similar strategy was also applied for the sequence homologues *ABCC1* and *ABCC3* for comparisons. As in humans, expression of these transcripts seems to be widespread in different tissues including some with importance in calcium homeostasis. In the chicken, *ABCC6* was found to be expressed in epiphyseal growth plate but also in the intestine and kidney, which are important organs that regulate calcium balance in vertebrates [442]. In reptiles, an EST was found in the kidney and in teleost fish *abcc6* transcripts were found in the craniofacial bone elements, fins and intervertebral discs. *ABCC1* and *ABCC3* seem to have a more dispersed distribution than *ABCC6* (Table 8-2).

Table 8-2. ABCC6; ABCC1 and ABCC3 expression analysis in human, bird, reptile, amphibianand teleost. ESTs were obtained from NCBI EST databases. Searches were also performed inotherdatabases:Geisha(http://geisha.arizona.edu/geisha/);Xenbase(http://www.xenbase.org/entry/);ExpressionAtlas(https://www.ebi.ac.uk/gxa/home),GeneCards(http://www.genecards.org/),Ensemblhttp://www.ensembl.org/index.html)andcomplemented with published data [113].

Tissue		ABC	CC6	ABCC1				ABCC3				
Tissue	Hsa	Gga	Aca	Dre	Hsa	Gga	Xtr	Dre	Hsa	Gga	Aca	Xtr
Adenocarcinoma cell line									Χ			
Adrenal gland					X				X			
Aorta					X							
Ascites					X							
Blood						X						
Brain					Χ	Х						
Bursa of fabricius						X						
Bursal lymphocyte						X						
Carcinoma, cell line									Χ			
Cerebrum	Х											
Cervix, tumor tissue									X			
Chondrocytes isolated from growth						X						
Chondrosarcoma lung metastasis cell lines					X				X			
Colon									X			
Connective tissue						X						
Cortex	X											
Craniofacial bone elements				Х								
Day 1 embryo								Χ				
Ductal carcinoma, cell line									Х			
Dura mater					Х							
EBV-transformed					X							
Embryonic stem cells, cell lines					Х							
Embryonic tissue						X						
Epididymis					X							
Epiphyseal growth plate		X				X						
Epithelioid carcinoma					Χ							
Esophageal, tumor tissue									Χ			

	ABCC6			ABCC1				ABCC3				
lissue	Hsa	Gga	Aca	Dre	Hsa	Gga	Xtr	Dre	Hsa	Gga	Aca	Xtr
Esophagus muscle					X							
Fins				X								
Gallbladder	X											
Gastroesophage					X							
Gonad		X				X						
Gonadal PGC					X	X						
Head (Geisha)		X				X						
Heart						X	X				X	X
Hepatocelular carcinoma, cell line	X											
Human embryonic stem cells					X							
Intestine							X					
Invertebral disc				X								
Kidney	X	X	X				Χ			X	X	Χ
Large cell carcinoma									X			
Large intestine	X											
Leukemia cell					Χ							
Leukocyte									X			
Liver	X	X				X						
Liver and Spleen									X			
Lung					Χ							
Lymph node					Χ							
Mitral valve					Χ							
Neuroblastoma					X				X			
Ovary		X			Χ	X			X			
Pancreas	X								Х			
Paratiroid gland					X							
Peripheral Nervous system									X			
Pooled colon, kidney, stomach									X			
Pterygium									X			
Renal cell adenocarcinoma									Х			
Retinoblastoma					Χ							
Skeletal muscle						X	Х					
Skin					X			X				
Small intestine		X										
Smooth muscle					X							
Spinal cord	Χ											
Spleen					Х	Х			Χ			
Splenocytes						Χ						
Stomach					X				Χ			
Testis					X			Χ				
Thalamus									Χ			
Thymus					X				Χ			
Thyroid					Х							
Tongue					Х							
Tongue, tumor tissue					Х				Х			
Trunks		Х										
Uterus					Х							
Vas deferens					Х							
Whole embryo						Χ	Χ	Χ				
Whole larva								X				
Whole body								Х				

Abbreviations: Hsa- Human, Gga- Chicken, Aca- Anole lizard, Dre- Zebrafish, Xtr- Xenopus.

#### 8.4.6 Expression of abcc6 and abcc1 during sea bream scale formation

According to the CT values (Supplementary table 8-6), both transcripts for *abcc6* and *abcc1* are expressed in the sea bream skin and, *abcc6* seems to be more expressed than *abcc1* (Supplementary table 8-6). Comparison of the Ct values between the regenerating and intact skin samples suggests that gene expression in both samples is similar and follows a similar trend, and there was no evidence for major changes in cycle number, indicating that *abcc6* and *abcc1* genes not have a role in skin regeneration and scale formation in the teleost. The same results were observed in figure 8-6A and 8-6B in which both intact and regenerating skin samples, the genes shows also a similar distribution profile.



Figure 8-6. Expression results of *abcc6* and *abcc1* in sea bream skin regeneration assay. A and B shows the profile of  $\Delta$ CT values in *abcc6* and *abcc1*;  $\Delta$ CT values were obtained subtracting the Ct of each gene by the housekeeping control gene *rps18*. C and D represent the relative expression of *abcc6* and *abcc1* genes in regenerating skin relative to intact skin.

Comparisons of the relative expression levels between regenerating ( $\Delta\Delta$ Ct method) and intact sea bream skin (Figure 8-6C and 8-6D) revealed that expression of *abcc6* and *abcc1* between regenerating and intact skin was similar.

#### **8.5.** Discussion

In the present study the evolution of the vertebrate ABCC6 gene was studied and the potential role of this gene in fish skin scale regeneration was tested. Orthologues of the human ABCC6 gene were explored in several vertebrate genomes and phylogenetic analysis revealed that human and other vertebrate ABCC6 genes shared common ancestry and that the abcc6 gene emerged early during the vertebrate radiation. The abcc6 gene was only found in bony vertebrates genomes and evidence suggests that this gene was deleted from non-bony vertebrate, as no putative abcc6 genes were retrieved from the cartilaginous fish elephant shark and the lamprey. The teleost duplication of the *abcc6* gene occurred but the gene duplicates only persisted in the genomes of some species, suggesting that lineage or speciesspecific gene deletion occurred during their radiation. In the mapping of the human PXE mutations we obtained nine amino acid positions, common between the fish and the mutated human MRP6 protein, located in cytoplasmatic and transmembrane regions. This could suggest that the amino acids that cause the disease in humans, may have an important role in the calcification process in fish. Expression analysis of *abcc6* gene during the mineralization process in scales in the sea bream regeneration model suggested that this gene may not be involved in scale formation, even though it was highly expressed in fish skin. Our results provide evidence for parallel evolution of the *abcc6* gene with the acquisition of a bony skeleton and highlights its potential association with calcium regulation, however the physiological role of the ABCC gene family in teleost skin remains to be determined.

Orthologues of the human *ABCC6* were found in the genomes of different vertebrates. The non-mammalian genes that shared high sequence and structure similarities with the human *ABCC6* gene were retrieved from birds and fish. In tetrapods and in the majority of teleosts and also in the coelacanth and spotted gar, a single *abcc6* gene was found, however in the stickleback and blind cave fish two paralogue genes persisted and in the zebrafish genome three were identified. During the vertebrate radiation, duplication and deletion events have greatly contributed to shape vertebrate genome content [449]. Early as the vertebrates emerged two whole round of genome tetraploidization occurred prior to the divergence of the jawless fish [450, 451]. In the teleosts, a subsequent genome duplication event occurred and this explains the presence of gene duplicates in teleost genomes relative to tetrapods [451].

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However, only some duplicates persisted and other were eliminated from the genome [452] potentially due functional redundancy [453]. The reason why duplicated *abcc6* genes persisted in stickleback, blind cave fish and zebrafish and were deleted from the genomes of other analyzed teleost is unknown, and it remains to be established if both gene copies are functional.

Although functional studies of the *abcc6* genes in teleosts are scarce, in zebrafish some studies exist [111-113]. The zebrafish skeleton shows high similarity with human bones in terms of cells, matrix proteins, and molecular signaling pathways [454]. A study revealed that, in zebrafish embryos, the duplicate *abcc6a* is expressed in the kupffer's vesicles and tail bud, while the second duplicate - *abcc6b*- is expressed in the enveloping layer and embryonic kidney proximal straight tubules [111]. In the same study, using morpholinos to "knockdown" *abcc6a* and *abcc6b* the authors suggested that *abcc6a* is an essential gene for normal fish development [111].

It is known that the absence of the MRP6 activity observed in patients with PXE or Abcc6-/observed in mice, cause ectopic mineralization [128, 415]. A study using zebrafish mutants revealed that disease causing *abcc6* mutations, that do not directly affect the transport and or ATP catalytic activity, resulted primarily in lower stability and or cytoplasmatic retention of the mutant proteins [112]. Mackay and Schulte-Merker identified, by next generating sequencing, the causative mutation in the *abcc6a* gene in a zebrafish line with a recessive mineralization disorder. The identified mutation resulted in the substitution of L1429R in a highly conserved region of NBD-2 that contains the Walker B motif, which is essential for binding to ATP [455]. In another study, the authors verified that in zebrafish this variant causes hypermineralisation of the axial skeleton, resulting in mineralised structures in the intervertebral space. According to Ensembl database, this variant could also occur in the cow (L1426R; rs440576475), but no phenotype information was available. In humans, in the corresponding variant (L1425P; rs150230403) a proline substitution occurs instead of an arginine, and is not associated with PXE or any other disease. However the Sift and PolyPhen rating suggest that this variant has a deleterious and damaging effect on the protein. The immediately preceding variant I1424T in humans is associated with PXE.

In our study, we show that *abcc6* and the related *abcc1* are expressed in teleost skin and we hypothesized that it could be involved in scale formation. However expression studies in a sea bream skin/scale regeneration model suggests that the gene expression varies across time but they were not significantly different from the control, and thus the potential role of *abcc6* in skin remains undefined. In zebrafish the *abcc6a* gene is expressed and functions at the site of

mineralization, secreting ATP from cells increasing PPi locally, suggesting that the transporter ligand in fish is not liver derived as occurs in humans [113].

A strong link between the *ABCC6* gene and reduced amounts of pyrophosphate has been established [129]. *ABCC6* overexpression induces nucleotide release in vitro, which is rapidly converted by ENPP1 into PPi [129]. It has been reported that PPi secretion from the livers of *Abcc6-/-* mice was dramatically lower compared to wild type mice, and the authors suggested that MRP6 is an ATP efflux transporter [397]. ATP is converted into AMP and PPi and represents the main source of mineralization inhibitor PPi in plasma, which fully explains why the absence of *ABCC6* results in the ectopic mineralization observed in patients with PXE [397].

Our preliminary expression analysis in a teleost skin regeneration mode revealed that the *abcc6* gene may not be involved in early stages of scale formation. In fact it should be noted that mineralization in PXE and its mouse model *Abcc6-/-*, is not noted at birth, but develops later in life. Probably the *abcc6* gene in fish skin acts as a potent inhibitor of pathological ectopic calcification through a PPi mechanism. Overall, the presence of the *abcc6* gene in teleost fishes and its absence in cartilaginous and lamprey genomes suggest that this gene possibly emerged associated with the need for more sophisticated mechanisms of control of PPi in cells. Future studies aimed at understand the function of *abcc6* in teleost skin will be required.

#### **8.6 Supplementary Material**

Supplementary table 8-1. Accession numbers of the *ABCC6*, *ABCC1* and *ABCC3* genes retrieved from vertebrates. Sequences were retrieved from Ensembl Genomes (<u>http://ensemblgenomes.org/</u>, accessed April 2015) database. The Elephant shark (*Callorhinchus milii*) orthologues were obtained from (<u>http://ensembl.fugu-sg.org/index.html</u>, accessed April 2015) database.

			Vertebrates		
Specie nome	Common nomo	Abbrowistures		Accession number	
Specie name	Common name	Abbieviatures	ABCC6	ABCC1	ABCC3
Homo sapiens	Human	Hsa	ENSG0000091262	ENSG00000103222	ENSG00000108846
Pan troglodytes	Chimpanzee	Ptr	ENSPTRG0000007815	ENSPTRG0000007812	ENSPTRG0000009406
Mus musculus	Mouse	Mmu	ENSMUSG0000030834	ENSMUSG0000023088	ENSMUSG0000020865
Canis lupus familiaris	Dog	Cluf	ENSCAFG0000018197	ENSCAFG0000018208	ENSCAFG00000017201
Bos taurus	Cow	Bta	ENSBTAG00000015191	ENSBTAG0000021090	ENSBTAG0000020070
Dasypus novemcinctus	Armadillo	Dno	ENSDNOG0000024923	ENSDNOG0000014990	ENSDNOG0000046300
Monodelphis domestica	Opossum	Mdo	ENSMODG0000005815	ENSMODG0000004194	ENSMODG0000020910
Ornithorhynchus anatinus	Platypus	Oan	ENSOANG0000005123	ENSOANG0000005124	ENSOANG0000013379
Gallus gallus	Chicken	Gga	ENSGALG0000006698	ENSGALG0000006646	ENSGALG0000007522
Anolis carolinensis	Anole Lizard	Aca	ENSACAG0000003478	ENSACAG0000005349	ENSACAG0000001396
Xenopus tropicalis	Xenopus	Xtr	ENSXETG00000026360	ENSXETG00000019661	ENSXETG00000012239
Latimeria chalumnae	Coelacanth	Lch	ENSLACG00000022117	ENSLACG0000001471	ENSLACG00000007209 ENSLACG0000006619
Contained and and bottom	C 4: -1-1 - 11-	Car	1) ENSGACG00000019172	ENSC A CC00000000424	ENSC A CC0000005001
Gasterosteus aculeatus	Stickleback	Gac	2) ENSGACG0000003037	ENSGACG000000434	EINSGACG00000005901
Dicentrarchus labrax	See bass	Dla	177430	195360	ni
Oryzias latipes	Medaka	Ola	ENSORLG00000013429	ENSORLG00000017141	ENSORLG0000020741
Tetraodon nigroviridis	Tetraodon	Tni	ENSTNIG00000012067	ENSTNIG0000005013	ENSTNIG0000004171
Oreochromis niloticus	Tilapia	Oni	ENSONIG0000018866	ENSONIG0000007824	ENSONIG0000019586
Xiphophorus maculatus	Platyfish	Xma	ENSXMAG0000004906	1) ENSXMAG00000017319 2) ENSXMAG0000007738	ENSXMAG00000012203
Gadus morhua	Cod	Gmo	ENSGMOG0000005748	ni	ENSGMG0000010029
			1) ENSDARG00000016750		1) ENSDARG0000007243
Danio rerio	Zebrafish	Dre	2) ENSDARG0000094901	ENSDARG00000104719	2) ENSD & PC0000006662
			3) ENSDARG0000095820	1	2) ENSDARG0000090002
A atu an an mania anna	Dlind agus fish	Ama	1) ENSAMXG0000004837	ENSAMYC0000002042	ENS A MY C00000016252
Astyanax mexicanus	Billiu cave fish	Alle	2) ENSAMXG0000003085	ENSAWIX00000002943	ENSAWAG0000010255
Lepisosteus oculatus	Spotted gar	Loc	ENSLOCG0000007152	ENSLOCG0000007196	ENSLOCG0000010918
Callorhinchus milii	Elephant shark	Cmi	ni	SINCAMG00000015787	ni
Petromyzon marinus	Lamprey	Pma	ni	ni	ENSPMAG0000000892

Abbreviations: ni- not identified

Supplementary table 8-2. Accession numbers of the ABCC genes retrieved from invertebrates.SequenceswereretrievedfromEnsemblMetazoadatabase(http://metazoa.ensembl.org/index.html, accessed April 2015).

	Invertebra	ates	
Su sois nome	Common anoma	Abbuenistion	Accession number
Specie name	Common name	Abbreviation	abcc1/3/6
			WBGene00003407
			WBGene00003408
			WBGene00003410
Caenorhabditis elegans	Roundworm	Cel	WBGene00003413
			WBGene00003409
			WBGene00003414
Daphnia pulex	Water flea	Dpu	DAPPUDRAFT_347281
			AGAP009835
	M1		AGAP008437
Anopheles gambiae	Malaria mosquito	Aga	AGAP027980
			AGAP028128
Tribolium castaneum	Red flour beetle	Тса	TC012253
Apis mellifera	Honeybee	Amel	GB53134
Drosophila melanogaster	Drosophila	Dme	FBgn0032456
	Leesh	I.I	HelroG163344
Helobaella robusta	Leech	Нго	HelroG157076
			LotgiG107213
Terrise sis marks a	Oral lines of	I -:	LotgiG105097
Lottia gigantea	Owr Impet	Lgi	LotgiG110718
			LotgiG153611
Strongylocentrotus purpuratus	Sea urchin	Spu	26395
	Ciana	Car	ENSCSAVG0000003792
Ciona intestinalis	Ciona	Csa	ENSCSAVG0000008135
			118638
			232174
Duran a bia atawa a dawi i	A	Del	118636
Branchiostoma floridae	Anpnioxus	BII	128060
			90918
			230771

			*	20	*	40	*	60	*	80	*	100		
ABCC6	Hsa	:	MAAPAEPCAG	OGVWNOTEPE	PAATSLLSI	.CFLRTAGV <mark>W</mark>	VPPMYLWVLG	PIYLLFIHHHG	RGYLRMSP-	LFKAKMVLGFA	IVLCTSSV	VALWK	:	93
ABCC6	Ptr	:											:	-
ABCC6	Mmu	:	MNRGRSMATPGEOCAG	LRVWNOTEOF	PAAYHLLSI	CFVRAASSW	VPPMYLWVLG	FIMLLYTHRHG	RCYLRMSH-	LFKTKMVLGLA	ILLYTFNV	VPLWR	:	99
ABCC6	Cluf	:	MAAPAEPCLG	OAVWNWTEPE	PTAAHLLNV	CELKTAGVW	MPPMYLWVLG	FIMLLYTHRRG	KGYLRMSP-	LFKAKMVLGLA	IILCTSSVS	SVALWR	:	93
ABCC6	Bta	:	MAGOGEPCAG	PGVWNOTEPE	PAAARLLSI	CFLKTAGVW	VPPMYLWVLG	PIHLLYTHRHD	KGYIOMSR-	LFKAKMVLGFA	IILCTSSVS	SVTLWR	:	93
ABCC6	Dno	:								OVLGFA	IVLSTSNVS	SVALWK	:	21
ABCC6	Mdo	:	-MVVVVGSGSGVCNPV	LGNWNWNETC	SLGLOMSSI	. LMNAAVA 🕅	LPSVYLWVIS	FMFLYRYNN	KGYIRMSC-	LFKTKMVLGFT	VLLCFSNI	FTLWK	:	98
ABCC6	Oan	:							MSR-	LFKVKMVSFA	MSLCFFNLC	FTLWK	:	29
ABCC6	Gơa	:	MAAGRLCGSREGS	AGLWDWNOTW	YTDSPRFTW	CFENTVLSWI	IPCAYLWICF	FVYLYDOHKN	KGYIRMSH-	IFKIKMVLGFL	VILCESNVE	FVLWE	:	96
ABCC6	Aca	:									FLAVYFASTC	TITME	:	19
ABCC6	Xtr Tub	:	NDORODUDGG			CFHNSVLNWI		FMVLYRRHG	RGYIRMSAL	SKAKT-CLIGAL	VLVCYTELI	TTVWN	:	66
ABCC6	Len	•	MDOFCRVDG5	DPFWDWNOTW	IFTDRPDFIG	CFOLLITYMI	LECTELWLCS	FYCWYTORHG	NRYIRMSKI	YKAKT-VIIGAL	LLCVSEF	TTVWE	:	93
ABCC6	Gaci	:	MDAFCRISGL	DPLWDWNRTW	YTANPDLIC	CFONTVLVW	VPCIYLWLLA	PFYCLH YCHD	-SGRIRMSC	LCCARTMLGFL	ASFGEVEF	TTTTT.	:	93
ABCC6	Gacz	÷	FWMEDLCSVSGL	DPLWDWNLTW	MINDDI UC	CFOHIVLYWS	SPCVYLWICS	FFILLY WLRP	DRGVIPLSK		ASFGLVEMI	TTTTT	:	96
ABCC6	DIa		-MDETINLIVLPOPLI	CRUCDUNDE	NTANPDLIC	CFONTVLVW	VECTY LWLLA	F CLH YCHD	-RGRIRMSC	LCIARMVIGFL	ASFGFVEFI	SATT TES	•	90
ABCCO	Ula	÷	MDA ECOL SCI			CFONTVLVW		FICLE ICED	UCD TOMOC	LCMARMVLGFL	ASFGEVELL		÷	34
ABCCO	Oni	÷	MDAFCOLSGL	DPLWDWNRIW	NULL NEDL C	CFONTVLVW	VICINING LA	FICLE ICED	-nGRIOMSG	LFARTIVILGFL	ASFGCVEFI		÷	30
ABCCO	Vma	÷	MDAFCRISGL	DELADANKIA	VTANEDL C		VICLI INLLA		-RGRIOMSC	LCSRRMVIIGFL	ASPGEVELL		•	30
ABCCO	Cmo	:	MDTFCKISCI					FICVHIICHD	NCDIDIGC	LCTREMMET	ASPCEVER		:	33
ABCCO	Dro1	:	MDTFCGIGCI			CFONTVL WW			DCDIDICC	LCNAKT LICER	ASPOPUEPI		:	22
ABCCO	Drei	:	MDIFCSLSGL	DEPADAHOIA	I IIIKE SLOV	CTONT V LVW2			MCD TO TO TO C	LCCARMONALC	ASTORIET		:	50
ABCCG	Dre3	:	MDTLCSLSGL		WTAHPDI	CEOHTTLVM	FECEVIMICA	FUCLVIKEVD	-NGRIDIDE	LCCAKTG ALC	ASEGELETY		:	93
ABCC6	Ame1	:	MDTECSLNGL		VTHTPELSE	CFOHTVLVW	APCIVIMICS	PROCLE VCHG	-RGRLPLST	LCSAKLUIGEE	ASEGEVEEL	TITY	:	93
ABCC6	Ame2	:	I.PI.EAVI.KSSEVTV	SVFONWNLTW	FTPNPDI.	CFOHTVLVM	FPCEVIMLCA	PRVFLVCFHD	-VGRISVSS	LCVTKTVICIS	AFFSLLETA	VILLVS	:	97
ABCC6	Loc	÷	MDAFCSLSGL	DPLWDWNRTW	VTPNPDI.	CFONTVLVW	VPCVYLWVCA	PECLY HCYD	-RGVIRVSC	LCCAKMVLGEL	ASEGEVEEL	TITY	;	93
ABCC1	Hsa	÷	MALRGFCSADGS	DPLWDWNVTW	NTSNPDFIK	CFONTVLVW	VPCFVIWACE	PEVELVISEHD	RGYTOMTPI	NKTKT-ALGEL	WTVCWADLE	VSFWE	÷	95
ABCC1	Ptr	÷		DWNVTW	NTSNPDFIK	CFONTVLVW	VPCEVIWACE	PEVELY SRHD	RGYTOMTPT	NKTKT-AUGET.	WIVCWADLE	VSFWE	÷	79
ABCC1	- 0- Mm11	÷	MALRSECSADGS	DPT.WDWNVTW	HTSNPDFIK	CFONTVLTW	VPCEVINSCE	DI.VFFY SRHD	RGYTOMTHI	NKTKT-ALGEF	WITCWADLE	VSFWE	÷	95
ABCC1	Cluf		MVLRGFCRADGS	DPFWEWDVSW	NTSNPDFIK	CFONTVLVW	VPCCYLWLCF	FUFLY SRHD	RGYIOMTYI	NKTKT-ALGEV	WIVCWADLE	YSFWE	÷	95
ABCC1	Bta	:		EWNVTW	NTSNPDF	CFONTVLVW	VPCSYLWVCF	FIFLY SHHD	RGYIOMTHI	NKAKT-AUGFL	WIVCWADLE	YSFWE	:	79
ABCC1	Dno	:	OOSRGDSYGOGFF	PLWKDWNVTW	HTDSPDF	CFONTVLVW	VECCULWACE	FUFLY SRHD	RGYIOMTHI	NKAKT-AUGFL	WIVCWADLE	YSFWE	:	96
ABCC1	Mdo	:	MALPRFCSADGS	DPLWDWNITW	HTDNPDF	CFONTVLVW	VECVYLWACE	FIFLYCRHN	RGYIOMIHI	NKAKT-ALGFL	WIVCWADLE	YSFWE	:	95
ABCC1	Oan	:											:	-
ABCC1	Gơa	:	MGIESLCSADAS	EPFWDWNLTW	HTENPDFIC	CFONTVLVW	VPCIYLWVCF	AMFLYRSHD	RGYIOMSII	NKAKT-ALGLI	WIVCWADLE	YSFWE	:	95
ABCC1	Aca	:		DWNLTW	NTPRPDFTF	CFONTVLAW	<b>FPCAFLWACF</b>	FYAFFORRHD	KGYIOMSRI	NKAKT-ALGFI	WIVCWADLE	YSFWE	:	79
ABCC1	Xtr	:	MESFCSYDGS	ERFWDSNLTW	TYTENPDF K	CFONTVLIW	IPCIYLWFCL	<b>PFYFAY</b> RKND	OGYIOMSHI	NKAKT-AIGFI	WLACWADLE	YSFWE	:	93
ABCC1	Lch	:	MWIEALCAKDGS	DPFWDWNOTW	YTENPDF K	CFONSVLVW	IPCVYLWVAS	LFYYLYRRYG	RGYIRMSWI	NKTKT-V AVL	WLICWVDI	IFFME	:	95
ABCC1	Gac	:	MGLHGFCSADTS	DPFWDWNRTW	YTTKPDF	CFONTVLVWI	LPCLYLWICA	PLYLLYRSHD	HGYIRMSHI	NRAKT-AVGLL	WIICWADVE	FSFWE	:	95
ABCC1	Dla	:		-MNTDWNRTW	YTANPDL C	CFONTVLVWI	LPCLYLWMCA	PLYLLYRGHD	RGYICMSHI	NKAKT-AVGLL	WIICWADVE	YSFWE	:	82
ABCC1	Ola	:	-SRRMGLDRFCSPNSS	EPFWDWNRSW	NTSNPDLTF	CFOSTVLVW	VPCLYLWLCA	PFYLMYMRSHN	RGYICMSHI	NKAKT-AVGFL	WIICWLDVE	YSFWE	:	98
ABCC1	Tni	:	MGFARFCTSNES	DLFWDWNRTW	YTDNPDFIC	CFONTVLVW	IPCLYLWICG	PIYMLYLHSHS	HGYICMNHI	NKAKT-AVCLL	WVLCWSDVE	YTFWE	:	95
ABCC1	Oni	:	MGFDOFCSVDRS	DPLWDWNRTW	YTDNPDFTC	CFONTVLVWI	LPCFYLWICA	PFYLVYLHTHD	HGYICMNHI	NKAKT-AVGFL	WIICWSDVE	YSFWE	:	95
ABCC1	Xma1	:											:	-
ABCC1	Xma2	:					CFYLFACL	TVOYFLNSISM	KEYRTRRHK	NKSONOVVGFL	WVVCWSDVI	YSFWE	:	54
ABCC1	Dre	:	MGIDSFCSLDGS	DPLWDWNRTW	OTYYPDLIF	CFONTVLVW	IPCLYLWLFA	PLYILYKSHD	RGYICMTHI	NRAKT-VIGFT	WLICWADVE	YSFWE	:	95
ABCC1	Ame	:	MGIDHFCSVDGS	DPFWDWNRTW	HTHNPDLTC	CFONTLLVV	VPCFYLWLFA	PFYFLYKSHD	RGYICMTHI	NKAKT-VT <sup>©</sup> FL	WIICWADVE	YSFWE	:	95
ABCC1	Loc	:	MGIDEFCSLDGS	DPFWDWNRTW	YTPNPDL C	CFONTVLVW	VPCVYLWVCA	PFYCLYHCND	RGYIRMSHI	NKAKT-VTEFL	WIVCWADVE	YSFWE	:	95
ABCC1	Cmi	:		DSNLTW	HTODPDFII	CFKKTVLIWI	IPCIFLWLCF	PFYTLFLYYRK	OGYIRMSNI	NKSKT-LLGFL	WLSCWSOVI	LNIILE	:	79

			*	:	120	*		140	*		160		*	180	)	*		200		
ABCC6	Hsa	:	IOOGTPEAPE	FLIHPTV	LT	-TMSFA	VFLIH	T <mark>E</mark> RKK <mark>G</mark> VO	SSGVI	FGYWLL	CFVLPATI	NA	AO <mark>O</mark> ASG	AGFOSI	DPV <mark>R</mark> HL:	STYLCL	SIVVA	FVL	:	183
ABCC6	Ptr	:												-GFOSI	DPVRHL:	STILCL	SIVVA	FVL	:	25
ABCC6	Mmu	:	IHOGVPOAPE	LHPTV	LT	TMSFA	TFLIH	MERRKGVI	RSSGVI	FGYWLL	CCILPGI	NT	OOASA	GNFRO	PLHHL	ATTLCL	SIVVA	LVL	:	189
ABCC6	Cluf	:	IORGMPOAPE	LHPTV	LT	-TMSFA	MFLTH	TERKKGVI	RASGVI	FGYWML	CF LPIT	ST	AOLTIC	GDFRS	PFSHL	ATYLCL	SVAA	FVL	:	183
ABCC6	Bta	:	IOOGTPOALE	FLHPTV	LT	TMS FA	VFLTH	AERKKGV	DASGVI	FGYWLL	CFFFPAT	SA	TOOASE	GDFOSI	PFRLS	SPYLYL	SIVA	FAL	:	183
ABCC6	Dno	:	IHRGTPOAPE	LYPTV	LT	TMS FA	MFVIH	MERRKGVO	DASGVI	FGYWLL	CC LPAT	NT	AOLVLR	GDFOR	DAFRHL	STLLCL	SVAV	DLVL	:	111
ABCC6	Mdo	:	IKKGIPOAPE	FL NPTV	LI	-TMILA	IFLIH	LERRRGIC	SSGVI	FIYWLL	CSFSMAV	TVSAT	VHOALC	GGFPEI	DTFRHL:	TTFHS	A IGA	FVL	:	191
ABCC6	Oan	:	IKOGTPOALE	LINPAM	LLI	TMSLT	VFLTH	FERLKGVC	SSGVI	FVYWLL	SF VTLV	FLSAT	OHALC	GGFPRI	AFRHIV	∕S⊻LYS	AUVGA	FVL	:	122
ABCC6	Gɑa	:	ISOGIPRPPA	FFISPAV	LGI	-TMILA	MFITO	VERMMGIC	DSSGIM	LIYWLL	TFSALV	MFSSK	ORGLE	RGFLE	FFHHV	ATTLYA	STVIG	LVL	:	189
ABCC6	Aca	:	ANHGIOODPG	ASCAL	DLA	TMILV	LF TO	TEROKGVO	SSGLI	LLYWLL	SFISATA	SLISK	OEARE	GGFRS	P FHHA	rsy iyf	TVSL	LGI	:	112
ABCC6	Xtr	:	M-THNVROAP	FLISPL	ILG	SMLLA	тспо	YERMOGVE	RSSALI	LFFWLL	AL CATE	OLRTK	TTAIS	EI	KLRYTI	LFVLYF	VFVA	SVI	:	156
ABCC6	Lch	:	INOGTLRALA	FLISPAI	LAFT	LVLA	TFLIH	YERVKGVC	SSGVI	LFYWLL	SLCAVE	PFRSK	OOAPF	DGSVI	ISFREG	MF∑SYF	AUVIA	DLIL	:	186
ABCC6	Gac1	:	R-SOEIEOHM	FLLSPI	IRS	MTVILA	LCITO	LERIRGCI	RSSVFI	FLFWVL	AVVCSLV	PLRAK	OLAMD	EGISS	)IVRYF/	AFFSYF	TIOIA	)LFL	:	186
ABCC6	Gac2	:	K-NEEIOKHS	LIVIGPL	IRS	LTLVLA	VITH	VERMKGCI	RSSFLI	FOFWIL	LV CSLV	PLKVD	EOIID	RGFSSI	DSSRLLI	LFFLCF	FOI	DLVL	:	189
ABCC6	Dla	:	R-SOEIOOHM	FLLSPI	IRS	MTVILA	LCITO	LERVRGCI	RSSVFI	FLFWVL	AVVCSLV	PLRAK	OLAMD	EGIAS	DIVRYL	AFESYF	TIOIA	LFL	:	191
ABCC6	Ola	:	R-SODIGHHM	FLLSPI	IRS	MTVILA	LCITO	LERIRG <mark>C</mark> I	RSSIFI	FLFWVL	SVVCSLV	PLRAK	OLAVE	EGIAS	DIVRYL	AFESYF	TIONA	LFL	:	187
ABCC6	Tni	:	R-SOEIHOHM	FLLSPI	IRS	MTVVIV	LCIIO	LERVRGCI	RSSVFI	FLFWVM	AVVCSLV	PLRAK	OLAMD	EGFASI	IVOYF	AFFSYF	TIOIA	LFL	:	186
ABCC6	Oni	:	R-SODIOHHM	FLLSPI	IRS	LTVILA	мстто	LERIRGCI	RSSIFI	FLFWVL	AVVCALVI	PLRAK	OLAMD	EGIAS	DIVRYL	AFFSYF	TIOIA	LFL	:	186
ABCC6	Xma	:	R-SODIOHHM	FLLSPI	IRS	MTVILA	LCITO	LERIRG <mark>C</mark> I	RSSVFI	FLFWVL	SVVCSLV	PLRAK	OLAID	EGIAS	DIVRYL	AFFSYF	SIOLA	LFL	:	186
ABCC6	Gmo	:	R-SGEIHOHM	FLLSPI	RS	VTVILA	LFIIO	LERLRGCI	RSSVFI	FLFWVL	AVVCSLV	PLRAK	OLAVE	EGIGS	VVRFL	AFFSYF	TIOIA	DLVL	:	186
ABCC6	Dre1	:	R-RLEIHOHL	FLLSPI	RS	LTVVLA	VCVIH	WERVRGCI	RSSVFI	FFFWLL	GV CSII	PLHAK	OLAVE	OGLSPI	DIV.YL	AFFSYF	AIOIA	<b>LFL</b>	:	186
ABCC6	Dre2	:	R-SRDIEHLM	FLLSPI	IRS	LTMILV	MLMTH	LERLRGFI	RSSVFI	FLFWML	SVVCSLV	PLRAN	OANIK	EGFSA	DPMRFA.	AFFTFF	SIOIA	DLIL	:	145
ABCC6	Dre3	:	R-RRDIEHHM	FLLSPI	IRS	LTMILA	MLMIH	LERLRGFI	RSSMFI	FLFWML	AVVCSLV	PLRAN	OAIIE	EGFSA	DAMRFV	AFFTFF	SIOA	DLIL	:	186
ABCC6	Ame1	:	R-NOEIHRHL	FLLSPI	RS	LTVVLA	vciio	WERVRGCI	RSSVVI	FLYWLL	GVICSLV	PLRAK	OLAVE	OGFSPI	DIVHYL.	AFFAYF	ATOTA	LFL	:	186
ABCC6	Ame2	:	R-SGELNNHM	FLLSPV	IRS	LTMVLT	VCVIH	LERMKGCI	RSSLFI	FVFWTL	AVVCSLVI	PLRAN	OAVVG	ESCSRI	SVISA	AFFTCF	SIOA	DLIL	:	190
ABCC6	Loc	:	R-NREIOOHL	FLLSPV	IRS	LTVVLA	VLIIO	FERVRGSI	RSSAFI	FLFWLL	AVVCSLVI	PLRAK	OLAID	EGFSA	DAVRYL	AFFSYF	TOA	<b>LFL</b>	:	186
ABCC1	Hsa	:	R-SRGIFLAP	FLVSPT	LLG	ITMLLA	TFLIO	LERRKGVC	SSGIM	LTFWLV	ALVCALA	ILRSK	MTALK	EDAOVI	DLFRDI	FYVYF	SLI	DLVL	:	188
ABCC1	Ptr	:	R-SRGIFLAP	FLVSPT	LLG	TMLLA	TFIIO	LERRKGVC	SSGIM	LTFWLV	ALVCALA	ILRSK	MTALK	EIT		-FYVYF	SLI	DLVL	:	163
ABCC1	Mmu	:	R-SOGVLRAP	LUSPT	LLG	ITMLLA	TFLIO	LERRKGVO	SSGIM	LTFWLV	AL CALA	ILRSK	ISALK	KDAHVI	VFRDS	FYLYF	TVV	DLVL	:	188
ABCC1	Cluf	:	R-SWGKILAP	FLVSPT	LLG	ITMLLA	TFIIO	LERRKGV	SSGIM	LTFWLI	AL CALA	ILRSK	MTALK	EDAEI	VFRDV	FTIYF	SVI	DLVL	:	188
ABCC1	Bta	:	R-SMGKLLAP	FLVSPT	LLG	ITMLLA	TFLIO	IERRRGVO	SSGIM	LTFWLI	AL CALA	ILRSK	MTALK	EDARVI	VFRDV	FTIYF	SVI	DLVL	:	172

ABCC1	Gac	:	RSYGSNVLAPTHISPTMLGFIMILLTILTOYERMKGVOSSGVMLLYWLLAL CATVTFGSKISRALDOPLTVSVWRYTTFYTYYALL VSLCI	:	189
ABCC1	Dla	:	RSHGSRVPAPYTVSPTLLGLTMIS	:	130
ABCC1	Ola	:	RSHSRN-VAATHUVSPTLLGLIMLLATILVOYERMKGVOSSGIMLIFWLLALLCASVTFRSKILOAODOPEAVSGWRYTTFYVYYALLALVI	:	191
ABCC1	Tni	:	RSOKSN-VPLVYTVSPTLLGLIMLICAALIOSERLKGVOSSGVIFIVULALISATFILRSKILHALEOSLTAFPWRHTTFIIVYGILJAAFVI	:	188
ABCC1	Oni	:	RSHVS-SPAPTR VSPTLLGLTMLLAVMLIHYERMKGAOSSGVMLIYULAL CATVTFRSKI FOALEOPOTVCVWRYTTFYIYYALL IALFI	:	188
ABCC1	Xma1	:		:	-
ABCC1	Xma2	:	RNHSSNSTAPTHEVSPTLLGLTMLLATFTTOYERLKGVOSCGITLIFWLIAL CATVSFRSKILOARNEPETVCIWKYTTFYIYYAFL VALII	:	148
ABCC1	Dre	:	R-SHGATVAPYYLVSPTMLGVTMLLATFLIOYERMKGVOSSGVMLNPWLITIVCATITFRSKIMHALNDPASVGVFRYTTFYIVYTLIISLII	:	188
ABCC1	Ame	:	R-GHGVASAPYYLVSPTILGIIMLLATLLIOYERIKGVOSSGIMLNFWLVATUCATVTFRSKILOAVNEPETUNVFRYSTFYLYYALLISLII	:	188
ABCC1	Loc	:	R-SOGOAKAPYYFVSPTLLGITMLLATFLVOYERMKGVOSSGVILNFWVIAVICGTISFRSKILOAFSETSGVDLFRYFTFIYFAILIIDFI	:	188
ABCC1	Cmi	:	K-SRGFGHATVLILGPAFLGVTMLLAVFILOFERLKGLRSSAVMFLFWLLTLLCSTIEFRST0MNLLYPPAHFDLVDHIIFFFNFTVVLAFVU	:	172

		*	220	*	240	*	260	*	280	*	300	
ABCC6 Hsa	:	SCLADOPEFFPEDPO	OSNPCPETGAAFE	SKATFWW	VSGLVWR <mark>G</mark>	- <mark>Y</mark> RRPLRPK	DLWSL <mark>GR</mark> ENSS	EELVSRLEK	EMMRNR-SAAR	HNKAIAFK	RKGGS :	278
ABCC6 Ptr	:	SCLADOPEFFPEDPO	<b>OSNPCPETGAAFE</b>	SK <mark>AT</mark> FWW	VSGLVWRG	-YRRPLRPK	dlwsl <mark>gr</mark> en <b>s</b> s	EELVSRLEK	EMMRNR-SAARI	RHNKAIAFK	RKGGS :	120
ABCC6 Mmu	:	SCLVDOPPFFSEDSO	PLNPCPEAEASFE	SKAMFWW	ASGLIWRG	-YKKLLGPK	dlwsl <mark>gr</mark> en <b>s</b> s	EELVSOLER	ENRRSCNGLPG		HKGHS :	276
ABCC6 Cluf	:	SCLVDOPRFFPKDPO	<mark>OS</mark> NPCP <mark>KAE</mark> ASFI	.SR <mark>AM</mark> FWW	VSGLVWRG	-YRRLLGPE	dlwsl <mark>gr</mark> en <b>s</b> s	EELVSOLOF	EWTRTR-SAAO	OHTKARDAK	RKGSR :	278
ABCC6 Bta	:	SCLADOCELFRKRPP	OANPCPKAGASFE	SKAMFWW	VSGLVWKG	-YRRPLGPK	DLWSL <mark>GSK</mark> NSS	EELVSOLEK	EWTRNR-SATO	RHTKATAFK	RKGSH :	278
ABCC6 Dno	:	SCLADWPEFFPKAPO	OPNPCPEAGASFE	SK <mark>AT</mark> FWW	VSGLVWRG	-YRRPLGPK	dlwsl <mark>gk</mark> ess	EELVSRLEF	ewtrnrraaori	RHLKAKASK	RKGGA :	207
ABCC6 Mdo	:	SFLADOPRFFSKIMH	DSNPCPESGASFE	SKV <b>T</b> FWW	FSRLVWOG	-YRKPLEMD	dlwsl <mark>gk</mark> en <b>s</b> s	EETISRLES	EWKRICNETOO	FKEEMGFER	GGGNR :	287
ABCC6 Oan	:	SFFADOPEFFAKVPO	ESNPCPESGASFE	SKV <mark>T</mark> FWW	FSRLVWOG	-YRRPLEPD	dlwsl <mark>or</mark> en <b>s</b> s	EELVSOLER	EWKKNHHOTPW	SPDAVALNR	ADGOLR :	218
ABCC6 Gơa	:	FCLVDHPPFFSKAVN	SSNOCPEASSSFI	SKI <mark>T</mark> YWW	FSGLVWKG	-CROSLGVI	DLWSV <mark>RK</mark> ED <b>S</b> S	EEIVAWAER	EWKKYNNRTKOI	KMES	ATF :	278
ABCC6 Aca	:	CCLVDOPPFFSKVDS	<b>DA</b> NPCP <b>ESR</b> ASFI	SRI <mark>T</mark> FWW	FAGTIWKG	-YWKPLORE	DLWSL <mark>AK</mark> EN <b>S</b> S	EEIVAKFKI	AWEKHCASAEDI	KFPMNLTTS	SEISES :	208
ABCC6 Xtr	:	CTFNDDPPFFSNLKK	ESNPCPVSESSFI	.SKV <b>T</b> F <mark>S</mark> W	FTEIMFRG	-YKOPLKAE	DVWSLRKSDTA	EEILTLFSK	GVEKECKKANL(	DN	:	240
ABCC6 Lch	:	CCFTEPPEFFSEERK	APNPCPESNASFI	SKV <b>T</b> FWW	FTGOVIKG	-YRRPLVAE	dlwsi <mark>rk</mark> en <mark>r</mark> s	DEIVRHLER	EWKKEYAKGKO	5	:	269
ABCC6 Gac1	:	CCFADKPGSTSKSAG	<b>DE</b> NPCP <b>VKD</b> ASFI	SKI <mark>l</mark> fw.	FTGLVVKG	-YRTPLEAE	DLWTL <mark>RE</mark> ED <b>T</b> S	RKITAELEE	DWTDECAKVONI	SLFSC-RC	EKALA :	281
ABCC6 Gac2	:	SCFCDLRELCAKOSY	<b>VONR</b> CP <b>EED</b> ASFI	.SNFFFSW	FSGLVVRG	-YR <b>H</b> PLOAA	DLWPLRDODSS	IRIMTDFEN	IL AONCKPLOE	EPDNVELTC	NWTOS :	285
ABCC6 Dla	:	CCFADOP-PEGKTIL	EKNPCP <b>VKD</b> ASFI	.SKI <mark>l</mark> FWW	FTGLVVKG	-YRTPLAAE	DLWTL <mark>RE</mark> ED <b>T</b> S	NKIISELOO	DWTAECAKIO-	КС	EKALA :	278
ABCC6 Ola	:	CCFADOP-POGKPNL	<b>EK</b> NPCP <b>VKD</b> ASFI	SKI <mark>l</mark> fw.	FTGLVVKG	-YRTPLEAT	DLWTL <mark>RE</mark> ED <b>T</b> S	HKIISDLOC	EWGAECAKLO-	КС	EKSLE :	274
ABCC6 Tni	:	CCFADOP-PVGKTIL	<b>EK</b> NPCP <b>VKD</b> ASFI	.SKL <mark>L</mark> FWW	FTGLVVKG	-YR <mark>N</mark> PLAAE	DLWTL <mark>RE</mark> ED <b>T</b> S	CKIIAELOC	DWTAECAKION	OGVRTHSGC	OKALA :	281
ABCC6 Oni	:	C FADOP-PEGKIIS	EKNPCP <mark>VKD</mark> ASFI	.SKI <mark>L</mark> FWW	FTGLVVKG	-YR <b>T</b> PLEAG	dlwti <mark>re</mark> ed <b>t</b> s	OKIISDLEC	DWTAECAKLO-	KI	MEPIA :	273
ABCC6 Xma	:	CCFADRP-POGKPVL	<b>ek</b> npcp <b>ved</b> asfi	SKI <mark>L</mark> FW.	FTGLVVKG	-YR <b>T</b> PLEAE	dlwtl <mark>rk</mark> ed <b>t</b> s	HKIISELOO	DWTDECAKLO-	КС	OKALA :	273
ABCC6 Gmo	:	VCFADRRXXXXXXX	XXNPCP <b>VKD</b> ASFI	SKI <mark>L</mark> FW.	FIGPDRO			-EKVLASGTA	LG		:	239
ABCC6 Dre1	:	SCFADOAPLGKAVHK	NACPVODASFI	SKI <mark>L</mark> FW.	FSGLIFKG	-YRSPLOAE	dlwsl <mark>re</mark> ed <b>t</b> s	ERIISDLEE	EWTAKRTKLOO	DENHMSI	SAALG :	278
ABCC6 Dre2	:	SCFADOREDTLKPVY	VKNPCP <b>VED</b> ASFI	.SKL <mark>L</mark> FWW	YGRLVVKG	-YRSPLKAE	dlwsi <mark>re</mark> ed <b>t</b> s	EKIICDLEK	EWAKOWAKLOOI	KKSSLNEAC	TLGFK :	241
ABCC6 Dre3	:	SCFADOREDTLKPVY	VKNPCP <b>VED</b> ASFI	.SKL <mark>L</mark> FWW	YGRLVVKG	-YRSPLKAE	dlwsi <mark>re</mark> ed <b>t</b> s	EKIICDLEK	Ewakowakloh:	TVALIKMF	LPSHT :	282
ABCC6 Ame1	:	SCFADOAPPGKVALK	NACPVODASFI	.SKL <mark>L</mark> FWW	FRGLVVKG	-YR <b>T</b> PLOAE	DLWSI <mark>RE</mark> ED <b>T</b> S	DKIISDLEE	EMAERTKLOO	IROETYLSS	SVALG :	280
ABCC6 Ame2	:	SCFADORSDDLKWVD	VKNPCP <b>VED</b> ASFI	SKI <mark>L</mark> FW.	FSGLVVKG	-YR <mark>S</mark> PL <mark>KAE</mark>	DLWSL <mark>RK</mark> ED <b>T</b> S	EKIIGDLER	EWTTOCAKLOOP	KMSYSTTOL	.РҮНТК :	286
ABCC6 Loc	:	SCFSDOPPYTRRPVK	VPNPCP <mark>VOD</mark> ASFI	SKI <mark>L</mark> FW.	FSGLVVKG	-YR <mark>K</mark> PLKAE	DLWSL <b>RE</b> ED <mark>R</mark> S	DRIISDLER	EWTAOCTKLOO	DE	:	270
ABCC1 Hsa	:	SCFSDRSPLFSETIH	<b>DP</b> NPCP <b>ESS</b> ASFI	SRI <mark>T</mark> FWW.	ITGLIVRG	-YROPLEGS	DLWSI <mark>NK</mark> ED <b>T</b> S	EOAABATAR	N#KKECAKTRK-		OP :	272
ABCC1 Ptr	:	SCFSDRSPLFSETIH	<b>DP</b> NPCP <b>ESS</b> ASFI	SRI <b>T</b> FWW.	ITGLIVRG	-YROPLEGS	DLWSL <mark>NK</mark> EDTS	EOAABATAR	N KKECAKTRK-		OP :	247
ABCC1 Mmu	:	SCFSDCSPLFSETVH	DRNPCPESSASFI	SRITFW	ITGMMVHG	-YROPLESS	DLWSINKEDTS	SEEVVPVLVN	N KKECDKSRK-		OP :	272
ABCC1 Cluf	:	SCFSDRPELFSETIH	<b>DL</b> NPCP <b>ESS</b> ASFI	SRVTFWW	ITGLMVRG	-YROPLESI	DLWSL <mark>NK</mark> EDTS	EOVVPVLVK	NAKKECAKSKR		00 :	272
ABCC1 Bta	:	SCFSDRSPLFSETIN	DPNPCPESSASFI	SRITFW	ITGMMVOG	-YROPLESI	DLWSINKEDTS	EOVVPVLVK	NAKKECAKSRK		OP :	256
ABCC1 Dno	:	SCFSDRSPLFSETIN	<b>DP</b> NPCP <b>ETS</b> ASFI	SRI <b>T</b> FWW.	ITGLVVRG	-YROPLEST	HLWSINREDTS	EEVVPVLVK	N©KKECARSRK		OP :	273
ABCC1 Mdo	:	SCFSDHSPLFSETIN	DPNPCPESGASFI	SRI <b>T</b> FWW	ISGLMVOG	-YKCPLEAI	DLWSLNREDTS	NOVVPVLVK	N©KKECAKTRK		OP :	278
ABCC1 Oan	:					-YKRPLEAS	DLWSINREDTS	DOAABALAR	N AKECTKSKK-		OS :	45
ABCC1 Gda	:	SCFPEKP LFSEAVN	DPKPCPEFSASFI	SRITFWW	TIGLMIOG	-HRRPLEAK	DLWSINKEDTS	EELVPGLAK	N AKEWAKTKR-		OP :	272
ABCC1 Aca	:	SCFPERPELFSETVH	DPSNR RIKTNV	KSOVLE	IKG LFFSYS	GYON I LEMA	FVFHINSSLPS	EELVVVKVK	DCKWDCVKKRKI		KW :	263
ABCCI Xtr	-	SAFP RP LFSERVN	DPNPCPESSASFI	SOLTEWW	ISRMMVOG	-FKRPLEAK	DLWSINKEDKS	LEVVPVLSK	N EKEYNKAKAI	1K	VP :	2/2
ABCCI Len	:	SCLTDOPPLFSEEVK	DENPCPEYSTSFI	SRITFWW		-YKOPLEAK	DMWSINKEDTS	AOVVPLLDR	O OKETAKTKK		GG :	2/2
ABCCI Gac	•	SOLTOOLELFSEAVK	DSNPCPERGANFI	SKITFWW		-YKRPLEEN	DIWSINSAURS	HKVVPELVG	RINVECORVER	ГВ	: 0	2/4
ABCCI DIA	:	SCLTDOPPLFSOAVK	DENPCPELGASFI	SKITFWW		-INHPLEEN	DINCINPEDRS		RWNAECOKVKR	88	В :	215
ABCCI UIA	:	SCLSDOMPLFSOAVK	DPNPCPEPGASFI	SRITFWW	ISGMMLSG	TANTIK	DLWSINPEDRS	HCVVPOLLE	RWTAECHKVKR	ГЕ	в:	2/6
ABCCI TRI	:	SCLTDOPELFCAVVK	NENPCPEPGASFI	SRITFWW		- IANILKK	SFELSS	upanport		೬U ೭೪	K :	251
ABCCI UNI	•	551100PELF5RDVK	DEMPCPEPGASFI	ISKTTLAM	TIRONNIC	- KRELEEK	DEWSENAEDCS	INV POLVE	K M TOCORPERS	26	: עי	213
ABCC1 Mmal	•			CDTTTW		עם דם מסעי				 rv		-
ABCC1 Dro	:	A T COOD T POPULATE	DENDCDESCASFI	CVITFWW		VVDDI PPV		PDU PO VE	R DORCUNVKR	1 10	: טי	233
ABCC1 Amo	÷	S I S OP I POM	DSNPCPESGASFI	SD T G FUUU		-TARE LEEK		UT DO VE	DUBCONVAR	 דח	: ע :	2/3
ABCC1 Log	•	S T S OP T FSOAVA	DSNPCPEICASEI	WW10ING		VDDDT PPD	DIVSINERAS		DINCODARTED	D9	: ·	2/3
ABCC1 Cmi	:	C ET DD FFOT TIC	-TNPCPESKASFI			VKDDT PAK	DIVSINENDES	FKT VDFT WV	THE RECORDER	DF	:	2/3
ADCCI CIILI	·	COLIDEELIOTID	- INT CERDIVADEI	ANTITWW		- CAN			BARNECONNER!			200

			* 320	*	340	*	360	*	380	*	400	
ABCC6	Hsa	:	GMKAP	TEPFLRO	EGSOWRPLLKA	IWOVFHSTFLI	LGTI <mark>S</mark> LIISDVF	RFTVEKLIS	LFLEFIGDPKPP	AWKGYLLA	<b>V</b> LMF	: 357
ABCC6	Ptr	:	GMEAP	ETEPFLRO	EGSOWRPLLKA	IWOVFHSTFLI	GTISLIISDVF	RETVEKLIS	LFLEFIGDPKPP	AWKGYLLA	VLMF	: 199
ABCC6	Mmu	:	SVGAP	TEAFLOP	ERSORGP LRA	IWRVFRSTFLI	GTISLVISDAF	RFAVEKLIS	LFLEFMGDRNSS	AWTGWLLA	VLMF	: 355
ABCC6	Cluf	:	DVEAP	EMEALLOO	EGSORGPULRA	IWOVSRSTFLI	LATFNLVICTVF	RFAVEKLFS	LFLEFIGNPTIP	AWKGYVLA	VLLF	: 357
ABCC6	Bta	:	NKEAP	ETETLLPO	ORGKRGP LRA	IWOVGRSAFLI	GTISLIVSDVF	RFTVEKLIS	LFLEFIGDPNTP	AWKGYLLA	VLMF	: 357
ABCC6	Dno	:	GPEVP	ETEAFLRO	EGSORGPULRA	IWOVSRVTFLI	GTISLVIGDAF	RFTVEKLIS	L <b>FLE</b> FI <b>G</b> D <b>PK</b> AP	AWKGYFLA	ALMF	: 286
ABCC6	Mdo	:	AEPALPP	BTETFLOG	HOSPRFPLLKA	IWKVFNGTFLI	GTISLIVCDVF	RFAVEKIIS	FFLEFISDPEAP	AWKGYFYA	VLLF	: 368
ABCC6	Oan	:	DEAADPW	TOP FLOS	ERTOSGPILKA	IWRVFGLSFII	GSUSLVACDIF	TFSIFKIIS	LFLEFISD <b>LA</b> AP	GWKGYFCA	VLLF	: 299
ABCC6	Gơa	:	KKSWKIGTDTAE	EETEVLLOS	EHSOSGP LOA	FWSMFGIYFLI	STICLVICDVF	LFSIFKIIS	LFLEFIEDOEAP	SWHGYFYA	FILV	: 366
ABCC6	Aca	:	ATCKREKRKSOT	RETALLLOP	ENSKSKL LKS	FWSVFGTYFII	GTICLVAGDVF	LFLIFKTIS	VFLDFISAPEAP	SWKGYFYA	AAMF	: 296
ABCC6	Xtr	:	KLIVAAESLGLGLPRETEKS	IELLKNRH	IOLSOKTLKV	IMRSFGLYFLI	SA LMTFYTAF	LFISPLLVR	LLLOLLK <mark>DPS</mark> AP	SWOGFLVA	VFLF	: 336
ABCC6	Lch	:	VETVOFSKKORHSGASLKOPE	TOVLMKROG	EOSNGTA LKA	LWRIYGNHFLI	GTICLVLSDVL	LFSIPOILD	SLLGFMSDPEAP	<b>V</b> WRGY <b>F</b> YA	ALMF	: 366
ABCC6	Gac1	:	AGAALGSRLPD	DACLERKLOK	EOSSGFFLLRT	MARKFGPYFL	GTIYIIFHDAF	MFAIPOVIS	LLL <mark>D</mark> FM <mark>R</mark> DEDAP	LWKGYFYA	TLMF	: 368
ABCC6	Gac2	:	TTSSGSLSRAWDFDAVTEKTOLLK	KKKKGOKGOK	GRGYGIFLHT	VACSFGPYFIC	GT WLLLHEVF	MFAVPOVIS	LLLAFI SDEDAA	MWKGFLFC	SLLF	: 385
ABCC6	Dla	:	SGVALGSRLPD	DACLERKLOK	EOSSGFFLLRT	LARKFGPYFL	GTICIIFHDAF	MFAIPOVIS	LLL <mark>G</mark> FM <mark>R</mark> DEDAP	LWKGYFYA	TLMF	: 365
ABCC6	Ola	:	SAPVLGSRLPD	DACLERKLOK	EOSSGFFLLRT	LARKFGPYFL	GTICIIFHDAF	MFAIPOVIS	LLL <mark>G</mark> FI <mark>R</mark> DPEAP	OWKGYFYA	TLMF	: 361
ABCC6	Tni	:	SNAALGSRLPD	ACLIRKLOK	EOSSGFFLLRT	LTRKFGPYFLS	<b>GTICIIFHDAF</b>	MFAIPOVIS	LLLGFMRDEDAP	LWKGYFYA	TLMF	: 368
ABCC6	Oni	:	LFLCOPDKOSSFKSSNCNADF	LKILILRSP	RLYWDHO YLT	ARKFGPYFL	GTICIIFHDAF	MEAIPOVIS	LLLDFMRDEDAP	LWKGYFYA	TLMF	: 370

	DHO	: VKIVYPA-KDPAKPKGGSKVDVNEEVDALIVR	SPOKERDPSEFKVLYKTFGPYFLM	ISFLFKALHDLMMFAGPELLKLLIS	SFVNDKOAPSWOGYFYTALLF :	372
ABCC1 N	Mdo	: VKIVYSP-KDPAKAEGGSKGDVNEEVEALILK	PTORERKPSIFKVIYKTFGPYFIN	ISFIFKALHDLMMFAGPETIKILIN	IFVNDNOAPDWOGYFYTALLF :	377
ABCC1 C	Oan :	: LKIVYAP-KDPVKLKTGSKGDVNEEVDALIVK	PSORDKEPS FKV YKT GPY IN	SFUFKALHDIMMBAGPETTKILIN	FVNDKDAPDWOGYLYTGLLF :	144
ABCC1 0	Gra	· INMIVSSKKOOKSSDSNGEVTERADATITK	CODSSEAST SKUT VKT FCDVFT	AS FURKAAHDTIMETCERTIKITIN		370
ADCCI C	eua .		SORSSERS SKV TRITGETTE			370
ABCC1 A	Aca	: LPMLYSPKKAPKGGVSSTEAMAAEEADALILR.	PAORDKKPS SKV YKTIGPYI M	ISF FKAFHDLMMDAGPEL KRL I	IFVSDOSAPNWOGYFYTALLF :	363
ABCC1 >	Xtr :	: LKMVYSPKKOTKKLNSKEDVREEADALIVK	PAPKELEPSILKAIYKTIGPYIFI	ISCFFKFFHDVLMFSGPOLIOILIF	KFVGDKDAPDWHGYLYTFLLF :	370
ABCC1 1	Lch :	: LOLMYSPKKPKSSKDEDGEAVEEAOTLIIK	RAEKDKEPSIFKALCRTFGPYFLM	4SFVYKAIHDLLMFVGPEIIRLLIC	FVNNKDAPNWHGYIYTALLF :	370
ABCC1 0	Gac	: RTLYSPREAPPSEGKEGRAVESEVLIV	KAOKAKEPS FWA CLT GPY 1	SCIYKIIODILMFVGPEIIRILIF	FVNNSSAPSWHGYFYTALLF :	369
ABCC1 I		· KTIVSPKOUP HSEDKDCPAUFESETTTUK	NOCKTKEDS TWATCITECOVET	SCI VKI TODITI MEVORETTRITT	FUNINGSA DEMOCYFYTATIE	312
ADCCI I						212
ABCC1 C	Ola :	: KMLYSPKOPPHGENKEVRAVEESDILIVK	SPKKSREPS LWA CLTFAPHFL	/SC_YKLIODILMEVGPEL_R_L_I	FVNDPDAPSWOGYFYAALLF :	373
ABCC1 7	Tni	: KNIYSSKVLLHSNRKEDRMVEESEILIVK	KOAKTKEPS FWALCLTFGPYFLI	ISCLYKLIODVLMFIGPEILRILIN	FVNNPEAPSWOGYFYTSLLF :	348
ABCC1 C	Oni	: KMLYSSKRVPHSENPOGOAVEESDILILR	PRKKNKEPSLLWALCLTFGPYFFI	ISCIYKLIODILMFVGPEIIRLLIC	FVNDSSAPSWOGYFYAALLF :	370
ABCC1 >	Xma1	:			:	-
ABCC1 >	Xma2	: OMVYSPKRALHGENREGOPVEESDILLLT	SPRKTKEPS LWA CLT GPY	SCIYKITODILMIYGPETTRILIH	IFVNDTSALSWOGYFYTALLE :	330
ABCC1 T	Dro	KTIVERKRET DERKKDEODURRETTIAK				270
ABCCII	Die .	. KILISEKKSIKGEKKDGOFVEESTILLKK	REORIGEP 3 FFR CRITCE IFIN	SSHIRI HIDVLOIVGELIKELI	I VINDS SKEIWIGTETTRUSE .	570
ABCC1 A	Ame	: KTMYSPKRPSMAEKKDGRPVEESDILLIK.	APOKSGDPS FLA CRTFGPYFL	/SSIYKIIHDVLMFVGPEL_RLLIC	FVNDSDAPSWHGYFYTALLF :	370
ABCC1 I	Loc	: KTMYSPKRSARAAAEEKKDGAPAEES VLIVO	EPRKAOEPSI AMAI CLAFGPHFIA	SFVYKIIHDVLMFVGPEILKLLII	FVNDPSAPSWOGYSYTALLF :	373
ABCC1 (	Cmi	:TVHTOOKEKTGANKEHENENTEOSEVLLI	OKKONMEPSILKAICRAFGPYLMI	ISFFFKIFHDVLVFASPEIMRLLLC	FVNNHFAPVWOGYFYAILLF :	352
		* 400 *	110 +	460 + 400	* 500	
		* 420 *	440 *	460 * 480	500	
ABCC6 H	Hsa	: LSACLOTIFECONMYRLKVLOMR-LRSAITGL	VY <mark>RK</mark> VLALS <mark>S</mark> GSRKASAVGDVV <mark>N</mark> I	LVS <mark>V</mark> DVORLTESVLYLNGLWLPLVV	/IV/CFVYLWOLLGPSALTAI :	456
ABCC6 H	Ptr	: LSACLOTLFECONMYRLKVLOMR-LRSAITGL	VYRK <mark>VLA</mark> LSSGSRKASAVG <mark>D</mark> VVNI	LVSVDVORLTESVLYLNGLWLPLVV	IVVCFVYLWOLLGPSALTAI :	298
ABCC6 N	Mmu	: AAACLOTLFEOOHMYRAKVLOMR-LRTAITGL	VYRK <mark>VLVLSSGSRKSSAA</mark> GDVVNI	LVSVDIORLAESIIYLNGLWLLFUV	IFVCFVYLWOLLGPSALTAV :	454
ABCC6 (	Cluf	: LSASLOSILEOHYMYKLKVLOMR-LRTAITGL	vyrk <mark>v</mark> lvissasrkasavedvvni	LVSVDVORLTECTIVLNGLWLPVIV	MITCFVYLWOLLGPSALTAT :	456
ABCCE	Bta	· ISACIOTIFFOOHMVDIKULOID-IDTATICI	WORNT AT COCORCEAUCDWWN	VSVDVORT TESUTVINCT WIRT	TWVCEVVINOTICPSALTAT	456
ADCCO I	Dua	I SACLOTIFECONMIRLAVEOLA	VIRNVLALSSSSRRSSAVCDVVII			400
ABCC6 I	Dno	: ISACLOTIFEOOHVYRMKVLOIR-LRTAITGL	VYRKVLALSSSSRKASAVGDVVNI	LVSVDVORLMDSIFFLNGLWLPLVV	(IIICFVFLWOLLGPSALTAV :	385
ABCC6 N	Mdo	: LSACLOTLFEORHMYVOMVLEIR-LRTAVMGL	VYRK <mark>VLALSNAM</mark> RK <b>TAA</b> VGEIINI	LVSVDVORLMDAVLYLNGLWLPVIV	IIICFTFLWOLLGPSALTAI :	467
ABCC6 C	Oan	: LINSLKILFEORYMYVCFVLGMR-LKTALVGL	VYRK <mark>V</mark> L <mark>ALSSAA</mark> RK <mark>ATA</mark> VGEIVNI	LVSVDVORLVDAVVYFNGIWICPI	IVICFIFLWOLLGPSALTAL :	398
ABCC6 C	Gơa	: LLACLOTIFEORYMYMCLVLGLR-LKTAVTGL	VYRK <mark>ILTVSNAS</mark> RK <mark>AVT</mark> VGEIVNI	LVSVDVOKLMDLIIYFNGTWLAPIF	RIIICFVFLWOLLGPSALASI :	465
ABCCE	Aca	· ILACIOTIFEOOVMVMCLVLGVR-LKTATTCL	VVRKI. UMSNAAKKEATVGET VNI	UVSVDVOKUMDI. TIVENGEWI.APTE	TVTCEVELVOLLOPSALMAV	395
ABCCC 1	v+v					125
ADCC6 /	AUI	. ICPCCOSLFLHOHDYICYVIGMR-LKRAIVGI	VINALMISSAGRAESSAGEIVNI	LISIDVOREMDERICVNIMWSRPVI	IIIVAMIFLWOILGIAVLAGV :	435
ABCC6 I	Lcn	: LFACLOSILVHOYMYMACIIGMR-LKTALTGL	IYRK <mark>I</mark> LVM <b>TSGA</b> KKTSTVGEVVNI	LVSVDIOKLMDLIIYFNGVWLAPL	LALCFYFLWOYLGPSSLAGV :	465
ABCC6 C	Gac1	: LLSCLOSLFNHOYMYTCFTVGMR-VKTAVMGL	VYRK <mark>S</mark> LVI <mark>NSSA</mark> RR <b>TCT</b> VGEIVNI	LVS <b>A</b> DTOKLMDFVVYFNAVWLAPIE	ISLCLFFLWOHLGPSALAGI :	467
ABCC6 0	Gac2	: LLSCLOSLLHHOYMFHCFSVGMR-LKTALIGL	VYRK <mark>C</mark> LLL <b>SSAA</b> RR <mark>RGD</mark> VGEIINI	LVSADTOKLMDFVVYFNSLWVTPII	ITLCFYFLWOLLGPSALAGI :	484
ABCC6 I	Dla	: LLSCLOSLFNHOYMYTCFTVGMR-VKTAVMGL	VYRK <mark>SLVINSAA</mark> RR <b>TCT</b> VGEIVNI	LVSADTOKLMDFVVYFNAVWLAPI	TALCLFFLWOHLGPSALAGI :	464
ABCC6 C	01a	ILSCLOSI FNHOVMVTOFTVOMP-VKTAVMGL	VVRKSLVINSA ARRTCTVCFIVNI	USADTOKI MDEVVVENAVWI A PIL	TGICLERINOHLOPSALACT	460
ADCCC C	m n i					400
ADCC6 1		: LLSCLOSLFNHOMMYICFIVGMR-VKIAVMGL	VIRNSLVINSASRRICIVGEIVNI	LVSADIOREMDFVVYFNAVWEAPIE	TAICLFFLWOOLGPSALAGI :	40/
ABCC6 C	Oni	: LLSCLOSLFNHOYMYTCFTVGMR-VKTAVMGL	VYRK <mark>S</mark> LVI <mark>NSSA</mark> RR <b>TCT</b> VGEIVNI	LVSADTOKLMDFVVYFNAVWLAPII	IALCLFFLWOHLGPSALAGI :	469
ABCC6 }	Xma	: LLSCLOSLFNHOYMYTCFTVGMR-VKTAVMGL	VYRK <mark>S</mark> LVI <mark>NSSA</mark> RR <b>TCT</b> VGEIVNI	LVS <b>ADTOKLMDFVVYFNA</b> VWLAPIE	IALCLFFLWOHLGPSALAGI :	459
ABCC6 C	Gmo	: LLSCLOSLFNHOYMYTCFTVGMR-VKTAVMGL	VYRK <mark>S</mark> LVI <mark>NSSA</mark> RR <b>TCT</b> VGEIVNI	LVSADTOKLMDFVVYFNAVWLAPII	IAICLFFLWOHLGPSALAGI :	419
ABCC6 I	Dre1	LLSCLOSVENHOVTYTCFTYGMR-VKTAVMGL	VYRK <mark>S</mark> LVM <mark>NSSARRTCT</mark> VGEIVNI	LVSADTOKIMDFVVYFNAVWLAPIF	VTLCLFFLWOHLGPSALAGI :	458
ABCCE	Dro?		UVDKSTUTNSAADKTCTUCETUNI		TAICLERINOHICRSTIACT	4.20
ADCCO I		• I SH DSTRNETOMY''''''''''''''''''''''''''''''''''''			TUTCHLINMOUTHOL DITUVOT	<b>TZU</b>
ABCC6 I	Dues	LLSCLOSLFNHOYMYTCLTVGMR-VKTAVMGL				400
	Dre3	: LLSCLOSLFNHOYMYTCLTVGMR-VKTAVMGL : LLSCLOSLFNHOYMYTCFAVGMR-VKTAVMGL	VYRK <mark>S</mark> LVI <mark>NSAA</mark> RK <b>TCT</b> VGEIVNI	LVS <b>ADTOKLMDFVV</b> YFNAVWLAPI	IAICLFFLWOHLGPSALAGI :	469
ABCC6 A	Dre3 Ame1	: LLSCLOSLFNHOYMYTCLTVGGR-VKTAVMGL : LLSCLOSLFNHOYMYTCFAVGMR-VKTAVMGL : LLSCLOSLFNHOYMYSCFTVGMR-VKTAVMGL	VYRK <mark>SLVI<mark>NSAA</mark>RKTCTVGEIVNI VYRK<mark>S</mark>LVI<mark>NSAA</mark>RRTCTVGEIVNI</mark>	LVSADTOKLMDFVVYFNAVWLAPII LVSADTOKLMDFVVYFNAVWLAPII	TALCLFFLWOHLGPS <mark>ALAG</mark> I : T <mark>ALCLFFLWOH</mark> LGPS <mark>A</mark> LAGI :	469 460
ABCC6 H ABCC6 H	Dre3 Ame1 Ame2	: DLSCLOSIFNHOYMYTCFAVGR-VKTAVMGL : DLSCLOSIFNHOYMYTCFAVGM-VKTAVMGL : LLSCLOSIFNHOYMYSCFTVGMR-VKTAVMGL : LLSCLOSIFNHOYMYSCFTVGMR-VKTAVMGL	VYRK <mark>SLVINSAARKTCTVGEIVNI</mark> VYRK <mark>SLVINSAARRTCTVGEIVNI</mark> VYRK <mark>A</mark> LVI <mark>SSAARRTC</mark> TVGEIVNI	LVS <mark>A</mark> DTOKLMDFVVYFNAVWLAPI LVSADTOKLMDFVVYFNAVWLAPI LVS <mark>A</mark> DTOKLMDFVVYFNAVWLAPI	TATCLFFLWOHLGPSALAGI : TATCLFFLWOHLGPSALAGI : TGTCLFFLWORLGPSALAGI :	469 460 478
ABCC6 A ABCC6 A ABCC6 I	Dre3 Ame1 Ame2 Loc	: LLSCLOS JFNHOIMYTELTVORL VKTAVNGL : LLSCLOS JFNHOIMYTEFAVGNR VKTAVNGL : LLSCLOS JFNHOIMYSEFTVORR VKTAVNGL : LLSCLOS JFNHOIMYSEFTVORR VKTAVNGL : LLSCLOS JFNHOIMYSEFTVORR VKTAVNGL	VYRKSLVI <mark>NSAARKTCT</mark> VGEIVN VYRKSLVI <mark>NSAARRTCT</mark> VGEIVNI VYRKALVISSAARRTCTVGEIVNI VYRKSLVI <mark>NSAA</mark> RRTCTVGEIVNI	LVSADTOKLMDFVVYFNAVMLAPT LVSADTOKLMDFVVYFNAVMLAPT LVSADTOKLMDFVVYFNAVMLAPT LVSADTOKLMDFVVYFNAVMLAPT LVSADTOKLMDFVVYFNAVMLAPT	TAICLFFLWOHLGPSALAGT : TAICLFFLWOHLGPSALAGT : TGICLFFLWORLGPSALAGT : TGICLFFLWORLGPSALAGT :	469 460 478 458
ABCC6 A ABCC6 A ABCC6 I ABCC1 H	Dre3 Ame1 Ame2 Loc Hsa	: LLSCLOSIFNHOIMYTELIVGNE VKTAVNGL : LLSCLOSIFNHOIMYTEFAVGNE VKTAVNGL : LLSCLOSIFNHOIMYSEFTVGNE VKTAVNGL : LLSCLOSIFNHOIMYSEFTVGNE VKTAVNGL : VTACLOSIFNHOIMYSEFTVGNR VKTAVNGL : VTACLOSIFNHOFNISFTVGNR IKTAVIG	VYRKSLVINSAARKTCTVGEIVNI VYRKSLVINSAARRTCTVGEIVNI VYRKALVISSAARRTCTVGEIVNI VYRKSLVINSAARRTCTVGEIVNI VYRKALVITNSARRSSTVGEIVNI	LVSADTOKLUDFVVYFNAVNLAP I LVSADTOKLUDFVVYFNAVNLAP I LVSADTOKLUDFVVYFNAVNLAP I LVSADTOKLUDFVVYFNAVNLAP I LVSADTOKLUDFVVYFNAVNLAP I LMSVPAORFVDLATYINMIVSAPIC	NARCLFFLWOHLGPSALAGT : NARCLFFLWOHLGPSALAGT : NGICLFFLWORLGPSALAGT : NGICLFFLWOHLGPSALAGT : NTIALYLWINLGPSVLAGV :	469 460 478 458 470
ABCC6 A ABCC6 A ABCC6 I ABCC1 H ABCC1 H	Dre3 Ame1 Ame2 Loc Hsa Ptr	ILSCIOSIFNHOIMYTEITVORL-VKTAVNGL ILSCIOSIFNHOIMYTEITVORL-VKTAVNGL ILSCIOSIFNHOIMYSOFTVORL-VKTAVNGL ILSCIOSIFNHOIMYSOFTVORL-VKTAVNGL ILSCIOSIFNHOIMYSOFTVORL-VKTAVNGL VTACIOTVLHOIFHIOFYSORL-IKTAVIGA	VYRK <mark>SLVINSAARNTCT</mark> VGEIVNI VYRK <mark>SLVINSAARRTCT</mark> VGEIVNI VYRKALVISSAARRTCTVGEIVNI VYRKALVISSAARRTCTVGEIVNI VYRKALVINSAARKSSTVGEIVNI VYRKALVITNSAARKSSTVGEIVNI	LVSADTOKLMDFVVVFMAVMDAPTE LVSADTOKLMDFVVVFMAVMDAPTE LVSADTOKLMDFVVVFMAVMDAPTE LVSADTOKLMDFVVVFMAVMDAPTE LVSADTOKLMDFVVVFMAVMDAPTE LMSVDAORFMDLATYTIMTVSAPTC	TAICLFFLWOHLGPSALAGI: TAICLFFLWOHLGPSALAGI: TGICLFFLWOHLGPSALAGI: TGICLFFLWOHLGPSALAGI: VIIALYLWLNLGPSVLAGV: VIIALYLWLNLGPSVLAGV:	469 460 478 458 470 376
ABCC6 A ABCC6 A ABCC6 I ABCC1 H ABCC1 H	Dre3 Ame1 Ame2 Loc Hsa Ptr	<ul> <li>LLSCLOSIFNHOIMYTELIVOM VKTAVNGL</li> <li>ILSCLOSIFNHOIMYTEFAVGMR-VKTAVNGL</li> <li>LLSCLOSIFNHOIMYSEFTVGMR-VKTAVNGL</li> <li>LLSCLOSIFNHOIMYSEFTVGMR-VKTAVNGL</li> <li>VLSCLOSIFNHOIMYSEFTVGMR-VKTAVNGL</li> <li>VTACLOTIVLHOIFHIEFVSGMR-IKTAVIGA</li> <li>VTACLOTIVLHOIFHIEFVSGMR-IKTAVIGA</li> </ul>	VYRKSLVINSAARNTCTVGEIVNI VYRKSLVINSAARRTCTVGEIVNI VYRKALVISSAARRTCTVGEIVNI VYRKSLVINSAARRTCTVGEIVNI VYRKALVITNSARRSSTVGEIVNI VYRKALVITNSARKSSTVGEIVNI VYRKALVITNSARKSSTVGEIVNI	LVSADTOKLMDFVVVFAAVADAPTE LVSADTOKLMDFVVVFAAVADAPTE LVSADTOKLMDFVVVFAAVADAPTE LVSADTOKLMDFVVVFAAVADAPTE LVSADTOKLMDFVVVFAAVADAPTE LMSVDAORFADLATYTIMTKSAPTC LMSVDAORFADLATYTIMTKSAPTC	TARCLFFLWOHLGPSALAGT : TARCLFFLWOHLGPSALAGT : TGICLFFLWOFLGPSALAGT : TGICLFFLWOFLGPSALAGT : VIIALYLWLNLGPSVLAGV : VIIALYLWLNLGPSVLAGV :	469 460 478 458 470 376
ABCC6 A ABCC6 A ABCC6 I ABCC1 F ABCC1 F ABCC1 M	Dre3 Ame1 Ame2 Loc Hsa Ptr Mmu	<ul> <li>LLSCLOSIFNHOIMYTEITVOM VKTAVNGL</li> <li>LLSCLOSIFNHOIMYTEFAVGMR VKTAVNGL</li> <li>LLSCLOSIFNHOIMYSEFTVOMR VKTAVNGL</li> <li>LLSCLOSIFNHOIMYSEFTVOMR VKTAVNGL</li> <li>VTACLOTIVLHOIFHIEFVSOMR VKTAVNGL</li> <li>VTACLOTIVLHOIFHIEFVSOMR IKTAVIGA</li> <li>VTACLOTIVLHOIFHIEFVSOMR IKTAVIGA</li> <li>VSACLOTIALHOIFHIEFVSOMR IKTAVIGA</li> </ul>	VYRKSLVINSAARKTCTVGEIVNI VYRKSLVINSAARRTCTVGEIVNI VYRKALVISSAARRTCTVGEIVNI VYRKSLVINSAARRTCTVGEIVNI VYRKALVITNSARKSSTVGEIVNI VYRKALVITNSARKSSTVGEIVNI VYRKALLITNAARKSSTVGEIVNI	LV SADTOKLUD FVVY FAAVADAPIE LV SVDAORFVDLATYIN WISAPIE LMSVDAORFVDLATYIN WISAPIE LMSVDAORFVDLATYIN WISAPIE	TAICLFFLWOHLGPSALAGT : TAICLFFLWOHLGPSALAGT : TGICLFFLWOHLGPSALAGT : TGICLFFLWOHLGPSALAGT : YUTALYLWINLGPSVLAGV : YUTALYLWINLGPSVLAGV : YUTALYLWINLGPSVLAGV :	469 478 458 470 376 471
ABCC6 A ABCC6 A ABCC6 I ABCC1 H ABCC1 H ABCC1 M ABCC1 O	Dre3 Ame1 Ame2 Loc Hsa Ptr Mmu Cluf	LLSCLOSIFNHO'MYTELTVORL-VKTAVNGL ILSCLOSIFNHO'MYSFTVORL-VKTAVNGL ILSCLOSIFNHO'MYSFTVORL-VKTAVNGL ILSCLOSIFNHO'MYSFTVORL-VKTAVNGL VTACLOTIVLHO'FNIOFVSCR-VKTAVNGL VTACLOTIVLHO'FNIOFVSCR-IKTAVIGA VSACLOTIVLHO'FHIOFVSCR-IKTAVIGA	VYRK <mark>SLV INSAARNTCT</mark> VGE I VNI VYRKSLV INSAARNTCTVGE I VNI VYRKAL V ISSAARNTCTVGE I VNI VYRKAL V INSAARNTCTVGE I VNI VYRKAL V ITNSARKSSTVGE I VNI VYRKALL I ITNSARKSSTVGE I VNI VYRKALL V ITNSARKSSTVGE I VNI VYRKAL V ITNSARKSSTVGE I VNI	LV SADTOKLMDFWVYFAVWDAP I LV SADTOKLMDFWVYFAVWDAP I LV SADTOKLMDFWVYFAVWDAP I LV SADTOKLMDFWYFAVDAP I LV SADTOKLMDFWYFAVDAP I LMSVDAORFWDLATYTAMTSAP I LMSVDAORFWDLATYTAMTSAPI LMSVDAORFWDLATYTAMTSAPI LMSVDAORFWDLATYTAMTSAPI LMSVDAORFWDLATYTAMTSAPI	TAICLFFLWOHLGPSALAGI : TAICLFFLWORLGPSALAGI : TGICLFFLWORLGPSALAGI : TGICLFFLWOHLGPSALAGI : YIIALYLWLNIGPSVLAGV : YIIALYLWLNIGPSVLAGV : YIIALYFLWLSLGPSVLAGV : YIIALYFLWLSLGPSVLAGV :	469 478 458 470 376 471 470
ABCC6 // ABCC6 // ABCC6 // ABCC1 // ABCC1 // ABCC1 // ABCC1 // ABCC1 //	Dre3 Ame1 Ame2 Loc Hsa Ptr Mmu Cluf Bta	<ul> <li>LLSCLOSIFNHOIMYTELIVORI, VKTAVNGL</li> <li>LLSCLOSIFNHOIMYTELIVORI, VKTAVNGL</li> <li>LLSCLOSIFNHOIMYSOFTVORR, VKTAVNGL</li> <li>LLSCLOSIFNHOIMYSOFTVORR, VKTAVNGL</li> <li>ILSCLOSIFNHOIMYSOFTVORR, VKTAVNGL</li> <li>VTACLOTIVLHOIFHIOFVSORR, IKTAVIGA</li> <li>VTACLOTIVLHOIFHIOFVSORR, IKTAVIGA</li> <li>ICACLOTIVLHOIFHIOFVSORR, IKTAVIGA</li> <li>ICACLOTIVLHOIFHIOFVSORR, IKTAVIGA</li> <li>ISACLOTIVLHOIFHIOFVSORR, IKTAVIGA</li> </ul>	VYRK <mark>SLVINSAARKTCT</mark> VGEIVNI VYRKSLVINSAARRTCTVGEIVNI VYRKSLVINSAARRTCTVGEIVNI VYRKSLVINSAARRTCTVGEIVNI VYRKALVITNSARKSSTVGEIVNI VYRKALLVITNSARKSSTVGEIVNI VYRKALVITNSARKSSTVGEIVNI VYRKALVITNAARKSSTVGEIVNI	LV SADT OKLMDFVVVFMAVMDAPTE LV SADTOKLMDFVVVFMAVMDAPTE LV SADTOKLMDFVVVFMAVMDAPTE LV SADTOKLMDFVVVFMAVMDAPTE LV SADTOKLMDFVVVFMAVMDAPTE LMSVDAORFMDLATYTMTVSAPTC LMSVDAORFMDLATYTMTVSAPTC LMSVDAORFMDLATYTMTVSAPTC	TAICLFFLWOHLGPSALAGI : TAICLFFLWOHLGPSALAGI : TGICLFFLWOHLGPSALAGI : TGICLFFLWOHLGPSALAGI : VIIALYLWLNLGPSVLAGV : VIIALYLWLNLGPSVLAGV : VIIALYLWLNLGPSVLAGV : VIIALYLWLNLGPSVLAGV :	469 478 458 470 376 471 470 454
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ABCC6	Ptr	:	AVFL	5LLPL1	NFFI 7	KKRN.	нное	EOMR	OKDS	RARL	ISSI	LRNS	K <b>t</b> ik	FHGW	E <mark>G</mark> A F	LERV	LGIR	GOET	GALF	TSGL	IFS	SLV	FOV	STFLV	7ALVVI	A−−VH	:	396
ABCC6	Mmu	:	AVFL	5LLPLN	(FFI)	KKRG	FHCE	EOMR	OKAS	RARL	rssm	LRTV	RTIK	SHG	E <b>H</b> A F	LERI	LHIR	GOET	SALF	TSTL	FS	SLV	FOV	STFLV	7ALVVI	`A – – ⊽H	:	552
ABCC6	Cluf	:	AVFM	5LLPL1	<b>TFFI</b>	KKRK	OHOE	EHMR	OKDS	RVRL	ISCI	IRNM	KMVK	SHG	E <mark>E</mark> AF	LERV	LHIR	GOET	GAME	TSSL	FS	SLV	5FOV	S <b>T</b> FL\	7ALVVI	R−−vH	:	554
ABCC6	Bta	:	AVFV	5LLPL1	<b>TFFI</b>	KKRN	нно	EOMR	OKDC	RARL.	ISCI	LRNV	R <b>T</b> VK	YHG	E <mark>G</mark> A F	LDRV	LHIR	AOET	GALF	TSSL	FS	SLV	5FOV	S <b>T</b> FL\	7ALVVI	R−−vH	:	554
ABCC6	Dno	:	AVFL	5LLPL1	<b>TFFI</b>	KKRK	HHOE	EOMR	OKDA	RARL	ISSI	LRHA	KLIK	FHG	E <mark>E</mark> AF	LDRV	LOSR	RREI	GALF	TSGL	FS	SLV	FOA	S <b>T</b> FL\	7ALVVI	R−−vH	:	483
ABCC6	Mdo	:	AVFL:	LLPL	VFI I I	KKRS	CFE	EOVO	HKDR	RARL.	TDSI	LRNM	KIIK	FHG	E <mark>E</mark> AF	MEKI	LTIR	KGET	OALF	NSGF	T FA	SLV	5 FHL	S <b>T</b> FL\	/ALVM	R−−vH	:	565
ABCC6	Oan	:	AVFL	LLPL	(FVI)	KKRS	R F E	EOMR	OKDH	RGTL	ISSI	LSNV	RIIK	FHG	E <b>K</b> A F	MEKV	LHIR	KEEI	OALF	KSGL	FS	SLV	5 FHL	S <b>T</b> FL\	/ALVM	r <b>a</b> vy	:	496
ABCC6	Gơa	:	AVFL	FIP-LN	VFMI 1	KKRS	H F E	AOMK	HKDE	RATL:	<b>FNA</b> I	ISDI	KVIK	LYG	EKTF	MEKV	HAIR	KOET	OALF	RSOI	FS	ASLA	5 FHS	STFLI	l AFVM	r <b>a</b> vy	:	562
ABCC6	Aca	:	VVF	LLPL	NFV I I	KKRT	OFŒ	AOVA	HKDS	RAKL	ISAI	ISDI	K <b>T</b> LK	LHGW	E <mark>E</mark> AF	VGRV	MGVR	TREI	OALF	RSOF	TFS	ASLV	FOS	S <b>T</b> FLI	SFIM	FAVY	:	493
ABCC6	Xtr	:	AVFI	INLPFN	4TVF#	VIIK	RVOE	оомк	OKDG	RIKI	ISEI	IOGI	KVLK	LYAW	E <mark>N</mark> A F	MKKV	TEFR	LMET	KAVF	TGAL	LSC	GALA	7FVA	SPFW	SLTM	GVF	:	533

Chapter VIII	
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	Amez .		570
ABCC6	roc :	: ATVILIEPLAGFIAKORSKLOEVOMKHMUGRIKIMNEIINGIKIIRFYAWBKAFLERVLGYROKEIKALKKSOIIYSISIASENSSTFLIAFAM-GVY :	556
ABCC1	Hsa :	: AVMVLVVPVNAVMAMKTKTYOVAHUKSKDNRIKLMNEIINGIKVLKLYAWELAFKDKVLAIROEELKVLKKSAYLSAVGTFTWVCTPFLVALCTFAVY :	568
ABCC1	Ptr :		474
ADGGI	1 01 ·		5.00
ABCCI	Mmu :	: RVMILMVPLNAVMAMKTKTYOVAHMKSKUN KIKIMNEIINGIKVLKLYAWBLAFODKVMSIROBBIKVLKKSAYLAAVGTFTWVCTPFLVALSTFAVF :	569
ABCC1	Cluf :	: AVMILMVPLNAVMAMKTKTYOVAHMKSKDNRIKIMNEIINGIKVLKLYAWELAFKDKVLAIROEEIKVLKKSAYDAAVGTFTWVCTPFLVALSTFAVY :	568
ABCC1	Bta :	: EVMVLUVPINAVUAMSTKTY VAHUSSKINKIKIMNEI NGIKVISLYAWELVKKKVLAIROBERKVIKKSAVIAANGTFUVCTPERVALSTEAVV :	552
ARCCI	Dro I		570
ABCCI	DHO :	: RVMILOVPINAVAANATATIOVAHUASAUNAIALMINEIINGIAVLALYAWBLAJOBAVSAIRABUAVIKASAILAAVGTPINVCTPELVALSTPAVY:	5/0
ABCC1	Mdo :	: AVMILMVPLNAVMAMKTKTYOVAHMKSKDNRIKIMNEIINGIKVLKLYAWBLAFKEKVLEIROEEIKVLKKSAYLAAVGTFTWVCTPFLVALSTFAVY :	574
ABCC1	Oan :	: AVMILAVITNAV MANGTKTY VAHUKSKIN SIKIMBII NGIKVIKLYAWELAEKKKVIETOEETKVIKKSAVI AAVGTFUVVCTPELVALSTEAVV :	341
ADGG1			5.67
ABCCI	Gua :	: RVMTLEVPTNAVAAMATATYOVAOMASAINAIKEMINEIINGIKVERLYAWBEAREKVEEIRONSEKVERKSATEAAUGTFEWVCAPEEVAESTPAVY:	56/
ABCC1	Aca :	: AVMILLVPVNAVIAMKTKTYOVAHMKSKDNRIKIMNEIINGIKVLKLYAWBLAFKEKVLGIRKEEIRVLKKSAYLAAIGTFTWVCAPFLISDAKCANCVF :	562
ABCC1	Xtr :	: EVMYVMEMI VAPCIESAAVTSVVOMKCKDNE IKTMNETINGIKVIKI VAWELAEKEKVIGIEK DETKVIKKSAVI AAVGEEUVCAPELVALSTEAVX :	567
ADGG1	Tab .		5.67
ABCCI	rcu :	: RVMVLOVPVNAPIAMKSKTYOTOMKSKUNKIKLMNEIINGIKVLKLYAWBLANDKVLEIROOJOVUKKAATAVVATFTWVCTPFLVALSTHTVY:	56/
ABCC1	Gac :	: AVMVLMVPINAVIAMKTKTYOVAOMKSKDSRIKIMNEMINGIKVIKLYAWELAFKDKVSKIRESEIOVIKKAAYLGAVSTFTWICAPFIVALSTFAVY :	566
ABCC1	Dla :	: EVMYLMYPYNAV AMKTKTY VAOMKSKUN KIKIMNEMINGI KVIKLYAWELA KOKVSETRESETRVI KKAAVI GAVSTFTAVCAPETAVALSTETVX :	509
ARCCI	010		570
ABCCI	UIA :	: RVMILWVPINAVIAMATATIOVAOMANADSKIKIMNEMINGIAVIALSIMAAAABAASSOIRENGIAVIAKAAAIGAVSTFIWVCAPEIVALSIPSVY:	5/0
ABCC1	Tni :	: GVMVLMVPVNAVIAMKTKTYOVAOMKNKDSRIKIMNEMINSIKVLKLYAWELAFKDKVSEIREHEIHVLKKAGYLGAVTTFTWICAPFLVALSTETVY :	545
ABCC1	Oni :	: EVMVLMVPVNAVTAMETKAY VAOMESKIN KIKTMNEMINGI KVIKLYAWELA EKGEVSETRESETRVI KKAAYI GAVSTETAVCAPETVALSTEAVA :	567
ABCCI	Vmal ·		
ADCCI	VIIIat :		-
ABCC1	Xma2 :	: AVMVLMVPINAVIAMKTKTYOVAOMKSKDSRIKIMNEMINGIKVIKLYAWBLAFKEKVSKIRESEIRVLKKTAYLGAISTFTWVCAPFIVALSTFAVY :	527
ABCC1	Dre :	: RVMVLMVPLNAVTAMKTKTYOVAOMKSKDNRIKIMNEVINGIKVLKLYAWELAEKGKVSAIRESEIRVLKKMAYIGAISTFTWVCAPFLVALSTEAVY :	567
ABCCI	1		567
ADCCI		. RYMY BOVE VIRY TRUNTKI I V ROUKSKUN KIRIMIREV INGINY IREI RUBANDU KUSI I REDI KVINKKARI OKTOT FI WVRFT I VALSI I RA-VI .	507
ABCC1	roc :	: AVMVFMVPVNAVIAMKSKTYOVAOMKSKDSRIKIMNEVINGIKVLKLYAWBLAFOGKVLGIRETEIRVLKKSAYLAAVSTFTWVCTPFLVALSTFAVY :	570
ABCC1	Cmi :	: RVMILLVPINSMIAMKTKDLOVTOMKEKDNRIKIMNEIINGIKVIKLYAWELAFKEKVMOIRRKEIKVLKNAAYFSAVSTFTWICAPFLVALSSFAVY :	549
ABCC6	Hsa :	: TLVAEN-AMNAEKA <mark>F</mark> VTLTVLNIINKAOAFLPFSLH <mark>S</mark> LVO <mark>A</mark> RVSFD <mark>R</mark> LVTFLCLEEVDPGVVDSSSSGSAAGKDCLTIHSATFAWSOESPPCLHRINL :	651
ABCC6	Ptr :	TIVAEN-AMDAEKAEVUTTULULINKAOAELESIHSI.VOARUSEDEUTUTELCLEEVDPGAVDSSSSGSTAGKDCUTUHSATEAUSORSPECIHEINI.	493
ADGGC			C 4 0
ABCC6	Mmu :	: TEVALDNAWDAENAFVTFTVLSTINKAOAFEPFSVHCTVOFRVSFDRIAAFTCLEEVDPNGWLASNSKRSSKDRISVHNGTHAWSOLSPPCHGUNL :	649
ABCC6	Cluf :	: TLVAEENAMDAEKAFVTLTVLSIINKAOVFMPFSINSVVOARVSFDRIAAFLCLEEIDLRAVDLSPSRCSAGETCLRVHDGTFAWSREGTPCLRRINL :	652
ABCC6	Bta :	: TEVARENAMDARKARVUTTUL VETNKAOA FERSIHSI VORUSEDETAARISLEETDPGAVDSSPSRCAAGEDCISIOEGTITUSOESAECIRRINE :	652
ADGGC	Dea .		501
ABCC6	Dno :	: TLVAEENAMDAEKAFVTITVLAIINKAOAFLPFSIHSVVOARVSFDRIAAFICLEEVDPGAVVSMPFRCPAGKAGITVRNGTPAVSRESPECIORITL :	281
ABCC6	Mdo :	: ALTDEKHVLDAEKAFVALTIININRAOAFLEFSINTIFOAWVSIARIAAFTHLEEVEPRAISTTPVGEESISVODGTEANSOENSPCLORINL :	659
ABCC6	Oan :	TISTENNVLDAOKARVATMUTNTINKAOGELELSTHITTOYKVSTARTAARTSLEETENAVDTSPKGSSGECITHENGTEAMSRESSECTREISL	592
	-		
ABCC6	Gda :	: TLVDNTHVLDAOKAFVSLTLINIDNTAHSFLPFSINAAVOAKVSLKRIAAFINLBEINPE-SSNRHTSDCG-ELFIIIRNGTFCWSKDTSPCLRRIDL :	658
ABCC6	Aca :	: TLADERNIFSAOKAFVSIALVNIINTAHSFLPFSINSVVOAKVSINRIAAFISLEDIDOTNAEPGSLDGTODCITIRNGTFTWSRESPECIKRINL :	589
ABCCE	Vtr ·	· TAT DEKNTLDA EKA EVETTUL VIT DED DE ME MA TELEA SSUST KEMUKEESA BETERESÜDENDIS.SSNLEHA TERHETERGESSERDE LOSINE ·	631
indee0			
ABCC6	Lcn :	: MLVDRSNVLDAOKAFVSMALVTLMKIPLSFLPFSISTTVOAGVSLKRISTFISHBELNPNNTDRSTTHSLGKOIVVENGTFSWSKDNPPCLTRINL :	659
ABCC6	Gac1 :	: VMLDDRNVLDAOKVFVSMALINIIKTPLSOLFAISTTMOAMVSIRRIGKYLCSEEIREDNVSKAPFCSDGEDVVIENGNFSWSAEGPPCIKRISI :	661
ABCCE	Gac2 ·		678
indee0			
ABCC6	DIA :	: VTLDDRNVLDAOKVFVSMALINIIKTPLSOLPFAISTTMOAMVSIRRIGKYLCSEEIRVDNVSKAPLSSDGEDVALENGTFSWSAEGPPCIKRINI :	658
ABCC6	Ola :	: VMLDERNVLDAOKVEVSMALINIIKTPLSOLFAISITMOALVSIRRIGKYLCSEEIKVDGVSKALSSSDGEDLVIENGTESWSKEGPECIKRISV :	654
ABCCE	Tni ·		661
ADCCO			001
ABCC6	Oni :	: VMLDDKNVLDAOKVFVSMALINIIKTPLSOLPFAISTTLOAVVSLKRLGKYLCSEEIKMENVSKAPLSSDGEDVVLENGTFSWSAEGPPCLKRISV :	663
ABCC6	Xma :	: VMLDDRNVLDAOKVEVSMALINTIKTPLSOLFFAISTTMOALVSIRRIGKYLCSEETRVDNVSKTLLSPDGEDVMLESGTESWTPEGPPCIKRINV :	653
ARCCE	Cmo ·		
ADCCO	. 01110	· VIIDARAVEDAONVEVSTALIATERIETSOLEEVANDIINGAAAAAANGKEICSEELKODAVIKAAISEDG====EDVSTDAGINOVOGEGEECKKIIVV ·	£13
ABCC6			613
	Dre1 :	: VLIDDKNVLDAOKIFVSMAIINIKTPLSOLPFANSITMOALVSLKRIGKFICODELKPDNVARESFKSDVDGVVFDNGTFSWSKDGPPCLKRISV :	613 652
ABCC6	Dre1 : Dre2 :	: VLIDDKAVLDAOKIFVSMAIINTIKTPISOLFFANSITMOALVSIKRIGKFICODENKPDNVARESFKSDVDGVVFDAGTSWSKDGPECIKRISV : : VLIDDKHVLDAOKIFVSMAIINTIKAPISOLFIAUSTTVOVVVSIKRIGTFIDODENKLDSVORVPYNPNIESVVINNGTSWSKDSTECIRRINV :	613 652 614
ABCC6	Dre1 : Dre2 : Dre3 :	: VLIDDKVULDAOKIEVSVAIIVILKTPLSOLIPAVSTI VOLVSVKUKTIKKICKTEODIKLDSVORVPVNPNDGVVPDVGTSVKKDCFEOTKRISV: : VLIDDKKULDAOKIFVSVAIIVILKAPLSOLPIAVSTI VOVVSVKUGTFIDDDIKLDSVORVPVNPNIESVVINNGTSVKKDSTEOTREINV: : VLIDDKKULDAOKIFVSVAIIVILKAPLSOLPIAVSTVOVVSVKUKKECODIKLDSVORVPVNPVGLVFSVVINNGTSVKKDSTEOTREINV:	613 652 614 667
ABCC6 ABCC6	Dre1 : Dre2 : Dre3 :	: VLIDDKIVLDAORIFVSMAIINIKTPLSOLFFANSTTUOALVSIKRIGKFICODEIKEDSVSKSDVDGVVFDNGTSSSKKDGPECIKRISV : : VLIDDKHVLDAORIFVSMAIINIKAPLSOLFFANSTTUOVVSIKRIGTFIDDDEIKLDSVGRVPYNPNIESVVINNGTSSSKKDSTECTRRINV : : VLIDDKHVLDAORIFVSMAIINIKAPLSOLFFANSTTUOVVSIKRIGKFICODEIKLDSVERVPYNPVGSLYPESVVINNGTSSSKKDSTECTRRINV :	613 652 614 667
ABCC6 ABCC6 ABCC6	Dre1 : Dre2 : Dre3 : Ame1 :	: VLIDDKÄVLDAORIFVSMAIINIIKTPISOLFFANSITMOALVSIKRIGKFICODEIKPDNÄRESFKSDVDGÄVFDÄGTESMSKDGPECIKRISV : : VLIDDKHVLDAORIFVSMAIINIIKAPISOLFIANSITMOVVSIKRIGTFIDODEIKLDSTORVPYNPNIESÄVINÄGTESMSKDSTECIRRINV : : VLIDDKHVLDAORIFVSMAIINIIKAPISOLFFANSITMOAVVSIKRIGKFICODEIKLDSTERVPYNPVGSLYFESÄVINÄGTESMSKDSTECIRRINV : : VLIDDKÄVLDAORIFVSMAIINIIKTPISOLFFANSITMOAVVSIKRIGKFICODEIKLDSTERVPYNPVGSLYFESÄVINÄGTESMSKDSTECIRRINV :	613 652 614 667 654
ABCC6 ABCC6 ABCC6 ABCC6	Dre1 : Dre2 : Dre3 : Ame1 : Ame2 :	: VLIDDK VLDAORIFYSMAIINI KTPLSOLIPAUSTI MOAVSIKRICKFI CODEIKEDN VARESFKSDVDGVVFDNGTESVSKDCPECIKRISV : : VLIDDKHVLDAORIFYSMAIINI KAPLSOLIPAUSTI MOVVSIKRIGFT DODEIKLDSVGRVPYNPNG	613 652 614 667 654 672
ABCC6 ABCC6 ABCC6 ABCC6 ABCC6	Dre1 : Dre2 : Dre3 : Ame1 : Ame2 :	: VLIDDK VLDAORIFVSMAIINIKTPLSOLFAVSTT JOALVSIKRIGKFICODEIKLDSVRAPFSPDGDGVVFDNGTSVSKDGPECIKRISV : : VLIDDKHVLDAORIFVSMAIINIKTPLSOLFAVSTT JOAVVSIKRIGKFICODEIKLDSVGRVPYNPNLGSVVINNGTSVSKDSTECIRRINV : : VLIDDKHVLDAORIFVSMAIINIKTPLSOLFAVSTT JOAVVSIKRIGKFICODEIKLDSVGRVPYNPVGSLYFESVVINNGTSVSKDSFECTRRINV : : VLIDDKVLDAORVFVSMAIINIKTPLSOLFAVSTT JOATVSIKRIGKFICODEIKLDSVGRVPYNPVGSLYFESVTINNGTSVSKDGPECTRRISV : : VLIDEKVLDAORVFVSMAIINIKTPLSOLFAVSTT JOATVSIKRIGKFICODEIKLDSVGRPFSPDGDSVTEDGTSSVSKDGPECTRRISV :	613 652 614 667 654 672 652
ABCC6 ABCC6 ABCC6 ABCC6 ABCC6	Dre1 : Dre2 : Dre3 : Ame1 : Ame2 : Loc :	: VLIDDKIVLDAOKIFVSNAIINIKTPISOLIPAVSTT XOLVSIKRICKFICODIKPDNVARESFKSDVDGVVPDNGTSWFKDGFCOTKRISV: : VLIDDKHVLDAOKIFVSNAIINIKAPISOLIPAVSTT XOLVSIKRIGTFIDDDIKLDSVRVPYNPAUSIV : VLIDDKHVLDAOKIFVSNAIINIKTPISOLIPAVSTT XOLVSIKRIGKFICODIKLDSVRVPYNPGSVYFNVGISVFSVKDSFCIRRINV: : VLIDDKNVLDAOKIFVSNAIINIKTPISOLIPAVSTT XOLVSIKRIGKFICODIKLDSVRPYNDGSLYFSVVDNGTSWFKDGFCKKTSV: : VLIDEKVVLDAOKVFVSNAIINIKTPISOLIPAVSTT XOLVSIKRIGKFICODIKLDSVRPYNDGSLYFSVTNOGTSWFKDGFCKKTSV: : VLIDEKVVLDAOKVFVSNAIINIKTPISOLIPAVSTT XOLVSIKRIGKFICODIKLDSVRPYNDGSLYFSVTNOGTSWFKDGFCKKTSV:	613 652 614 667 654 672 652
ABCC6 ABCC6 ABCC6 ABCC6 ABCC6 ABCC1	Dre1 : Dre2 : Dre3 : Ame1 : Ame2 : Loc : Hsa :	: VLIDDK VLDAORIFYSKAIINI KYPLSOLIPAVSTT MOALVSIKRICKFI CODEIKLDDN ARESFKSDVDG VFPNGT SWEKDGP CIKRISY : : VLIDDKHVLDAORIFYSKAIINI KAPLSOLIPAVST MOAVSIKRICFFI DODEIKLDSVGRVPYNPNESVUNNGT SWEKDSFECTRINV : : VLIDDKHVLDAORIFYSKAIINI KAPLSOLIPAVST MOAVSIKRICKFI CODEIKLDSVGRVPYNPVGSLYFESVUNNGT SWEKDSTECTRINV : : VLIDDKVLDAORIFYSKAIINI KTPLSOLIPAVST MOAVSIKRICKFI CODEIKLDSVGRVPYNPVGSLYFESVUNGT SWEKDSFECTRINV : : VLIDDKVLDAORIFYSKAIINI KTPLSOLIPAVST MOAVSIKRICKFI CODEIKLDSVGRVPYNPGSLYFESVUNGT SWEKDGPECIRRISV : : VLIDDKVLDAORIFYSKAIINI KTPLSOLIFAVST MOAVSIKRICKFI CODEIKLDSVGRPSVERDEDSVVENGT SWEKDGPECIRRISV : : VLIDEKVLDAORVFYSKAIINI KTPLSOLIFAVST MOAVSIKRICKFI CODEIKLDSVGRPSGEGSVVENGT SWEKDGPECIRRISV : : VLIDEKVLDAORVFYSKAIINI KTPLSOLIFAVST MOAVSIKRICKFI CODEIKLDSVGRAPFSDGGSVVENGT SWEKDGPECIRRISV : : VLIDEKVLDAORVFYSKAIINI KTPLSOLIFAVST MOAVSIKRICKFI CODEIKLDSVGRAPFSDGGSVVENGT SWERDGPECIRRISV : : VLIDEKVLDAORVFYSKAIINI KTPLSOLIFAVST MOAVSIKRICKFI CODEIKLDSVGRAPFSDGGSVVENGT SWERDSFERRINV : : VLIDEKVLDAORVFYSKAIINI KTPLSOLIFAVST MOAVSIKRICKFI CODEIKLDSVGRAPFSDGGSVVENGT SWERDSFERRINV : : VLIDEKVLDAORVFYSKAIINI KTPLSOLIFAVST MOAFVSIKRICKFI CODEIKLDSVGRAPSJEGGSVVENGT SWERDSFERRINV : : VLIDEKVLDAORVFYSKAIINI KTPLSOLIFAVST MOAFVSIKRICKFI CODEIKLDSVERRAFGSFG	613 652 614 667 654 672 652 666
ABCC6 ABCC6 ABCC6 ABCC6 ABCC6 ABCC1 ABCC1	Dre1 : Dre2 : Dre3 : Ame1 : Ame2 : Loc : Hsa : Ptr :	: VIIDDK VUDAORIFYSMAIINIKTPLSOL FAVSTT JOALVSIKRICKFICODEIKLDSVORVYNPNDGVVFDIGTSVSKDGPECIKRISV : VIIDDKHVUDAORIFYSMAIINIKTPLSOL FAVSTT JOVVSIKRICKFICODEIKLDSVORVYNPNDGVVFDIGTSVSKDGPECIKRISV : VIIDDKHVUDAORIFYSMAIINIKTPLSOL FAVSTT JOAVVSIKRICKFICODEIKLDSVORVYNPNGSLYFSVVINNGTSVSKDSFECIRRINV : VIIDDKVUDAORIFYSMAIINIKTPLSOL FAVSTT JOAVVSIKRICKFICODEIKLDSVORVYNPVGSLYFSVVINNGTSVSKDSPECIRRINV : VIIDDKVUDAORIFYSMAIINIKTPLSOL FAVSTT JOAPVSIKRICKFICODEIKLDSVORPYNPVGSLYFSVVINNGTSVSKDSPECIRRINV : VIIDEKVUDAORYFYSMAIINIKTPLSOL FAVSTT JOAPVSIKRICKFICODEIKLDSVORAPFSPDGDSVVERGTSVSKDGPECIRRISV : VIIDEKVUDAORYFYSMAIINIKTPLSOL FAVSTT JOAPVSIKRICKFICODEIKLDSVORAPFSPDGGSVVERGTSVSRDSPECIRRINV : VIIDEKVUDAORYFYSMAIINIKTPLSOL FAVSTT JOAPVSIKRICKFICODEIKLDSVORAPFSPDGGSVVERGTSVSRDSPECIRRINV : VIIDEKVUDAORYFYSMAIINIKTPLSOL FAVSTT JOAPVSIKRICKFICODEIKLDSVORAPFSPDGGSVVERGTSVSTSVERGSFECIRRINV : VIIDEKVUDAORYFYSMAIINIKTPLSOL FAVSTT JOAPVSIKRICKFICODEIKLDSVERAPSDFGGSVVERGTGTSVSRDSPECIRRINV : VIIDEKVUDAORYFYSMAIINIKTPLSOL FAVSTT JOAFVSIKRIEN SHEELEPDSIERRPVKDGGGTNSTTVRNATET JARSDFTINGTT : VIIDENNILDAOTAFVSIAIFNILFPLNILDMVISSIVOSVERKIRIFISHEELEPDSIERRPVKDGGGTNSTTVRNATET JARSDFTINGTT : VIIDENNILDAOTAFVSIAIFNILFPLNILDMVISSIVOSVEKRIRIFISHEELEPDSIERRPVKDGGGTNSTTVRNATET JARSDFTINGTT	613 652 614 667 654 672 652 666 572
ABCC6 ABCC6 ABCC6 ABCC6 ABCC6 ABCC1 ABCC1 ABCC1	Drel : Dre2 : Dre3 : Amel : Loc : Hsa : Ptr : Mmu :	: VIIDDKVUDAORIFVSKATINIIKTPLSOLIPAVSTIJOLVSIKRIGKFICODIKPDNVARESFKSDVDGVVPDNGTSVKKDGFCOKKRSV: : VIIDDKHUDAORIFVSKATINIIKTPLSOLIPAVSTIJOOVSIKRIGTTDODIKLDSVGRVPYNPNIESVVINGTSVSKDGFCOKRISV: : VIIDDKHUDAORIFVSKATINIIKTPLSOLIPAVSTIJOOPVSIKRIGKFICODIKLDSVGRVPYNPVGSLYFESVVINGTSVSKDSTFCTRRINV: : VIIDDKNUDAORIFVSKATINIIKTPLSOLIPAVSTIJOOPVSIKRIGKFICODIKLDSVGRVPYNPVGSLYFESVVINGTSVSKDSTFCTRRINV: : VIIDDKNUDAORIFVSKATINIIKTPLSOLIPAVSTIJOOPVSIKRIGKFICODIKLDSVGRVPYNPVGSLYFESVVINGTSVSKDSTFCTRRINV: : VIIDEKVUDAORIFVSKATINIIKTPLSOLIPAVSTIJOOPVSIKRIGKFICODIKLDSVGRVPYNPVGSLYFESVVINGTSVSKDSTFCTRRINV: : VIIDEKVUDAORIFVSKATINIIKTPLSOLIPAVSTIJOOPVSIKRIGKFICODIKLDSVGRPYNDGEDSVTFEDGTSSVSRDGPFCTRRISV: : VIIDEKVUDAORVFVSKATINIIKTPLSOLIPAVSTIJOOPVSIKRIGKFICOBIKADNVERAPLSPEGGSVVENGTSSVSRDGPFCTRRINV: : VIIDEKVUDAORVFVSKATINIITTRPLSOLIPAVSTIJOAVSIKRIGKFICOBIKADNVERAPLSPEGGSVVENGTSSVSRDGPFCTRRINV: : VIIDEKVUDAORVFVSKATINIITTRPLSOLIPAVSTIJOAFVSIKRIRIFISHBETEPDSTERRPVKDGG-GTNSTVRNATTTVARSDPFTNGTFF: : VIIDENNIDAOTAFVSTATINIIFTRPLNILMVISSIVOASVSIKRIRIFISHBETEPDSTERRPVKDGG-GTNSTVRNATTTVARSDPTTNGTFF: : VTIDENNIDAACAFVSTATINITRPLNILMVISSIVOASVSIKRIRIFISHBETEPDSTERRSVKDGG-GTNSTVRNATTVARSDPTTNGTFF: : VTIDENNIDAACAFVSTATINITRPLNILMVISSIVOASVSIKRIRIFISHBETEPDSTERRSIKSGE-CG-STVINATTVARAGEPTINGTFF:	613 652 614 667 654 672 652 666 572 666
ABCC6 ABCC6 ABCC6 ABCC6 ABCC6 ABCC1 ABCC1 ABCC1	Drel : Dre2 : Dre3 : Amel : Ame2 : Loc : Hsa : Ptr : Mmu :	: VIIDDK VIDAOKIFYSKATINI KTYPLSOLI PAVETT MOAVSIKRICKFI CODETKEDDVARESFKSDVDGVPPNGTESVEKDGPECTKRISV : : VIIDDKHVIDAOKIFYSKATINI KTXPLSOLI PAVETT MOAVSIKRICKFI CODETKIDSVERVPYNPNIESVVINGTESVEKDSTECTRINV : : VIIDDKVIDAOKIFYSKATINI KTPLSOLI PAVETT MOAVSIKRICKFI CODETKIDSVERVPYNPVGSLYPESVINGTESVEKDSTECTRINV : : VIIDDKVIDAOKIFYSKATINI KTPLSOLI PAVETT MOAVSIKRICKFI CODETKIDSVERVPYNPVGSLYPESVINGTESVEKDSTECTRINV : : VIIDDKVIDAOKVFYSKATINI KTPLSOLI PAVETT MOAVSIKRICKFI CODETKIDSVERVPYNPVGSLYPESVINGTESVEKDSFECTRRINV : : VIIDDKVIDAOKVFYSKATINI KTPLSOLI PAVETT MOAVSIKRICKFI CODETKIDSVERVPYNPGGSLYPESVINGTESVEKDSPECTRRINV : : VIIDDKVIDAOKVFYSKATINI KTPLSOLI PAVETT MOAVSIKRICKFI CODETKIDSVERVPYNDGEDSVVENGTESVERGPECTRRINV : : VIIDEKVIDAOKVFYSKATINI KTPLSOLI PAVETT MOAVSIKRICKFI CODETKIDSVERAPSPGGSVVENGTESVERGSECTRRINV : : VIIDEKVIDAOKVFYSKATINI KTPLSOLI PAVETT MOAVSIKRICKFI CODETKIDSVERAPSPGGSVVENGTESVERGSECTRRINV : : VIIDENVILDAOTAFVSIATINI KTPLSOLI PAVEST MOAVSIKRIKFI SHEETEPDSTERRVKDGGGTNSTVRIATETARSPETINGTF : : VTIDENVILDAOTAFVSIATINI KTPLNIL MVISSI VOASVSIKRIRI INI SHEETEPDSTERRVKDGGGTNSTVRIATETARSPETINGTF : : VTIDENVILDAOTAFVSIATINI FYLLIPPINILE MVISSI VOASVSIKRIRI INI SHEETEPDSTERRSIKSGE-GNSTVRIATETARSPETINGTF : : VTIDENVILDAOTAFVSIATINI FYLNEPPINIEMVISSI VOASVSIKRIRI FI SHEETEPDSTERRSIKSGE-GNSTVRIATETARSPETINGTF : : VTIDENVILDAOTAFVSIATINI FYLNEPPINIEMVISSI VOASVSIKRIRI FI SHEETEPDSTERRSIKSGE-GNSTVRIATETARSPETINGTF :	613 652 614 667 654 672 652 666 572 666
ABCC6 ABCC6 ABCC6 ABCC6 ABCC6 ABCC1 ABCC1 ABCC1 ABCC1	Drel : Dre2 : Dre3 : Amel : Ame2 : Loc : Hsa : Ptr : Mmu : Cluf :	: VLIDDK VLDAORIFYSKAIINI KTPLSOL FAVSTT JOALVSIKRICKFI CODEIKLDSVORVFNROMDGVFDNGT SVSKDGP CIKRISY : : VLIDDKHVLDAORIFYSKAIINI KAPLSOL FAVSTT JOVVSIKRICKFI CODEIKLDSVORVFNROMEGVFNNGT SVSKDSP CIRRINY : : VLIDDKHVLDAORIFYSKAIINI KAPLSOL FAVSTT JOAVVSIKRICKFI CODEIKLDSVORVFNROEDSVVENGT SVSKDSP CIRRINY : : VLIDDKVLDAORIFYSKAIINI KTPLSOL FAVSTT JOAVVSIKRICKFI CODEIKLDSVORVFNROEDSVVENGT SVSKDSP CIRRINY : : VLIDEK VLDAORVFVSKAIINI KTPLSOL FAVSTT JOAVVSIKRICKFI CODEIKLDSVORVFNROEDSVVENGT SVSKDSP CIRRINY : : VLIDEK VLDAORVFVSKAIINI KTPLSOL FAVSTT JOAVVSIKRICKFI CODEIKLDSVORAPSPDGGSVVENGT SVSRDSPCTRRINY : : VLIDEK VLDAORVFVSKAIINI KTPLSOL FAVSTT JOAPVSIKRICKFI CODEIKADSVERAPSPDGGSVVENGT SVSRDSPT SVSRDSPCTRRINY : : VLIDEK VLDAORVFVSKAIINI KTPLSOL FAVSTT JOAPVSIKRICKFI CODEIKADSVERAPSPDGGSVVENGT SVSRDSPT SVSRDSPT TRANST : VLIDEK VLDAORVFVSKAIINI KTPLSOL FAVST JOAPVSIKRICKFI CODEIKADSVERAPSPDGGSVVENGT SVSRDSPT TARSVER : VLIDEK VLDAORVFVSKAIINI KTPLSOL FAVST JOAPVSIKRICKFI CODEIKADSVERAPSPDG	613 652 614 667 654 672 652 666 572 666 666
ABCC6 ABCC6 ABCC6 ABCC6 ABCC6 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1	Dre1       :         Dre3       :         Ame1       :         Ame2       :         Loc       :         Ptr       :         Mmu       :         Cluff       :         Bta       :	: VIIDDKVUDAORIEVSKATINIIKTPLSOLIPAVETT KOLVSTKRICKFICODIKPDNVARESFKSDVDGVVPDNGTSVKKDGFCVKRISV : : VIIDDKHVUDAORIFVSKATINIIKAPLSOLIPAVETT KOLVVSTKRIGFT DODIKLDSVGRVPYNPNIESVVINGTSVKKDSTFCTRRINV : : VIIDDKNVUDAORIFVSKATINIIKTPLSOLIPAVETT KOLVVSTKRIGKFICODIKLDSVGRVPYNPVGSLYFESVTNNGTSVSKDSTFCTRRINV : : VIIDDKNVUDAORIFVSKATINIIKTPLSOLIPAVETT KOLVSTKRIGKFICODIKLDSVGRVPYNPVGSLYFESVTNGTSVSKDSTFCTRRINV : : VIIDDKNVUDAORIFVSKATINIIKTPLSOLIPAVETT KOLVSTKRIGKFICODIKLDSVGRVPYNPVGSLYFESVTNGTSVSKDSTFCTRRINV : : VIIDDKNVUDAORIFVSKATINIIKTPLSOLIPAVETT KOLVSTKRIGKFICODIKLDSVGRVPYNPVGSLYFESVTNGTSVSKDSTFCTRRINV : : VIIDDKNVUDAORIFVSKATINIIKTPLSOLIPAVETT KOLVSTKRIGKFICODIKLDSVGRVPYNPVGSLYFESVTNEGSFCTRRINV : : VIIDEKVUDAORVFVSKATINIIKTPLSOLIPAVETT KOLVSTKRIGKFICODIKLDSVGRVPKNDEDSVTNEGTSVSRDPFCTRRISV : : VIIDEKVUDAORVFVSKATINIIKTPLSOLIPAVETT KOLVSTKRIGKFICODIKLDSVGRPVSNGGEGNSTVRATTARSPFTNGTF : : VIIDEKVUDAORVFVSKATINIIKTPLSOLIPAVESTVOAVSSKRIRIFISHEDIEDSTERRVKDGGGNSTVRNATTTARSPFTNGTF : : VIIDENTUDAOTAFVSTATINITETTEPINILPAVISSIVOASVSKRIRIFISHEDIEDSTERRVKDGGGNSTVRNATTTARSPFTNGTF : : VTVDENTUDAKAFVSTATINITETTEPINILPAVISSIVOASVSKRIRIFISHEDIEDSTERRSKSGEGNSTVRNATTARSPFTNGTF : : VTVDENTUDAORAFVSTATINITERPINILPAVISSIVOASVSKRIRIFISHEDESTERRSKSGEGANSTVKNATTARSPFTNGTF : : VTVDENTUDAORAFVSTATINITERPINILPAVISSIVOASVSKRIRIFISHEDESTERRSKSGEGANSTVKNATTARSPFTNGTF : : VTVDENTUDAORAFVSTATINITERPINILPAVISSIVOASVSKRIRIFISHEDESTERRSKSGEGANSTVKNATTARSPFTNGTF : : VTVDENTUDAORAFVSTATINITERPINILPAVISSIVOASVSKRIRIFISHEDESTERRSKSGEGANSTVKNATTARSPFTNGTF : : VTVDENTUDAORAFVSTATINITERPINILPAVISSIVOASVSKRIRIFISHEDESTERRVKDGGGANSTVKNATTARSPFTNGTF : : VTVDENTUDAORAFVSTATINITERPINILPAVISSIVOASVSKRIRIFISHEDESTERRVKDGGGANSTVKNATTARSPFTTAGTF :	613 652 614 667 654 672 652 666 572 666 666 650
ABCC6 ABCC6 ABCC6 ABCC6 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1	Dre1 : Dre2 : Dre3 : Ame1 : Ame2 : Loc : Hsa : Ptr : Cluf : Bta : Dno :	: VIIDDK VIDAORIFYSKATINI KYPLSOL FAVSTI MOAUVSIKRICKFI CODETKPDN ARESFKSDVDG VFPNGT SWEKDGP CIKR SV : : VIIDDKHVIDAORIFYSKATINI KAPLSOL FAVSTI MOAVVSIKRICKFI CODETKIDSVGRVPYNPNEG VFPNGT SWEKDGP CIKR SV : : VIIDDK VIDAORIFYSKATINI KAPLSOL FAVSTI MOAVVSIKRICKFI CODETKIDSVERVPYNPVGSLYFES VINNGT SWEKDSTCTRRINV : : VIIDDK VIDAORIFYSKATINI KTPLSOL FAVSTI MOAVVSIKRICKFI CODETKIDSVERVPYNPVGSLYFES VINNGT SWEKDSFCTRRINV : : VIIDDK VIDAORIFYSKATINI KTPLSOL FAVSTI MOAVVSIKRICKFI CODETKIDS VERVPYNPVGSLYFES VINNGT SWEKDSFCTRRINV : : VIIDDK VIDAORVFYSKATINI KTPLSOL FAVSTI MOAVVSIKRICKFI CODETKIDS VRAPFSPGDS VVENGT SWEKDGP CIKR SV : : VIIDEK VIDAORVFYSKATINI KTPLSOL FAVSTI MOAVVSIKRICKFI CODETKIDS VRAPFSPGGS VVENGT SWERDGP CIRRISV : : VIIDEK VIDAORVFYSKATINI KTPLSOL FAVSTI MOAVVSIKRICKFI CODETKIDS VRAPFSPGGS VVENGT SWERDSFCTRRINV : : VIIDEK VIDAORVFYSKATINI KTPLSOL FAVSTI MOAVVSIKRICKFI CODETKIDS VRAPFSPGGS VVENGT SWERDSFCTRRINV : : VIIDEN VIDAORVFYSKATINI KTPLSOL FAVSTI MOAVVSIKRICKFI CODETKIDS VRAPFSPGGS VVENGT SWERDSFCTRRINV : : VIIDEN VIDAORVFYSKATINI KTPLSOL FAVSTI MOAVVSIKRI KFI SHEETEPDS ERRPKNDGGGNS TVRNATTWARSPFTING TF : : VTIDEN VIDAORAFVSIAFNI FYN TRFPINIL MVISSI VOASVSIKRI RIFT SHEETEPDS ERRPVKDGGGNS TVRNATTWARSPFTING TF : : VTUDEN VIDAORAFVSIAFNI FFI RYPINIL MVISSI VOASVSIKRI RIFT SHEETEPDS ERRPVKDGGGANS TVRNATTWARSPFTING TF : : VTUDEN VIDAORAFVSIAFNI RFPINIL MVISSI VOASVSIKRI RIFT SHEETEPDS ERRPVKDGGGANS TVRNATTWARSPFTING TF : : VTUDEN VIDAORAFVSIAFNI RFPINIL MVISSI VOASVSIKRI RIFT SHEETEPDS ERRPVKDGGGANS TVRNATTWARSPFTING TF : : VTUDEN VIDAORAFVSIAFNI RFPINIL MVISSI VOASVSIKRI RIFT SHEETEPDS ERRPVKDGGGANS TVRNATTWARSPFTING TF : : VTUDEN VIDAORAFVSIAFNI RFPINIL MVISSI VOASVSIKRI RIFT SHEETEPDS ERRPVKDGGGANS TVRNATTWARDSPTING TF : : VTUDEN VIDAORAFVSIAFNI RFPINIL MVISSI VOASVSIKRI RIFT SHEETEPDS ERRPVKDGGGINSI TVRNATTWARDSPTING TF : : VTUDEN VIDAORAFVSIAFNI RFPINIL MVISSI VOASVSIKRI RIFT SHEETEPDS ERRPVKDGGGINSI TVRNATTWARDSPTING TF : : VTUDEN VIDAOR	613 652 614 667 654 672 652 666 572 666 666 650 668
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ABCC6 ABCC6 ABCC6 ABCC6 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1	Dre1 : Dre2 : Dre3 : Ame1 : Loc : Hsa : Ptr : Cluf : Bta : Dno : Mdo : Oan :	: VIIDDK VIDAORIFYSKATINI KTPLSOL FAVSTI GOLVSIKRICKFI COD TKPDN ARESFKSDVDG VFPNGT SVEKDGP CIKR SV : : VIIDDK VIDAORIFYSKATINI KTPLSOL FAVSTI GOVVSIKRIGKFI COD TKLDSVORVFYNPNESVVINGT SVEKDST CIRRINV : : VIIDDK VIDAORIFYSKATINI KTPLSOL FAVSTI GOAVSIKRIGKFI COD TKLDSVORVFYNPNGLYFSV VINGT SVEKDST CIRRINV : : VIIDDK VIDAORIFYSKATINI KTPLSOL FAVSTI GOAVSIKRIGKFI COD TKLDSVORVFYNPNGELDSVVENGT SVEKDSFCIRRINV : : VIIDDK VIDAORIFYSKATINI KTPLSOL FAVSTI GOAVSIKRIGKFI COD TKLDSVORPFYNDGEDSVVENGT SVEKDGP CIRRISV : : VIIDDK VIDAORIFYSKATINI KTPLSOL FAVSTI GOAVSIKRIGKFI COD TKLDSVORPFYNDEDSVVENGT SVERDGP CIRRISV : : VIIDEK VIDAORVFYSKATINI KTPLSOL FAVSTI GOAVSIKRIGKFI COD TKLDSVORPFYNDEGSVVENGT SVERDGP CIRRISV : : VIIDEN VIDAORVFYSKATINI KTPLSOL FAVSTI GOAVSIKRIGKFI COD TKLDSVORPFYNDE	613 652 614 667 654 672 666 572 666 650 668 671 438
ABCC6 ABCC6 ABCC6 ABCC6 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1	Dre1 : Dre2 : Dre3 : Ame1 : Ame2 : Loc : Hsa : Ptr : Cluf : Bta : Dno : Mdo : Gan : Gaa :	: VIIDDK VIDAORIEVSKAIINIERPISCI FAVSTI VOLVSIKRICKFICODIKEDN VARESKSDVDGV PD.GTSVKKOGF OKKRISV : : VIIDDKHVIDAORIFVSKAIINIERPISCI FAVSTI VOLVSIKRICKFICODIKEDSVGRVPYNPNIESVVNNGTSVSKDSTECTRINV : : VIIDDKIVIDAORIFVSKAIINIERPISCI FAVSTI VOLVSIKRICKFICODIKEDSVGRVPYNPNGEDSVVDSGTSVKKDSTECTRINV : : VIIDDKIVIDAORIFVSKAIINIERPISCI FAVSTI VOLVSIKRICKFICODIKEDSVGRVPYNPNGEDSVVDSGTSVKKDSTECTRINV : : VIIDEKVIDAORIFVSKAIINIERTISTERPISCI FAVSTI VOLVSIKRICKFICODIKEDSVGRVPYNPVGSUYFSVVNNGTSVSKRDSTECTRINV : : VIIDEKVIDAORIFVSKAIINIERTISTERPISCI FAVSTI VOLVSIKRICKFICODIKEDSVGRVPYNPVGSUYFSVVNNGTSVSKRDSTECTRINV : : VIIDEKVIDAORIFVSKAIINIERTISTERPISCI FAVSTI VOLVSIKRICKFICODIKEDSVGRPVPVGGEDSVVDSGTSVSRGPFCTRRISV : : VIIDEKVIDAORVFVSKAIINIERTISTERPISCI FAVSTI VOLVSIKRICKFICODIKEDSVGRPVKDGE	613 652 614 667 654 672 652 666 572 666 650 668 671 438 663
ABCC6 ABCC6 ABCC6 ABCC6 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1	Dre1 : Dre2 : Dre3 : Ame1 : Loc : Hsa : Ptr : Mmu : Cluf : Bta : Dno : Mdo : Goan : Gda :	: VIIDDK VIDAORIFYSKATINIERT LSOLFAKST WOLVSTKRICKF CODETKEDN ARESFKSDVDG VFD GT SVEKDGF CTKRISY : VIIDDKHVLDAORIFYSKATINIERT SUCKED FAKST WOLVSTKRICKF CODETKLDSVGRVPYNPNDG VFD GT SVEKDGF CTKRISY : VIIDDK VIDAORIFYSKATINIERT SUCKED FAKST WOLVSTKRICKF CODETKLDSVGRVPYNPNGSLYFS VIN GT SVEKDSTCTRENV : VIIDDK VIDAORIFYSKATINIERTESST WOLVSTKRICKF CODETKLDSVGRVPYNPNGSLYFS VIN GT SVEKDSTCTRENV : VIIDDK VIDAORVFVSKATINIERTESST WOLVSTKRICKF CODETKLDSVGRVPYNPNGDEDS VVD GT SVEKDSFCTRENV : VIIDDK VIDAORVFVSKATINIERTESST WOLVSTKRICKF CODETKLDSVGRVPYNPNGDEDS VVD GT SVERDFECKRISV : VIIDEK VIDAORVFVSKATINIERTESST WOLVSTKRICKF CODETKLDSVGRAPSPGGS VVD GT SVERDFECKRISV : VIIDEK VIDAORVFVSKATINIERTESST WOLVSTKRICKF CODETKLDSVGRAPSPGGS VVD GT SVERGFECTRENV : VIIDEK VIDAORVFVSKATINIERTESST WOLVSSTKRICKF CODETKLDSVGRAPSPGGS VVD GT SVERGS CTRENV : VIIDEK VIDAORVFVSKATINIERTESST WOLVSSTKRICKF CODETKLDSVGRAPSPGGS VVD GT SVERGS CTRENV : VIIDEK VIDAORVFVSKATINIERTESST WOLVSSTKRICKF CODETKLDSVGRAPSPGGS VVD GT SVERGS CTRENV : VIIDEK VIDAORVFVSKATINIERTESST WOLVSSTKRICKF SKRIGKF CODETKLDSVGRAPST TREATTARSDFT TOR TF : VTTDENILDAOFAFVSTATINIERTESST WOLVSSTKRICKF SKRIGKF CODETKLDSVGRAPSTATING TF STRATTTARSDFT TOR TF : VTTDENILDAOFAFVSTATINIERTESST WOLVSSTKRICKF SKRIGKF CODETKLDSVGGGNSTVRATTTARSDFT TOR TF : VTTDENILDAORAFVSTATINIERTESST WOLVSSTKRICKF SKRIGFT SKRIGEF SKRIGGGNSTVRATTTARSDFT TAGT F : VTTDENILDAORAFVSTATINIERTESST WOLVSSTKRICKF SKRIGT SKRIGGGNSTVRATTARSDFT TARSDFT TAGT F : VTTDENILDAORAFVSTATINIERTESST WOLVSSTKRICKF SKRIGT SKRIGGGNSTVRATTARSDFT TARSDFT TAGT F : VTTDENILDAORAFVSTATINIERTESST WOLVSSTKRICKFT SKRIGEFSSTRRVKDGGGNSTVRATTARDSFT SG TF : VTTDENILDAORAFVSTATINIERTESST WOLVSSTKRICT SKRIGT SKRIGG SVRATTSTARATTARSDFT TOR TF : VTTDENILDAORAFVSTATINIERTESST WOLVSSTKRICT SKRIGT SKRIGT SKRIGG SVRATTSTRATTTARSDFT TOR TF : VTTDENILDAORAFVSTATINTESST WOLVSSTKRICT SKRIGT SKRIGT SKRIGG SVRATTSTRATTSTRATTTARSDFT TOR TF : VTTDENILDAORAFVSTATINTERTINGST VSTKRICT SKRIGT SKRIGT SKRIGT STORST STRATTSTRATT	613 652 614 667 654 672 652 666 572 666 572 666 650 668 671 438 652
ABCC6 ABCC6 ABCC6 ABCC6 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1	Dre1 : Dre2 : Dre3 : Ame1 : Ame2 : Loc : Hsa : Ptr : Mmu : Dno : Mmu : Cluf : Bta : Dno : Gda : Gda : Aca :	: VLIDDKIVLDAOKIFVSKATI NILKYPLSOL FAVSTT MOLVSIKRICKFICODIKPDNVARESKSDVDGVVPDGTSVEKDGFOKKISV : VLIDDKHVLDAOKIFVSKATI NILKAPLSOL FAVST MOLVVSIKRIGKFICODIKLDSVERVPYNPNIESVVINGTSVEKDSFCIRRINV : VLIDDKHVLDAOKIFVSKATI NILKAPLSOL FAVST MOLVSIKRIGKFICODIKLDSVERVPYNPNGLYPSVINGTSVEKDSTFCIRRINV : VLIDDKNVLDAOKIFVSKATI NILKAPLSOL FAVST MOLVSIKRIGKFICODIKLDSVERVPYNPNGLYPSVINGTSVEKDSTFCIRRINV : VLIDDKNVLDAOKIFVSKATI NILKAPLSOL FAVST MOLVSIKRIGKFICODIKLDSVERVPYNPNGLYPSVINGTSVEKDSTFCIRRINV : VLIDDKNVLDAOKIFVSKATI NILKAPLSOL FAVST MOLVSIKRIGKFICODIKLDSVERVPYNPNGLYPSVINGTSVEKDSTFCIRRINV : VLIDEKVLDAOKVFVSKATI NILKAPLSOL FAVST MOLVSIKRIGKFICODIKLDSVERVPYNPNGLYPSVINGTSVERSFORRINV : VLIDEKVLDAOKVFVSKATI NILKAPLSOL FAVST MOLVSIKRIGKFICODIKLDSVERVPYNPGGGSVVENGTSVERGSFCIRRINV : VTIDENILDAOTAFVSIATINILKAPLSOL FAVST MOLVSIKRIGKFICODIKLDSVERAPKDGGGSVVENGTSVERGSFCIRRINV : VTIDENILDAOTAFVSIATINILKAPLSOL FAVST MOLVSIKRIGKFICODIKLDSVERAPKDGGGSVVENGTSVERGSFCIRRINV : VTIDENILDAOTAFVSIATINILKAPLSOL FAVST MOLVSIKRIGKFICODIKLDSVERAPKDGG-GTNST TVRNATTARSDFTING TF : VTIDENILDAOTAFVSIATINILKAPLSVENTING VSVENTRIFISHEEPDS ERRPVKDGG-GTNST TVRNATTARSDFTING TF : VTIDENILDAOKAFVSIATINITRPINILMVISSI VOASVSKRIRIFISHEEPDS ERRPVKDGG-GANSTVKNATTVARSDFTING TF : VTIDENILDAOKAFVSIATINITRPINILMVISSI VOASVSKRIRIFISHEEPDS ERRPVKDGG-GANSTVKNATTVARDSFTING TF : VTIDENILDAOKAFVSIATINITRPINILMVISSI VOASVSKRIRIFISHEEPDS ERRPVKDGG-GANSTVKNATTVARDSFTING TF : VTIDENILDAOKAFVSIATINITRPINILMVISSI VOASVSKRIRIFISHEEPDSVRRPVKDGG-GANSTVKNATTVARDSFTISGTTF : VTIDENILDAOKAFVSIATINITRPINILMVISSI VOASVSKRIRIFISHEEPDSVRRPVKDGG-GTNSTVKNATTVARDSFTISGTTF : VTIDENILDAOKAFVSIATINITRPINILMVISSI VOASVSKRIRIFISHEEPDSVRRPVKDGG-GTNSTVKNATTVARDSFTISGTTF : VTIDENILDAOKAFVSIATINITRPINILMVISSI VOASVSKRIRIFISHEEPDSVRRPVKDGG-GTNSTVKNATTVARDSFTISGTTF : VTIDENILDAOKAFVSIATINITRPINILMVISSI VOASVSKRIRIFISHEEPDSVRRPVKDGG-GTNSTVKNATTVARDSFTISGTTF : VTIDENILDAOKAFVSIATINITRPINILMVISSI VOASVSKRIRIFISHEEPDSVRRPVKDGG-GTNSTVKNATTVARNDFTINGTTF : VTIDENILDAOKAFVSIATINITRPINILMVISSI VOASVSKRIRIFISHEEP	613 652 614 667 654 652 666 572 666 650 668 671 438 663 663
ABCC6 ABCC6 ABCC6 ABCC6 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1	Dre1 : Dre2 : Dre3 : Ame1 : Loc : Hsa : Hra : Cluf : Bta : Dno : Cluf : Cluf : Cluf : Cluf :	: VIIDDK VIDAORIFYSKATINIERTESCH FAVSTT GOLVSIKRICKF CODIKEDN VARESKSDVDGV PD/GT SVEKDGF O'KRUSY : VIIDDKHVLDAORIFYSKATINIERTESVEKRUST GOLVSIKRICKF ODDIKLDSVERVPYNPNDGV PD/GT SVEKDGF O'KRUSY : VIIDDKVLDAORIFYSKATINIERTESVERGE FAVSTT GOLVSIKRICKF ODDIKLDSVERVPYNPNCSIYFS VINNGT SVEKDSTFCTRENV : VIIDDKVLDAORIFYSKATINIERTESVERGE FAVSTT GOLVSIKRICKF CODIKLDSVERVPYNPVGSLYFS VINNGT SVEKDSTFCTRENV : VIIDDKVLDAORIFYSKATINIERTESVERGE FAVSTT GOLVSIKRICKF CODIKLDSVERVPYNPVGSLYFS VINNGT SVEKDSTFCTRENV : VIIDEKVUDAORVFVSKATINIERTESVERGE FAVSTT GOLVSIKRICKF CODIKLDSVERVPYNPVGSLYFS VINNGT SVEKDSFCTRENV : VIIDEKVLDAORVFVSKATINIERTESVERGE FAVSTT GOLVSIKRICKF CODIKLDSVERVPYNPVGSLYFS VINGT SVEKDGFCIRKESV : VIIDEKVLDAORVFVSKATINIERTESVERGE FAVST GOLVSIKRICKF CODIKLDSVERVPNVGGGGNSTVENGT SVERDEFCIRKESV : VIIDEKVLDAORVFVSKATINIERTESVERGE FAVST GOLVSIKRICKF CODIKLDSVERVENDSVERGE	613 652 614 667 654 672 666 572 666 650 668 671 438 663 652 661
ABCC6 ABCC6 ABCC6 ABCC6 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1	Dre1 : Dre2 : Dre3 : Ame1 : Ame2 : Loc : Hsa : Ptr : Dr : Bta : Dno : Mdo : Cluf : Gda : Aca : Lch :	: VIIDDK VIDAORIFYSKATINIERTPLSOL FAVET MOLVESTKRICKF CODETKEDN ARESFKSDVDG VFD GT SVEKDOF CIKR SV : : VIIDDKHVLDAORIFYSKATINIERTPLSOL FAVET MOLVESTKRICKF CODETKLDSVGRVPYNPNDG VFD GT SVEKDOF CIKR SV : : VIIDDK VIDAORIFYSKATINIERTPLSOL FAVET MOLVESTKRICKF CODETKLDSVGRVPYNPNGELYPES VENNGT SVEKDST CIRR NV : : VIIDDK VIDAORIFYSKATINIERTPLSOL FAVET MOLVESTKRICKF CODETKLDSVGRVPYNPOGSLYPES VENNGT SVEKDSF CIRR SV : : VIIDDK VIDAORIFYSKATINIERTPLSOL FAVET MOLVESTKRICKF CODETKLDSVGRVPYNPOGSLYPES VENGT SVEKDOF CIRR SV : VIIDEK VIDAORVFVSTATINIERTPLSOL FAVET MOLVESTKRICKF CODETKLDSVGRVPYNPOGSLYPES VENGT SVEKDOF CIRR SV : VIIDEK VIDAORVFVSTATINIERTPLSOL FAVET MOLVESTRICKF CODETKLDSVGRPSTRODEGS VVENGT SVERDOF CIRR SV : VIIDEK VIDAORVFVSTATINIERTPLSOL FAVET MOLVESTROL VENGT SVERTERFT CODETKLDSVGROF CIRR SV : VIIDEK VIDAORVFVSTATINIERTPLSOL FAVET MOLVESTVOLVESTROL VENGT SVERDEF CODETKLDSVERPVKDGGGINST VENGT SVERDEF CIRR SVERTER : VIIDEK VIDAORVFVSTATINIERTERPLNIERVISSI VOLVESTVOLVESTVOLVESTROL VENGT SVERTERFT SKEDTER SVERGE	613 652 614 667 654 652 666 572 666 650 668 671 438 663 662 661 663
ABCC6 ABCC6 ABCC6 ABCC6 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1	Dre1 : Dre2 : Dre3 : Ame1 : Ame1 : Loc : Ptr : Ptr : Dno : Dno : Oan : Gaa : Xtr : Lch :	: VIIDDK VUDAORIEVSKAIINIERPLOIPAVET UOLVSTKRICKE CODIKEDWARESKSDVDGVPDVGTSVEKDGF-CKRISV : : VIIDDKHVUDAORIEVSKAIINIERPLOIPAVET UOLVSTKRICKE CODIKEDSVERVPYNPNIESVVINGTSVEKDSTFCTRENV : : VIIDDKNVUDAORIEVSKAIINIERPLSOIPAVET UOLVSTKRICKE CODIKEDSVERVPYNPNDSVVDNGTSVEKDSTFCTRENV : : VIIDDKNVUDAORIEVSKAIINIERPLSOIPAVET UOLVSTKRICKE CODIKEDSVERVPYNPVGSLYFESVINGTSVEKDSTFCTRENV : : VIIDDKNVUDAORIEVSKAIINIERPLSOIPAVET UOLVSTKRICKE CODIKEDSVERVPYNPVGSLYFESVINGTSVEKDSTFCTRENV : : VIIDEKVUDAORIEVSKAIINIERPLSOIPAVET UOLVSTKRICKE CODIKEDSVERVPYNPVGSLYFESVINGTSVERGECIKERSV : : VIIDEKVUDAORIEVSKAIINIERPLSOIPAVET UOLVSTKRICKE CODIKEDSVERPVNDGEDSVTEDGTSSVERDEFCIKERSV : : VIIDEKVUDAORVEVSKAIINIERPLSOIPAVET UOLVSTVARKE KEE CODIKEDSVERPVNDGEGSVVDEGTSVERGESCIKERSV : : VIIDEKVUDAORVEVSKAIINIERPLSOIPAVET UOLVSTVARKEE CODIKEDSVERPVNDGEGSVVDEGTSVERGESCIKERSV : : VIIDEKVUDAORVEVSKAIINIERPLSOIPAVET UOLVSTVARVEKEE CODIKEDSVERPVNDGEGSVVDEGTSVERGESCIKERV : : VIIDENIUDAORAFVSIAIFNIERPLNIERVISSI VOASVSIKERIETSHEELEPDSVERREVKDGGGTNSTVENATETVARSDEFTINGTF : : VTVDENIUDAORAFVSIAIFNIERPLNIERVISSI VOASVSIKERIETSHEELEPDSVERREVKDGGGANSTVENATETVARSDEFTINGTF : : VTVDENIUDAORAFVSIAIFNIERPLNIERVISSI VOASVSIKERIETSHEELEPDSVERREVKDGGGANSTVENATETVARSDEFTINGTF : : VTVDENIUDAORAFVSIAIFNIERPLNIERVISSI VOASVSIKERIETSHEELEPDSVERREVKDGGGANSTVENATETVARDEFTINGTF : : VTVDENIUDAORAFVSIAIFNIERPLNIERVISSI VOASVSIKERIETSHEELEPDSVERREVKDGGGANSTVENATETVARDEFTINGTF : : VTVDENIUDAORAFVSIAIFNIERPLNIERVISSI VOASVSIKERIETSHEELEPDSVERREVKDGGGANSTVENATETVARDEFTINGTF : : VTVDENNUDAORAFVSIAIFNIERPLNIERVISSI VOASVSIKERIETSHEELEPDSVERREVKDGGGANSTVENATETVARDEFTINGTF : : VTVDENNUDAORAFVSIAIFNIERPLNIERVISSI VOASVSIKERIETSHEELEPDSVERREVKDGGGANSTVENATETVARDEFTINGTFF : : VTVDENNUDAORAFVSIAIFNIERPLNIERVISSI VOASVSIKERIETSHEELEPDSVERSVERVELOGSI VERVIATESSENDFTINGTFF : : VTVDENNUDAORAFVSIAIFNIERPLNIERVISSI VOASVSIKERIETSHEELEPDSVERSVERVELOGSI VERVIATESSENDFTINGTFF : : VVUDENNUDAORAFVSIAIFNIERPLNNESI VOASVSIKERERVETSHEELEPESVERESVERDUG	613 652 614 667 654 672 652 666 572 666 650 668 671 438 663 652 661 662 663
ABCC6 ABCC6 ABCC6 ABCC6 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1	Dre1 : Dre2 : Dre3 : Ame1 : Loc : Hsa : Hsa : Ptr : Dno : Dno : Mdo : Gaa : Xtr : Lch : Gaz :	: VIIDDK_VIDAORIFYSKATINIERTPLSOL FAVETT 00.7 VSTKRICKFT CODETKEDN VARESFKSDVDGV VFD.GT.SVKKDCF-CTKRISV : VIIDDKHVIDAORIFYSKATINIERTPLSOL FAVETT 00.7 VSTKRICKFT CODETKLDSVCRVPYNPNDGV VFD.GT.SVKKDCF-CTKRISV : VIIDDKVIDAORIFYSKATINIERTPLSOL FAVETT 00.7 VSTKRICKFT CODETKLDSVCRVPYNPNDGV VFD.GT.SVKKDSTFCTRRINV : VIIDDKVIDAORIFYSKATINIERTPLSOL FAVETT 00.7 VSTKRICKFT CODETKLDSVCRVPYNPVGSLYFES VINNGT SVKKDSTFCTRRINV : VIIDDKVIDAORIFYSKATINIERTPLSOL FAVETT 00.7 VSTKRICKFT CODETKLDSVCRVPYNPVGSLYFES VINNGT SVKKDSFFCTRRINV : VIIDEKVIDAORVFVSKATINIERTPLSOL FAVETT 00.7 VSTKRICKFT CODETKLDSVCRVPYNPVGSLYFES VINNGT SVKKDSFFCTRRINV : VIIDEKVIDAORVFVSKATINIERTPLSOL FAVETT 00.7 VSTKRICKFT CODETKLDSVCRAPFSPDGGSVVENGT SVKRDGFCJKRISV : VIIDEKVIDAORVFVSKATINIERTPLSOL FAVETT 00.7 VSTKRICKFT CODETKLDSVCRAPFSPDGGSVVENGT SVKRDGFCJKRISV : VIIDEKVIDAORVFVSKATINIERTERPLNIL MVISSI VOAVSTKRICTIST SHEETED SERREVKDGGGNSTTVRNATTTARSDFTINGTF : VTIDENTILDAOTAFVSTATFNIERPLNIL MVISSI VOASVSTKRIRIFT SHEETED SERREVKDGGGNSTTVRNATTTARSDFTINGTF : VTVDENTILDAORAFVSTATFNIERPLNIL MVISSI VOASVSTKRIRIFT SHEETED SERREVKDGGGNSTTVRNATTTARDFTTARTSFT SGTF : VTVDENTILDAORAFVSTATFNIERPLNIL MVISSI VOASVSTKRIRIFT SHEETED SERREVKDGGGNSTTVRNATTTARNPTTRATT SGTF : VTVDENTILDAORAFVSTATFNIERPLNIL MVISSI VOASVSTKRIRIFT SHEETED SERREVKDGGGNSTVRNATTWRSDFTTTGT F: : VTVDENTILDAORAFVSTATFNIERPLNIL MVISSI VOASVSTKRIRIFT SHEETED SERREVKDGGGNSTVNATTWRSDFTTWRTTTARSDFTTNGTF : : VTVDENTILDAORAFVSTATFNIERPLNIL MVISSI VOASVSTKRIRVFT SHEETED SERREVKDGGGNSTVRATTWRSDFTTWRTTTRATTVSDFTTTGT F: : VTVDENTILDAORAFVSTATFNIERPLNKIL MVISSI VOASVSTKRIRVFT	613 652 614 667 654 672 652 666 572 666 650 666 650 665 651 438 652 661 663 663
ABCC6 ABCC6 ABCC6 ABCC6 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1	Dre1 : Dre2 : Dre3 : Ame1 : Ame2 : Loc : Hsa : Ptr : Bta : Dtr : Bta : Gaa : Aca : Xtr : Gac : D1a :	: VLIDDK VLDAORIEVSKAI I NI KYPLSOL FAVSTI VOLVSIKRICKFI CODIKPDN VARSSKSDVDGV PD.GT.SVKKDGF-C/KRISV : VLIDDKHUDAORIFVSKAI I NI KAPLSOL FAVST VOLVSIKRICKFI CODIKLDSVRVPYNPNIES V NNGT SVKKDSTFCJRRINV : VLIDDKHUDAORIFVSKAI I NI KAPLSOL FAVST VOLVSIKRICKFI CODIKLDSVRVPYNPVGSLYPES VI NNGT SVKKDSTFCJRRINV : VLIDDKNUDAORIFVSKAI I NI KAPLSOL FAVST VOLVSIKRICKFI CODIKLDSVRVPYNPVGSLYPES VI NNGT SVKKDSTFCJRRINV : VLIDDKNUDAORIFVSKAI I NI KAPLSOL FAVST VOLVSIKRICKFI CODIKLDSVRVPYNPVGSLYPES VI NNGT SVKRDSTFCJRRINV : VLIDEK VUDAORVFVSKAI I NI KAPLSOL FAVST VOLVSIKRICKFI CODIKLDSVRAPFSPDGDSVT ED GT SVSRDPFCJRRINV : VLIDEK VUDAORVFVSKAI I NI KAPLSOL FAVST VOLVSIKRICKFI CODIKLDSVRAPFSPDGDSVT ED GT SVSRDPFCJRRINV : VI DENNILDAORVFVSKAI I NI KAPLSOL FAVST VOLVSIKRICKFI CODIKLDSVRAPFSPDGDSVT ED GT SVSRDPFCJRRINV : VT DENNILDAORVFVSKAI I NI KAPLSOL FAVST VOLVSIKRICKFI CODIKLDSVRAPFSPDGDSVT ED GT SVSRDPFCJRRINV : VT DENNILDAORAFVSIAI FNI RFPLNIL MVISSI VOLVSIKRICKFI CODIKADNVERAPLSPEGGSVVEDGT SVRAGFTING TF : VT DENNILDAORAFVSIAI FNI RFPLNIL MVISSI VOLSVIKRIR IFI SHEELEDSSVERRPVKDGGGTNST TVRNAT TARSDPT TING TF : VT DENNILDAORAFVSIAI FNI RFPLNIL MVISSI VOLSVIKRIR IFI SHEELEDSSVERRPVKDGGGNST TVRNAT TARGFTINGT FF : VT DENNILDAORAFVSIAI FNI RFPLNIL MVISSI VOLSVIKRIR IFI SHEELEDSSVERRPVKDGGGNST TVRNAT TARGFTINGT FF : VT DENNILDAORAFVSIAI FNI RFPLNIL MVISSI VOLSVIKRIR IFI SHEELEDSSVERRPVKDGGGNST TVRNAT TARDFT TARSDPT TING TF : VT DENNILDAORAFVSIAI FNI RFPLNIL MVISSI VOLSVIKRIR IFI SHEELEDSSVERRPVKDGGGNST TVRNAT TARNDFT THGT FF : VT VENNVLDAORAFVSIAI FNI RFPLNIL MVISSI VOLSVIKRIR IFI SHEELEDSSVERRPVKDGGGNST TVRNAT TARNDFT TING TF : VT DENNILDAORAFVSIAI FNI RFPLNIL MVISSI VOLSVIKRIR IFI SHEELEDSSVERRPVKDGGGNST TVRNAT TARDFT TARDFT TING TF : VT DENNILDAORAFVSIAI FNI RFPLNIL MVISSI VOLSVIKRIR IFI SHEELEDSSVERRPKDRGSSVENAAGNST TVRNAT TARSDPT TING TF : VT DENNILDAORAFVSIAI FNI RFPLNIL MVISSI VOLSVIKRIR IFI SHEELEDSSVERRPKDRGSSVENAA	613 652 614 667 654 672 656 572 666 650 668 671 438 663 652 661 663 662 605
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ABCC6 ABCC6 ABCC6 ABCC6 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1	Dre1 : Dre2 : Dre3 : Ame1 : Ame2 : Loc : Hsa : Ptr : Mmu : Cluf : Bta : Dno : Mdo : Cluf : Bta : Cluf : Dno : Mdo : Cluf : Dno : Cluf : Cluf : Dno : Mdo : Cluf : Dno : Mdo : Cluf : Dno : Cluf : Dno : Mdo : Cluf : Dno : Cluf :	<ul> <li>VUIDDANT VUDAOKT VOMAT INTERPLSOEPA, SET MOALVSTRATKER COPERED WARESREDVDG, VPD, GT, SCKDGPC, CKR, SV</li> <li>VUIDDANT VOMAT INTERPLSOEPA, SET MOAVVSTRATGET DODER LDSCRAVPYNPNES VUDGTSCRAVGET SCRETNV</li> <li>VUIDDANT VOMAT INTERPLSOEPA, SET MOAVVSTRATGET COPERED SCREVPYNVGDEDS, VUDGTSCRAVGET SCRETCRAVST</li> <li>VUIDDER VUDAOR VOMAT INTERPLSOEPA, SET MOAVVSTRATGET COPERED SCREVPYNVGDEDS, VUDGTSCRAVGET SCRETCRAVST</li> <li>VUIDDER VUDAOR VORMAT INTERPLSOEPA, SET MOAVVSTRATGET COPERED SCREAPPYRODEDS, VUDGTSCRAVGET SCREEPCER, ST</li> <li>VUIDDER VUDAOR VORMAT INTERPLATED VOR VARANT SCRETCOPERED SCREAPPYRODEDS, VUDGTSCRED SCREEPCER, ST</li> <li>VUIDDER VUDAOR VORMAT INTERPLATER VOR STANDAVSTRATGET COPERED SCREAPPYRODESC VUDGTSCRED SCREEPCER, ST</li> <li>VUIDDEN VUDAOR VORMAT NELKTPLSOEPA, SET MOAFVSTRATGET COPERED SCREAPPYROGEGNS TURNATET ARBOPTING TF</li> <li>VUIDDEN VUDAOR VORMAT NELKTPLSOEPA, SET MOAFVSTRATGET SCRETCHORE SCREEPTING TO TARATTAR SCRETT ARBOPTING TF</li> <li>VUIDDEN VUDAORAVSTATENT REPENTERPLATER VENDEST VOR VERSTRAVENDEGGNS TURNATET ARBOPTING TF</li> <li>VUIDENNILDAORAVSTATENT REPENTERPLATER VERSTRAVENDEGGNS TURNATET ARBOPTING TF</li> <li>VUVDENNILDAORAVSTATENT REPENTERPLATERVEST VOR SCRETT SCRETT</li></ul>	613 652 667 654 667 654 662 666 650 668 663 663 663 662 663 662 663 663 663 663
ABCC6 ABCC6 ABCC6 ABCC6 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1	Dre1 : Dre2 : Dre3 : Ame1 : Loc : Hsa : Ptr : Hsa : Cluf : Bta : Dno : Dno : Dno : Ado : Cluf : Cluf : Bta : Dno : Cluf :	<pre>V UDDOKAVLDAOK IZVSIAT IIIKTPLSOT FALST TORVISIKAT KAREFKSDVDC VYD, GT SYEKDEPC TAR ISV : VIDDKAVLDAOK IZVSIAT IIIKAPLSOT FALST TORVVSIKAT GTFIDODIKLDSVORVPYNPNESVV TALGT SYEKDST CTRAINV : VIDDKAVLDAOK IZVSIAT IIIKAPLSOT FALST VORVSIKAT GKFIDODIKLDSVORVPYNPVSLYFSV VID.GT SYEKDST CTRAINV : VIDDKAVLDAOK IZVSIAT IIIKTPLSOT FALST VORVSIKAT GKFICODE KLDSVCRAPFSPDGDSVV ELGT SYEKDST CTRAINV : VIDDKAVLDAOK IZVSIAT IIIKTPLSOT FALST VORVSIKAT GKFICODE KLDSVCRAPFSPDGDSVV ELGT SYEKDST CTRAINV : VIDDKAVLDAOK VIVSIAT IIIKTPLSOT FALST VORVSIKAT GKFICODE KLDSVCRAPFSPDGDSVV ELGT SYEKDST CTRAINV : VIDEKAVLDAOK VIVSIAT IIIKTPLSOT FALST VORVSIKAT GKFICODE KLDSVCRAPFSPDGDSVV ELGT SYEKDST CTRAINV : VIDEKAVLDAOK VIVSIAT FILKFPLANT FALST VORSYSIKAT FALST COETKADNVERAPFSPDGDSVV ELGT SYEKDSC CTRAINV : VIDEKAVLDAOK VINSIAT FILKFPLANT MAVISS VORSYSIKAT FILT SHEETEPDSTERRPVKDGG-GTNST VR ATT ARGEP TING TF : VTDERNILDAC AFVSIAT FILKFPLANT MAVISS VORSYSIKAT FILT SHEETEPDSTERRPVKDGG-GTNST VR ATT ARGEP TING TF : VTDERNILDACKAFVSIAT FILKFPLANT MAVISS VORSYSIKAT FILT SHEETEPDSTERRPVKDGG-GANST VK AATT ARGEP TING TF : VTDERNILDACKAFVSIAT FILKFPLANT MAVISS VORSYSIKAT FILSHEETEPDSTERRPVKDGG-GANST VK AATT ARGEP TING TF : VTDENNILDAOKAFVSIAT FILKFPLANT MAVISS VORSYSIKAT FILSHEETEPDSTERRPVKDGG-GANST VK AATT ARGEP TING TF : VTDENNILDAOKAFVSIAT FILKFPLANT MAVISS VORSYSIKAT FILSHEETEPDSTERRPVKDGG-GANST VK AATT ARGEP TING TF : VTDENNILDAOKAFVSIAT FILKFPLANT MAVISS VORSYSIKAT RIFT SHEETEPDSTERRPVKDGG-GANST VK AATT ARGEP TING TF : VTVDENNILDAOKAFVSIAT FILKFPLANT MAVISS VORSYSIKAT RIFT SHEETEPDSTERRPVKDGG-GANST VK AATT ARGEP TING TF : VTVDENNILDAOKAFVSIAT FILKFPLANT MAVISS VORSYSIKAT RIFT SHEETEPDSTERRPVKDGG-GANST VK AATT ARGEP TING TF : VTVDENNILDAOKAFVSIAT FILKFPLANT MAVISS VORSYSIKAT RIFT SHEETEPDSTERPVKDGG-GANST VK AATT ARGEP TING TF : VTVDENNILDAOKAFVSIAT FILKFPLANT MAVISS VORSYSIKAT RIFT SHEETEPDSTERPVKDGG-GANST VK AATT ARGEP TING TF : VTVDENNILDAOKAFVSIAT FILKFPLANT MAVISS VORSYSIKAT RIFT SHEETEPDSTERPVKDGG-GANST VK AATT</pre>	613 652 667 654 672 652 666 650 668 650 668 663 663 662 663 662 663 662 663 663 663
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ABCC6 ABCC6 ABCC6 ABCC6 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1	Dre1 : Dre2 : Dre3 : Ame1 : Loc : Hsa : Ptr : Hsa : Ptr : Dno : Dno : Dno : Dno : Dno : Aca : Xtr : Cac : Ola : Ola : Ola : Tni : Cni : Xma1 : Zxma2 : Dre : Loc : Cmi :	<pre>* VLTD DK VLDAGGT VSKALT IIIKTPLSOLF PAST GT VOTVOSKT (GKT CODENK PM QARSKSDVGVPD (GT SG SKDST CLRR NV : VLTD DK VLDAGGT VSKALT IIIKTPLSOLF PAST TOVVOSKT (GTT CODENK DS ORVPYNPN</pre>	613 652 667 654 672 652 666 650 668 660 668 663 663 662 663 662 663 662 663 664 663 664 663 664 663 664 663
ABCC6 ABCC6 ABCC6 ABCC6 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1	Dre1 : Dre2 : Dre3 : Ame1 : Ame2 : Hsa : Hsa : Ftr : Cluf : Bta : Dno : Mdo : Cluf : Bta : Dno : Mdo : Cluf : Gac : Xtr : Cluf : Gac : Tni : Cluf : Cla : Cl	: VLTD DK.VLDAOKT VSKALT IIIKTPLSOLPAST ST.VOLVESKIKKIGFTOD SIKKSPV	613 652 667 654 672 666 572 666 572 666 650 668 671 438 663 662 663 663 662 663 662 663 672 663 6645 772 663 6645
ABCC6 ABCC6 ABCC6 ABCC6 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC2 ABCC2 ABCC3 ABCC3 ABCC3 ABCC3 ABCC3 ABCC3 ABCC4 ABCC4 ABCC4 ABCC4 ABCC4 ABCC4 ABCC4 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC5 ABCC5 ABCC5 ABCC5 ABCC5 ABCC5 ABCC5 ABCC5 ABCC5 ABCC5 ABCC5 ABCC5 ABCC5 ABCC5 ABCC5 ABCC5 ABCC5 ABCC5 ABCC5 ABCC5 ABCC5 ABCC5 ABCC5 ABCC5 ABCC5 ABCC5 ABCC5 ABCC5 ABCC5 ABCC5 ABCC5 ABCC5 ABCC5 ABCC5 ABCC5 ABCC5 ABCC5 ABCC5 ABCC5 ABCC5 ABCC5 ABCC5 ABCC5 ABCC5 ABCC5 ABCC5 ABCC5 ABCC5 ABCC5 ABCC5 ABCC5 ABCC5 ABCC5 ABCC5 ABCC5 ABCC5 ABCC5 ABCC5 ABCC5 ABCC5 ABCC5 ABCC5 ABCC5 ABCC5 ABCC5 ABCC5 ABCC5 ABCC5 ABCC5 ABCC5 ABCC5 ABCC5 ABCC5 ABCC5 ABCC5 ABCC5 ABCC5 ABCC5 ABCC5 ABCC5 ABCC5 ABCC5 ABCC5 ABCC5 ABCC5 ABCC5 ABCC5 ABCC5 ABCC5 ABCC5 ABCC5 ABCC5 ABCC5 ABCC5 ABCC5 ABCC5 ABCC5 ABCC5	Dre1 : Dre2 : Dre2 : Ame1 : Loc : Hsa : Ftr : Muu : Cluf : Bta : Dno : Can : C	<pre>VIIIDBK_ULDAGT_TSUSAT_TILTEPISCT_FA_ST_MOT_VSIK_TICKTERCTEDODETKEDS_WARESFYSUSDC_TY_SUSACES_CTRANST V VIIIDBKKULDAGT_TSUSAT_TILTAPISCT_FA_ST_MON_VSIK_TICKTTCDDDETKLDS_URVPYNPNTES_VIN_CT_SUSACE_CTRANST V VIIIDBKKULDAGT_TSUSAT_TILTAPISCT_FA_ST_MON_VSIK_TICKTTCDDETKLDS_URVPYNPVGSUSYFSUFN_CT_SUSACE_CTRANST V VIIIDBKKULDAGT_TSUSAT_TILTAPISCT_FA_ST_MON_VSIK_TICKTTCDDETKLDS_URVPYNPVGSUSYFSUFN_CT_SUSACE_CTRANST V VIIIDBKKULDAGT_TSUSAT_TILTAPISCT_FA_ST_MON_VSIK_TICKTTCDDETKLDS_URVPYNPVGSUSYFSUFN_CT_SUSACE_CTRANST V VIIIDBKKULDAGT_TSUSAT_TILTAPISCT_FA_ST_MON_VSIK_TICKTTCDDETKLDS_URVPYNPVGSUSYFSUFN_CT_SURGE_CTRANST V VIIIDBKKULDAGT_TSUSAT_TILTAPISCT_FA_ST_MON_VSIK_TICTUSETETEDES_URRPVNDGCGTNS_TUR_AT_T_ARSDET_UNG_TF_ VIIIDBKKULDAGT_TSUSAT_TILTAPISCT_FA_ST_MON_VSIK_TILTUSEETEPES_BRRSTKDGE_GTNS_TUR_AT_T_ARSDET_UNG_TF_ VIIIDBKKULDAGT_SUSAT_TILTAPISCT_TVSUS_VSIK_TILTUSEETEPES_BRRSTKDGE_GTNS_TUR_AT_T_ARSDET_UNG_TF_ VIIIDBKKULDAGT_SUSAT_FILTAPINITURVUSS_TVOSVSIK_TILTUSEETEPES_BRRSTKDGC_GANS_TUK_AT_T_ARSDET_UNG_TF_ VIIIDBKKULDAGT_SUSAT_FILTAPINITURVUSS_TVOSVSIK_TILTUSEETEPES_BRRSTKDGC_GANS_TUK_AT_T_ARSDET_UNG_TF_ VIIIDBKKULDAGT_SUSAT_FILTAPINITURVUSS_TVOSVSIK_TILTUSEETEPES_BRRSTKDGC_GANS_TUK_AT_T_ARSDET_UNG_TF_ VIIIDBKKULDAGT_SUSAT_FILTAPINITURVUSS_TVOSVSIK_TILTUSEETEPES_BRRSTKDGC_GANS_TUK_AT_T_ARSDET_UNG_TF_ VIIIDBKKULDAGT_SUSAT_FILTAPINITURVUSS_TVOSVSIK_TILTUSEETEPES_URRFVKDGG_GANS_TUK_AT_T_ARSDET_UNG_TF_ VIIIDBKKULDAGT_SUSAT_FILTAPINITURVUSS_TVOSVSIK_TRITUSEETEPES_URRFVKDGG_GANS_TUK_AT_T_SRDET_TIGGTFF VIIIDBKKULDAGT_SUSAT_FILTAPINITURVUSS_TVOSVSIK_TRITUSEETEPES_URRFVKDGUSA</pre>	613 652 667 654 667 652 666 652 666 650 668 660 668 660 668 662 661 662 663 662 663 663 663 663 6645 750 592
ABCC6 ABCC6 ABCC6 ABCC6 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1	Dre1 : Dre2 : Dre3 : Ame1 : Hsa : Hsa : Ptr : Dre : Dno : Dno : Dno : Dno : Dno : Dno : Dno : Cluf : Dno : Dno : Dno : Cluf : Dno : Dna :	<pre>VIDID&amp; UDDAGET EVSLAT TELEVISTATION VEST TWO VUSIKENEST CONTREDUCTION DATES TO CONTREDUCT SUPPORT</pre>	613 652 667 654 667 654 666 572 666 650 666 668 671 438 663 663 663 662 665 665 665 665 666 667 666 672 666 672 666 672 666 672 666 672 666 672 666 672 666 667 666 672 666 667 666 667 666 667 666 667 666 667 666 667 666 666 667 666 667 666 667 666 666 667 666 666 667 666 666 666 667 666 666 666 666 666 666 666 666 666 667 666 666 666 666 666 666 666 666 666 666 666 666 666 666 666 666 666 666 666 666 666 666 666 666 666 666 666 666 666 666 666 666 666 666 666 666 666 666 666 666 666 666 666 666 666 666 666 666 666 666 666 666 666 666 666 666 666 666 666 666 666 667 666 667 666 666 666 666 667 666 667 666 666 666 667 666 667 666 667 666 667 666 667 666 667 666 667 666 667 667 666 667 666 667 666 667 666 667 667 667 666 667 667 667 667 667 667 667 667 667 667 667 667 667 667 667 667 667 667 667 667 750 750 748
ABCC6 ABCC6 ABCC6 ABCC6 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC2 ABCC6 ABCC6 ABCC6 ABCC6 ABCC6 ABCC6 ABCC6 ABCC6 ABCC6 ABCC6 ABCC6 ABCC6 ABCC6 ABCC6 ABCC6 ABCC6 ABCC6 ABCC6 ABCC6 ABCC6 ABCC6 ABCC6 ABCC6 ABCC6 ABCC6 ABCC6 ABCC6 ABCC6 ABCC6 ABCC6 ABCC6 ABCC6 ABCC6 ABCC6 ABCC6 ABCC6 ABCC6 ABCC6 ABCC6 ABCC6 ABCC6 ABCC6 ABCC6 ABCC6 ABCC6 ABCC6 ABCC6 ABCC6 ABCC6 ABCC6 ABCC6 ABCC6 ABCC6 ABCC6 ABCC6 ABCC6 ABCC6 ABCC6 ABCC6 ABCC6 ABCC6 ABCC6 ABCC6 ABCC6 ABCC6 ABCC6 ABCC6 ABCC6 ABCC6 ABCC6 ABCC6 ABCC6 ABCC6 ABCC6 ABCC6 ABCC6 ABCC6 ABCC6 ABCC6 ABCC6 ABCC6 ABCC6 ABCC6 ABCC6 ABCC6 ABCC6 ABCC6 ABCC6 ABCC6 ABCC6 ABCC6 ABCC6 ABCC6 ABCC6 ABCC6 ABCC6 ABCC6 ABCC6 ABCC6 ABCC6 ABCC6 ABCC6 ABCC6 ABCC6 ABCC6 ABCC6 ABCC6 ABCC6 ABCC6 ABCC6 ABCC6 ABCC6 ABCC6 ABCC6 ABCC6 ABCC6 ABCC6 ABCC6 ABCC6 ABCC6 ABCC6 ABCC6 ABCC6 ABCC6 ABCC6 ABCC6	Dre1 : Dre2 : Dre3 : Ame1 : Ame2 : Loc : Hsa : Ptr : Hsa : Dno : Mdo : Cluf : Gac : Aca : Xtr : Cluf : Gac : Tni : Dna : Cluf : Cmi : Chaf : Cmi : Cmi : Cmi :	<pre>VLTDDK_VLDAGT_VSTAT_TITUTPLSCUTPA_SIT_VGT_VGT_VGTACUTATED_ADDEALDESCOVE_VDT_ADDEALDESCOVE_VDT_ADDEALDESCOVE_VDT_ADDEALDESCOVE_VDT_ADDEALDESCOVE_VDT_ADDEALDESCOVE_VDT_ADDEALDESCOVE_VDT_ADDEALDESCOVE_VDT_ADDEALDESCOVE_VDT_ADDEALDESCOVE_VDT_ADDEALDESCOVE_VDT_ADDEALDESCOVE_VDT_ADDEALDESCOVE_VDT_ADDEALDESCOVE_VDT_ADDEALDESCOVE_VDT_ADDEALDESCOVE_VDT_ADDEALDESCOVE_VDT_ADDEALDESCOVE_VDT_ADDEALDESCOVE_VDT_ADDEALDESCOVE_VDT_ADDEALDESCOVE_VDT_ADDEALDESCOVE_VDT_ADDEALDESCOVE_VDT_ADDEALDESCOVE_VDT_ADDEALDESCOVE_VDT_ADDEALDESCOVE_ADDEALDESCOVE_VDT_ADDEALDESCOVE_ADDEALDESCOVE_VDT_ADDEALDESCOVE_ADDEALDESCOVE_ADDEALDESCOVE_ADDEALDESCOVE_ADDEALDESCOVE_ADDEALDESCOVE_ADDEALDESCOVE_ADDEALDESCOVE_ADDEALDESCOVE_ADDEALDESCOVE_ADDEALDESCOVE_ADDEALDESCOVE_ADDEALDESCOVE_ADDEALDESCOVE_ADDEALDESCOVE_ADDEALDESCOVE_ADDEALDESCOVE_ADDEALDESCOVE_ADDEALDESCOVE_ADDEALDESCOVE_ADDEALDESCOVE_ADDEALDESCOVE_ADDEALDESCOVE_ADDEALDESCOVE_ADDEALDESCOVE_ADDEALDESCOVE_ADDEALDESCOVE_ADDEALDESCOVE_ADDEALDESCOVE_ADDEALDESCOVE_ADDEALDESCOVE_ADDEALDESCOVE_ADDEALDESCOVE_ADDEALDESCOVE_ADDEALDESCOVE_ADDEALDESCOVE_ADDEALDESCOVE_ADDEALDESCOVE_ADDEALDESCOVE_ADDEALDESCOVE_ADDEALDESCOVE_ADDEALDESCOVE_ADDEALDESCOVE_ADDEALDESCOVE_ADDEALDESCOVE_ADDEALDESCOVE_ADDEALDESCOVE_ADDEALDESCOVE_ADDEALDESCOVE_ADDEALDESCOVE_ADDEALDESCOVE_ADDEALDESCOVE_ADDEALDESCOVE_ADDEALDESCOVE_ADDEALDESCOVE_ADDEALDESCOVE_ADDEALDESCOVE_ADDEALDESCOVE_ADDEALDESCOVE_ADDEALDESCOVE_ADDEALDESCOVE_ADDEALDESCOVE_ADDEALDESCOVE_ADDEALDESCOVE_ADDEALDESCOVE_ADDEALDESCOVE_ADDEALDESCOVE_ADDEALDESCOVE_ADDEALDESCOVE_ADDEALDESCOVE_ADDEALDESCOVE_ADDEALDESCOVE_ADDEALDESCOVE_ADDEALDESCOVE_ADDEALDESCOVE_ADDEALDESCOVE_ADDEALDESCOVE_ADDEALDESCOVE_ADDEALDESCOVE_ADDEALDESCOVE_ADDEALDESCOVE_ADDEALDESCOVE_ADDEALDESCOVE_ADDEALDESCOVE_ADDEALDESCOVE_ADDEALDESCOVE_ADDEALDESCOVE_ADDEALDESCOVE_ADDEALDESCOVE_ADDEALDESCOVE_ADDEALDESCOVE_ADDEALDESCOVE_ADDEALDESCOVE_ADDEALDESCOVE_ADDEALDESCOVE_ADDEALDESCOVE_ADDEALDESCOVE_ADDEALDESCOVE_ADDEALDESCOVE_ADDEALDESCOVE_ADDEALDESCOVE_ADDEALDESCOVE_ADDEALDESCOVE_ADDEALDESCOVE_ADDEALDESCOVE</pre>	613 652 667 654 667 654 666 572 666 666 666 668 671 438 663 662 663 663 662 663 663 672 663 664 572 663 664 572 750 592 7748

ABCC6 Oni	: SVPRGSLVAVVGPVG	9 <mark>5</mark> GKSSLLSAMLGE	<b>te<mark>krs</mark>govt</b> vkgsvay	VPOOAWION <b>A</b> TV <mark>OD</mark> NI	IFG <mark>REKLKT</mark> WY <mark>HR</mark> VLF	EACAL <mark>L</mark> PDL <mark>DI</mark> LP <b>A</b> G-	DATEIGEKG : 76	2
ABCC6 Xma	: RVPRGSLVAVVGHVG	9 <mark>5</mark> GKSSLLSAMLGE	<b>te<mark>krs</mark>govt</b> vkgsvay	VPOOAWION <mark>A</mark> TV <mark>OD</mark> NI	LFG <mark>RDKLKT</mark> WY <mark>OR</mark> VLF	ACALLPDI <mark>DI</mark> LP <b>A</b> G-	DATEIGEKG : 75	2
ABCC6 Gmo	: HVPRGSLVAVVGHVG	9 <mark>5</mark> GKSSLLSAMLGE	<b>te<mark>rrt</mark>ghvt</b> vkgslay	vpooawion <mark>a</mark> tv <mark>od</mark> nv	VVFG <mark>REKLKT</mark> WY <mark>OC</mark> VLE	ACALLPDI <mark>DI</mark> LP <b>A</b> G-	DATEIGEKG : 71	2
ABCC6 Dre1	: KVPCGSLVAVVGHVG	9 <mark>5</mark> GKSSLLSAMLGE	TEK <mark>RS</mark> GTVSVKGSIAY	VPOOAWION <mark>A</mark> SI <mark>OD</mark> NI	LFG <mark>REKKES</mark> WY <mark>OR</mark> VLE	ACALLPDI <mark>DN</mark> LP <b>A</b> G-	DATEIGEKG : 75	1
ABCC6 Dre2	: KVORGSLVAVVGHVG	9 <mark>5</mark> GKSSLLSAMLGE	MEKKSGHITITGSVGY	VPOOAWION <mark>A</mark> TI <mark>KD</mark> NI	LFG <mark>C</mark> EKKDSLYOKVLE	ACAL <mark>L</mark> PDL <mark>EI</mark> LP <mark>AR-</mark>	DATEIGEKG : 71	3
ABCC6 Dre3	: KVORGSLVAVVGHVG	S <mark>S</mark> GKSSLLSAMLGE	MEKKSGHIKI <mark>T</mark> GSVAY	VPOOAWION <mark>A</mark> TI <mark>KD</mark> NI	LFG <mark>CEKKDSL</mark> Y <mark>OK</mark> VLE	ACAL <mark>L</mark> PDL <b>EI</b> LP <b>AR-</b>	DA <mark>TEIGEKG</mark> : 76	6
ABCC6 Ame1	: RVPCGCLVAVVGHVG	9 <mark>8</mark> GKSSLLSAMLGE	TERRSGNVSIKGSVAY	VPOOAWION <mark>A</mark> TI <mark>OD</mark> NI	LFG <mark>RE</mark> KKKTWY <mark>OR</mark> VLE	ACAL <mark>L</mark> PDL <b>EI</b> LP <b>A</b> G-	DA <mark>TEIGEKG</mark> : 75	3
ABCC6 Ame2	: KVPRGCLVAVVGHVG	9 <mark>5</mark> GKSSLLSAMLGE	TEK <mark>KS</mark> G <mark>N</mark> VTVKGSVAY	VPOOAWION <mark>A</mark> TI <mark>RE</mark> NI	VFG <mark>O</mark> EKKESWY <mark>OT</mark> VLF	ACALVRDINILPAR-	DATEIGEKG : 77	1
ABCC6 Loc	: RVPOGALLAVVGHVG	9 <mark>5</mark> GKSSLLSAILGE	TEKRSGRVLVKGSVAY	VPOOAWION <mark>A</mark> TL <mark>RE</mark> NV	7IFG <mark>R</mark> EKKEAWY <mark>OR</mark> VVI	ACAL <mark>L</mark> PDL <b>EI</b> LP <mark>A</mark> G-	DATEIGEKG : 75	1
ABCC1 Hsa	: SIPEGALVAVVGOVG	- CGKSSLLSALLAE	MDKVEGHVAIKGSVAY	VPOOAWION <mark>D</mark> SL <mark>RE</mark> NI	LFGCOLEEPYYRSVIC	DACALLPDIEILPSG-	DRTEIGEKG : 76	5
ABCC1 Ptr	: SIPEGALVAVVGOVG		MDKVEGHVAIKGSVAY	VPOOAWION <mark>D</mark> SLRENI	LFGCOLEEPYYRSVIC	DACALLPDIEILP <mark>S</mark> G-	DRTEIGEKG : 67	1
ABCC1 Mmu	: SIPEGALVAVVGOVG	CGKSSLLSALLAE	MDKVEGHVTLKGSVAY	VPOOAWIONDSLRENI	LFGHPLOENYYKAVM	ACALLPDIETLP <mark>S</mark> G-	DRTEIGEKG : 76	5
ABCC1 Cluf	: STPEGSLVAVVGOVG	CGKSSLLSALLAE	MDKVEGHVATKGSVAV	VPOOAWTONDSURENT	LFGROLOERYYKAVTE	ACALEPDIETLPSG-	DRTEIGEKG : 76	5
ABCC1 Bta	SVPEGSLVAVVGOVG	CCKSSLLSALLAF	MDKVECHVTVKCSVAV	VPOOAWTONTSLEENI	LEGROLOERVYKAVVI	ACALEDDEETLPSG-	DRTEIGEKG · 74	.9
ABCC1 Dro	· SUPECALVAVVOVO	CCKSSIISAIIAF	MDKVECHAAIKCSVAV	VPOOAWTONDST PENT	I FOROLOFRCVKAVT	ACALEDDIETIPEC.	DRIFICERC : 74	7
ABCC1 Mdo	. TWDOCALWAWLCOW	COVCCTICATIAE	MDUTEOUUCTVOSUAV	VDOOAWTONNET DENU	III GROBOERCIKAVII	CALED DISTURIC	DRIEIGENG : 70	,
ABCC1 Mao	· AWDECCITAWWOWC	CORSSILSALLAR	MDRIEGHVOIRGSVAI	VPOONUTONASI PENI	LFGROPOERFIRIVII	ACALTEDIETIESC-	DWTEICEKC · 52	7
ABCCI Uali	. AVPEGSLIAVVGOVG		MDRVEGHVAIRGSIAI	VPOORWIONASLRENI	LFGROPEERNIKOVII	ACALEPDIEILP <mark>B</mark> G-	DWIEIGERG : 55	,
ABCCI Gda	: TVPEGSLIAVVGOVG	GKSSLLSALLGE		VPOOAWIONATLEDNI	IFGREMNESRYKRVII	ACALLPDIETLPMG-	DRTEIGERG : 76	2
ABCCI ACa	: AVPEHRLVAVVGOVG	GKSSLLSALLGE	MERREGLVSLKGSVAY	VPOOAWIONATIKENI	LFGREAREROYNCVVI	ACALLPDLEVLPSG-	DOTEIGEKG : 75	T
ABCC1 Xtr	: SIPEGSLVAVVGOVG	GKSSLLSALLGE	MEKODGYVAMKGSVGY	V <b>S</b> OOAWIONASLKDNV	LFGRESNESMYKKVII	ACALLPDLEILPTG-	DRIEIGEKG : 76	0
ABCC1 Lch	: TIPEGALVAIVGHVG	3 <mark>C</mark> GKSSMLSALLGE	MEKOEGHVAVKGSVAY	VPOOAWION <b>A</b> TL <mark>KD</mark> NI	LFGOEMNENWYRCVVI	ACALLPDLEILPAG-	DSTEIGEKG : 76	2
ABCC1 Gac	: CIPEGSLVAVVGHVG	S <mark>S</mark> GKSSLLSALLGE	MDKLEGSVAVKGSVAY	VPOOAWIONATL <mark>RE</mark> NI	MFG <b>OESREA</b> WY <b>OR</b> VVI	EACAL <mark>O</mark> PDLEILPAG-	DETEIGEKG : 76	1
ABCC1 Dla	: HIPEGSLVAVVGHVG	9 <mark>8</mark> GKSSLLSALLGE	MDKLEGTVTVKG <mark>W</mark> VAY	VPOOAWION <mark>S</mark> TL <mark>KE</mark> NI	MFG <b>O</b> ERRDSWYOCVVI	ACAL <mark>R</mark> PDL <b>EI</b> LP <b>A</b> G-	DETEIGEKG : 70	4
ABCC1 Ola	: RIPEGSLVAVVGHVG	S <mark>S</mark> GKSSLLSALLGE	MDK <mark>ME</mark> G <mark>S</mark> VSVKGSVAY	VPOOAWI <mark>LNA</mark> TL <mark>KN</mark> NI	. V FG <b>OKRKEA</b> WY <mark>HR</mark> VVI	EACAL <mark>HO</mark> DL <b>EI</b> LP <b>A</b> G-	DETEIGEKG : 76	5
ABCC1 Tni	: FVLIER CTPCNGCI	LDKNHLESVTNREK	FVGLIMCVIVOGLVAY	VPOOAWION <mark>S</mark> TL <mark>KE</mark> NI	VFG <mark>OEFRES</mark> WY <b>HS</b> VIF	FIYVCNLILKVIFDK	FNMOCHSOG : 70	2
ABCC1 Oni	: NIPEGSLVAVVGHVG	9 <mark>5</mark> GKSSLLSALLGE	MDK <mark>LEG</mark> SVTVKGSVAY	VPOOAWION <mark>S</mark> SL <mark>KD</mark> NI	IFGHERROSWYOHVVI	EACAL <mark>O</mark> PDL <b>EI</b> LP <b>A</b> G-	DDTEIGEKG : 76	2
ABCC1 Xma1	:	GKSSLLSALLGE	MDK <mark>VE</mark> G <mark>S</mark> VVVKGSVAY	VPOOAWION <mark>S</mark> TL <mark>KE</mark> NI	VFG <mark>OKRRED</mark> WY <mark>NH</mark> VVI	VCAL <mark>O</mark> PDLEILPAG-	DETEIGEKG : 8	3
ABCC1 Xma2	:						:	-
ABCC1 Dre	: SIPEGALVAVVGHVG	G <mark>S</mark> GKSSL <u>LSALLGE</u>	MHKOEGSVSIKGSVAY	VPOOAWIONATLKDNI	LFGRETKDSWYOKVVF	ACAL <mark>L</mark> PDL <mark>EI</mark> LP <mark>G</mark> G-	DTTEIGEKG : 76	2
ABCC1 Ame	: RIPEGALVAVVGHVG	S <mark>S</mark> GKSSLLSALLGE	MHK <mark>OE</mark> G <mark>D</mark> VSIKGSVAY	VPOOAWION <mark>A</mark> TL <mark>RE</mark> NI	MFG <mark>O</mark> EKKESWY <mark>O</mark> KVLE	ACAL <mark>L</mark> PDL <b>EI</b> LP <mark>G</mark> G-	DTTEIGEKG : 76	2
ABCC1 Loc	: RIPEGALVAVVGHVG	S <mark>S</mark> GKSSLLSALLGE	MEK <mark>OE</mark> G <mark>O</mark> VSVKGSVAY	VPOOAWION <mark>A</mark> TL <mark>RE</mark> NV	7IFG <mark>R</mark> EKKEAWY <mark>O</mark> RVVI	ACAL <mark>L</mark> PDL <b>EI</b> LP <mark>A</mark> G-	DATEIGEKG : 76	5
ABCC1 Cmi	: AILEGSLVAVVGHVG	- CGKSSLISALLGE	MEK <mark>OE</mark> G <mark>Y</mark> VAVKGTVAY	VSOOAWIONTTLKDNI	IFG <b>ODWHKG</b> WYNRVIF	SCALLPDIEMLPAG-	DESEIGEKG : 74	4
	*	820	* 840	* 860	) *	880 *	900	
ABCC6 Hsa	MNLSCGOKORLSLAR	AVYRKAAVYLLDD.	PL <mark>A</mark> ALDAH <mark>V</mark> G <mark>O</mark> HVF <mark>N</mark> O	VIGEGGLIOGTIR	ILVTHALHILPOADWII	VLANGAIAEMGSYOE	LI <mark>O</mark> RKGALM : 84	8
ABCC6 Ptr	MNLSGGOKORLSLAF	RAVYRKAAVYLLDD	PLAALDAHVGOHVFNO	VIGEGGLIOGTTRI	LVTHALHILPOADWII	VLANGATAEMGSYOE	LIORKGALM : 69	0
ABCC6 Mmu	MNLSGGOKORLSLAF	RAVY <mark>KKAA</mark> IYLLDD	PL <mark>A</mark> ALDAHV <mark>SOO</mark> VFKO	VIGPSGLIOGTTRI	LVTH <b>TUHV</b> LPOADRII	VLANGTIAEMGSYOD	LIORNGALV : 84	6
ABCC6 Cluf	MNLSGGOKORLSLAF	RAVY <mark>SKAA</mark> VYLLDD	PLVALDAHVGOSVFNO	VIGP <mark>G</mark> GLI <mark>HGT</mark> TRI	LVTHALHVLPOADWIN	VLEDGATAEMGRYOE	LIHRKGALV : 84	9
ABCC6 Bta	MNLSGGOKORLSLAR	RAVYRKAAVVI.I.DD	PLAALDAOVGOHVENR	VIGPDGLIOGTTRI	T.VTHATHTT.POADWTS	VIEDGATAEMGSFOE	TTHRKGALV : 84	9
ABCC6 Dno	MNLSGGOKORLSLAF	RAVVRKAAVVI.I.DD	PLAALDAHVGOOVESR	VIGPDGLIOG-TTRI	L.V.THARHVI.POADRT	VLADCATAEMOSVOE	TTHRKGALA · 77	
ADGGC MAL								0
ARCC6 MOO	<ul> <li>INLSGGOKORTSTAR</li> </ul>	2 A U V K K A A T V T. T. D D	PLAALDAHVCOHTEDR	VIGPCGITHCTTRI	T.VTHAWHTI.POADVT	MMADCAVVESCSVOE	TORNEPOT · 85	6
ABCC6 Mdo	INLSGGOKORLSLAF	RAVY <mark>KKAA</mark> IYLLDD	PL <mark>A</mark> ALDAHVG <mark>OHIF</mark> DR	VIGE <mark>G</mark> GLI <mark>HGT</mark> TRI	LVTH <mark>AVHI</mark> LPO <mark>A</mark> DYII	MMADGAVVESGSYOE	LIORNGPFT : 85	6
ABCC6 Mdo ABCC6 Oan	: INISGGOKORUSLAF	RAVY <mark>KKAA</mark> IYLLDD RAVY <mark>RRAS</mark> VYLLDD	PL <mark>A</mark> ALDAHVG <mark>O</mark> HIF <mark>DR</mark> PLSAVDAHVGOHIFDH	VIGP <mark>G</mark> GLL <mark>HGT</mark> TRI IIGPDGLLKDTTRI	LVTHAVHILPOADYII LVTHAVSVLPRVDSIV	MMADGAVVESGSYOE MLVDGALAEIGSYRE	LIORNGPFT: 85 LVRRKGAFV: 78	6 9
ABCC6 Mdo ABCC6 Oan ABCC6 Gga	INISGGOKORUSLAR INISGGOKORVSLAR INISGGOKORVSLAR	RAVY <mark>KKAA</mark> IYLLDD RAVY <mark>RRAS</mark> VYLLDD RAVY <mark>ORSS</mark> IYLLDD	PL <mark>A</mark> ALDAHVG <mark>OHIFDR</mark> PLSAVDAHVGOHIFDH PLSAVDAHVGOHIFEH	VIGP <mark>G</mark> GLL <mark>HGT</mark> TRI IIGPDGLLKDTTRI VLGPNGLLKDKTRV	LVTHAVHILPOADYII LVTHAVSVLPRVDSIV VLVTHMISVCHOVDTIV	MMADCAVVESGSYOE MLVDCATAEIGSYRE VLVDCTTAEIGSYOE	LI <mark>ORNGP</mark> FT : 85 LVRRKGAFV : 78 LSORSGAFA : 85	6 9 5
ABCC6 Mdo ABCC6 Oan ABCC6 Gga ABCC6 Aca	: INLSGGOKORUSLAF : INISGGOKORVSLAF : INISGGOKORVSLAF : VNLSGGOKORVSLAF	RAVY <b>KKAA</b> IYLLDD RAVY <mark>RRAS</mark> VYLLDD RAVY <mark>ORSS</mark> IYLLDD RAVY <mark>TKAE</mark> VYLLDD	PI <mark>A</mark> ALDAHVGOHIFDR PLSAVDAHVGOHIFDH PLSAVDAHVGOHIFEH PLSAVDAOVGOHIFKH	VIGPGGLLHGTTRI IIGPDGLLKDTTRI VLGPNGLLKDKTRV VLGPTGLLKNKTRI	LVTHAUHILPOADYII LVTHAVSVLPRVDSIV VLVTHAISVLHOVDTIV LVTHAISVLHOVDTIV	MMADCAVVESGSYOE MLVDCATAEIGSYRE VVLVDCTTAEIGSYOE VVMNCEISETGSWOE	LIORN CPET: 85 LVRRK CAFV: 78 ISORS CAFA: 85 LVARN CAFA: 78	6 9 5 6
ABCC6 Mdo ABCC6 Oan ABCC6 Gga ABCC6 Aca ABCC6 Xtr	INLSGGOKORLSLAF INISGGOKORVSLAF INISGGOKORVSLAF VNLSGGOKORVSLAF	RAVY <mark>KKAA</mark> IYLLDD RAVY <mark>RRAS</mark> VYLLDD RAVY <mark>ORSSIYLLDD RAVY<mark>TKAE</mark>VYLLDD RAVY<mark>TKAE</mark>VYLLDD</mark>	PI <mark>A</mark> ALDAHVGOHIF <b>DR</b> PLSAVDAHVGOHIFDH PLSAVDAHVGOHIF <mark>EH</mark> PLSAVDAOVGOHIFKH PLSAVDAHVGOHLFEO	VIGE <mark>GLLHGTTRI</mark> IIGEDGLLKDTTRI VLGENGLLKDKTRV VLGETGLLKNKTRI VIGESGLLKDKTRI	LVTHAVHILPOADYII LVTHAVSVLPRVDSIV VLVTHMISVIHOVDTIV LVTHAVHLPRMDRII VLVTHGVSFLPOMDMII	MMADCAVVESCSYOE MUVDCATAEICSYRE VUVDCTTAEICSYOE VVMNCEISEICSWOE VMSDCRVSEVGTYNE	LIORN CPET: 85 LVRRK GAEV: 78 LSORS GAEA: 85 LVARN GAEA: 78 LIORN GAES: 82	69568
ABCC6 Mdo ABCC6 Oan ABCC6 Gda ABCC6 Aca ABCC6 Xtr ABCC6 Lch	INLSGOKORUSLAR INISGOKORVSLAR INISGOKORVSLAR VNLSGOKORVSLAR VNLSGOKORVSLAR	RAVYKKAAIYLLDD RAVYRRASVYLLDD RAVYORSSIYLLDD RAVY <mark>TKAB</mark> VYLLDD RAVYRNCDVYLLDD RAVCRRSAVYLLDD	PI <mark>A</mark> ALDAHVGOHTF <b>DR</b> PLSAVDAHVGOHTFDH PLSAVDAHVGOHTFEH PLSAVDAOVGOHTFKH PLSAVDANVGOHTFEO PLSAVDARVGOSTFEK	VIGE <mark>G</mark> GLI <mark>HGTTRI</mark> IIGEDGLLKDTTRI VLGENGLLKDKTRV VLGETGLLKNKTRI VIGESGLLKDKTRV VIGENGLLK <b>DKT</b> RV	LVTHAVHILPOADYII LVTHAVSVLPRVDSIV VLVTHMISVLHOVDTIV LVTHAVHLPRMDRII VLVTHGVSFLPOMDMII VLVTHAVSVLPOADSII	MMADCAVVESCSYOE MLVDCALAEIGSYRE VLVDCTLAEIGSYOE VVMNCEISETGSWOE VMSDCRVSEVCTYNE VMSDCGISENGSYKE	LLORN CP FT : 85 LVRRK GAFV : 78 LSORS GAFA : 85 LVARN GAFA : 78 LLORN GAFS : 82 LLERG GAFA : 85	695686
ABCC6 Mdo ABCC6 Oan ABCC6 Gda ABCC6 Aca ABCC6 Aca ABCC6 Xtr ABCC6 Lch ABCC6 Gac1	INISGOOKORLSLAM INISGOOKORVSLAM VNLSGOOKORVSLAM VNLSGOOKORVSLAM VNLSGOOKORVSLAM LNLSGOOKORVSLAM	RAVYKKAAIYLLDD RAVYRRASVYLLDD RAVYORSSIYLDD RAVYRKAEVYLLDD RAVYRNCDVYLLDD RAVYCRRSAVYLLDD RAVYCRRSAVYLLDD	PIAALDAHVOOHIADR PLSAVDAHVOOHIADH PLSAVDAHVOOHIADH PLSAVDAOVOOHIADH PLSAVDAHVOOHIAD PLSAVDAHVOOHIAD PLSAVDARVOOSIAD	VIGPGGLIHGTTRI IIGPDGLLKDTTRI VIGPNGLLKDKTRV VIGPTGLLKNKTRI VIGPSGLLKDKTRV VIGPNGLLKHKTRV VIGPKGVLRDKTRI	LVTHAVHILPOADYI LVTHAVSVLPRVDSI VLVTHMISVLHOVDTI LVTNAVHLIPRMORI VLVTHGVSFLPOADMI VLVTHAVSVLPOADSI LVTHGMSFLPOADFI	MMADCAVVESGSYOE MLVDCATABIGSYRE VLVDCTHABIGSYOE VMNCEISETGSWOE VMSDCRVSEVGTYNE VMSNCGISEMGSYKE VVSNCGISEMGSYKE	LLORN OF FT : 85 LVRRKGAFV : 78 LSORSGAFA : 85 LVARNGAFA : 78 LVARNGAFS : 82 LLERGGAFA : 85 LSRHGAFA : 85	56956868
ABCC6 Mdo ABCC6 Oan ABCC6 GGa ABCC6 Aca ABCC6 Xtr ABCC6 Gac1 ABCC6 Gac2	INDSGOKORUSLAN INI SGOKORVSLAN VNLSGOKORVSLAN VNLSGOKORVSLAN VNLSGOKORVSLAN VNLSGOKORVSLAN LNLSGOKORVSLAN LNLSGOKORVSLAN	RAVYKKAAIYLLDD RAVYRRASVYLLDD RAVYORSSIYLLDD RAVYTKAEVYLLDD RAVYRNCDVYLLDD RAVCRRSAVYLLDD RAVYRKADVYLMDD (SVYRRSDVYLLDD	PI <mark>A</mark> ALDAHVCOHIEDR PLSAVDAHVCOHIEDH PLSAVDAHVCOHIERH PLSAVDAVCOHIERH PLSAVDAHVCOHIERC PLSAVDAHVCOHIEC PLSAVDAHVCOHIEDR PLSAVDAHVCOHIEDR	VIGPGGLIHGTTRI IIGPDGLLKDTTRI VIGPNGLLKDKTRI VIGPGILKNKTRI VIGPGLLKKDKTRI VIGPNGLLKHKTRI VIGPKGVLRDKTRI VIGPRGLLKEKTRI	LVTHAVHI LPOADYI LVTHAVSVIPRVISI LVTHMISVIHOVII LVTHMISVIHOVII LVTHAVSIHOMI LVTHAVSVIPOADSI LVTHAVSVIPOADSI LVTHGSFLPOADFI LVTHGISFLSKTDLI	MADCAVYESCSYOE MIVDCATACICSYR VVDCTACISYR VVMNCEISETCSYOE VMSDCRVSVCTVMS VMSDCRVSVCTVMS VMSDCRSVCTVS VMSNCGISEMCSYR VLCDCEITESCSYOE VMLECHTSPMCSYRD	LI ORN CPET : 85 I VRRK GAFV : 78 I SORS GAFA : 85 I VARN GAFA : 85 I VARN GAFA : 82 I I CKN GAFA : 85 I I ERG GAFA : 85 I I SRH GAFA : 85 I U DRK CN FA : 87	0 9 5 6 8 6 8 5
ABCC6 Mdo ABCC6 Oan ABCC6 Aca ABCC6 Aca ABCC6 Xtr ABCC6 Lch ABCC6 Gac1 ABCC6 Gac2 ABCC6 Dla	1 INISGOKORUSLAH INISGOKORVSLAH VILSGOKORVSLAH VILSGOKORVSLAH VILSGOKORVSLAH LILSGOKORVSLAH LILSGOKORVSLAH INISGOKORVSLAH	RAVYKKAA YYLLDD RAVYRRAS VYLLDD RAVYORSS TYLLDD RAVYNCDSS TYLLDD RAVYRKAB VYLLDD RAVYRKAD VYLDD RAVYRKAD VYLDD SVYRRSD VYLLDD RAVYRKAD VYLLDD	PI <mark>A</mark> ALDAHVCOHIEDR PLSAVDAHVCOHIEDH PLSAVDAHVCOHIEDH PLSAVDAOVCOHIERO PLSAVDAHVCOHLEO PLSAVDAHVCOHIERO PLSAVDAHVCOHIEDR PLSAVDAHVCOHIEDR PLSAVDAHVCOHIEDR	VIGPGGLIHGTTRI IIGPDGLLKDTTRI VIGPNGLLKDKTRV VIGPGLLKDKTRI VIGPSGLLKDKTRI VIGPNGLLKHKTRI VIGPKGVLRDKTRI VIGPRGLLKEKTRV VIGPKGVLRDKTRI	LVTHAVHI LPOADYI LVTHAVSVIPRVDSI VIVTHISVIHOVDTI VIVTHISVIHOVDTI VIVTHOSFIPOMOMI VIVTHOSFIPOMOMI VIVTHOSFIPOADFI VIVTHGISFIPOADFI VIVTHGISFIPOADHI LVTHGSFIPOADHI	MADCAVVESCSVOE MIVDCATACICSVRE VIVDCTTACICSVRE VVMCETSCTOSVOE VMSDCRVSEVCTVN VMSDCRVSEVCTVN VMSNCGSSMCSVRE VICCETTESCSVOE VMLCCHISBNCSVRD VILVDCETTESCSVOE	LLORN CPET : 85 LVRRKGAFV : 78 LSORSGAFA : 85 LVARNGAFA : 85 LLOKNGAFA : 82 LLERGGAFA : 85 LISRHGAFA : 85 LNDRKCNFA : 87 LSRHGAFA : 85	0 9 5 6 8 6 8 5 5 5
ABCC6 Mdo ABCC6 Oan ABCC6 Ga ABCC6 Aca ABCC6 Xtr ABCC6 Cac1 ABCC6 Gac2 ABCC6 Dla ABCC6 Ola	1 INISGOKOKUSLAH 1 NISGOKORVSLAH 1 NISGOKORVSLAH VNLSGOKORVSLAH 1 VNLSGOKORVSLAH 1 NLSGOKORVSLAH 1 LNLSGOKORVSLAH 2 LNLSGOKORVSLAH 1 LNLSGOKORVSLAH	A AVYKKAA YYLLDD AAVYRAS YYLDD AAVYCRSS YLLDD AAVYRNCD YYLLDD AAVYRNCD YYLLDD AAVYRKAD YYLDD AVYRKAD YYLDD SVYRSD YYLDD AVYRKAD YYLDD AAVYRKAD YYLLDD	PI <mark>A</mark> ALDAHVOOHIEDR PLSAVDAHVOOHIED PLSAVDAHVOOHIEB PLSAVDAHVOOHIEBO PLSAVDAHVOOHIEBO PLSAVDARVOOSIER PLSAVDAHVOOHIEDR PLSAVDAHVOOHIEDR PLSAVDAHVOOHIEDR PLSAVDAHVOOHIEDR	VIGPGGLIHGTTRI IIGPDGLLKDTTRI VLGPTGLLKDKTRI VIGPSGLLKDKTRI VIGPSGLLKDKTRI VIGPGLKHKTRI VIGPKGVLRDKTRI VIGPKGVLRDKTRI VIGPKGVLRDKTRI	LVTHAVHILPOADYI LVTHAVSVLPRVDSI VLVTHAVSVLPRVDSI VLVTHAVSVLHOVDI VLVTHAVSVLHOVDI VLVTHAVSVLPOADSI LVTHAVSVLPOADSI LVTHASSLPOADHI LVTHASSLPOADHI LVTHASSLPOADHI	MADCAVVESCSVOE MIVDCATAEICSVR VIVDCTIAEICSVOE VVNDCTIAEICSVOE VVNDCRVSEVCTVN VNSDCRVSEVCTVN VNSDCGTEESSVOE VVICCETESSVOE VVICCETESSVOE VILDCETESCSVOE	LLORN CPET : 85 LVRRK GAFV : 78 LSORS GAFA : 85 LVARN GAFA : 85 LLOKN GAFA : 82 LLERG GAFA : 85 LLISRH GAFA : 85 LN DRK CNFA : 87 LLISRH GAFA : 85	6 9 5 6 8 6 8 5 5 1
ABCC6 Mdo ABCC6 Ga ABCC6 Ga ABCC6 Aca ABCC6 Lch ABCC6 Gac1 ABCC6 Gac2 ABCC6 Dla ABCC6 Ola ABCC6 Ola	1 INISGGOKORISLAH 1 NISGGOKORVSLAH 2 VNLSGGOKORVSLAH 2 VNLSGGOKORVSLAH 2 VNLSGGOKORVSLAH 2 INLSGGOKORVSLAH 2 INLSGGOKORVSLAH 2 INLSGGOKORVSLAH 3 INLSGGOKORVS	A AVYKKAA YYLLDD AAVYRAS YYLDD AAVYORSS YLLDD AAVYCRE YLLDD AAVYRKA YYLDD AAVYRKA YYLDD SVYRKA YYLDD AAVYKAD YYLDD AAVYRKAD YYLDD AAVYRKAD YYLDD	PIAALDAHWOOHIED PLSAVDAHWOOHIED PLSAVDAWGOHIEH PLSAVDAWGOHIEH PLSAVDAWGOHIEH PLSAVDAWGOHIED PLSAVDAWGOHIED PLSAVDAHWOOHIED PLSAVDAHWOOHIED PLSAVDAHWOOHIED PLSAVDAHWOOHIED	VIGPGGLIHGTTRI IIGPDGLLKDTTRI VIGPNGLLKDKTRI VIGPSGLLKDKTRI VIGPSGLLKHKTRI VIGPKGVLRDKTRI VIGPKGVLRDKTRI VIGPKGVLKDRTRI VIGPKGVLKDRTRI VIGPKGVLKDKTRI	LVTFAVHLEPOADY LVTFAVSVLPAVSIV VLVTFAVSVLPAVSIV LVTNAVHLEPRMRI VLVTFAVSVLPOADSI LVTFAVSVLPOADSI LVTFGSFLPOADFI VLVTGSFLPOADLI LVTFGSFLPOADLI LVTFGSFLPOADLI	MADCAVVESCION MUDCATALIGSVC VLVDCTALIGSVC VVMCETSTCSVC VMCETSTCSVC VMSCCTSCCTV VMSCCTSCCTV VMSCCTSCCTV VMSCCTSCCTV VMCCTSSC VMCCTSSC VMCCTTSSC VMCCTTSSC VMCCTTSSC VMCCTTSSC VMCCTTSSC VMCCTTSSC VMCCTTSSC VMCCTTSSC VMCCTTSSC VMCCTTSSC VMCCTTSSC VMCCTTSSC VMCCTTSSC VMCCTTSSC VMCCTTSSC VMCCTTSSC VMCCTTSSC VMCCTTSSC VMCCTTSSC VMCCTTSSC VMCCTTSSC VMCCTTSSC VMCCTTSSC VMCCTTSSC VMCCTTSSC VMCCTTSSC VMCCTTSSC VMCCTTSSC VMCCTTSSC VMCCTTSSC VMCCTTSSC VMCCTTSSC VMCCTTSSC VMCCTTSSC VMCCTTSSC VMCCTTSSC VMCCTTSSC VMCCTTSSC VMCCTTSSC VMCCTTSSC VMCCTTSSC VMCCTTSSC VMCCTTSSC VMCCTTSSC VMCCTTSSC VMCCTTSSC VMCCTTSSC VMCCTTSSC VMCCTTSSC VMCCTTSSC VMCCTTSSC VMCCTTSSC VMCCTTSSC VMCCTTSSC VMCCTTSSC VMCCTTSSC VMCCTTSSC VMCCTTSSC VMCCTTSSC VMCCTTSSC VMCCTTSSC VMCCTTSSC VMCCTTSSC VMCCTTSSC VMCCTTSSC VMCCTTSSC VMCCTTSSC VMCCTTSSC VMCCTTSSC VMCCTTSSC VMCCTTSSC VMCCTTSSC VMCCTTSSC VMCCTTSSC VMCCTTSSC VMCCTTSSC VMCCTTSSC VMCCTTSSC VMCCTTSSC VMCCTTSSC VMCCTTSSC VMCCTTSSC VMCCTTSSC VMCCTTSSC VMCCTTSSC VMCCTTSSC VMCCTTSSC VMCCTTSSC VMCCTTSSC VMCCTTSSC VMCCTTSSC VMCCTTSSC VMCCTTSSC VMCCTTSSC VMCCTTSSC VMCCTTSSC VMCCTTSSC VMCCTTSSC VMCCTTSSC VMCCTTSSC VMCCTTSSC VMCCTTSSC VMCCTTSSC VMCCTTSSC VMCCTTSSC VMCCTTSSC VMCCTTSSC VMCCTTSSC VMCCTTSSC VMCCTTSSC VMCCTTSSC VMCCTTSSC VMCCTTSSC VMCCTTSSC VMCCTTSSC VMCCTTSSC VMCCTTSSC VMCCTTSSC VMCCTTSSC VMCCTTSSC VMCCTTSSC VMCCTTSSC VMCCTTSSC VMCCTTSSC VMCCTTSSC VMCCTTSSC VMCCTTSSC VMCCTTSSC VMCCTTSSC VMCCTTSSC VMCCTTSSC VMCCTTSSC VMCCTTSSC VMCCTTSSC VMCCTTSSC VMCCTTSSC VMCCTTSSC VMCCTTSSC VMCCTTSSC VMCCTTSSC VMCCTTSSC VMCCTTSSC VMCCTTSSC VMCCTTSSC VMCCTTSSC VMCCTTSSC VMCCTTSSC VMCCTTSSC VMCCTTSSC VMCCTTSSC VMCCTTSSC VMCCTTSSC VMCCTTSSC VMCCTTSSC VMCCTTSSC VMCCTTSSC VMCCTTSSC VMCCTTSSC VMCCTTSSC VMCCTTSSC VMCCTTSSC VMCCTTSSC VMCCTTSSC VMCCTTSSC VMCCTTSSC VMCCTTSSC VMCCTTSSC VMCCTTSSC VMCCTTSSC VMCCTTSSC VMCCTTSSC VMCCTTSSC VMCCTTSSC VMCCTTSSC VMCCTTSSC VMCCTTSSC VMCCTTSSC VMCCTTSSC VMCCTTSSC VMCCTTSSC VMCCTTSSC VMCCTTSSC VMCCTTSSC VMCCTTSSC VMCCTTSSC VMCCTTSSC VMCCTTSSC VMCCTTSSC VMCCTTSSC VMCCTTSSC VMCCTTSSC VMC	LILORN CPET         :         85           LURRKGARV         :         78           LURRKGARV         :         85           LORNGARA         :         85           LURRKGARV         :         85           LURRGARA         :         85           LURRGARA         :         85           LURRGARA         :         85           LUSRKARA         :         87           LUSRKARA         :         87           LUSRKARA         :         85           LUSRKARA         :         85           LUSRHGARA         :         85	0 9 5 6 8 6 8 5 5 1 7
ABCC6         Made           ABCC6         Gaa           ABCC6         Aca           ABCC6         Gac1           ABCC6         Dla           ABCC6         Ola           ABCC6         Ola           ABCC6         Ola           ABCC6         Ola	1 INISGGOKORVSLAR INISGGOKORVSLAR VNLSGGOKORVSLAR VNLSGGOKORVSLAR VNLSGGOKORVSLAR UNLSGGOKORVSLAR LNLSGGOKORVSLAR LNLSGGOKORVSLAR LNLSGGOKORVSLAR LNLSGGOKORVSLAR LNLSGGOKORVSLAR	A AVYKKAA YYLLDD AAVYRAAS VYLLDD AAVYCASS YYLLDD AAVYCAE VYLLDD AAVYRAB VYLLDD AAVYRAD VYLLDD AAVYRAD VYLLDD AAVYRAD VYLLDD AAVYRAD VYLLDD AAVYRAD VYLLDD AAVYRAD VYLLDD	PIAALDAHWOOHIED PLSAVDAHWOOHIED PLSAVDAHWOOHIEH PLSAVDAWOOHIEK PLSAVDAHWOOHIEK PLSAVDAHWOOHIED PLSAVDAHWOOHIED PLSAVDAHWOOHIED PLSAVDAHWOOHIED PLSAVDAHWOOHIED PLSAVDAHWOOHIED	VIGPGGLIHGTTRI IIGPDGLLKDTTRI VIGPTGLLKDKTRI VIGPGLLKHKTRI VIGPGLLKHKTRI VIGPKGVLRDKTRI VIGPKGVLRDKTRI VIGPKGVLRDKTRI VIGPKGVLRDKTRI VIGPKGVLRDKTRI	LVTFAVHLEPOADY LVTFAVSVERVOSU VLVTRAVSVERVOSU LVTNAVHLERMORI LVTRAVSFEPOADY LVTFAVSVEPOADY LVTFAVSVEPOADY LVTFGSFISKT LUTFGSFIPOADH LVTFGSFIPOADH LVTFGSFIPOADU	MADCAVVESCIVOE MUVDCATAPICSVR VVDCTAPICSVR VVMSCRVSVCSVOE VMSCRVSVCSVOE VMSCRVSVCSVN VMSCGISPMCSVK VTGDCETTSSSVOE VMLCHTSSSVOE VLDCETTSSSVOE VLDCETTSSSVOE	LI ORN CPET         :         85           LURRKGARV         :         78           LORNGARA         :         85           LORNGARA         :         85           LUARNGARA         :         85           LUARNGARA         :         85           LUARNGARA         :         85           LUSRGARA         :         85           LUSRHGARA         :         86	5 6 9 5 6 8 6 8 5 5 1 7 0
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ABCC6         Man           ABCC6         Gaa           ABCC6         Gaa           ABCC6         Xtr           ABCC6         Xtr           ABCC6         Lch           ABCC6         Gac1           ABCC6         Dla           ABCC6         Dla           ABCC6         Ia           ABCC6         Ola           ABCC6         Stat           ABCC6         Stat           ABCC6         Ola           ABCC6         Stat	INLEGGOKORUS LAR           INISGCOKORUS LAR           INISGCOKORUS LAR           VNLSGCOKORUS LAR           VNLSGCOKORUS LAR           VNLSGCOKORUS LAR           INLSGCOKORUS LAR           LNLSGCOKORUS LAR	A AVYKKAA YYLLDD AAVYRAAS VYLLDD AAVYORSS YYLLDD AAVYCKAS VYLLDD AAVYKAB VYLLDD AAVYRKAD VYLLDD	PIAALDAHWOOIIER PLSAVDAHWOOIIER PLSAVDAHWOOIIER PLSAVDAWOOIIER PLSAVDAWOOIIER PLSAVDAWOOIIER PLSAVDAWOOIIER PLSAVDAHWOOIIER PLSAVDAHWOOIIER PLSAVDAHWOOIIER PLSAVDAHWOOIIER PLSAVDAHWOOIIER PLSAVDAHWOOIIER PLSAVDAHWOOIIER PLSAVDAHWOOIIER PLSAVDAHWOOIIER PLSAVDAHWOOIIER	VIGPGGLIHGTTRI IIGPDGLLKDTTRI VIGPTGLLKDKTRI VIGPGLLKDKTRI VIGPGLLKHKTRI VIGPGLLKHKTRI VIGPKGVLRDKTRI VIGPKGVLRDKTRI VIGPKGVLRDKTRI VIGPKGVLRDKTRI VIGPKGULRDKTRI VIGPKGILRDKTRI VIGPGGLKKKOTRV VIGPRGLKKNKTRI	LVTHAVHLEPOADY LVTHAVSVERVOSU VLVTHAVSVERVOSU VLVTHAVSVEPOADY LVTNAVHLERMORI VLVTHAVSVEPOADY LVTHAVSVEPOADY LVTHGSSISKTDLI LVTHGSSISKTDLI LVTHGSSEPOADHI LVTHGSSEPOADII LVTHGSSEPOADII VLVTHGSSEPOADII VLVTHGSSEPOADII VLVTHGSSEPOADII VLVTHGSSEPOADII VLVTHGSSEPOADII VLVTHGSSEPOADII VLVTHGSSEPOADII	MADCAVVESCIVOE MILVDCATACICSVC VVMCCTACICSVC VVMCCTCSTCSVOE VMSCCVCSVCTVN VMSCCVCSVCTVN VMSCCSCVCTVN VMSCCTSSVOE VLCCCTTSSSVOE VLLDCCTTSSSVOE VLLDCCTTSSSVOE VLLDCCTTSSSVOE VLLDCCTTSSSVOE VLLDCCTTSSSVOE VLLDCCTTSSSVOE VLLDCCTTSSSVOE VLLDCCTTSSSVOE VLLDCCTTSSSVOE VLLDCCTTSSSVOE VLLDCCTTSSSVOE VLLDCCTTSSSVOE VLLDCCTTSSSVOE VLLDCCTTSSSVOE VLLDCCTTSSSVOE	LI ORN OP FT : 85 LVRRK GA FV : 78 LVRRK GA FV : 78 LVARN GA FA : 85 LVARN GA FA : 85 LVARN GA FA : 85 LI SRH GA FA : 81 LI SRH GA FA : 81	。 69568685517000934
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ABCC6         Made           ABCC6         Can           ABCC6         Gaa           ABCC6         Xtr           ABCC6         Xtr           ABCC6         Cat           ABCC6         Gac1           ABCC6         Gac2           ABCC6         Gac1           ABCC6         Gac1           ABCC6         Gac2           ABCC6         Gac1           ABCC6         Ola           ABCC6         Ola           ABCC6         Oni           ABCC6         Jmc1           ABCC6         Jmc1           ABCC6         Jmc1           ABCC6         Jmc1           ABCC6         Jmc2           ABCC6         Jmc2           ABCC6         Jmc2           ABCC6         Jmc2           ABCC6         Amc1           ABCC6         Amc2	INLEGGORORUS LAR           INISGORORVS LAR           INISGORORVS LAR           VNLSGORORVS LAR           VNLSGORORVS LAR           INLSGORORVS LAR           INLSGORORVS LAR           INLSGORORVS LAR           INLSGORORVS LAR           LNLSGORORVS LAR	A AVYKKAA YYLLDD AVV RRAS YYLLDD AVV RRAS YYLLDD AVV RRAS YYLLDD AVV RRAS YYLLDD AVV RRAS YYLLDD AVV RKAD YYLLDD	PIAALDAHWOOHIEDR PLSAVDAHWOOHIEDR PLSAVDAHWOOHIERH PLSAVDAWOOHIERH PLSAVDAWOOHIER PLSAVDARWOOHIER PLSAVDARWOOHIEDR PLSAVDAHWOOHIEDR PLSAVDAHWOOHIEDR PLSAVDAHWOOHIEDR PLSAVDAHWOOHIEDR PLSAVDAHWOOHIEDR PLSAVDAHWOOHIERR PLSAVDAHWOOHIERR PLSAVDAHWOOHIERR PLSAVDAHWOOHIERR PLSAVDAHWOOHIERR PLSAVDAHWOOHIERR PLSAVDAHWOOHIERR	VIGPGGLIHGTTRI IIGPDGLLKDTTRI VIGPNGLLKDKTRI VIGPGLLKDKTRI VIGPGLLKDKTRI VIGPKGVLRDKTRI VIGPKGVLRDKTRI VIGPKGVLRDKTRI VIGPKGVLRDKTRI VIGPKGVLRDKTRI VIGPKGULRDKTRI VIGPKGILKDKTRI VIGPKGILKNKTRV VIGPKGILKNKTRV VIGPKGILKNKTRV	LVTHAVHILPOADYI LVTHAVSVIPRVISI UVTHMISVIHPOTI UVTHMISVIHPOTI UVTHAVSVIPOADSI UVTHAVSVIPOADSI UVTHAVSVIPOADSI UVTHASSIPOADHI UVTHGSFIPOADHI UVTHGSFIPOADHI UVTHGSFIPOADHI UVTHGSFIPOADHI UVTHGSFIPOADHI UVTHGSFIPOADHI UVTHGSFIPOADHI UVTHGSFIPOADHI UVTHGSFIPOADHI UVTHGSFIPOADHI UVTHGSFIPOADHI UVTHGSFIPOADHI UVTHGSFIPOADHI UVTHGSFIPOADHI	MADCAVVESCYOE MIVDCATACICSVE VVDCTACSVE VVDCTACSVE VDCCTSCSVC VDCCTSCSVC VDCCTSCSVC VDCCTSCSVC VDCCTSCSVC VDCCTSSSVC VDCCTSSSVC VDCCTSSSVC VDCCTTSSSVC VDCCTTSSSVC VDCCTTSSSVC VDCCTTSSSVC VDCCTTSSSVC VDCCTTSSSVC VDCCTTSSSVC VDCCTTSSSVC VDCCTTSSSVC VDCCTTSSSVC VDCCTTSSSVC VDCCTTSSSVC VDCCTTSSSVC VDCCTTSSSVC VDCCTTSSSVC VDCCTTSSSVC VDCCTTSSSVC VDCCTTSSSVC VDCCTTSSSVC VDCCTTSSSVC	LI ORN CPET : 85 LVRRK GAEV : 78 LORRK GAEV : 78 LORRK GAEA : 85 LVARN GAEA : 85 LVARN GAEA : 85 LI SRH GAEA : 81 LI SRH GAEA : 84 LI SRK AEA : 86 LI SRK AEA : 86	6956868551700093419
ABCC6         MAD           ABCC6         Gan           ABCC6         Gan           ABCC6         Kr           ABCC6         Xtr           ABCC6         Lch           ABCC6         Gac1           ABCC6         Gac2           ABCC6         Cla           ABCC6         Cla           ABCC6         Ola           ABCC6         Ola           ABCC6         Gmo           ABCC6         Gmo           ABCC6         Gmo           ABCC6         Gmo           ABCC6         Gmo           ABCC6         Ame1           ABCC6         Ame2           ABCC6         Ame2           ABCC6         Ame2           ABCC6         Loc	1 INISGOKORVSLAH 1 NISGOKORVSLAH 2 VNLSGOKORVSLAH 2 VNLSGOKORVSLAH 2 VNLSGOKORVSLAH 2 VNLSGOKORVSLAH 2 NLSGOKORVSLAH 3 LNLSGOKORVSLAH 3 LNLSGOKORVSL	A VYKKAA YYLLDD AXV RAS VYLLDD XXV RAS VYLLDD XXV RAS VYLLDD XXV RAS VYLLDD XXV RAS VYLLDD XXV RAS VYLLDD XXV RAD VYLDD XXV RAD VYLDD	PIAALDAHWOOHIED PLSAVDAHWOOHIED PLSAVDAWOOHIEH PLSAVDAWOOHIEH PLSAVDAWOOHIEH PLSAVDAWOOHIEC PLSAVDAWOOHIED PLSAVDAHWOOHIED PLSAVDAHWOOHIED PLSAVDAHWOOHIED PLSAVDAHWOOHIED PLSAVDAHWOOHIED PLSAVDAHWOOHIED PLSAVDAHWOOHIER PLSAVDAHWOOHIER PLSAVDAHWOOHIER PLSAVDAHWOOHIER PLSAVDAHWOOHIER PLSAVDAHWOOHIER PLSAVDAHWOOHIER PLSAVDAHWOOHIED	VIGPGGLIHGTTRI TIGPDGLLKDTTRI VIGPNGLLKDKTRI VIGPSGLLKHKTRI VIGPSGLLKHKTRI VIGPSGLLKHKTRI VIGPKGVLRDKTRI VIGPKGVLRDKTRI VIGPKGVLRDKTRI VIGPKGVLRDKTRI VIGPKGVLRDKTRI VIGPKGVLRDKTRI VIGPKGULRDKTRI VIGPKGILRDKTRI VIGPKGILKMKTRI VIGPKGLLKMKTRI VIGPKGLLKMKTRI	LVTFAVSVLPCAVSU LVTFAVSVLPCVSU LVTFAVSVLPCVSU LVTFAVSVLPCAVSU LVTFAVSVLPCAVSU LVTFAVSVLPCAVSU LVTFAVSVLPCAVSU LVTFAVSVLPCAVSU LVTFGSFLPCAVL LVTFGSFLPCAVL LVTFGSFLPCAVL LVTFGSFLPCAVL LVTFGSFLPCAVL LVTFGSFLPCAVL LVTFGSFLPCAVL LVTFGSFLPCAVL LVTFGSFLPCAVL LVTFGSFLPCAVL LVTFGSFLPCAVL LVTFGSFLPCAVL LVTFGSFLPCAVL LVTFGSFLPCAVL	MADCAVVESCYOE MUVDCATALIGSYR VLVDCTIALIGSYR VLVDCTIALIGSYR VMCETSTCSVOE VMSCGISENCSYK VMSCGISENCYK VTCCETTSSSVOE VLDCETTSSSVOE VLDCETTSSSVOE VLVDCETTSSSVOE VLVDCETTSSSVOE VLVDCETTSSSVOE VLVDCETTSSSVOE VLVDCETTSSSVOE VLVDCETTSSSVOE VLVDCETTSSSVOE VLVDCETTSSSVOE VLVDCETTSSSVOE VLVDCETTSSSVOE	LI ORN CPET : 85 LVRRKGARV : 78 ISORSAFAA : 78 ISORSAFAA : 78 ILORNGAFS : 82 ILORNGAFS : 82 ILERGAFA : 85 ILSRHGAFA : 85 ILSRHGAFA : 85 ILSRHGAFA : 85 ILSRHGAFA : 85 ILSRHGAFA : 81 ISRRGAFA : 81 ISRRGAFA : 85 ILSRHGAFA : 85 ILSRHGAFA : 85 ILSRHGAFA : 85 ILSRHGAFA : 85 ILSRHGAFA : 85 ILSRHGAFA : 84	069568685517000934199
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ISORS A FA         :         78           ISORS A FA         :         78           ISORS A FA         :         85           IVARN GAES         :         82           IDERC A FA         :         82           IDERC A FA         :         85           ISORS A FA         :         82           IDERC A FA         :         85           ISORS A FA         :         85           ISORS A FA         :         85           ISORG A FA         :         86           ISORG A FA         :         86           INRN A FA         :         86           INRN A FA         :         86           INR A FA         :         86           INR A FA         :         86           INR A FA         :         86           INGR A FA         :         86           IARD GA FA         :         86 <td>695686855170009341993933</td>	695686855170009341993933
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ABCC6 MGO           ABCC6 Ga           ABCC6 Ga           ABCC6 Ca           ABCC6 Dre3           ABCC6 Ame1           ABCC6 Ame2           ABCC6 Loc           ABCC6 Ame1           ABCC6 Loc           ABCC1 Hsa           ABCC1 Hsa           ABCC1 Mmu           ABCC1 Ca           ABCC1 Ca           ABCC1 Ca           ABCC1 Aca           ABCC1 Loc           ABCC1 Loc           ABCC1 Loc           ABCC1 Ja           ABCC1 Ja           ABCC1 Ca           ABCC1 Ca           ABCC1 Ca           ABCC1 Ca           ABCC1 Ca           ABCC1 Ca	INLEGGORORUS LAR           INISGORORUS LAR           INISGORORUS LAR           VILSGORORUS LAR           VILSGORORUS LAR           VILSGORORUS LAR           INISGORORUS LAR           INLSGORORUS LAR           INLSGORORUS LAR           LILSGORRUS LAR           LILSGORRUS LAR           LILSGORORUS LAR           LINLSGORORUS LAR           VILSGORORUS LAR <t< td=""><td>A VYKKAA YYLLDD XAV PRAS VYLLDD XAV PRAS VYLLDD XAV PRAS VYLLDD XAV PRAS VYLLDD XAV PRAS 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ABCC6         MAD           ABCC6         Gan           ABCC6         Gan           ABCC6         Kar           ABCC6         Kar           ABCC6         Kar           ABCC6         Gac1           ABCC6         Gac1           ABCC6         Gac1           ABCC6         Gac1           ABCC6         Gac1           ABCC6         Gac2           ABCC6         Gac1           ABCC6         Gac1           ABCC6         Gac1           ABCC6         Gac3           ABCC6         Dre3           ABCC6         Dre3           ABCC6         Dre3           ABCC6         Ame1           ABCC6         Ame2           ABCC6         Ame2           ABCC6         Loc           ABCC1         Ha           ABCC1         Mat           ABCC1         Ama           ABCC1         Ama           ABCC1         Ama           ABCC1         Cac           ABCC1         Cac           ABCC1         Cac           ABCC1         Cac	INLESGOKORUSLAH           INISGOKORVSLAH           INISGOKORVSLAH           VILSGOKORVSLAH           VILSGOKORVSLAH           VILSGOKORVSLAH           VILSGOKORVSLAH           INISGOKORVSLAH           INISGOKORVSLAH           INLSGOKORVSLAH           VILSGOKORVSLAH	A VYKKAA YYLLDD XAV PRAS YYLLDD XAV PRAS YYLLDD XAVY PRAS YYLLDD XAVY RKAS YYLLDD XAVY RKAS YYLLDD XAVY RKAD YYLLDD XAVY CDS DYYL FDD XAVY CDS YYLLDD XAVY CDR YYLLDD	PLAALDAHWOOTI DR PLSAVDAHWOOTI DR PLSAVDAHWOOTI DH PLSAVDAWOOTI DH PLSAVDAWOOTI DK PLSAVDAWOOTI DK PLSAVDAWOOTI DK PLSAVDAWOOTI DK PLSAVDAWOOTI DK PLSAVDAWOOTI DK PLSAVDAWOOTI DK PLSAVDAWOOTI DK PLSAVDAWOOTI DR PLSAVDAWOOTI DR PLSAVDAWOOT	V IGPGGLING TR I I IGPGGLIKD TR I V IGPNGLIKD KTR V V IGPSGLIKD KTR V V IGPSGLIKD KTR V V IGPGGLIKB KTR V V IGPGGLIKD KTR V V IGPKGVLRD KTR V V IGPKGLIKN KTR V V IGPGGLIKN KTR V V IGPGGLIKD KTR V V IGPGGLIKD KTR V V IGPGILKD KTR V V IGPGGLIKD KTR V V IGPGGL	LVTHAUHLIPOADYI LVTHAUSYIPOADYI LVTHAUSYIPOADYI LVTHAUSYIPOADYI LVTHAUSYIPOADYI LVTHAUSYIPOADYI LVTHGSFIPOADHI LVTHGSFIPOADHI LVTHGSFIPOADHI LVTHGSFIPOADHI LVTHGSFIPOADHI LVTHGSFIPOADHI LVTHGSFIPOADHI LVTHGSFIPOADHI LVTHGSFIPOADHI LVTHGSFIPOADHI LVTHGSFIPOADHI LVTHGSFIPOADHI LVTHGSFIPOADHI LVTHGSFIPOADHI LVTHGSFIPOADHI LVTHGISFIPOADHI LVTHGSFIPOADHI LVTHGSFIPOADHI LVTHGSFIPOADHI LVTHGSFIPOADHI LVTHGSFIPOADHI LVTHGSFIPOADHI LVTHGSFIPOADHI LVTHSISYIPOYDI LVTHSISYIPOYDI LVTHSISYIPOADHI LVTHGSYIPOADHI LVTHGSYIPOADHI LVTHGSYIPOADHI LVTHGSFIPOADHI LVTHGSFIPOADHI LVTHGSFIPOADHI LVTHGSFIPOADHI LVTHGSFIPOADHI LVTHGSFIPOADHI LVTHGSFIPOADHI LVTHGSFIPOADHI LVTHGSFIPOADHI LVTHGSFIPOADHI LVTHGSFIPOADHI LVTHGSFIPOADHI LVTHGSFIPOADHI LVTHGSFIPOADHI LVTHGSFIPOADHI LVTHGSFIPOADHI LVTHGSFIPOADHI LVTHGSFIPOADHI LVTHGSFIPOADHI LVTHGSFIPOADHI LVTHGSFIPOADHI LVTHGSFIPOADHI LVTHGSFIPOADHI LVTHGSFIPOADHI LVTHGSFIPOADHI LVTHGSFIPOADHI LVTHGSFIPOADHI LVTHGSFIPOADHI LVTHGSFIPOADHI LVTHGSFIPOADHI LVTHGSFIPOADHI LVTHGSFIPOADHI LVTHGSFIPOADHI LVTHGSFIPOADHI LVTHGSFIPOADHI LVTHGSFIPOADHI LVTHGSFIPOADHI LVTHGSFIPOADHI LVTHGSFIPOADHI LVTHGSFIPOADHI LVTHGSFIPOADHI LVTHGSFIPOADHI LVTHGSFIPOADHI LVTHGSFIPOADHI LVTHGSFIPOADHI LVTHGSFIPOADHI LVTHGSFIPOADHI LVTHGSFIPOADHI LVTHGSFIPOADHI LVTHGSFIPOADHI LVTHGSFIPOADHI LVTHGSFIPOADHI LVTHGSFIPOADHI LVTHGSFIPOADHI LVTHGSFIPOADHI LVTHGSFIPOADHI LVTHGSFIPOADHI LVTHGSFIPOADHI LVTHGSFIPOADHI LVTHGSFIPOADHI LVTHGSFIPOADHI LVTHGSFIPOADHI LVTHGSFIPOADHI LVTHGSFIPOADHI LVTHGSFIPOADHI LVTHGSFIPOADHI LVTHGSFIPOADHI LVTHGSFIPOADHI LVTHGSFIPOADHI LVTHGSFIPOADHI LVTHGSFIPOADHI LVTHGSFIPOADHI LVTHGSFIPOADHI LVTHGSFIPOADHI LVTHGSFIPOADHI LVTHGSFIPOADHI LVTHGSFIPOADHI LVTHGSFIPOADHI LVTHGSFIPOADHI LVTHGSFIPOADHI LVTHGSFIPOADHI LVTHGSFIPOADHI LVTHGSFIPOADHI LVTHGSFIPOADHI LVTHGSFIPOADHI LVTHGSFIPOADHI LVTHGSFIPOADHI LVTHGSFIPOADHI LVTHGSFIPOADHI LVTHGSFIPOADHI LVTHGSFIPOADHI LVTHGSFIPOADHI LVTHGSFIPOADHI LVTHGSFIPOADHI LVTHGSFIPOADHI LVTHGSFIPOADHI LVTHGSFIPOADHI LVTHGSFIPOADHI LVTHGSFIPOADHI LVTHGSFIPOADHI LVTHGSFIPOADH	MAD CAVYESCYOP           MILVD CATAPICSYNE           VIND CATAPICSYNE           VID CATAPICSYNE	II ORN CPET         :         85           IVRRKGARY         :         78           IORN CARY         :         85           IORN CARS         :         82           IIERG CARA         :         85           IISRH CARA         :         86           IISRH CARA         :         81           IISRH CARA         :         86           IISRH CARA         :         86           IISRGARA         :         86           IIARD CARA         :         86 </td <td>695686855170009341993375850980923001-00</td>	695686855170009341993375850980923001-00
ABCC6 MGO ABCC6 Ga ABCC6 Ga ABCC6 Ca ABCC6 Ca ABCC1 CA AB	INLSGOKORVSLAH           INISGOKORVSLAH           INISGOKORVSLAH           VILSGOKORVSLAH           VILSGOKORVSLAH           VILSGOKORVSLAH           INISGOKORVSLAH           VILSGOKORVSLAH	A VYKKAA YYLLDD XAV RAS YYLLDD XAV RAS YYLLDD XAVYRAS YYLLDD XAVYRAS YYLLDD XAVYRAS YYLLDD XAVYRAD YYLDD XAVYRAD YYLDD XAVYCDS YYLDD XAVYCDA YYLDD XAVYCDRA YYLDD	PIAALDAHWOOTI DR PLSAVDAHWOOTI DR PLSAVDAHWOOTI DH PLSAVDAWOOTI DH PLSAVDAWOOTI DK PLSAVDAWOOTI DK PLSAVDAWOOTI DK PLSAVDAWOOTI DK PLSAVDAWOOTI DK PLSAVDAHWOOTI DR PLSAVDAHWOOTI DR DR PLSAVDAHWOOTI DR DR DR DR DR DR DR DR DR DR DR DR DR D	V IGPGGLIMG TTR I I IGPGGLIKD TTR I V IGPNGLIKD KTR V V IGPSGLIKD KTR V V IGPSGLIKM KTR V V IGPGGLIKM KTR V V IGPKGVIRD KTR V V IGPKGULKD KTR V V IGPKGILKN KTR V V IGPKGLIKN KTR V V IGPGGLIKD	LVTHANHI LPOADYI LVTHAVSVIPRVISI VIVTENSVIPRVISI VIVTENSVIPRVISI VIVTENSVIPOADSI JVTENSVIPOADSI JVTENSVIPOADSI JVTENSVIPOADSI JVTENSVIPOADSI JVTENSPIPOADII JVTENSPIPOADII JVTENSPIPOADII JVTENSPIPOADII VIVTENSPIPOADII VIVTENSPIPOADII VIVTENSPIPOADII VIVTENSPIPOADII VIVTENSPIPOADII VIVTENSPIPOADII JVTENSVIPOADII JVTENSVIPOADII JVTENSVIPOADII JVTENSVIPOADII JVTENSVIPOADII JVTENSVIPOADII JVTENSVIPOADII JVTENSVIPOADII JVTENSVIPOADII JVTENSVIPOADII JVTENSVIPOADII JVTENSVIPOADII JVTENSVIPOADII JVTENSVIPOADII JVTENSVIPOADII JVTENSVIPOADII JVTENSVIPOADII JVTENSVIPOADII JVTENSVIPOADII JVTENSVIPOADII JVTENSVIPOADII JVTENSVIPOADII JVTENSVIPOADII JVTENSVIPOADII JVTENSVIPOADII JVTENSVIPOADII JVTENSVIPOADII JVTENSVIPOADII JVTENSVIPOADII JVTENSVIPOADII JVTENSVIPOADII JVTENSVIPOADII JVTENSVIPOADII JVTENSVIPOADII JVTENSVIPOADII JVTENSVIPOADII JVTENSVIPOADII JVTENSVIPOADII JVTENSVIPOADII JVTENSVIPOADII		II ORN CPET         :         85           IVRRKGARY         :         78           IORN CARY         :         78           IORN CARY         :         78           IORN CARY         :         78           IORN CARS         :         85           IORN CARS         :         85           IORN CARS         :         85           IORN CARA         :         85           ISREGARA         :         86           ISREGARA         :         86           ISREGARA         :         81           ISREGARA         :         86	0       0       0       0       0       0       0       0       0       0       0       0       0       0       0       0       0       0       0       0       0       0       0       0       0       0       0       0       0       0       0       0       0       0       0       0       0       0       0       0       0       0       0       0       0       0       0       0       0       0       0       0       0       0       0       0       0       0       0       0       0       0       0       0       0       0       0       0       0       0       0       0       0       0       0       0       0       0       0       0       0       0       0       0       0       0       0       0       0       0       0       0       0       0       0       0       0       0       0       0       0       0       0       0       0       0       0       0       0       0       0       0       0       0       0       0       0       0       0
ABCC6         MAD           ABCC6         Gan           ABCC6         Gan           ABCC6         Kr           ABCC6         Kr           ABCC6         Can           ABCC6         Kr           ABCC6         Gac1           ABCC6         Can           ABCC6         Dre3           ABCC6         Dre3           ABCC6         Ame           ABCC6         Ame           ABCC6         Ame           ABCC6         Ame           ABCC6         Ame           ABCC6         Ame           ABCC1         Ma           ABCC1         Ma           ABCC1         Can           ABCC1 <td>INLISGOKORVSLAH           INISGOKORVSLAH           INISGOKORVSLAH           VILLSGOKORVSLAH           VILLSGOKORVSLAH           VILLSGOKORVSLAH           INISGOKORVSLAH           INLSGOKORVSLAH           VILSGOKORVSLAH           VILSGOKORVSLAH</td> <td>A VYKKAA YYLLDD XAVY RAAS VYLLDD XAVY RAS VYLLDD XAVY RAS VYLLDD XAVY RAS VYLLDD XAVY RKAD YYLDD XAVY SDAD YYLDD XAVY CDS VYLLDD XAVY CDRAVYLDD XAVY CDRAVYLDD</td> <td>PIAALDAHWOOTI EDR PLSAVDAHWOOTI EDR PLSAVDAHWOOTI EDR PLSAVDANWOOTI ENR PLSAVDANWOOTI ENR PLSAVDAWOOTI ENR PLSAVDAWOOTI ENR PLSAVDANWOOTI DR PLSAVDAHWOOTI DR PLSAVDAHWOOTI DR PLSAVDAHWOOTI DR PLSAVDAHWOOTI DR PLSAVDAHWOOTI DR PLSAVDAHWOOTI DR PLSAVDAHWOOTI ENR PLSAVDAHWOOTI ENR PLS</td> <td>V IGPGGLLMG TTR I I IGPGGLLKD TTR I V IGPNGLLKD KTR V V IGPSGLLKD KTR V V IGPGGLLKH KTR V V IGPGGULKEK KTR V V IGPGGVLRD KTR V V IGPKGVLRD KTR V V IGPKGULRD KTR V V IGPKGLLKN KTR V V IGPGLLKD KTR V V IGPGULKD KTR V V IGPGULKD</td> <td>LVTHANHLIPOADYI LVTHAVSVIPRVISI VIVTENSVIPRVISI VIVTENSVIPRVISI VIVTENSVIPOADSI JVTENSVIPOADSI LVTENSVIPOADSI LVTENSFIPOADI LVTENSFIPOADI LVTENSFIPOADI LVTENSFIPOADI LVTENSFIPOADI LVTENSFIPOADI LVTENSFIPOADI LVTESSIPOADI LVTESSIPOADI LVTESSIPOADI LVTESSIPOADI LVTESSIPOADI LVTESSIPOADI LVTESSIPOADI LVTESSIPOADI LVTESSIPOADI LVTESSIPOADI LVTESSIPOADI LVTESSIPOADI LVTESSIPOADI LVTESSIPOADI LVTESSIPOADI LVTESSIPOADI LVTESSIPOADI LVTESSIPOADI LVTESSIPOADI LVTESSIPOADI LVTESSIPOADI LVTESSIPOADI LVTESSIPOADI LVTESSIPOADI LVTESSIPOADI LVTESSIPOADI LVTESSIPOADI LVTESSIPOADI LVTESSIPOADI LVTESSIPOADI LVTESSIPOADI LVTESSIPOADI LVTESSIPOADI LVTESSIPOADI LVTESSIPOADI LVTESSIPOADI LVTESSIPOADI LVTESSIPOADI LVTESSIPOADI LVTESSIPOADI LVTESSIPOADI LVTESSIPOADI LVTESSIPOADI LVTESSIPOADI LVTESSIPOADI LVTESSIPOADI LVTESSIPOADI LVTESSIPOADI LVTESSIPOADI LVTESSIPOADI LVTESSIPOADI LVTESSIPOADI LVTESSIPOADI LVTESSIPOADI LVTESSIPOADI LVTESSIPOADI LVTESSIPOADI LVTESSIPOADI LVTESSIPOADI LVTESSIPOADI LVTESSIPOADI LVTESSIPOADI</td> <td>MAD GAVYESCYOP           MAD GAVYESCYOP           MILVD GATAPICSYNE           VLVD GTTAPICSYNE           VLVD GTTAPICSYNE           VMSD GYSEVGTYNE           VMD GETTES GSYOE           VLD GETTES GSYOE           VMD GETTES GSYOE           VMD GETTES GSYOE           VMD GETTES GSYOE           VMD GETTES GSYOE           VMS GKISEMGSYOE           VMS GKISEMGSYOE</td> <td>LI ORN CPET : 85 LVRRK GAEV : 78 LVRRK GAEV : 78 LVARN GAEA : 85 LVARN GAEA : 85 LVARN GAEA : 85 LI SREGAEA : 86 LI REGAEA :</td> <td>6       9       5       6       8       5       5       1       7       0       0       9       3       4       1       9       9       3       9       3       7       5       8       5       0       9       2       3       0       0       1       -       0       0       3       2       3       0       0       1       -       0       0       3       2       3       0       0       1       -       0       0       3       2       3       0       0       1       -       0       0       3       2       3       0       0       1       -       0       0       3       2       3       0       0       1       -       0       0       3       3       7       5       8       5       0       9       2       3       0       0       1       -       0       0       3       4       1       9       9       3       7       5       8       5       0       9       2       3       0       0       1       -       0       3       4       1       9       3</td>	INLISGOKORVSLAH           INISGOKORVSLAH           INISGOKORVSLAH           VILLSGOKORVSLAH           VILLSGOKORVSLAH           VILLSGOKORVSLAH           INISGOKORVSLAH           INLSGOKORVSLAH           VILSGOKORVSLAH	A VYKKAA YYLLDD XAVY RAAS VYLLDD XAVY RAS VYLLDD XAVY RAS VYLLDD XAVY RAS VYLLDD XAVY RKAD YYLDD XAVY SDAD YYLDD XAVY CDS VYLLDD XAVY CDRAVYLDD XAVY CDRAVYLDD	PIAALDAHWOOTI EDR PLSAVDAHWOOTI EDR PLSAVDAHWOOTI EDR PLSAVDANWOOTI ENR PLSAVDANWOOTI ENR PLSAVDAWOOTI ENR PLSAVDAWOOTI ENR PLSAVDANWOOTI DR PLSAVDAHWOOTI DR PLSAVDAHWOOTI DR PLSAVDAHWOOTI DR PLSAVDAHWOOTI DR PLSAVDAHWOOTI DR PLSAVDAHWOOTI DR PLSAVDAHWOOTI ENR PLSAVDAHWOOTI ENR PLS	V IGPGGLLMG TTR I I IGPGGLLKD TTR I V IGPNGLLKD KTR V V IGPSGLLKD KTR V V IGPGGLLKH KTR V V IGPGGULKEK KTR V V IGPGGVLRD KTR V V IGPKGVLRD KTR V V IGPKGULRD KTR V V IGPKGLLKN KTR V V IGPGLLKD KTR V V IGPGULKD	LVTHANHLIPOADYI LVTHAVSVIPRVISI VIVTENSVIPRVISI VIVTENSVIPRVISI VIVTENSVIPOADSI JVTENSVIPOADSI LVTENSVIPOADSI LVTENSFIPOADI LVTENSFIPOADI LVTENSFIPOADI LVTENSFIPOADI LVTENSFIPOADI LVTENSFIPOADI LVTENSFIPOADI LVTESSIPOADI LVTESSIPOADI LVTESSIPOADI LVTESSIPOADI LVTESSIPOADI LVTESSIPOADI LVTESSIPOADI LVTESSIPOADI LVTESSIPOADI LVTESSIPOADI LVTESSIPOADI LVTESSIPOADI LVTESSIPOADI LVTESSIPOADI LVTESSIPOADI LVTESSIPOADI LVTESSIPOADI LVTESSIPOADI LVTESSIPOADI LVTESSIPOADI LVTESSIPOADI LVTESSIPOADI LVTESSIPOADI LVTESSIPOADI LVTESSIPOADI LVTESSIPOADI LVTESSIPOADI LVTESSIPOADI LVTESSIPOADI LVTESSIPOADI LVTESSIPOADI LVTESSIPOADI LVTESSIPOADI LVTESSIPOADI LVTESSIPOADI LVTESSIPOADI LVTESSIPOADI LVTESSIPOADI LVTESSIPOADI LVTESSIPOADI LVTESSIPOADI LVTESSIPOADI LVTESSIPOADI LVTESSIPOADI LVTESSIPOADI LVTESSIPOADI LVTESSIPOADI LVTESSIPOADI LVTESSIPOADI LVTESSIPOADI LVTESSIPOADI LVTESSIPOADI LVTESSIPOADI LVTESSIPOADI LVTESSIPOADI LVTESSIPOADI LVTESSIPOADI LVTESSIPOADI LVTESSIPOADI LVTESSIPOADI LVTESSIPOADI LVTESSIPOADI	MAD GAVYESCYOP           MAD GAVYESCYOP           MILVD GATAPICSYNE           VLVD GTTAPICSYNE           VLVD GTTAPICSYNE           VMSD GYSEVGTYNE           VMD GETTES GSYOE           VLD GETTES GSYOE           VMD GETTES GSYOE           VMD GETTES GSYOE           VMD GETTES GSYOE           VMD GETTES GSYOE           VMS GKISEMGSYOE	LI ORN CPET : 85 LVRRK GAEV : 78 LVRRK GAEV : 78 LVARN GAEA : 85 LVARN GAEA : 85 LVARN GAEA : 85 LI SREGAEA : 86 LI REGAEA :	6       9       5       6       8       5       5       1       7       0       0       9       3       4       1       9       9       3       9       3       7       5       8       5       0       9       2       3       0       0       1       -       0       0       3       2       3       0       0       1       -       0       0       3       2       3       0       0       1       -       0       0       3       2       3       0       0       1       -       0       0       3       2       3       0       0       1       -       0       0       3       2       3       0       0       1       -       0       0       3       3       7       5       8       5       0       9       2       3       0       0       1       -       0       0       3       4       1       9       9       3       7       5       8       5       0       9       2       3       0       0       1       -       0       3       4       1       9       3

ABCC6	Xtr	:	EFINTYARKSVVFEES	: 877
ABCC6	Lch	:	ELIRTYTNAEOSESTG	: 914
ABCC6	Gac1	•	DE HT FANAFRKE	908
ADCCC	Cago	:		
ADCCO	Gacz	·	AVITATINGRAKKG	. 926
ABCC6	DIa	:	DTHITFASTERKEOLIGSAIORAGSRRSNARLSMVDFMPFSRDLSOEOLIG:	: 902
ABCC6	Ola	:	DETHTFASTEKKEOLIGYINSRSELES :	: 912
ABCC6	Tni	:	DETHTFARTERKE	: 901
ABCC6	Oni	:	DETHTFASTERKEOLIGSAIORGKETFOTLAGSRRSNARLSMVDFMPFSRDLSOEOLIG:	: 915
ABCC6	Xma	•	DITHTFASTERKEOLIGSVIORAGSRRSNARLSMVDFMPFSRDLSOFOLIG	: 897
ABCCE	Gmo			. 845
ADCCO	Omo 1	:		. 015
ABCC6	Drei	:	D. HTFANSERKESKSVRLSVIDIMFSKDLSUED	: 894
ABCC6	Dre2	:	ELKAFSVSERKMHEVLGTRKSVSFLSIKDFSTDLIRG	: 850
ABCC6	Dre3	:	ETVKAFSVSERKESATHKGKIKFTLTTVKIHVNLGOTSLLTSLKSNSSG :	: 913
ABCC6	Ame1	:	DETERT FASSERKERSCARLSVTDYMLFSRDLSOEO	: 894
ABCC6	Ame2	:	DEVOTFAGNERKEISTNKGKOGFPLTENKDSLGNLHSTCNESLTHLKD:	: 917
ABCC6	Loc	:	DURY FASSDRKESAVHRGPRKSSSRLSVTDYMPVSRDLSOEQ::	: 892
ABCC1	Hga		TENDERVASTEOFONDE	• 929
APCCI	Dtr	:		
ABCCI	FUI	÷		. 044
ABCCI	Mmu	:	ETTRTYANAKODLASEDDSV5G5GKESKPVENGMLVTDTVGKHLORHLSN5SSH5GDTSOOHS	926
ABCC1	Cluf	:	E TRTYASGDOEOAEODDGLTGVSSPGKEVKOMENGMLVTDVAGKOLOROLSNSSSYSGDVSLHHT	: 929
ABCC1	Bta	:	EDTRTYASAEOEOGOPEDGLAGVGGPGKEVKOMENGMLVTDTAGKOMOROLSSSSSYSGDVSRHHTEDGLAGVGGPGKEVKOMENGMLVTDTAGKOMOROLSSSSSYSGDVSRHHT	: 913
ABCC1	Dno	:	ETTRTYAGAEOEOAAEGDGPTGVSGPAKEAKOMENGMLVMDAAGKOLOROLSSSSSYSGVVS	: 927
ABCC1	Mdo	:	ETRTYANAEONMEDEGTNGPVVKEVKOMENGVLISETAGKOLKROLSNSSSYSTEPGKHN	: 929
ABCC1	Oan	:	EURTYANAEOSPDDGDVKKGEGNOPLEEEEGSNSPAVKEVKPMENGVLVMEGSAKOLHROLSNSSTYSTDTGKHOT	: 712
ABCC1	Gga	•	RUTRTYANAFOSMESSDASSPSGKEGKPVENGVLVNDAPGKLMHROLSNSSTYSRETGKSOHOS	924
ABCC1	Ace			· 025
ADCCI	Aca V+~	÷		. 923
ADCCI	AUT	•	ENTATEMARGUMARGOEVESG	. 925
ABCC1	ьсn	:	EMPRITARAROMAREMERAVGLCFVNSFTFKEGPLLENGLVFLOKOLFROSTTSFSSOPDTTEPLLOKN	. 928
ABCC1	Gac	:	E CRTYAAVEHADHDENVNSPEVSRVSKPGOTG	: 921
ABCC1	Dla	:	E ORTYSAVDHTDNN	: 836
ABCC1	Ola	:	ETTRMYAANEOSEETEWTGLDFSSENWLYVYHEKSLSSCLEPVPNSPTKPMENGVGPGFTGSSOSASNVSKGSV:	: 937
ABCC1	Tni	:	WNFLVHLEPLKISNKIVALSNVKIIVKVWEENVRNRSTRTAYLSLSLSLCSSAPGNLSIMAOPG:	: 864
ABCC1	Oni	:	ENTRAYDKTDNSG	: 920
ABCC1	Xma1	•	RETRTYATUDOTDDGVOHUPUASSRSCFFTLONLKTAPKSGSKAUENGDLPALIGEPAUKTETOKPHKTDN	252
ABCCI	Vma2			
ADCCI	Dwo	:		• • • •
ABCCI	Dre	÷	BI TRITINI BOEDEDESLIGDAVP	. 916
ABCCI	Ame	:	DTRTYANAKODGEPDGMTUGAP	: 916
ABCC1	Loc	:	ETTRTYANADOGEEEDOPEDGDENEG-KDKPEDRSSSPGREOKGLENGGPAALRONSLTSSVGSDSAKALLKSG :	: 936
ABCC1	Cmi	:	EVIOAYAHKETSEFEVESESEDIVLLEVEDAEDDGPNRPRHKKRRLSTISSASEMONOAKSRAVLRRHHSPSVHRDPSTTROOYLSPSYROGSSYRROES	: 942
			* 1020 * 1040 * 1060 * 1080 * 1100	
ABCCE	Hca		· · · · · · · · · · · · · · · · · · ·	• 892
ABCC6	Hsa	:	IK :	: 892
ABCC6 ABCC6	Hsa Ptr	:	IK :	: 892 : 734
ABCC6 ABCC6 ABCC6	Hsa Ptr Mmu	::		: 892 : 734 : 887
ABCC6 ABCC6 ABCC6 ABCC6	Hsa Ptr Mmu Cluf	:::::::::::::::::::::::::::::::::::::::		: 892 : 734 : 887 : 893
ABCC6 ABCC6 ABCC6 ABCC6 ABCC6	Hsa Ptr Mmu Cluf Bta	: : : :		: 892 : 734 : 887 : 893 : 893
ABCC6 ABCC6 ABCC6 ABCC6 ABCC6 ABCC6	Hsa Ptr Mmu Cluf Bta Dno	:::::::::::::::::::::::::::::::::::::::		: 892 : 734 : 887 : 893 : 893 : 822
ABCC6 ABCC6 ABCC6 ABCC6 ABCC6 ABCC6 ABCC6	Hsa Ptr Mmu Cluf Bta Dno Mdo	:::::::::::::::::::::::::::::::::::::::		: 892 : 734 : 887 : 893 : 893 : 822 : -
ABCC6 ABCC6 ABCC6 ABCC6 ABCC6 ABCC6 ABCC6 ABCC6	Hsa Ptr Mmu Cluf Bta Dno Mdo Oan	:::::::::::::::::::::::::::::::::::::::		: 892 : 734 : 887 : 893 : 893 : 822 : - : 834
ABCC6 ABCC6 ABCC6 ABCC6 ABCC6 ABCC6 ABCC6 ABCC6 ABCC6	Hsa Ptr Mmu Cluf Bta Dno Mdo Oan Gga	:::::::::::::::::::::::::::::::::::::::		: 892 : 734 : 887 : 893 : 893 : 893 : 822 : - : 834 : 898
ABCC6 ABCC6 ABCC6 ABCC6 ABCC6 ABCC6 ABCC6 ABCC6 ABCC6 ABCC6 ABCC6	Hsa Ptr Mmu Cluf Bta Dno Mdo Oan Gga Aca	: : : : : : : : : : : : : : : : : : : :		: 892 : 734 : 887 : 893 : 893 : 822 : - : 834 : 898 : 843
ABCC6 ABCC6 ABCC6 ABCC6 ABCC6 ABCC6 ABCC6 ABCC6 ABCC6 ABCC6 ABCC6 ABCC6	Hsa Ptr Mmu Cluf Bta Dno Mdo Oan Goa Aca Xtr	: : : : : : : : : : : : : : : : : : : :		: 892 : 734 : 887 : 893 : 893 : 822 : - : 834 : 898 : 843 : -
ABCC6 ABCC6 ABCC6 ABCC6 ABCC6 ABCC6 ABCC6 ABCC6 ABCC6 ABCC6 ABCC6 ABCC6 ABCC6	Hsa Ptr Mmu Cluf Bta Dno Mdo Oan Gga Aca Xtr Lch	: : : : : : : : : : : : : : : : : : : :		: 892 : 734 : 887 : 893 : 893 : 822 : - : 834 : 898 : 843 : - : -
ABCC6 ABCC6 ABCC6 ABCC6 ABCC6 ABCC6 ABCC6 ABCC6 ABCC6 ABCC6 ABCC6 ABCC6 ABCC6 ABCC6	Hsa Ptr Mmu Cluf Bta Dno Mdo Oan Goa Aca Xtr Lch Gacl			: 892 : 734 : 887 : 893 : 822 : - : 834 : 898 : 843 : - : - : 910
ABCC6 ABCC6 ABCC6 ABCC6 ABCC6 ABCC6 ABCC6 ABCC6 ABCC6 ABCC6 ABCC6 ABCC6 ABCC6 ABCC6	Hsa Ptr Mmu Cluf Bta Dno Mdo Oan Gga Aca Xtr Lch Gac1 Gac2			: 892 : 734 : 887 : 893 : 893 : 822 : - : 834 : 898 : 843 : - : - : 910
ABCC6 ABCC6 ABCC6 ABCC6 ABCC6 ABCC6 ABCC6 ABCC6 ABCC6 ABCC6 ABCC6 ABCC6 ABCC6 ABCC6	Hsa Ptr Mmu Cluf Bta Dno Mdo Oan Gga Aca Xtr Lch Gac1 Gac2			: 892 : 734 : 887 : 893 : 893 : 822 : : 834 : 898 : 843 : - : - : 910 : 932
ABCC6 ABCC6 ABCC6 ABCC6 ABCC6 ABCC6 ABCC6 ABCC6 ABCC6 ABCC6 ABCC6 ABCC6 ABCC6 ABCC6 ABCC6	Hsa Ptr Mmu Cluf Bta Dno Mdo Oan Gaa Aca Xtr Lch Gac1 Gac2 Dla			: 892 : 734 : 887 : 893 : 822 : : 834 : 898 : 843 : : 910 : 932 : 904
ABCC6 ABCC6 ABCC6 ABCC6 ABCC6 ABCC6 ABCC6 ABCC6 ABCC6 ABCC6 ABCC6 ABCC6 ABCC6 ABCC6 ABCC6	Hsa Ptr Mmu Cluf Bta Dno Mdo Oan GGa Aca Xtr Lch Gac1 Gac2 Dla Ola			: 892 : 734 : 887 : 893 : 822 : - : 834 : 834 : 843 : 843 : 843 : 910 : 910 : 932 : 904 : 923
ABCC6 ABCC6 ABCC6 ABCC6 ABCC6 ABCC6 ABCC6 ABCC6 ABCC6 ABCC6 ABCC6 ABCC6 ABCC6 ABCC6 ABCC6 ABCC6 ABCC6	Hsa Ptr Mmu Cluf Bta Dno Mdo Oan Gga Aca Xtr Lch Gac1 Gac2 Dla Ola Tni			: 892 : 734 : 887 : 893 : 893 : 822 : - : 834 : 898 : 843 : - : 910 : 932 : 904 : 923 : 903
ABCC6 ABCC6 ABCC6 ABCC6 ABCC6 ABCC6 ABCC6 ABCC6 ABCC6 ABCC6 ABCC6 ABCC6 ABCC6 ABCC6 ABCC6 ABCC6 ABCC6 ABCC6	Hsa Ptr Mmu Cluf Bta Dno Mdo Oan GGa Aca Xtr Lch Gac1 Gac2 Dla Ola Tni Oni			: 892 : 734 : 887 : 893 : 893 : 822 : : 834 : 834 : 834 : 834 : 834 : 834 : 910 : 910 : 910 : 901 : 902 : 903 : 903 : 917
ABCC6 ABCC6 ABCC6 ABCC6 ABCC6 ABCC6 ABCC6 ABCC6 ABCC6 ABCC6 ABCC6 ABCC6 ABCC6 ABCC6 ABCC6 ABCC6 ABCC6 ABCC6 ABCC6	Hsa Ptr Mmu Cluf Bta Dno Mdo Oan Goa Aca Xtr Lch Gac1 Gac2 Dla Ola Tni Oni Xma			: 892 : 734 : 887 : 893 : 822 : - : 834 : 843 : 843 : 843 : 910 : 932 : 904 : 904 : 903 : 903 : 903 : 907 : 899
ABCC6 ABCC6 ABCC6 ABCC6 ABCC6 ABCC6 ABCC6 ABCC6 ABCC6 ABCC6 ABCC6 ABCC6 ABCC6 ABCC6 ABCC6 ABCC6 ABCC6 ABCC6 ABCC6 ABCC6	Hsa Ptr Mmu Cluf Bta Dno Mdo Oan Gaa Aca Xtr Lch Gac1 Gac2 Dla Ola Tni Oni Xma Gmo			: 892 : 734 : 887 : 893 : 822 : : 834 : 834 : 843 : : : 910 : 932 : 904 : 923 : 903 : 917 : 889 : 850
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ABCC6	Cluf :	: LVPEKDGTTSEAOTGAPLAGPEWAGRPAGEDGTONGRVKATMYLSYFOAVGVPLCVYALFLFLCOOVASFCHGYWLSLWADDP-TVDGROTOAALRGSLF :	992
ABCC6	Bta :	: LVPEKDSAASEAOTGLPLDDPEGPGOPKGKDGTOYERVKATMYLTYLRAVCTPLCLYALFLELCOOVASFCRG7WLSLWADDP-IVDCOOTHVALRGWVF :	992
ABCC6	Dno :	: HGVERDSTTSKTOSGATLEDPEG-TAPTGG SMPYCRVKASMYLSULAVCAPICLYALFLFLAOOVASFCRGYWLSLWADDP-VVCRAAAALGWVF :	920
ABCC6	Mdo :	:KGRTTLOSRAEGTKMAGOTTEGTRVHY RVNATOYLATLAVCMPTCLSVVPTDLCOMISSSRGVULSLWADDP-VVNCTOHTGLRVGVT :	989
ABCC6	Oan :	: TAPTIMGKDATASKHOSEVHPDVSGRUTEEDEVOTGEVNLALVLTVMRAATPGCLITILEDLCOOVASESSWULSLWUDDP-DTDGVOHTELETGVE :	933
ABCCE	Gra ·		997
ABCCC	ana .		942
ADCC6	ACa :	EVSABRSSKSBARSVINASDLEIAELABEDAGIIGRANISIILSIEVASSLAWAIIVLEITCOOVASGCAUWLSVAADE VNATPAILELKAGVE	942
ABCC6	Xtr :	:ETDDVANEIEADAGKITEADVALTERVKLSVYLEMCKIMCKWYLLISALMALVOOAASLSYMWIGLWADDP-PVNETOHTSLKIGVY :	965
ABCC6	Lch :	:NGTPELGKOEGRAAKDAGK MEADTAOSERVKLAVYOEVFKKLCSFLFLYVIW HICOOAASFSASYWLSLWADDP-VVNGTOHVDVRIGVF :	1006
ABCC6	Gac1 :	: TTNTNLONMEPVSETDOEPVPEDICKITEADKARSGRVRLATYNKIFKTICLAIIVPIVFLYAFOOGASLAYNYWLSVWADDP-IVNGTOTDTDLKIIVF :	1009
ABCC6	Gac2 :	: IONKINPAHVSMAPGFSWGSRRDAGAVVESGGORHEOVKLOMYREUFRTVCPTIIAAIVFICAFOOAASLAYSWUSLWADEE-AIN-ATRSHOLRIGVF :	1030
ABCC6	Dla :	: TTNTNLONMEPVSETDOEOVPEDLEKITEADKARTERVRLEMYOKUFKTICLAILIPIVFLYAFOOGASLAYMYWLSMWADDP-VVNGTOIDTDLKITVF :	1003
ABCC6	01a :		1022
ABCCG	Tni ·		1002
ADCCO			1002
ABCC6	Uni :	TTNTNLONMEVSETDOOVPEDIGKTFADKARTGRVREDMIKKIFKTICEATITPTVFTAFOOCASIATMIWISKMADDZ-VNGTTDTDEKTTVF	1016
ABCC6	xma :	TTNTNLONMEPVSETDODOIPEDLGKITEVDKARTERVRLTLYKKYFKTICLAIIILLVFLYAFOOGASLAYNYWLSMWADDF-VVNETOIDTDLKISVF	998
ABCC6	Gmo :	: STNTNLONMESVPESEOEOVPEDLGRLTEVDKARTGRVRLDMYMEVFKTIGVALVVPIVLMYAFOOGASLTYNYWLSLWADGP-IVNGTOOGTDLKLAVF :	949
ABCC6	Dre1 :	: GDTNSIAIEPLPDSDE-DHIPEDLGKLTKVDKARIGRVKLEMYIEYFRTIGLPLIISIVFLYAF00AASLSNNYWLSLWADOF-VINGTOLNTDLKIGVY :	995
ABCC6	Dre2 :	: LGSASIOTMEAISDPKLNODRDEVGRITOADKAHTGRVKLEMYVEIFRTICLAFIIPIIFLYAFOOVASLAYNYWLSLWADDP-VINGTOVNTDLKIGVY :	950
ABCC6	Dre3 :	: MGSASIOTMETISDTEOETDNEEVGRITOADKAHTGRVKLEMYVENFRTISLALIIPIIFLYAFOOAASLAYNYWLSLWADDP-VINGTOVNTDLKTGVY :	1015
ABCC6	Ame1 :	: GDTNSVAMOSLEAD I EOFOT PEDLOCITEVIDEAE T CRUKTENVI EVERTICIALI VETUELVA FOOAASTA VNVULSMUADE - VI NOTOTNTDUKTOVY :	996
ABCCE	1mo2 ·		1018
ABCCC	Tog i		000
ADCCO	цос .		1010
ABCCI	nsa :	:STAELORAEAKKEETWA MEADKADTGOVALSV WWMAALCIFISFISIFIJMCNH SALASMWISSUTDDP-IVNGTCEHTKVKISVY :	1019
ABCC1	Ptr :	:STAELOKAEAKKEETWKIMEADKAOTGOVKLSVYWDMMKAICLFISFLSIFLFMCNHVSALASMYWLSLWTDDP-IVNGTOCHTKVKISVY :	934
ABCC1	Mmu :	:SIAELOKAGA-KEETWKIMEADKAOTGOVOLSVYWNYMKAIGLFITFLSIFLFLCNHVSALASNYWLSLWTDDPPVVNGTOANRNFRISVY :	1016
ABCC1	Cluf :	:STAELOKAGPKNEDAWKIVEADKAOTGOVKLSVYWDIMKAICLFISFLSIFLFLCNHVASLVSNYWLSLWTDDP-IVNGTOEHTKIRISVY :	1019
ABCC1	Bta :	:staelrkpgp-teetwkiveadkaotgovklsvywdymkaiclfisflstflelcnhmaslvsnywlslwtddp-ivngtoehtovrisvy :	1002
ABCC1	Dno :	:TAELOKAGAEKEDTWKIMEADKAOTGOVKLSVYWDIMKAICLFISFLSIFLFLCNHVAALASNYWLSLWTDDR-VVNGTOEHTOVRISVY :	1016
ABCC1	Mdo :	:STADMO-KSEAOKDAWKIMEADKAKTGOVKLSVYWDIMKAI CLFTSFLSTFIICNHVASLASNYMISIMTDDD-VVNCTOHTNVRTSVY :	1018
ABCC1	Oan :	:STGRLH-KAGTDKNAWKIMRADKAKTGOVKLSVVWRVMKALCLETSFLSTELETCNHVAATASNVMLSLWTDDP-VVNGTOVTDVRTGVV :	801
ABCCI	Gra ·		1013
ADCCI	lan i		1015
ABCCI	ACa .		1015
ABCCI	Atr :	:DINSSERDDWKITEADKAKTERVSYTFYYYMDPDIWMKTTFTENEOLISGSYGLIOTNTAGPDHSEANEAE	996
ABCC1	Lch :	:AADTPKOOKSSGKITEADKAOTGKVKFSVFWEVMKAIGLFLFFLSIFLFTCHHVASLASNYWLSLWTDDP-LINGTOOHTKVRIGVY :	1014
ABCC1	Gac :	:EEDKVPGKKAKOAEGCKITEADKASTGRVKLSVFGSILKAICVLISCVSILMFLAOHLGSLSSNYWLSLWTDDP-VVNGTOPNRRMRIGVY :	1011
ABCC1	Dla :	· · · · · · · · · · · · · · · ·	-
ABCC1	Ola :	:SEONVEOKNSKNAEAGKTTDADKALTGRVKLSVFFSZLKAICVLJSIISLFFLSHNLLSLFANVWLSLWTDDF-VVNGTOPNRLWRIGVY :	1027
ABCC1	Tni :	:OATKOPGIMAKKSEAGKITEADKASTERVKLSVIWANLKAICVLISSISILMIFTHHGVELFSNVMLSLWTDDP-VVNCTOPYRVMTGVV :	954
ABCC1	Oni :	:KADEELSNKPKNPEVGKITEADKASTCOVKLSVFWAMPKSICVLISCISILIELAHHLISLFSNYWLSLWTDDP-VVNCTOPNRLMRDGVV :	1010
ABCC1	Xma1	:ARELNKKTKNSEMGKUTRADKASTGOVKLSVEWAVLKATGVLJSCISTLLELTHHLVSLESNVMLSLWTDDL-VVNGTOPVRLRSLAVV :	340
ABCC1	Xma2		_
			1000
ABCC1	Dre :		IUUb
ABCC1	Dre :		1005
ABCC1 ABCC1	Dre : Ame :	ANDDAARIKIKSABASKI LEADKARI CAVARSY WE MARLE LE'SIFISIFIAR CARLSO LESNI IDE VIAL OFAREMARY : :S-DITOAKKIKSPDAKKITEADKANTERVKLAV BEYMARI CVFISIFISIL RLAHHVSIGSNYWLSLWTDDP-VIATOFAREMARY : 	1005
ABCC1 ABCC1 ABCC1 ABCC1	Dre : Ame : Loc : Cmi :	S-NDDAAAIKIKSABASKI LEADKANI CAVARSY WEIMARI CEPSIFSIFIARCARISSI ELSANI NDEPVINT OFRAEMRIG H :S-NDTOAKKIKSPDAAKITEADKANTORVKLAVEWMARI CEPSIFSI ELEAHHVSSIGSNYMISLWTDDPVINT OFRAEMRIG Y :S-AETPSKPGAGKEAGRITEADKANTORVKLSVIWEIMI AI CIFISFFSI ELESHSASIASNYMISLWTDDH-IINCTOPYEWKI 5 - SSNGI SOBACORI DNNTERKAGKITWA KAOTORVKISVINEVINI KUTAI CUCTSCI TWANTORVKAI FENERUSI SUTDDI-IINCTOPYEWKI 5 COM	1005 1025 1141
ABCC1 ABCC1 ABCC1 ABCC1	Dre : Ame : Loc : Cmi :	:SIDDAAIKISABASKIIBADKANISAYND YMEYMAALEPSIISIFHFFFANDSEGSNYHESMIDDPVINTOFKEWRIG'I :S-NDTOAKKTKSPDAAKITEADKANTERVKLAVEWEYMAAICYFISFISILLFLAHHVSSLGSNYHESMIDDPVINTOFKEWRIG'I :S-AETPSKPGAGKEAGRITEADKAKTEKVKLSVYWEYMAAICIFISFISIFIFLSHHSASLASNYHESMIDDP-INCTOPFNKLRIG'I : RSNVGLSOFAGOOELDNNTEEKAGGKITVADKAOTERVKFSVIKYIAAICVFISIIIVAYICOHVAAIFSNFWLSLWTDDP-INCTOPFNKLRIG'I	1006 1005 1025 1141
ABCC1 ABCC1 ABCC1 ABCC1	Dre : Ame : Loc : Cmi :	:SINDAAAIKIKSABASKIIBADKANICKUKASYIMBI MARIELPISISIFAFAHADSELGSNIMISUMIDDPUUNATOFAKEMARIG'I :SINDTOAKKKSPDAAKITEADKANTEKUKLSUMEYMIAICUFISFISIILFLAHHUSELGSNIMISUMTDDPUINETOPSREMARIG'I :SINDTOAKKKSPDAAKITEADKANTEKUKLSUMEYMIAICIFISFISIFIFLSHHSASLASNYMISUMTDDPUINETOPSREMARIG'I : RSNUGLSOFAGOOELDNNTEEKAGGKITUADKAOTERUKPSUMIKIIKAICUCTSCLIUVATICOHUAALFSNFWISIMTDDPUINETOPFNKLRIG'I	1006 1005 1025 1141
ABCC1 ABCC1 ABCC1 ABCC1 ABCC1	Dre : Ame : Loc : Cmi :		1006 1005 1025 1141
ABCC1 ABCC1 ABCC1 ABCC1	Dre : Ame : Loc : Cmi :		1006 1005 1025 1141
ABCC1 ABCC1 ABCC1 ABCC1 ABCC1	Dre : Ame : Loc : Cmi :		1006 1005 1025 1141 1088
ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC6 ABCC6	Dre : Ame : Loc : Cmi : Hsa : Ptr :	*       120       *       1240       *       1260       *       1280       *       1300         *       1220       *       1240       *       1260       *       1280       *       1300         *       1220       *       1240       *       1260       *       1280       *       1300         *       1220       *       1240       *       1260       *       1280       *       1300         *       1220       *       1240       *       1260       *       1280       *       1300         *       1220       *       1240       *       1260       *       1280       *       1300         *       1220       *       1240       *       1260       *       1280       *       1300         *       1220       *       1240       *       1260       *       1280       *       1300         *       1220       *       1240       *       1260       *       1280       *       1300         *       1240       *       1260       *       1280       *       1300       *       * <t< td=""><td>1006 1005 1025 1141 1088 930</td></t<>	1006 1005 1025 1141 1088 930
ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC6 ABCC6 ABCC6	Dre : Ame : Loc : Cmi : Hsa : Ptr : Mmu :	*	1008 1005 1025 1141 1088 930 1083
ABCC1 ABCC1 ABCC1 ABCC1 ABCC6 ABCC6 ABCC6 ABCC6	Dre : Ame : Loc : Cmi : Hsa : Ptr : Cluf :		1008 1005 1025 1141 1088 930 1083 1089
ABCC1 ABCC1 ABCC1 ABCC1 ABCC6 ABCC6 ABCC6 ABCC6 ABCC6 ABCC6	Dre : Ame : Loc : Cmi : Hsa : Ptr : Cluf : Bta :		1008 1005 1025 1141 1088 930 1083 1089 1089
ABCC1 ABCC1 ABCC1 ABCC1 ABCC6 ABCC6 ABCC6 ABCC6 ABCC6 ABCC6 ABCC6	Dre : Ame : Loc : Cmi : Hsa : Ptr : Cluf : Bta : Dno :	*	1008 1005 1025 1141 1088 930 1083 1089 1089 1017
ABCC1 ABCC1 ABCC1 ABCC1 ABCC1 ABCC6 ABCC6 ABCC6 ABCC6 ABCC6 ABCC6 ABCC6	Dre : Ame : Loc : Cmi : Ptr : Mmu : Cluf : Bta : Dno : Mdo :		1008 1005 1025 1141 1088 930 1083 1089 1089 1017 1086
ABCC1 ABCC1 ABCC1 ABCC1 ABCC6 ABCC6 ABCC6 ABCC6 ABCC6 ABCC6 ABCC6 ABCC6	Dre : Ame : Loc : Cmi : Hsa : Ptr : Bta : Dno : Mdo : Oan :		1008 1005 1025 1141 1088 930 1083 1089 1089 1017 1086 1030
ABCC1 ABCC1 ABCC1 ABCC1 ABCC6 ABCC6 ABCC6 ABCC6 ABCC6 ABCC6 ABCC6 ABCC6 ABCC6 ABCC6	Dre : Ame : Loc : Cmi : Ptr : Bta : Dno : Mdo : Oan : Gqa :		1008 1005 1025 1141 1088 930 1083 1089 1089 1017 1086 1030 1094
ABCC1 ABCC1 ABCC1 ABCC1 ABCC6 ABCC6 ABCC6 ABCC6 ABCC6 ABCC6 ABCC6 ABCC6 ABCC6 ABCC6	Dre : Ame : Loc : Cmi : Ptr : Bta : Dno : Mdo : Gaa :		1008 1005 1025 1141 1088 930 1083 1089 1089 1017 1086 1030 1094 1039
ABCC1 ABCC1 ABCC1 ABCC1 ABCC6 ABCC6 ABCC6 ABCC6 ABCC6 ABCC6 ABCC6 ABCC6 ABCC6 ABCC6 ABCC6 ABCC6 ABCC6	Dre : Ame : Loc : Cmi : Ptr : Dtr : Bta : Dno : Mdo : Gaa : Aca :		1008 1005 1025 1141 1088 930 1083 1089 1017 1086 1030 1094 1039
ABCC1 ABCC1 ABCC1 ABCC1 ABCC6 ABCC6 ABCC6 ABCC6 ABCC6 ABCC6 ABCC6 ABCC6 ABCC6 ABCC6 ABCC6 ABCC6 ABCC6	Dre : Ame : Loc : Cmi : Ptr : Mmu : Cluf : Bta : Dno : Oan : Goa : Aca : Xtr :		1008 1005 1025 1141 1088 930 1083 1089 1089 1017 1086 1030 1094 1039 1062
ABCC1 ABCC1 ABCC1 ABCC1 ABCC6 ABCC6 ABCC6 ABCC6 ABCC6 ABCC6 ABCC6 ABCC6 ABCC6 ABCC6 ABCC6 ABCC6	Dre : Ame : Loc : Cmi : Ptr : Dno : Dno : Mdu : Oan : Gaa : Xtr : Lch :		1008 1005 1025 1141 1088 930 1083 1089 1089 1089 1017 1086 1030 1094 1039 1062 1103
ABCC1 ABCC1 ABCC1 ABCC1 ABCC6 ABCC6 ABCC6 ABCC6 ABCC6 ABCC6 ABCC6 ABCC6 ABCC6 ABCC6 ABCC6 ABCC6 ABCC6 ABCC6	Dre : Ame : Loc : Cmi : Ptr : Mmu : Cluf : Dno : Dno : Mdo : Oan : Gaa : Aca : Lch : Gacl :		1008 1005 1025 1141 1088 930 1083 1089 1089 1089 1089 1089 1089 1030 1094 1039 1062 1103
ABCC1 ABCC1 ABCC1 ABCC1 ABCC6 ABCC6 ABCC6 ABCC6 ABCC6 ABCC6 ABCC6 ABCC6 ABCC6 ABCC6 ABCC6 ABCC6 ABCC6 ABCC6	Dre : Ame : Cmi : Cmi : Ptr : Mmu : Cluf : Bta : Dno : Mdo : Gaa : Aca : Xtr : Gac1 : Gac2 :	<ul> <li></li></ul>	1005 1025 1141 1088 930 1083 1089 1087 1086 1030 1094 1039 1062 1103 1106 1127
ABCC1 ABCC1 ABCC1 ABCC6 ABCC6 ABCC6 ABCC6 ABCC6 ABCC6 ABCC6 ABCC6 ABCC6 ABCC6 ABCC6 ABCC6 ABCC6 ABCC6 ABCC6 ABCC6	Dre : Ame : Cmi : Cmi : Cmi : Cmi : Cmi : Chuf : Dha : Aca : Xtr : Lch : Gac1 : Gac2 : Dla :	<ul> <li></li></ul>	1005 1025 1141 1088 930 1083 1089 1017 1086 1030 1094 1039 1062 1103 1106 1127 1100
ABCC1 ABCC1 ABCC1 ABCC1 ABCC6 ABCC6 ABCC6 ABCC6 ABCC6 ABCC6 ABCC6 ABCC6 ABCC6 ABCC6 ABCC6 ABCC6 ABCC6 ABCC6 ABCC6 ABCC6	Dre : Ame : Loc : Cmi : Ptr : Dra : Dra : Dra : Ada : Ada : Xtr : Lch : Gac1 : Gac2 : Dla : Ola :	<ul> <li></li></ul>	1005 1025 1141 1088 930 1083 1089 1089 1089 1089 1089 1030 1094 1039 1062 1103 1106 1127
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ABCC1 Cmi : SALGLG G---FFVLCSSVLVCAGGITASKWTHADLINDVLOSPUNFFERTPSGNLVNRFARDIDTIDSMIETVIKMFLGSLENVLIACIVILLATETVA : 1238

	* 1320	* 1340	* 1360	* 1380 *	1400
ABCC6 Hsa	: VAILPLFLLYAGFOSLYVVSSCOLR	LESASY <mark>S</mark> SVCSHMAETFO <mark>G</mark>	STVV <mark>RA</mark> F <mark>R</mark> T <mark>O</mark> APFVAONNARVI	ESORISFPRLVADRWLAANVE	LLGN : 1180
ABCC6 Ptr	: VAILPLFLLYAGFOSLYVVSSCOLRR	LESASYSSVCSHMAETFOG	STVVRAFRTOAPFVAONNARVI	ESORISFPRLVADRWLAANVE	LLGN : 1022
ABCC6 Mmu	· MATLPINVLYAGFOSLYVATSCOLR	LESARYSSVCSHMAETFOG	SLVVRAFRACASFTACHDALMI	ENORVSFPKLVADRWLATNLE	LLGN : 1175
ABCC6 Bta	: VAILPILLLYAGFOSLYVASSCOLR	LESARYSYVCSHVAETFOG	GPVVRAFRVOGPFTAONDAHVI	ESORVSFPRLVADRWLAANLE	LVGN : 1181
ABCC6 Dno	: AVILPILLLY <mark>AGF</mark> OSLYVASSCOLRR	le <b>sa</b> shspv <mark>c</mark> sh <mark>va</mark> etfog	SPVVRAF <mark>RA</mark> OGPFVAOSNAHVI	KSORVSFSRLVADSWVTSAVG	LRGK : 1109
ABCC6 Mdo	: VMVLPIMALYVGLOSLYVASSCOLRR	LESASRSPIYSHISETFOG	NAVIRAFOAODOFIAONDSRII	EHORASFPRLVADRWLATNME	LLGN : 1178
ABCC6 Oan	: LVILPILLFYGVFOSFYVASSCOLRR	LESASOSPIYSHISMIFOG	SGVIRAFRAOSRFVSRSDGHVI	ENORVSFPRLVADRWLATNLE	LLGN : 1122
ABCC6 Aca	: VAIVPITVLYAVSONFFIATSCOLKR	LEAASRSPIYSNISETFEG	SNSIRAYKACORFVLONDFNVI	ENERICIPGAVADRWIAINIE	FLGN : 1131
ABCC6 Xtr	: VAFIPIGLLY <mark>FFLO</mark> RFYVASS <mark>R</mark> OLKR	l <b>dav</b> sksplyth <b>fneslo</b> g	VYVIRAFRECERFIODNNMRLN	MNORFYFCSFVAN-RWISVRCD	FLSN : 1154
ABCC6 Lch	: VIIVPLTVMYCVIOSFYVATSCOLRR	LESVSRSPIFSH <mark>VN</mark> ETYOG	ASVIRAFGEOMRFLSONDSKVI	ENOKAYYPSVVANRWLAVNILE	FIAN : 1195
ABCC6 Gac1	: VVILPLALLYAFVOSFYVATSCOLRR	LEAVSRSPIYTHFNETVOG	ASVIRAFGEOSRFILOTNKRVI	FNOTSYFPRFVATRWLAVNLE	FVGN : 1198
ABCC6 Dla	: VIILPIAFLYAFVOSFYVATSCOLR	LEAVSRSPIYTHFNETVOG	ASVIRAFGEOPRFILOANORVI	FNOTSYFEREVATRWIAVNIE	FVGN : 1192
ABCC6 Ola	: VIILPIAFLYAFVOSFYVATSCOLRR	le <mark>avsr</mark> spiythfnetvog	ASVIRAF <mark>GE</mark> OSRFI <mark>MOA</mark> NERVI	FNOTSYFPRFVATRWLAVNLE	FVGN : 1211
ABCC6 Tni	: VIILPIAFLYACVOSFYVATSCOLRR	le <mark>av</mark> srspiythfnetvog	ASVIRAFGEOPRFILOANKRVI	FNOTSYFPRFVATSCIHRWLAVNLE	FIGN : 1195
ABCC6 Oni	: VIILPISFLYAFVOSFYVATSCOLRR	LEAVSRSPIYTHFNETVOG	ASVIRAFGEOSRFILOANDRVI	FNOTSYFPRFVATRWLAVNLE	FVGN : 1205
ABCC6 Ama	: VIILPIAFLYAFVOSFYVATSCOLRR	LEAVSRSPIYTHFNETVOG	ASVIRAFGEOPRFILOANERVI	INOTAVEEFVATEWIAVNEE	FVGN : 1187
ABCC6 Dre1	: VIILPMVFLYGFIOSFYVATSCOLRR	LESVSRSPIYTH <mark>LNETVO</mark> G	ASVIRAFNEOSRFIMGANHKVI	HNOTAYFPRFIATRWIGVNLE	FLGN : 1184
ABCC6 Dre2	: VIILPE <mark>TLLYAFIOSFYVATSC</mark> OLRR	le <b>sv</b> srspiyth <mark>fn</mark> etvog	ASVIRAFGEOPRFILOANCRVI	LNOTSYFPRFVASRWLAVNLE	FLGN : 1139
ABCC6 Dre3	: VIILPLALLYAFIOSFYVATSCOLRR	LESVSRSPIYTHFNETVOG	ASVIRAFGEOPRFILOANCRVI	LNOTSYFPRFVATRWLAVNLE	FLGN : 1204
ABCC6 Amel	: AIIFPLALLYAFVOSFYVATSCOLRR	LESVSRSPIYTHFNETVOG	ASVIRAFSEOSRFILOANRRVI ASVIRAFSEOPRILOANCRVI	VNOTSYFPRFVATRWLAVNLE	FLGN : 1185
ABCC6 Loc	: VVILPIALFYCFIOSFYVATSCOLRR	LESVSRSPITTHFNETVOG	VSVIRAFREOPRFILOANHRVI	YNOT SYFPRFVATRWLAVNLE	FLGN : 1185
ABCC1 Hsa	: IIIPPI <mark>GL</mark> IY <b>FFVORF</b> YVASS <mark>R</mark> OLKR	LESVSRSPVYSHFNETLLG	VSVIRAFEEOERFIHOSDLKVI	ENOKAYYPSIVAN-RWLAVRLE	CVGN : 1208
ABCC1 Ptr	: IIIPPIGLIYFFVORFYVASSROLKR	le <mark>sv</mark> srspvyshfnet <mark>ll</mark> g	VSVIRAFEEOERFIHOSDLKVI	ENOKAYYPSIVAN-RWLAVRI.E	CVGN : 1123
ABCC1 Mmu	: VIIPPIGLVYFFVORFYVASSROLKR	LESVSRSPVYSHFNETLLG	VSVIRAFEEOERFIHOSDLKVI VSVIDAFEEOERFIHOSDLKVI	ENOKAYYPSIVAN-RWLAVRLE	CVGN : 1205
ABCC1 Bta	: VIIPPIGLIYFFVORFYVASSROLAR	LESVSRSPVISHFNETLLG	VSVIRAFEEOERFIROSDLKVI	ENORATIPSIVAN-RWIAVRID	CVGN : 1208
ABCC1 Dno	: VIIPPI <mark>GLIYFLVORF</mark> YVASS <mark>R</mark> OLKR	LESVSRSPVYSHFNETLLG	VSVIRAFEEOERFIROSDLKVI	ENOKAYYPSIVAN-RWLAVRLE	CVGN : 1205
ABCC1 Mdo	: IIIPPLGLIYFFVORFYVASSROLKR	LESVSRSPVYSHFNETLLG	VSVIRAFEEO <mark>ORFIR</mark> OSD <b>LK</b> VI	ENOKAYYPSIVAN-RWLAVRLE	CVGN : 1210
ABCC1 Oan	: VVIPPLGLIYFFVORFYVTSSROLKR	LESVSRSPVYSHFNETLLG	VSVIRAFEEOKRFI <mark>O</mark> OSDMKVI	ENOKAYYPSIVAN-RWLAVRLE	CVGN : 990
ABCC1 Gda	: VATPPIALVYFFVORFYVATSROLKR	LESVSRSPVYSHFNETLLG	VSVIRAFEEORFIKONDMKVI	ONOKAYYPSIVAN-RWLAVRLE	FVGN : 1202
ABCC1 Xtr	: VIIPPLGLVYFFVORFYVATSROLKR	LESVSRSPVYSHFNETLLG	SSVIRAFGEOKRFIOISDFKVI	ENORAYYPSIVSNSRWLAIRLE	FVGN : 1189
ABCC1 Lch	: VIIPPIGLLYFFVOVYCAHTCMLOSP	FN			: 1139
ABCC1 Gac	: IIIPFLGVLYFFVORFYVASSROLKR	LESVSRSPIYTHFNETLLG	TSVIRAFGEOERFICESDORVI	LNOKAYYPGIVANRWLAVR-LE	FVGN : 1200
ABCC1 DIa ABCC1 Ola	ITTPFICVIVFFVORFVVASSBOLKE	TESVSRSPTVTHESPTT.C	TSVIRAFGEOERETHESDORVI		: -
ABCC1 Tni	: AITPFLGLLYFFVOVNALYLN			ILHL YR-SC	<b>V</b> VGN : 1085
ABCC1 Oni	: IIIPFIGLLY <mark>FFVORF</mark> YVASS <mark>R</mark> OLKR	LESVSRSPIYTHFNETLLG	TSVIRAFGEOERFIHESDORVI	HNOKAYYPSIVANRWLAIR-LE	FVGN : 1199
ABCC1 Xma1	:				: -
ABCC1 Xma2 ABCC1 Dre	TITPPICILVERVOREVVASSBOMKE	TESVSRSPVVTHENETT.C	TSVIRAFGEOORETKESDGRUI	HNCKAVEPSTVANEWLAVE_	: -
ABCC1 Ame	: IIIPPIGLLYFFVORFYVASSROLKR	LESVSRSPVYTHFNETLLG	TSVIRAFGEOORFIGESDRRVI	HNOKAYFPSIVANRWLAVR-LE	FVGN : 1194
ABCC1 Loc	: VIIPPL <mark>GLLY</mark> FFVORFYVATSROLKR	le <b>sv</b> srspvyshfnetllg	TSVIRAF <mark>OD</mark> OERFIKESDSRVI	YNOKAYYPSIVANRWLAVR-LE	Y <mark>VGN</mark> : 1214
ABCC1 Cmi	: VTFLPIGFVYFFVOKFYVATSROLKR	LESVSRSPIYSHFNETLLG	VSVIRAFGEODRFLOENDLRVI	ENOKAYYPSIVAN-RWLAVRLE	FVGN : 1330
	* 1420	* 1440	* 1460	* 1480 *	1500
ABCC6 Hsa	: GLVFAAATCAVLSKAHLSAGLV <mark>G</mark> FSV	SAALOVTOTLOWVVRNWTD	LENSIVSVE <mark>R</mark> MODYAMTPKEAE	WRLPTCAAOPPWPOG <mark>C</mark> OIEF <mark>R</mark> DFGL <mark>R</mark> Y <mark>R</mark> P	E PL : 1280
ABCC6 Ptr	CINFRAATCAVISKAHLSAGLVGFSV	SAALOVTOTLOWVVRNWTD	LENSIVSVERMODYAWTPKEAS		E PL : 1122
ABCC6 Cluf	: MLVLAAAMCAVISKAHLSAGLVGFSV	SAALOVIOILOWAVRSWID	LASSVVSVERMKDYVOTPKEAE	WRLPACAARSPWPHGGOVE FRD FGLRHHP	E PL : 1281
ABCC6 Bta	: GLVFVAAI <mark>CA</mark> VLS <mark>KAH</mark> LSPGLVG <mark>F</mark> SV	SAALOVTOMLOWAVRSWTD	LESSIVSVERLKDYAOTPKEAE	WKPLTCAAHPPWPRRGOIEFRDLGLRYRP	E PL : 1281
ABCC6 Dno	GGTGSOOACVIJGVLGOAAHPIWSSF	PTSIEVTOTLOWAVRSWID	LE <mark>SSIVAVERVOE</mark> YARTPKEAE	WRLPSCAARPPWPROGOIEFRCFGLRYRP	E PL : 1209
ABCC6 Mdo	CUVISAAFFAVISKPYLRPGIVGFSV	SVALOVIEILHWAVRSWID	LENNIVSVERMRDYTRTPKEAE I ENNIVSVEDVMEVSDUDKEAE		E AL : 1278
ABCC6 Gda	: GIVLFAALFATIGRTHLSPGTAGFSI	SYALOITGVLNWMVRSWTE	IENNIVSVERVSEYSRIPKEAE	WTLNDKLOGOV LTECR EFRNYS RYRP	NEL: 1286
ABCC6 Aca	: GIVLFAAI <mark>la</mark> vkskpylspglvgfsi	SYALOITGILNWMVRALAE	IDNNIVSVERVRDYSGTPKEAE	WTSDNKFFHENWPTEGOIAFRGYSLRYRP	G EL : 1231
ABCC6 Xtr	: FIVFTVAIVGVLFRDNITPGLVGLAV	VNSI RI I GVI KEAVHVATD	METNSVSVERVKEYCDAEPEAE	WTSDNASDPSNWPSKGKIEFONYGLRYRP	DDL : 1254
ABCC6 Lch	VIVLFAAILAVNGKGRLSPGVVGLSV	SHALOVT <mark>GILS</mark> WIVR <mark>SWID</mark>	IENNIVSVERVKEYSETPKEDE	WILNTNFLPEPWPSEGRVEFRNYGLRYRO	D DL : 1295
ABCC6 Gaci	TIVIAAATISVMGRGTLSPGIVGLAV	THSLOVIGILSWIVRSWID	VENNIVSVERVNEYADTPKEAS VENNIVSVERVKEVDSTDKEGO	WYPGGNKIPADWPATCNIOFEGYGIBYRK	GEL: 1298
ABCC6 Dla	: GVVLAAAILSVMGKNTLSPGIVGLAV	SHSLOVT <mark>GILS</mark> WIVRSWID	VENNIVSVERVNEYADTA <u>KEA</u> S	WSVEGSSLPLAWPORGTLEFODYGLOYRK	G EL : 1292
ABCC6 Ola	: GVVLAAAVLSVIGKSTVSPGIVGLAV	SHSLOVTGILSWIVRSWTD	vennivsvervneyadtpkeas	WNTEGSALPLAWPOSGTIEFODYGLOYRK	G EL : 1311
ABCC6 Tni	GVVLAAAILSVMGRNTLSPGIVGLAV	SHSLOVTAILSWIVRSWTD	VENNIVSVERVNEYADTAKEAS	WTVEGSSLPMDWPLKGTLEFOEYGLOYRK	G EL : 1295
ABCC6 Vma	GVVLAAAILSVMGKSTLSPGIVGLAV VVVLAAATLSVMGDSTLSDGIVGLAV	SHSLOVIGILSWIVRSWID	VENNIVSVERVNEYADTPKEAS VENNIVSVERVNEVADTPKEAS	WSIESSLFOAWFONGTIEFODYGIOYRK	G EL : 1305
ABCC6 Gmo	: GVVLAAAILSVMGKUTLSPGIVGLAV	SHSLOVTGILSWIVRSWID	VENNIVSVERVKEYADTAKEAE	WTVEGSSLPPDWPORGTIEFODYGTOYRK	GDL: 1237
ABCC6 Dre1	: GIVLAASILSVMAKGTLSPGMVGLAV	SHSLOVT <mark>GFLSWIVRSW</mark> TD	VE <mark>N</mark> NIV <mark>SVERVKEYADTP</mark> KEAA	WSIEGSSLPPSWPOTGTIEFODYGLOYRK	G EL : 1284
ABCC6 Dre2	: LLVLAAAILSVMGRATLSPGTVGLAV	SHSLOVTGILSWIVRSWTD	VENNIVSVERVKEYAETAKEAE	WIFEDSPLPSDWPRSGSIGFOAYGIOYRK	G DW : 1239
ABCC6 Dre3	CUVIAAAILSVMGRATLSPGIVGLAV	SHSLOVTGILSWIVRSWID	VENNIVSVERVKEYAETAKEAE	WI'LEDSPLPSDWPRCGSIGFOAYGIOYRK	G DW : 1304
ABCC6 Ame1 ABCC6 Ame2	: LIVLAAAILSVUGKEILSPGIVGLAV	SHSLOVIALSWIVRSWID	VENNIVSVERVKEYAETPKEAE	WTIENRSLPSAWPOTGSIEFOOYGIOYR	G DW : 1307
ABCC6 Loc	: ALVLAAAILSVIGKGTLSPGIVGLAV	SHSLOVTGILSWIVRSWTD	VE <mark>N</mark> NIV <mark>SVERVKEYVETA</mark> KEAA	WTVESSPVPPAWPOTGTIELRGYGLOYRK	G DW : 1285
ABCC1 Hsa	: CIVLFAALFAVISRHSLSAGLVGLSV	SYSLOVTTYLNWLVRMSSE	ME <mark>T</mark> NIV <mark>A</mark> VERLKEYSETEKEAE	WOIOETAPPSSWPOVGRVEFRNYCLRYRE	D DF : 1308
ABCC1 Ptr	: CIVLFAAIFAVISRHSLSAGLVGLSV	SYSLOVTTYLNWLVRMSSE	ME <mark>TNIVA</mark> VERIKEYSETEKEAE	WOIOETAPPSSWPOVGRVEFRNYCLRYRE	D DF : 1223

ABCC1	Tni	: IIV <mark>SFAALCA</mark> VI <mark>ARON</mark> LSPGIMGLSIS <mark>YA</mark> L	OLT <mark>AS</mark> LTWLVRMSSDLET	IIV <mark>A</mark> VEKV <b>KE</b> Y <mark>SE</mark> TOKEA <mark>E</mark>	WTHKPTSLPSNWPNKGCI	DIRGFSLRYRDDLDL : 1185
ABCC1	Oni	CIVSFAALFAVVAROSLSPGIMGLSISYAL	OLTTSLTWLVRMSSDVET	IIVAVEKVKEYSDTEKEA	WEHEPSTLSPGWETNGCI	EMRSEGURYROD DL : 1299
ABCC1	Xma1	:				
ABCCI	Vmol	•				
ABCCI	Alliaz					
ABCC1	Dre	CIVTFAALFAVMARNNLSPGIMGLSISYAL	OVTASLNWLVRMSSELET	II VAVERVKEYGDTEKEAE	SWKLENSNLPPGWPTAGHI	EIHKFGLRYREDLEL : 1295
ABCC1	Ame	: CIVTFAALFAVMARANLSPGIMGLSISYAL	OVTASLNWLVRMSSELET	IIV <mark>A</mark> VERV <b>KEYED</b> T <mark>E</mark> KEA <mark>E</mark>	WKLEOSSVPAGWPTAGHT	EVRNFGLRYREDLEL : 1294
ABCC1	Loc	CIVLFASLFAVMARDRLSPGSMGLSISYAI	OITASLNWLVRMSSEMET	IIVAVERVKEYGDTEKEAE	WOLEKSAPPRGWETACRI	EIRDFGLRYREDIEL : 1314
ABCC1	Cmi	CIVLFAALFAVAYRLKLSAGLVGLSISYAT	OVTATINWLVRMSSEVET	IIVAVERVKEYSEMEKEAE	MFSNNNSPTSNNIOR T	OFIGUSARVRAD DL : 1430
	0					
		* 1520 *	1540	* 1560	* 1580	* 1600
ABCC6	Hsa	: AVOGVSFKIH- <mark>A</mark> GEKVGI <mark>VG</mark> R <mark>TGA</mark> GKS <mark>S</mark> LA	.S <mark>GILR</mark> LOEAAE <mark>G</mark> GIWIDGV	PIAHVG <mark>L</mark> HTLRSR <mark>I</mark> SIIF	ODPILF <mark>PG</mark> SL <mark>R</mark> MNLDLLO	EHSDEAIWAALETVO : 1379
ABCC6	Ptr	: AVOGVSFKIH-AGEKVGIVGRTGAGKSSIA	SGLLRIOEAAEGGIWIDG	PIAHVGLHTLRSRISII	PODFILF <mark>P</mark> GSLRMNLDLLO	EHSDEATWAALETVO : 1221
ABCC6	Mm11	AVOGUSTRTH-AGERVGTVGRTGAGKSSTA	WGLLRTOEAAEGNTWIDG	PTTHVGLHTLRSRITII	PODPVI.FPGSIRMNI.DLLO	EHUDEGIWAALETVO : 1374
ABCCC	Cluf	AVDOUGEVILL A CENUCINCIDECA CUCCI	COLUMNER			ENTREMINENT INVO : 1390
ADCCO	CIUI D+-	NURSUSTRIN-AGERVGIVGRIGAGRSSIA	GGIERIEERREGGIWIDG			ENTLERIMERTERVO . 1380
ABCC6	вта	: AVRGVSFKIN-AGEKVGIVGRTGAGKSSIA	GellRIVEAAEGGIWIDG	PIAOVGLHTLRSRVTIII	PODPILFPGSLRMNLDMLO	EHIDEALWEVLETVO : 1380
ABCC6	Dno	: AVRGVSFKIO-AGEKVGIVGRTGAGKSSLA	RGLLRLLEAAEGGIWIDG	PIAHVGLHTLRSRITII	PODPILF <mark>P</mark> GSLRMNLD <mark>LLH</mark>	EHADKAIWAALETVO : 1308
ABCC6	Mdo	: ALONITIKIL-POEKVGIVGRTWAGKSSIS	IGLLRLIEATECGSDRWG-	-EYOSKWAPCPEVOITIIE	ODPILF <mark>P</mark> GSVRMNLD <mark>LLD</mark>	EHSDDEIWGALEMVO : 1376
ABCC6	Oan	: AIRDVTVTIL-POEKVGVVGRTGAGKSSIA	VGLLRIFEAAEGHIRIDG	NVARIGLHHLRSKITILE	PODPILF <mark>P</mark> GSLRMNLD <mark>LLH</mark>	EHPDGDIWTALEMVO : 1321
ABCC6	Gσa	AIKHINLTIN-GKEKIGITGRTGAGKSTIA	AGLERIVEAAEGVILIDG	DIAOLGLHDLRMKITVIF	PODPVLF <mark>S</mark> GTLRMNLD <mark>PLN</mark>	OYTDADIWTALELTO : 1385
ABCCE	Aca	• ALKNUNTOTK-GKEKUGTAGETGAGKSSLA	MGLURIVENARGETLIDG	DVAOTGI.HDI.RSKITVII		RHUDEDINAALSTML • 1330
ADCCO	NCu Vt-					
ADCCO	AUI	. ALKIVIASIO-OGERVGIVGRIGRGRSSLI	LGLFRILEPRIGRICIDE	DISELGLAELKSKIIIII	ODFVLFSGILRMNLDFFD	NISDNDIWVALOLAH : 1353
ABCC6	Lcn	: AVKNINVKID-KEEKVGIVGRTGAGKSSIT	MGLFRIMEASTGEVFIDG	NTATLGLHDLRSRLSII	PODPVLF <mark>C</mark> GSLRMNLD <b>PFD</b>	NYSDKDVWRALELAH : 1394
ABCC6	Gac1	: Alkgitlovh-erervgivgrtgagkssla	LGIFRILEAAK <mark>GK</mark> ILIDG	DIADVGLHDLRSRITIIF	PODPVLF <b>S</b> GSLRMNLD <b>PFD</b>	TYTDEEVWRSLELAH : 1397
ABCC6	Gac2	: ALNNICVNIO-DREKVGIVGRTGAGKSSLA	LGIFRILEAAKGRIFIDG	NIA <mark>E</mark> IGLH <mark>D</mark> LRSRITIIF	ODPVLF <mark>S</mark> GSLRMNLD <b>PFD</b>	VCSDEDLWKALELAH : 1418
ABCC6	Dla	: AIKGITLNIH-ERERVGIVGRTGAGKSSIA	LGIFRILEAAKGKIFIDG	NIA <mark>D</mark> IGLH <mark>D</mark> LRSRITIIE	PODPVLF <mark>S</mark> GSLRMNLD <b>PFD</b>	TYTDEEVWRSLELAH : 1391
ABCC6	01a	ATKGTTLOTO-KREKTGTVGRTGAGKSSTA	LGTERTLEAAKGRIETDG	NTARTGIHDIRSBITTI	PODPVI.FSGSI.RMNI.DPFD	TYTDEE WSSIELAH : 1410
ABCCC	mni.	ATTOTAL PREVOTION CONCLOSED	I CIEDILEN KOKIETOCI			
ABCCO	1111	AIRGIILMIH-ERERVGIVGRIGRGRSSIA	LGIFKILERAKGKIFIDG	NIRDIGLADLRSRITII	COF V LF SGS LKMN LDFFD	TTTDED WRSTELAH . 1394
ABCC6	Oni	: ALKGITLHIH-EREKVGIVGRTGAGKSSLA	LGIFRILEAAKGKIFIDG	DIADIGLHDLRSRITII	PODPVLFSGSLRMNLDPFD	TYTDEEVWSSLELAH : 1404
ABCC6	Xma	: AIKDITLHIN-PKEKVGIVGRTGAGKSSIA	LGIFRILEAAK <mark>GK</mark> IFIDG	NIA <mark>D</mark> IGLH <mark>D</mark> LRSRITIIF	PODPVLF <b>S</b> GSLRMNLD <b>PFD</b>	TYTDEEIWSSLELAH : 1386
ABCC6	Gmo	: AIKGITLSIO-EREKVGIVGRTGAGKSSLA	LGIFRILEAAKGKIFVDG	DLA <mark>D</mark> IGLH <mark>D</mark> LRSRITIIF	ODPVLF <mark>S</mark> GSLRMNLD <b>PFD</b>	NYTDOEVWSSLELAH : 1336
ABCC6	Dre1	: AIKGISVHIH-EREKIGIVGRTGAGKSSIA	LGIFRILEAAKGEIYIDG	NIA <mark>E</mark> IGLH <mark>D</mark> LRSRITIIE	PODPVLF <mark>S</mark> GSLRMNLD <b>PFN</b>	AYSDEEVWNALELAH : 1383
ABCCE	Dre2	• ATKETSTSUN-EREKVGTUGETGAGKSSTA	LGTERTLEAAKGKTETDG	NTARTGIHEIRSRITTIF	PODPVI.FSGSI.RINI.DPFD	RVTDEEVERST.ET.AH · 1338
ABCCE	Drog	ATVETCICUN PREVUCTUCE CACKESTA	ICTEDITENAKCKIETDC	NTARTCIURIDEDTTI		DVTDEFWDGIETAU · 1403
ADCCO	Dies	AIKEISISVN-EREKVGIVGRIGRGRGRSSIA	IGIPRILERARGRIFIDG.			NITUEEVWRSTELAII . 1405
ABCC6	Amei	: ALKGISLHIO-RREKIGIVGRTGAGKSSLA	LGIFRILEAAKGKIYIDG	DIAOLGLHDLRSRITIIF	ODPVLFSGSLRMNLDPFD	AYSDEEVWGALELSH : 1384
ABCC6	Ame2	: Alkeitlnvo-erekvgivgrtgagkssla	LGIFRILEAAKGEIYIDG	'NIA <mark>O</mark> IGL <mark>OD</mark> LRSRITIII	PODPILF <mark>S</mark> GSLRMNLD <b>PFD</b>	GYSDEDVWRALELAH : 1406
ABCC6	Loc	: AIKGITVOIR-EOEKVGIVGRTGAGKSSIA	LGIFRILEAAKGEIYIDG <sup>v</sup>	NIA <mark>E</mark> IGLH <mark>D</mark> LRSRITIIF	PODPVLF <mark>S</mark> GSLRMNLD <b>PFD</b>	SYSDEEVWNALELAH : 1384
ABCC1	Hsa	VIRHINVTIN-GGEKVGIVGRTGAGKSSIT	LGLFRINESAEGEIIIDG	NIA <mark>K</mark> IGLH <mark>D</mark> LR <b>F</b> KITIIF	PODPVLF <mark>S</mark> GSLRMNLD <b>PFS</b>	OYSDEEVWTSLELAH : 1407
ABCC1	Ptr	VIRHINVTIN-GGEKVGIVGRTGAGKSSLT	LGLFRINESAEGETIIDG	NIAKIGLHDLRFKITIIF	PODPVLFSGSLRMNLDPFS	OYSDEEVWTSLELAH : 1322
ABCC1	Mm11	VINHINUTIF-CCFKVCIVCDTCACKSSIT	TCIERINESAECEITIDC	NTAKTCIHNIPEKTTII	ODDVI FSCSI DMNI DDFS	OVSDEEWWMALELAH · 1404
ADCCI	aluf.		LOIPDING PORTIDO			OVODERU MARIELAN . 1404
ABCUI	CIUL	VIKHINITIN-GGERVGIVGRIGAGRSSII	LGLERINESAEGEIIIDD.		PODPVLFSGSLRMMLDPFS	OYSDEEVWISLELAH : 1407
ABCC1	Bta	: VIKHINVTID-GGEKVGIVGRTGAGKSSLT	LGLFRIKESAEGEIIIDD	NIA <mark>K</mark> IGLH <b>D</b> LR <b>F</b> KITIII	PODPVLF <mark>S</mark> GSLRMNLD <b>PFS</b>	OYSDEEVWTSLELAH : 1390
ABCC1	Dno	: FVEHRLYTLGPGDTAVGIVGRTGAGKSSLT	LGLFRI <mark>NESAE</mark> GEIVIDG	'NIA <mark>H</mark> IGLH <mark>D</mark> LR <mark>F</mark> RITIIF	PODPVLF <mark>S</mark> GSLRMNLD <b>PF</b> S	OYSDDDVWTSLELAH : 1405
ABCC1	Mdo	: VIKHVNVTIE-GGEKVGIVGRTGAGKSSLT	LGLFRINESAGGEIIIDG	NIA <mark>K</mark> IGLH <mark>H</mark> LR <mark>F</mark> KITIIF	PODPVLF <mark>S</mark> GSLRMNLD <mark>PFD</mark>	OYSDEDIWTSLELAH : 1409
ABCC1	Oan	VIKNINVTID-GGEKVGIVGRTGAGKSSLT	LGLFRINESAEGEIIIDGV	NIA <mark>K</mark> IGLH <mark>H</mark> LR <b>F</b> KITIIF	PODPVLF <mark>S</mark> GSLRMNLD <b>PFD</b>	OYSDED WRSTELAH : 1189
ABCC1	Gra	VINTNITTN-CORVCTVCRTCACKSSIT	T.GI.FRINEAAEGETTIDG	NTARTGLHDLREKTTTT	ONPTT.FSGSLRMNL.DPFD	OHSDEDTWRST.ET.AH · 1401
ABCCI	lan .	VIDNIETE CORVEYOR COMOLOGIC			CODDUL POCCIDANI DEFE	OVED FEWERE FLAM : 1404
ABCCI	ACa .	VIENIIIIISGGERRVGIVGRIGRGRSSLI	LGLFRINEAREGOILIDG	DIASIGLADLAFRVIIII	ODFVLFSGSLRMNLDFFE	OTSDEEVWRSLELAH : 1404
ABCCI	Xtr	: ALKNINVTIO-GGEKVGIVGRTGAGKSSLT	LELFRINEAAAGEIVIDG	NLAKIGLHDLRFRVTIIF	PODPVLFSGTLRMNLD <b>PFD</b>	KYTDDDIWTSLELAH : 1388
ABCC1	Lch	:				: -
ABCC1	Gac	: AIRNITLVINRGELKVGIVGRTGAGKSSLT	LALFRIIEASECHIFIDG	DIA <mark>L</mark> LGLH <mark>E</mark> LRSRITIIF	PODPVLF <mark>S</mark> GSLRMNLD <b>PFD</b>	CYSDEEVWRALELSH : 1400
ABCC1	Dla	:				: -
ABCC1	Ola	AIRNINVDISGGEKVGIVG-RTGAGKSSLT	LGIFRITEPAEGNIFIDG	DIAKLGLHELRSRITIIF	PODPVLFSGTLRMNLDPFD	SYSDED KA PFSH : 1415
ABCCI	Tni	ATDNITTSINCCERVCTUCDTC-ACKSSIT	TCIERTENARCHIETDC			KVSDEFTWKSTEVSH · 1284
ADCCI	0					CULDREWDAL FROM : 1209
ABCCI		. AIRNVIISINGGERVG-IVGRIGRGRSSLI	IGIFKIIERREGHIFIDG	DIARLGLAEDRSKIIIII	ODE V LE SGSLKMN LDE FD	STIDEEVWRRGEFSH . 1398
ABCC1	Xmal					
ABCC1	Xma2	:				: -
ABCC1	Dre	: AICDISVNIAGGEKVGIVG-RTGAGKSSLT	LGLFRIIEAAEGEIRIDG	'NIA <mark>D</mark> LGLH <mark>E</mark> LRSRITIIF	ODPVLF <mark>S</mark> GSLRMNLD <mark>PFD</mark>	GYTDEEVWRSLELAH : 1394
ABCC1	Ame	: ATHDITVIIEGGEKVGIVG-RTGAGKSSIT	LGLFRIIEAAOGEICIDG	NIANLGLHDLRSRITIIF	PODPVLF <mark>S</mark> GSLRMNLD <b>PFD</b>	GYSDEDVWRALELAH : 1393
ABCC1	Loc	: AIRDIAVTIEGGEKVGIVG-RTGAGKSSLT	LGLFRITEPAOGOTCIDG	<b>DVST</b> LGLHDLRSRITIIF	PODPVLF <mark>S</mark> GSLRMNLD <b>PFD</b>	SYSDEEVWNALELAH : 1413
ABCC1	Cmi	VINTTITTK-CCFKVCTVCPTCACKSSTA	T GT EP TTEPAEGT TVI DG	NISETCINDIDEETTII	OFDUVESCSIDMNIDEF	HHSDNDIWNALETAH · 1529
ADCCI	CILL		HOLINIILI REGULLUDG.			IIIODADIWAANDHAH : 1525
		* 1620 *	1640	* 1660	* 1680	* 1700
ABCC6	Hsa	: LKALVASLPGOLOY <mark>K</mark> CAD <mark>R</mark> GEDL <mark>S</mark> V <mark>GO</mark> K	OLLCLARALLRKT <mark>O</mark> I L <mark>II</mark> LI	EATAAVD <mark>PGTELO</mark> MO <mark>AM</mark> I	.GSWFAOCTVLLIAH <mark>R</mark> LRS	VMDCARVLVMDKGOV : 1477
ABCC6	Ptr	: IKALVASIEGOLOYKCADRGEDISVGOK	OLLCLARALLRKT <mark>O</mark> ILII	EATAAVDPGTELOMOAMI	GSWFAOCTVILIAHRIRS	VMDCARVLVMDKGOV : 1319
ABCC6	Mmu	: LKAFVTSLFGOLOYECAGOGDDLSVGOK	OLLCLARALLRKTOILIL	EATASVDPGTEMOMOAAT	ERWFTOCTVLLIAHRIRS	VMDCARVLVMDEGOV : 1472
ABCCE	Cluf	· IRPLWASI POOLOVECTDOGSDIS- WOOM	OLICIARALIPKTOTITI	FATAAVDPOTELOMOAA	GSWI. AOCTVITIANDIDG	VIDCARVIVMPKCOU · 1479
ADCCO	D+-		OTICIANALINATIONIC	THINK VOLUTIONCAR		
ADCUD	Dud	WINTER PROPERTY AND A STREET AN	OLLCLARALLERTOILILI			VEDCARVEVIDEGOV : 14/8
ABCC6	Dno	: THALVISTEGO OYECAEOGDDISVGOK	OLLCLARALLRKT <mark>O</mark> ILILI	deataavd <b>pgtelo</b> mo <b>aa</b> i	.GSWLAGCTVLLIAHRLPS	VMDCAR : 1397
ABCC6	Mdo	: LKTFILGLEGODOYECLDOGDNLR				: 1400
ABCC6	Oan	: LKAFVADLPGHLDHVCSDOGENVSVGOK	OLLCLARALLRKT <mark>K</mark> ILVLI	)EATAAVD <mark>POTDLO</mark> IO <mark>AT</mark> I	RTOFANCTVLTIAHRLNT	VMDCNRVLVMDDGOV : 1419
ABCC6	Gơa	LKNFVADLPEOLEYKCTDOGENLSTGOK	OLVCLARALIOKAKVLILI	EATAAIDIETDLOIOTAI	RTOFKESTVLTIAHRINT	IMDCDRDLVTENCOI : 1483

ABCC6	Mdo	:	LKTFILGLEGOLOYECLDOGDN1R	:	1400
ABCC6	Oan	:	lka <mark>fvadleghidhycsdo</mark> genvsvgokollclarallrktkilvldeataavd <mark>potdloioatirtofanctvlt</mark> iahrintvmb <mark>cn</mark> rvlvmddgov	:	1419
ABCC6	Gơa	:	lkn <mark>fv&amp;dlfeoteykctdo</mark> genis <mark>t</mark> gokolvclarallox <mark>&amp;k</mark> vlildeataaid <b>ietdlo</b> to <b>ta</b> trtofkestvltiahrintimdCdrdluvlensot	:	1483
ABCC6	Aca	:	lkn <mark>fvsdlegolayecser</mark> egulsvgorolici <mark>t</mark> rallre <mark>gnvvf</mark> ldeataavd <b>metdloiosa</b> irsofrdctvltiahrvStlmdcdriivmeseov	:	1428
ABCC6	Xtr	:	lkv <mark>fAscleegisyictec</mark> genisvgorolvclaralirktkilvldeataavd <b>letddl</b> ion <b>t</b> irkef <mark>ed</mark> ctiittiahrintimdytri	:	1443
ABCC6	Lch	:	lk <mark>n</mark> fvsslpdrlsyecseggenlsvgorolvclarallrkskilvldeataavd <b>letddl</b> iostirtof <mark>ed</mark> ctvltiahrintimd <mark>ct</mark> rvmvldrg <mark>o</mark> i	:	1492
ABCC6	Gac1	:	L <mark>ON</mark> FVSNLEDKINHECSEGENLSLGOROLVCLARALLRKTKILVLDEATAAVDLETDALIOSTIRTOFEDCTVLTVAHRINTIMDYTRVIVMDREH	:	1495
ABCC6	Gac2	:	L <mark>SS</mark> FV <b>SA</b> LE <mark>OKLNHOCCEG</mark> GENLSLGOROLLCLARALLRKTRILVLDEATAAVD <mark>LKTDOL</mark> IOSTIRTOFDDCTVLTIAHRINTIMDYNRVIVMDRGY	:	1516
ABCC6	Dla	:	lk <mark>n</mark> fv <b>snledkinhecseg</b> genislgorolvclarallrktkilvldeataavd <b>letdti</b> lostirtofedctultiahrintindytrvivmdreh	:	1489
ABCC6	Ola	:	LK <mark>D</mark> FVSNLPDKLNHECSECGENLSLGOROLVCLARALLRKTKILVLDEATAAVDLETDTLIOSTIRTOFEDCTVLTIAHRINTIMDYTRVIVMDRGYI	:	1508
ABCC6	Tni	:	LK <mark>T</mark> FV <mark>ANLPDKLNH</mark> EC <b>SEG</b> GENLS <mark></mark> LGOROLVCLARALLRKTKILVLDEATAAVD <b>LETDTL</b> IOSTIRTOF <mark>ED</mark> CTVL <b>T</b> IAHRINTIMDYTRVIVMDKC <mark>H</mark> I	:	1492
ABCC6	Oni	:	LK <mark>NFVSNLPDKLNHECTEG</mark> GENLSLGOROLVCLARALLRKTKILVLDEATAAVD <mark>LETDTL</mark> IO <b>STIRTOFED</b> CTVL <b>T</b> IAHRLNTIMDYTRVIVMDRC <mark>H</mark> V	:	1502
ABCC6	Xma	:	LK <mark>TFVSNLPDKLNY</mark> EC <b>SEG</b> GENLSLGOROLVCLARALLRKTKILVLDEATAAVD <b>LETDTL</b> IOSTIRTOF <mark>EH</mark> CTVL <b>T</b> IAHRINTIMDYTRVIVMDRGH	:	1484
ABCC6	Gmo	:	lk <mark>nfvsnledklsh</mark> ecsecgenls <mark>l</mark> gorolvclarallrktkilvldeataavdletdtliostirtofedctultiahri <mark>n</mark> timdytrvivmdks <mark>l</mark> i	:	1434
ABCC6	Dre1	:	lk <mark>n</mark> fvs <mark>e</mark> lf <b>dklnhecseg</b> genlslgorolvclarallrktkvlvldeataald <b>letdtl</b> iostirsofedo <mark>a</mark> vltiahrlntimdytkvivmdkgh	:	1481

ABCC1 Gơa	:	$Lk_{NFVSSLPDKLNHECSEGGENLS-vGOROLVCLARALLRKSKILVLDEATAAVDLETDNLIOSTIKSOFEECTVLTIAHRLNTIMDYTRVLVLDRGEV$	: :	1499
ABCC1 Aca	:	LK <mark>AFVSALPDKLLH</mark> ECAEGENLSVGOROLVCISRALLRRSKILVLDEATAAVDLETDCLIOATIRROFEGCTVLTIAHRLNTIMDYTR	: :	1493
ABCC1 Xtr	:	$Lk_{R} \texttt{FVAN} LPDRINHECAEGGENLSIGOROLVCLARALLRKTKILVLDEATAAVDLETDGLIOSTIRKE \texttt{FOD}CTVITIAHRINTINDYTKVIVLDKGOV$	: 3	1486
ABCC1 Lch	:		:	-
ABCC1 Gac	:	LOSFVSGLPNKLSHECSEGGENLSVGOROLLCLARALLRKTKILVLDEATAAVDMETDNLIOSTLRSOFEDCTVLTIAHRINTVMDYTRILVLDKGEM	: 3	1498
ABCC1 Dla	:		:	-
ABCC1 Ola	:	LKSFVSGLPDKLGHECSEGGENLSLGOROLLCLARALLRKTKVLVLDEATAAIDMETDDLIOTTIRSOFEGCTVLTIAHRLMTIMDYTRVLVLDKGOM	: :	1513
ABCC1 Tni	:	LK <mark>T</mark> FVS <mark>GLPNKINHECSEG</mark> GENLSVGOROLLCLARALLRKSKVLVLDEATAAVDMETDHLIOATIRSOFEDCTVLTIAHRINTIMDYSRVLVLDKGEL	: 3	1382
ABCC1 Oni	:	lk <mark>t</mark> fvSSlenklnhdcsecgenlsvgorollclarallrktrilvldeataavdmetdnliostirSofedctvltiahrlntindytrvlvleng <mark>a</mark> m	: :	1496
ABCC1 Xma1	:		:	-
ABCC1 Xma2	:		:	-
ABCC1 Dre	:	LKTFVSGLPDKINHECSEGGENLS-LGOROLVCLARALLRKTKILVLDEATAAVDLETDNLIOSTIRTOFEDCTVLTIAHRINTINDYTRVLVLDKGOM	: 3	1492
ABCC1 Ame	:	$Lk \mathbf{N} \mathbf{F} \mathbf{v} \mathbf{S} \mathbf{G} \mathbf{L} \mathbf{P} \mathbf{K} \mathbf{i} \mathbf{N} \mathbf{H} \mathbf{C} \mathbf{S} \mathbf{E} \mathbf{G} \mathbf{G} \mathbf{E} \mathbf{N} \mathbf{I} \mathbf{C} \mathbf{F} \mathbf{G} \mathbf{E} \mathbf{D} \mathbf{C} \mathbf{T} \mathbf{i} \mathbf{I} \mathbf{A} \mathbf{H} \mathbf{I} \mathbf{N} \mathbf{I} \mathbf{M} \mathbf{T} \mathbf{X} \mathbf{V} \mathbf{I} \mathbf{V} \mathbf{I} \mathbf{K} \mathbf{K} \mathbf{K} \mathbf{K} \mathbf{K} \mathbf{K} \mathbf{K} K$	: 3	1491
ABCC1 Loc	:	LK <mark>T</mark> FVSGLPDKINHECSEGGENLS-LGOROLVCLARALLRKTKVLVLDEATAAVDLETDNLIOSTIRSOBEECTVLTIAHRINTINDYTRVLVIDKCOI	: :	1511
ABCC1 Cmi	:	lk <mark>t</mark> fvsdlentlnhecseggenlsvgoroliclarallrkskvlvldeataavdlvrdkliostikshidostvltiahrdhtindytrvlvldkg <mark>e</mark> i	: :	1627

			* 1720 *		
ABCC6	Hsa	:	AESCSPACE LAOKCLEVE AOESCEV	:	1503
ABCC6	Ptr	:	AESGSFAOLIAOKGLFYRLAOESGLV	:	1345
ABCC6	Mmu	:	AESGS AOLIAOKCLFYRIAHESGIA	:	1498
ABCC6	Cluf	:	AESGSFAOLIAOKGLFYRLAOESGLV	:	1504
ABCC6	Bta	:	AESGSFAOLIAOKGLFYRLAOESGLV	:	1504
ABCC6	Dno	:		:	-
ABCC6	Mdo	:		:	-
ABCC6	Oan	:	VEFDSPARLLTRKGLFYRLAEESGLV	:	1445
ABCC6	Gơa	:	AEFDTEKOITAOKELFYKIMEESCIA	:	1509
ABCC6	Aca	:	SECDTFONLIARKCMFYTMAKESGIA	:	1454
ABCC6	Xtr	:		:	-
ABCC6	Lch	:	VEFDAPAKLLLOKCLFYRLASDAGITOLSPKTPEYO	:	1528
ABCC6	Gac1	:	SEMDTPANLIAORCOFYRMCREAGIM	:	1521
ABCC6	Gac2	:	AEIDSPSELIRLOGFFYOMCAEAGLV	:	1542
ABCC6	Dla	:	SEMDSPANLIAORCOFYRMCREAGLV	:	1515
ABCC6	Ola	:	SEMDSPANLISORCOFYRMCREAGIV	:	1534
ABCC6	Tni	:	SEMDSFGNLIAORCOFYRMCREAGIV	:	1518
ABCC6	Oni	:	SEMDSPANLISORCOFYRMCREAGLV	:	1528
ABCC6	Xma	:	SEMDSPANLISORCOFYRMCLEAGIV	:	1510
ABCC6	Gmo	:	SETDSPANLITORCOFYRMCREAGLV	:	1460
ABCC6	Drel	:	VEMDSPSNLIAKRCOFYYMCREAGIL	:	1507
ABCC6	Dre2	:	TEIDSPSNLISOHCOFYRMCREAGLV	:	1462
ABCC6	Dre3	:	TEVDSPSNLISOHCOFYRMCREAGLV	:	1527
ABCC6	Amel	:	AEMDTFANLIAORCOFYRMCREAGIA	:	1508
ABCC6	Ame2	:	TEMDSFTNLIAORCOFYCMCREAGIA	:	1530
ABCC6	Loc	:	TEMDTPSNLIASRCOFYRMCREAGIV	:	1508
ABCC1	Hsa	:	OEYGAFSDILOORGLFYSMAKDAGIV	:	1531
ABCC1	Ptr	:	OEYGAPSDLLOORGLFYSMAKDAGIV	:	1446
ABCC1	Mmu	:	RECGARSELLOORCIFYSMAKDAGLV	:	1528
ABCC1	Cluf	:	RECGOPSDLLOORGLFYSMAKDAGLV	:	1531
ABCC1	Bta	:	OEWGSPSDLLOORGLFYSMAKDSGLV	:	1514
ABCC1	Dno	:	REFGSPSELLOORCLFYSMARDANLA	:	1531
ABCC1	Mdo	:	VECDSPPVLIOKKCIFYSMAKDAGLV	:	1533
ABCC1	Oan	:	VECGSPSDLLOKKCIFYSMARDASLI	:	1313
ABCC1	Gơa	:	VECDSPDNLLOAKCLFYSMAKDSGLA	:	1525
ABCC1	Aca	:		:	-
ABCC1	Xtr	:	VEFDSPSNLLOOOGIFFNMAKDSGLV	:	1512
ABCC1	Lch	:		:	-
ABCC1	Gac	:	AEFDARHNLLAORCAFYKMAKDAGIV	:	1524
ABCC1	Dla	:		:	-
ABCC1	Ola	:	AEFDSFSNLIAOKCAFYRMAKDSGLI	:	1539
ABCC1	Tni	:	VEFASPSNLLAEKCSFYOMAKDAGLV	:	1408
ABCC1	Oni	:	AEFDSPSNLISORCAFYKMAKDSGLV	:	1522
ABCC1	Xma1	:		:	-
ABCC1	Xma2	:		:	-
ABCC1	Dre	:	AEFDSPSNLIAKKGIFYKMAKDSGLV	:	1518
ABCC1	Ame	:	AEFDSFASLIAKKCIFYKMAKDSGLV	:	1517
ABCC1	Loc	:	VEFDSFSNLLAKKCIFYKMAKDSGLL	:	1537
ABCC1	Cmi	:	IEFDTPANLLAKKGVFYHMAADSGLL	:	1653

Supplementary figure 8-1. Sequence alignments of the MRP1 and MRP6 proteins in vertebrates. Conserved amino acids in the sequence alignment are shaded in dark grey. The selected 139 amino acids mutated in PXE disease analyzed in this study are coloured in red. Accession numbers are given in the supplementary table 8-1. Due to its size the alignment of all species (including invertebrates and the other ABCC family members) is not demonstrated but is available by request.



Supplementary figure 8-2. Phylogenetic tree of the vertebrate and invertebrate ABCC6, 1 and 3 with the other human ABCC family members. The phylogenetic tree was built using the ML method with PhyML 3.0 software with 100 bootstrap replicates using JTT+I+G+F substitution model given by Protest and was rooted using the invertebrate ABCC-like branch. To facilitate interpretation, the three major vertebrate ABCC clades are boxed with different colours.

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Supplementary table 8-3. List of genes and their accession numbers used for linkage analysis. Data was retrieved from Ensembl Genomes genome database except the Elephant shark (*Callorhinchus milii*) orthologues that were obtained from (<u>http://ensembl.fugu-sg.org/index.html</u>, accessed August 2015).

Specie/Gene	NDE1	MYH11	FOPNL	ABCC1	NOMO3	
Human	ENSG0000072864	ENSG00000133392	ENSG00000133393	ENSG00000103222	ENSG00000103226	
Opossum	ENSMODG0000004385	ENSMODG0000004360	ENSMODG0000004204	ENSMODG0000004194	ENSMODG0000005682	
Platypus	ENSOANG0000005121	ENSOANG0000005134	ENSOANG0000005132	ENSOANG0000005124	ENSOANG0000005122	
Chicken	ENSGALG0000006500	ENSGALG0000006520	ENSGALG0000006532	ENSGALG0000006646	ENSGALG0000006730	
Xenopus	ENSXETG0000005528	ENSXETG00000019650	ni	ENSXETG00000019661	ENSXETG00000019683	
Coelacanth	ENSLACG0000006656	ENSLACG0000007990	ni	ENSLACG0000022117	ENSLACG00000012305	
Zebrafish	ENSDARG0000037900	ENSDARG0000009782	ENSDARG00000071198	ENSDARG00000059874	ENSDARG0000078592	
Stickleback	ENSGACG00000019165	ENSGACG00000019168	ENSGACG00000019170	ENSGACG0000000434	ENSGACG0000019191	
See bass	DLAgn_00177400	DLAgn_00177410	DLAgn_00177420	DLAgn_00195360	DLAgn_00177480	
Medaka	ENSORLG00000013552	ENSORLG0000013536	ENSORLG0000013435	ENSORLG00000017141	ENSORLG00000013299	
Tetraodon	ENSTNIG0000011286	ENSTNIG0000012065	ENSTNIG0000012066	ENSTNIG0000005013	ENSTNIG0000012072	
Spotted gar	ENSLOCG0000007273	ENSLOCG0000009053	ENSLOCG0000007248	ENSLOCG0000007196	ENSLOCG0000006964	
Elephant Shark	SINCAMG0000015553	SINCAMG0000015577	SINCAMG0000015784	SINCAMG0000015787	SINCAMG0000015915	
Specie/Gene	ABCC6	XYLT1	RPS15A	ARL6IP1	COQ7	
Human	ENSG0000091262	ENSG00000103489	ENSG00000134419	ENSG00000170540	ENSG00000167186	
Opossum	ENSMODG0000005815	ENSMODG0000005904	ENSMODG0000005920	ENSMODG0000005944	ENSMODG0000006166	
Platypus	ENSOANG0000005123	ENSOANG0000009533	ENSOANG0000012228	ni	ENSOANG0000003221	
Chicken	ENSGALG0000006698	ENSGALG0000006757	ENSGALG0000006771	ENSGALG0000006780	ENSGALG0000006861	
Xenopus	ENSXETG00000026360	ENSXETG00000019693	ENSXETG0000002942	ENSXETG0000002943	ENSXETG0000002946	
Coelacanth	ENSLACG0000001471	ENSLACG0000008838	ENSLACG00000011476	ENSLACG00000010670	ENSLACG0000005333	
	ENSDARG0000016750					
Zebrafish	ENSDARG00000094901	ENSDARG0000061248	ENSDARG00000010160	ENSDARG00000054578	ENSDARG0000062594	
	ENSDARG0000009582					
Stickloback	ENSGACG0000003037	ENSCACC0000010187	ENSCACC0000010181	ENSCACC0000014008	ENSGACC0000010175	
SUCKIEDACK	ENSGACG00000019172	EN30AC00000019187	EN30AC00000019181	ENSOAC00000014908	ENSOAC00000019175	
See bass	DLAgn_00177430	DLAgn_00177470	DLAgn_00177460	DLAgn_00194490	DLAgn_00177440	
Medaka	ENSORLG00000013429	ENSORLG00000013339	ENSORLG00000013347	ENSORLG0000001074	ENSORLG00000013378	
Tetraodon	ENSTNIG0000012067	ENSTNIG00000012071	ENSTNIG00000012070	ENSTNIG00000011302	ENSTNIG0000012068	
Spotted gar	ENSLOCG0000007152	ENSLOCG0000006998	ENSLOCG0000007017	ENSLOCG0000007049	ENSLOCG0000007132	
<b>Elephant Shark</b>	ni	SINCAMG0000015951	SINCAMG0000015952	SINCAMG0000015955	SINCAMG0000016019	

Abbreviations: ni- not identified, *NDE1*- Neurodevelopment protein 1, *MYH11*- Myosin heavy chain 11, *FOPNL*- FOP related protein, *ABCC1,6*- ATP binding cassette subfamily C member 1,6, *NOMO3*- Nodal modulator 3, *XYLT1*- Xylosyltransferase 1, *RSPS15A*- Ribosomal protein S15A, *ARL6IP1*- ADP ribosylation factor like protein 6 interacting protein 1, *COQ7*- Coenzyme Q7.

# Supplementary table 8-4. Percentage of amino acid sequence identity/similarity of the *ABCC6* and *ABCC1* sequences in comparison with human sequence by GeneDoc program.

Specie name	Common name	Abbreviation	% Identity/Similarity with Hsa			
			ABCC6	ABCC1		
Homo sapiens	Human	Hsa	X	Х		
Pan troglodytes	Chimpanzee	Ptr	88/89	92/93		
Mus musculus	Mouse	Mmu	78/86	87/95		
Canis lupus familiaris	Dog	Cluf	80/89	91/96		
Bos taurus	Cow	Bta	83/90	90/95		
Dasypus novemcinctus	Armadillo	Dno	73/81	86/93		
Monodelphis domestica	Opossum	Mdo	57/70	83/91		
Ornithorhynchus	Platypus	Oan	59/74	71/78		
Gallus gallus	Chicken	Gga	52/69	77/89		
Anolis carolinensis	Anole Lizard	Aca	50/68	68/80		
Xenopus tropicalis	Xenopus	Xtr	40/60	69/82		
Latimeria chalumnae	Coelacanth	Lch	48/67	49/59		
Castonostous apulaatus	Stickloback	Caa	44/64	66/80		
Gasierosieus acuieaius	SUCKIEDACK	Gae	43/60	00/80		
Dicentrarchus labrax	See bass	Dla	42/60	36/44		
Oryzias latipes	Medaka	Ola	45/63	64/80		
Tetraodon nigroviridis	Tetraodon	Tni	45/64	52/66		
Oreochromis niloticus	Tilapia	Oni	45/63	65/81		
Vinhonhoma manilatua	Dlatufiah	Vma	15/61	12/16		
Alphophorus maculalus	Platylish	Allia	43/04	24/29		
Gadus morhua	Cod	Gmo	43/62	XX		
			45/64			
Danio rerio	Zebrafish	Dre	44/62	68/81		
			44/62			
A atu au au au ani a arrest	Dlind cove fi-1	Ama	46/64	69/91		
Astyanax mexicanus	Dinu cave iish	Ame	44/62	68/81		
Lepisosteus oculatus	Spotted gar	Loc	47/65	68/81		
Callorhinchus milii	Elephant shark	Cmi	X	56/71		
Petromyzon marinus	Lamprey	Pma	X	X		

Supplementary table 8-5. Size of the exons and introns deduced from Ensembl for the Human and spotted gar *ABCC6* orthologues genes. The sizes of human pseudogenes are also indicated. Bold represents the exons with the same size than human *ABCC6* gene (accessed August 2015).

		Human (Chr1	Spotted gar (LG13)		
Exons	ABCC6	ABCC6P1	ABCC6P2	abcc6	
E1	66	124	36	42	
<i>I1</i>	1567	1565	1565	4807	
E2	183	184	183	177	
<i>I</i> 2	1701	1259	1259	354	
E3	126	116	116	126	
I3	139	325	325	2569	
E4	129	126	126	138	
I4	5104	139	139	3025	
E5	126	129	129	126	
<i>I5</i>	2077	5055	ni	1531	
E6	62	126	ni	62	
<i>I6</i>	3325	2070	ni	802	
E7	132	62	ni	132	
<i>I7</i>	5114	3338	ni	897	
E8	204	132	ni	201	
<i>I</i> 8	1231	5166	ni	1105	
E9	178	204	ni	178	
<i>I9</i>	3818	1231	ni	126	
E10	162	178	ni	162	
<i>I10</i>	5098	4050	ni	335	
E11	93	1562	ni	93	
<i>I11</i>	2462	ni	ni	989	
E12	204	ni	ni	204	
<i>I12</i>	1189	ni	ni	256	
E13	114	ni	ni	147	
<i>I13</i>	1619	ni	ni	304	
E14	88	ni	ni	88	
<i>I14</i>	2089	ni	ni	865	
E15	127	ni	ni	70	
<i>I15</i>	215	ni	ni	114	
E16	177	ni	ni	127	
116	3446	ni	ni	308	
E17	177	ni	ni	177	
<i>I17</i>	3446	ni	ni	609	
E18	168	ni	ni	168	
<i>I18</i>	1171	ni	ni	423	
E19	175	ni	ni	184	
<i>I19</i>	1465	ni	ni	268	
E20	76	ni	ni	82	

Enona		Human (Chr1	Spotted gar (LG13)		
EXONS	ABCC6	ABCC6P1	ABCC6P2	abcc6	
I20	2506	ni	ni	108	
E21	121	ni	ni	118	
I21	3430	ni	ni	237	
E22	208	ni	ni	208	
I22	3712	ni	ni	572	
E23	311	ni	ni	311	
I23	2430	ni	ni	438	
E24	200	ni	ni	200	
I24	1428	ni	ni	223	
E25	127	ni	ni	127	
I25	1854	ni	ni	282	
E26	102	ni	ni	102	
I26	1672	ni	ni	340	
E27	147	ni	ni	147	
I27	2631	ni	ni	349	
E28	159	ni	ni	159	
I28	78	ni	ni	403	
E29	167	ni	ni	167	
I29	3855	ni	ni	174	
E30	195	ni	ni	195	
<i>I30</i>	336	ni	ni	691	
E31	109	ni	ni	109	

Abbreviations: Chr- chromosome.

Supplementary table 8-6. CT values for the control gene *rps18* and *abcc6* and *abcc1* genes in intact and regenerating skin at 0-96 hours.

TIME	Int	tact skin		Regenerating skin			
	Control	abcc6	abcc1	Control	abcc6	abcc1	
0h	25,96	28,65	31,71				
6h	25,47	28,27	33,06	25,10	27,35	33,58	
24h	25,54	27,72	31,22	24,07	26,49	30,86	
48h	26,09	27,07	31,40	24,85	26,36	30,35	
72h	24,80	26,41	29,83	24,26	25,84	29,40	
96h	25,72	26,45	30,51	25,25	25,85	30,95	

## CHAPTER IX: GENERAL DISCUSSION AND CONCLUSIONS

### 9. GENERAL DISCUSSION AND CONCLUSIONS

This study was conducted in the Azores, a Portuguese archipelago located in the middle of the Atlantic Ocean, in a small island with only 56.467 inhabitants (Census, 2011). The high rate of consanguineous marriage and the high probability of common ancestry increases the possibility of finding diseases caused by a single gene. The coexistence of DISH with Chondrocalcinosis (CC) is very common on this island and seems to be an endemic manifestation. Previous studies, undertaken by our group, led to the identification and characterization of twelve families with early onset CC and/or DISH leading the group to suggest that both diseases, designated as DISH/CC phenotype, could share the same pathogenic mechanism [23]. These families may represent a familial type of pyrophosphate arthropathy with a phenotype that includes peripheral and axial enthesopathic calcifications. A similar phenotype has been described in several other studies in different populations [25, 26]. The meticulous analysis of twelve pedigrees pointed toward a Mendelian disease with autosomal-dominant mode of inheritance [23]. Eight of the probands of these families were born in the same or nearby villages and this phenotype has higher in specific zones of the island, raising the possibility of an unknown environmental factor or a genetic founder effect. In fact, founder effects have been used to explain the presence of high-frequency Mendelian diseases in many isolated populations [456, 457]. Since isolated populations have proven particularly valuable for the purposes of mapping genes involved in rare Mendelian monogenic disorders, studying DISH/CC in this island population will increase the likelihood of identifying the causative mutation. For a number of years the group that hosted the present study has been looking for a possible major gene in the aethiopathogenesis of the DISH/CC phenotype. The involvement of the ANKH gene, the only monogenic disease causing gene yet known for chondrocalcinosis, has already been discarded by a previous study [110]. A whole genome linkage analysis followed by an "Identity-by-state/descent" was performed and two zones, in chromosomes 12 and 20, seemed relevant for further investigation. In line with these results, two genes were considered to be good candidate genes for DISH/CC; RSPO4 on chromosome 20, and LEMD3 on chromosome 12. Several gene variants were identified and nucleotide modifications located in the regulatory region of the RSPO4 gene were more frequent in controls than in the DISH/CC group (p-values; 0.03 and 0.05). RSPO4 mutations, especially those located in the highly conserved exons 2 and 3 of the gene encoding the furin/like cysteine/rich domain of R/spondin 4, causes autosomal-recessive anonychia [351]. The specific variant Gly67Arg causes anonychia by disrupting the Wnt/ $\beta$ -catenin signaling Chapter IX

pathway [458]. The effects on the protein of the two regulatory variants found in our study have not been defined. However, the variants are located in the regulatory region of the gene and so may alter the expression of the *RSPO4* gene, although the modification in gene expression and why these variants are protective to DISH/CC is unknown. According to our results, neither *RSPO4* nor *LEMD3* are the main genetic causes for the development of the DISH/CC phenotype. These genes, in particular *RSPO4* may, however, have a modest role which should be further investigated.

To further identify candidate genes or variants associated with DISH/CC phenotype we performed Whole Exome Sequencing on four unrelated DISH/CC patients, followed by association studies of selected variants. Our focus on the "exome" was due to the common belief that the coding regions contain the most functionally relevant variants and because many coding mutations have been found to cause phenotypic effects [459]. For instance, missense mutations in ANKH gene causing gain or loss of function of ANK protein leads to development of chondrocalcinosis (CCAL2; MIM 118600) [343-345] the or Craniometaphyseal dysplasia (CMDD; MIM #123000) [109, 346], respectively. Other example is the coding mutations in the ACVR1 which cause a disruption of the glycine/serinerich domain of the activin A receptor 1 leading to the progressive ossification disease (FOP; MIM #135100) [460, 461]. Mutations in ABCC6 gene normally occur in cytoplasmatic regions of the protein [406], and cause a loss of function of the protein leading to the Pseudoxanthoma elasticum disease (PXE; MIM #264800) [126]. In fact the mutations that cause Mendelian diseases occur primarily in coding regions, and mutations that causes amino acids substitutions are the most frequent type of disease mutations (~60%) [462]. The candidate genes selected for the analysis in this study were those directly or indirectly related to mineralization or ossification, in which coding or splice-site mutations were found.

*BMP4* is a member of the BMP family and belongs to the transforming growth factor- $\beta$  (TGF- $\beta$ ) superfamily, which is involved in osteoblast differentiation and bone formation [463]. One common missense variant in this gene, rs17563 T>C (p.V152A), was found in three out of four of the investigated patients (WES). After typing this variant in a group of DISH/CC patients and controls we observed that the C allele is statistically more frequent in the DISH/CC group than in controls. This variant is very frequent in all populations (MAF=0.37) which does not invalidate a role on the susceptibility to DISH/CC, since common variants associated with disease risk are not uncommon. In OPLL disease, for

instance, the majority of susceptibility variants associated are common variants [61] [33, 146] [61]. The rs17563 is one of the most functional SNP of BMP4 gene [464]. This SNP causes a change in the mRNA structure and the levels of BMP4 mRNA are significantly higher in Tallele carriers when compared with C-allele carriers [381]. The T-allele has been associated with OPLL disease [160, 161], and mRNA and expression of BMP4 protein were significantly increased in OPLL cells derived from ossified spinal ligament when compared to non OPLL cells [382]. The rs17563 variant has been largely studied as associated with nonsyndromic cleft lip with or without palate (NSCL/P), however the results were inconsistent. For some the C allele is a risk factor for the disease [465, 466] and for others the C allele is protective [467]. To clarify this association a meta-analysis was performed and the authors conclude that the rs17563 variant could play a different role during the development of NSCL/P based on ethnicity diversity [464]. NSCL/P is a complex genetic disorder with a variable phenotype, largely attributed to the interactions of the environment and multiple genes, each potentially having certain effects [468]. In our case it is very difficult to state that this single variant is the responsible for the DISH/CC phenotype, but rather this variant could contribute to the DISH/CC phenotype by interacting with other moderate effect genes and/or with unknown environmental factors. At this moment we do not know how the C variant contributes to the DISH/CC phenotype and thus there is a need for further research in this area.

The main candidate gene investigated in this thesis was the *ABCC6* gene, a member of the ATP-Binding Cassette family of transporters that has been extensively related to dermal ectopic calcification and has recently become a new member of the calcification regulators in mammals [122]. Loss-of-function mutations within the *ABCC6* gene cause PXE and in some cases GACI, both heritable disorders related to soft tissue calcification. PXE and GACI are rare disorders and none of the patients investigated in this study were diagnosed with these conditions. The exact function of the protein encoded by this gene and the substrate(s) that it transport remain unknown [469], but evidences suggests that it may be involved in the metabolism of pyrophosphate. In PXE disease MRP6 deficiency leads to strong reduced plasma PPi levels that lead to a reduced PPi/Pi ratio and this favours pathological mineralization [397]. The same occurs in *abcc6*<sup>-/-</sup> mice, in which PPi levels were lower than in wild type mice [397]. It is now widely accepted that Pi and PPi levels are determinants for the development of rheumatic calcifying disorders. One missense rare variant in the *ABCC6* gene, rs41278174 C>T (p. R1064W), was present in one of the DISH/CC patients. A large

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number of other variants were found in this gene, but no differences were identified between DISH/CC and controls. The rs41278174 variant is highly conserved between mammals, and according to the algorithms used (SIFT and PolyPhen) is deleterious and damaging to the protein. We observed that this variant had a higher frequency in the DNA samples of our island population and it was more frequent in male controls than in male patients with disorders that are characterized by ectopic calcification, such as DISH/CC and Ankylosing Spondylitis. This variant is located in the transmembrane domain of the MRP6 protein, which plays a role in the substrate specificity of ABC transporters [412]. Mutations in the transmembrane domain can also affect the integration of the protein into the cell membrane leading to a loss of function [308]. We hypothesize that the variant - rs41278174 - in males, may change the specificity of the MRP6 transporter, conferring a protective effect via an unknown mechanism.

In humans, the *ABCC6* gene has highest expression in the liver and kidneys and localizes to the plasma membrane [470]. However, several other studies show that *ABCC6* is expressed in other tissues as well, albeit in much lower abundance, including the skin and the blood vessel walls, which are sites of pathology in PXE [125, 471, 472]. In fish, the *abcc6a* gene functions locally at the site of mineralization and in zebrafish the gene is also expressed in intervertebral disc regions, structures that are affected by hypermineralization caused by a specific mutation in *abcc6a* gene [113]. In this study, we found expression of *ABCC6* in human cartilage tissues and the gene was also expressed in fish skin (normal and regenerating). In fish skin, no difference was found between normal skin and regenerating skin, and the function of this gene in fish skin remains an open question. The retention of the gene in the genome of the bony fishes but its loss from the genome of the cartilaginous fish, from which they derived, suggests that the gene has an important function. Furthermore, comparative genomics analysis indicated that the *abbc6* gene emerged at the same time as bone vertebrates indicating it is most likely linked to specific innovations in the vertebrates.

In human cartilage tissues we found very different levels of the *ABCC6* transcript between patients. When grouped by disease we found that, in general, the level of expression was increased in coxoarthrosis, and was more evident in DISH and CC patients when compared with the only available control. In vitro, the overexpression of *ABCC6* induces nucleotide release [129]. Although MRP6 does not directly transport ATP, it is thought that ATP is secreted via an MRP6 dependent mechanism. In the liver, ATP is converted into AMP and

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PPi by ENPP1 and PPi is the main inhibitor of mineralization, in plasma [397]. The Pi:PPi ratio is a determinant factor that can lead to pathological mineralization or its inhibition [473]. In general, conditions which favour PPi increase promote CPP crystal formation, while decreases in PPi promotes hydroxyapatite crystal formation [474]. In line with this hypothesis we postulate that, in our patients, the PPi levels are higher, favouring CPP formation instead of hydroxyapatite crystals. In CC the deposited salts are normally composed of CPP, though other calcium salts can also be found including hydroxyapatite [256, 475]. In some cases, CPP can also occur in the spinal ligaments [257, 258], but it is usually difficult to distinguish from ossification [46]. In fact, in our patients the involvement of CPP deposition was already known, since CPP crystals were identified from knee effusions in 13 patients from the 12 DISH/CC families previously characterized [24].

Putting it all together, our results raise a question in relation to the monogenic or polygenic nature of the DISH/CC disease coupled with the possible involvement of environmental factors. The association of the rs17563 variant in the *BMP4* gene, found in our study, has probably a minor effect on disease development. As suggested for OPLL [152], it seems that the association of different genes and variants are important and that it is unlikely that there is only one major gene responsible for the disease. Rather, it seems most likely that a number of variants in a variety of different genes may be associated with DISH, and therefore predispose for the development of the disease in patients. The former facts explain the failure in previous studies to identify causative genes, as the studies assumed a single gene inheritance pattern.

The studies carried out and reported in this thesis have several limitations **1**) DISH is currently lacking a validated set of diagnostic and classification criteria in order to better describe and establish homogeneous cohorts of patients. This is particularly important because DISH is characterized not only by the ossification of the anterior spinal ligaments but also by generalized symmetrical enthesopathic calcifications. Much has been debated about the importance of diagnostic and classification criteria for DISH, but no agreement has been reached so far [40]. In our opinion, a well validated set of classification criteria for DISH, is of extreme importance for genetic studies in order to have a homogeneous phenotype group for investigations; **2**) the small sample size, especially the control group with only 36 individuals gives very low statistical power of the study. The low sample number for the control group is linked to the need in the asymptomatic population to carry out radiographic examinations to identify those affected by the pathology; **3**) All the filtering strategies

employed involved previous knowledge on the genes. The biggest limitation in this strategy is that genes that were not labeled yet or have unknown functions were not investigated in this study and may be relevant; 4) of course it cannot be assumed that any gene variant will necessarily have a negative impact on protein expression and function, but by focusing on the coding region we aimed to eliminate the synonymous and intronic variants. Normally the variants in the human genome with deleterious effects on the protein are the basis for the development of diseases, however variations that modify protein structure do not necessarily lead to a detectable human-disease phenotype, and a mutation that predispose an individual to a disease is not necessarily a deleterious variation. The synonymous variants are now widely acknowledged to cause changes in protein expression, conformation and function [476]. Sometimes the altered nucleotide is part of a splicing enhancer or suppressor and the change affects splicing or in other cases they do not affect splicing but the alternative codon could require an alternative transfer RNA that is in short supply, and this therefore changes the kinetics of translation [477]. For instance synonymous variants in the CFTR gene causes aberrant splicing in patients with Cystic Fibrosis [478] [479]. Thus, synonymous mutations within protein-coding regions may be associated with noncoding functions, acting pretranscriptionally at the DNA level or post-transcriptionally at the RNA level [480]. An example of this is found with the dopamine receptor gene (DRD2) in which a synonymous variant is associated with schizophrenia and alcoholism by modulating receptor production through differences in messenger RNA (mRNA) folding and stability [481]. Also the intronic variants could be of interest. Transcript variants within an intron may regulate genes; through modifying alternative splicing of the mRNA or by changing the binding site of enhancers that act on the gene they are found in or could possibly enhance the expression of many genes. Disease associated intronic variants in the ErbB4 gene are related to altered ErbB4 splicevariant expression in the brains in schizophrenia [482]; 5) the study population comprised only Azorean individuals and we cannot generalize our conclusion to other ethnic populations. Thus, the present findings need to be replicated and validated in a greater number of samples including other ethnic groups. The public health risk posed by the risk alleles is likely to show wide variation across populations simply as a function of its frequency, and this risk difference may be amplified by gene-gene and gene-environment interactions; 6) our expression studies were preliminary and with a reduced sample size.

In the future further studies will be required to overcome the limitation of the present study this could include; **1**) arranging groups according to the calcified tissue regions, since there is no exact classification criteria for DISH currently available, obviously this will greatly

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decrease the sample size, and thus more patients will be necessary; 2) look more closely at the unknown genes and to the synonymous and intronic variants obtained in the WES results in order to verify if there is a possible association with DISH/CC (extra filtering of the results); 3) perform additional studies with an enlarged number of samples and expression studies to clarify the association of the *BMP4* gene variant (rs17563) with our phenotype; 4) confirm if *ABCC6* overexpression is related to the formation of CPP deposition in DISH and CC patients. Clearly in the future it will be important to extend the biobank and collect the necessary cartilage samples to ensure a bigger sample size that will generate more robust data.

In conclusion, the findings of our study lead us to suggest that DISH/CC is polygenic, being influenced by the interaction of multiple small effect gene variants and possibly by unknown environmental factors. Exome sequencing combined with Sanger sequencing is confirmed by this study to be an efficient strategy to search for disease causing genes of both monogenic and polygenic diseases. Therefore, it seems most likely that DISH/CC phenotype has many potential different mutations in various genes in different chromosomes involved in its inheritance, pathology, and expression.

# **CHAPTER X: BIBLIOGRAPHY**

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# APPENDIX



# Gitelman's Syndrome Associated with Chondrocalcinosis: A Case Study from the Azores Islands (Portugal)

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#### Abstract

Gitelman syndrome (GS) is a rare autossomal recessive inherited tubulopathy, characterized by defective tubular reabsorption of magnesium and potassium, mostly caused by mutations in the *SLC12A3* gene. The association of GS with chondrocalcinosis (CC) has been described in the literature as a typical example of hypomagnesemia-induced crystal deposition disease.

We are presenting one case where the genetic cause for GS was identified in a proband with secondary early onset CC. A 60 years-old male patient with CC, hypomagnesemia and hypokalemia was identified in our hospital as a result of clinical and laboratory assessments. The clinical diagnosis of GS was performed and *SLC12A3* gene was screened in the proband; variants detected were further searched in family members.

The proband was homozygous for the S615L mutation; additionally, only one from the seven family members which were heterozygous presents CC. The presence of CC in two other individuals is most likely sporadic, in agreement with their advanced age.

**Keywords:** Chondrocalcinosis; Calcium pyrophosphate dehydrate; Genetic studies

#### Introduction

Gitelman Syndrome (GS, OMIM 263800; ORPHA358) is a rare autossomal recessive tubulopathy, with a prevalence of approximately 1:40 000 in the Caucasian population. Onset is usually in adult life, but cases with onset in childhood are also known [1]. GS is characterized by hypomagnesemia, hypokalemia, metabolic alkalosis, hypocalciuria and hyperreninemic hyperaldosteronism. The clinical spectrum is wide and includes: cramps, myalgies, muscle weakness, tetania, and paralysis [2]. GS is mostly caused by loss of function mutations in the solute carrier family 12, member 3 (*SLC12A3* gene) which consists of 26 exons and is located on the long arm of 16<sup>th</sup> chromosome [1]; this gene encodes the thiazide-sensitive sodium-chloride cotransporter (NCCT), expressed in the distal convoluted tubule of the kidney [3].

NCCT is a polypeptide which consists of 1021 amino acids. Its 2-D structure is predicted to contain 12 transmembrane domains and intracellular amino and carboxyterminal regions [3]. At present, according to the Human Gene Mutation Database (http://www.hgmd.cf.ac.uk/), more than 100 different variants have been identified in patients with GS. They are missense, non-sense, frameshift, and splice-site variations and are scattered throughout the transporter protein with a possible clustering of variations in the carboxy-terminal tail [4].

The association of GS with chondrocalcinosis (CC) has been described in the literature as a typical example of hypomagnesemiainduced crystal deposition disease [2]. CC is characterized by deposition of crystals of calcium pyrophosphate dihydrate (CPPD) in articular hyaline and fibro-cartilage [2]. Seventeen cases of GS associated with CC due to CCPD have been published in the literature, including 10 females and 7 males with a mean age of  $51.4 \pm 15.9$  years [2,5-15]. The role of hypomagnesemia in the development of CCPD is, however, not fully understood [16]. Magnesium is an important cofactor for alkaline pyrophosphatase, an enzyme that plays a key role by converting inorganic pyrophosphate (PPi) to orthophosphate (Pi). A reduction in the activity of this enzyme due to hypomagnesemia could induce CCPD by raising extracellular levels of PPi. Both PPi and calcium are crucial precursors for crystal nucleation. CCPD may be found in other conditions associated with hypomagnesemia, such as short bowel syndrome or in liver transplantation patients [16].

#### **Case with Genetic Analysis**

The proband, a 60 year-old caucasian male was first observed in the Rheumatic Diseases Clinic - HSEIT when he was 48 years old; he was born in Terceira island as well as both his parents. Symptoms started when he was 33 years old, mainly affecting knees, ankles, wrists, elbows and achilles tendons. In the proband, PPi crystals were identified in the synovial fluid aspirated from a right knee effusion. Since then he was under treatment with colchicine, NSAIDS (Nonsteroidal anti-inflammatory drugs), and oral potassium and

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magnesium. Laboratory tests revealed normal leukocyte, erythrocyte and platelet count.

Blood urea was 33 mg/dl, creatinine 0.9 mg/dl and glucose 177 mg/dl. Serum electrolyte concentrations were as follows: sodium 139 mEq/L, potassium 3.2 mEq/L, calcium 9.8 mg/dl, and magnesium 1.1 mg/dl (Table 1). In spite of the treatment with colchicine, patient still maintain hypokalemia and hypomagnesemia, however he showed some improvements. Using the diagnostic criteria of Bettinelli et al. [17] a clinical diagnosis of GS was suspected, and a diagnosis of knee

CC was made after the identification of bilateral knee cartilage calcification (Figure 1). SLC12A3 sequence analysis in the proband revealed that he was homozygous for a missense substitution in exon 15, previously described as associated to GS [18]. This mutation (CM014403), a C to T transition at position c.1869, changes the small size and polar amino acid serine to a medium size and hydrophobic leucine at position 615 (S615L), has a SIFT score of 0 and a Polyphen value of 0.996, both values suggestive of a deleterious variation.

Individuals	Sex	Age	Magnesium levels <sup>a</sup>	Potassium levels <sup>b</sup>	сс	Pathogenic mutation S615L
111.2	м	60	1.1	3.2	+	S615L/S615L
III.12	М	75	2.1	4.7	-	S615L/WT
III.13	F	67	2.2	4.1	-	WT/WT
III.16	м	75	2.0	4.6	+	WT/WT
III.19	F	79	1.9	4.7	+	S615L/WT
IV.1	м	35	2.3	3.7	-	S615L/WT
IV.2	F	54	2.2	4.2	-	S615L/WT
IV.4	м	46	1.9	4.0	-	S615L/WT
IV.14	F	51	1.9	4.0	-	WT/WT
IV.16	F	49	2.2	4.1	-	WT/WT
IV.17	F	45	1.9	4.3	-	WT/WT
IV.21	м	37	2.1	4.1	-	S615L/WT
IV.22	F	36	2.0	3.7	-	S615L/WT
V.1	F	25	2.0	4.7	-	WT/WT
<sup>a</sup> Normal serum magnesium 1.5-2.5 mg/dL; <sup>b</sup> Normal serum potassium: 3.3-5.1 mmol/L; M:Male: F:Female: CC:Chondrocalcinosis: WT:Wild Type						

Table 1: Characteristics and *SLC12A3* gene variants identified in the proband and in thirteen individuals of his family pedigree. The proband is indicated by bold.



**Figure 1:** X-rays of proband showing classical chondrocalcinosis in knees.

Thirteen additional family members were investigated (5M: 8W; [25-79]; mean age 51); blood tests and x-rays were obtained for all of them (data not shown). The pedigree with investigated individuals is shown in Figure 2. The biochemical data in these patients show normal levels of serum magnesium ranging from 1.9 to 2.3 mg/dL and normal levels of potassium ranging from 3.7-4.7 mmol/L (Table 1).

When the S615L mutation was searched in the thirteen relatives of the proband, seven family members were found to be heterozygous, of which only one presented CC. Furthermore six individuals were wildtype homozygous; noteworthy, one of them (III.16) presented CC (Table 1 and Figure 2).

### Discussion

The GS patient described in this study has the S615L variation in homozygosity, while the other cases of GS with this variation were reported in compound heterozygotes [2]. In our study, seven individuals heterozygous for the S615L did not have either hypokalemia or hypomagnesemia, confirming that they were asymptomatic carriers of this variation.



**Figure 2:** Pedigree with 14 investigated individuals (6 males and 8 females). The CC affected individuals and the presence of the mutation S615L are also indicated. The proband with GS is denoted by the arrow.

Hypomagnesemia and hypocalciuria are found in most cases of GS, however, some cases with mutations in the NCCT do not show these conditions [19]. It is believed that hypomagnesemia causes CC by increasing formation and reducing solubility of CCP crystals [16]. Excess of PPi is the main precursor for CPPD crystal nucleation. Because the magnesium is a necessary cofactor for numerous enzymes, such as pyrophosphatases, and considering the fact that it increases the solubility of CPPD crystals, low levels of magnesium could induce CPPD deposition disease by raising PPi and/or reducing the saturation product of CPPD crystals [14]. The prevalence of CC increases with age (10-15% for people between 65 and 75 years) and is hence called sporadic in patients older than 60 years, whereas in younger individuals there are several putative underlying disorders causing CPPD deposition disease, such as hemochromatosis, hyperparathyroidism, hypomagnesemia or hypophosphatemia [20].

The assumption that GS is caused by a defect in the NCCT cotransporter in the renal distal tubule has been proven by the identification of numerous variations in the SLC12A3 gene in patients with GS [1,4,19,21]. In the present study the specific involvement of this cotransporter in the etiology of this disorder is further substantiated by the finding that the proband is homozygous for the S615L variation. The S615L identified in this study was previously described by Cruz and co-workers [18] in a study involved 36 kindreds from the United States, Canada and England and later reported in a study by Syrén et al. [22]. Although the SLC12A3 variations reported in previous studies are distributed throughout the whole protein [4,23], the study of Lemmink (1998) indicates that the carboxyterminal end represents a hot spot for variations [4]. S615L is located at the intracellular C-terminal end of the SLC12A3 protein. It is conceivable that structural alterations due to SLC12A3 variations in the C-terminal domain interfere with phosphorylation of the NCCT protein and as such with its regulation [4].

Evidence for an association between CC and GS comes from uncontrolled case reports, case series and only one cross-sectional study. As a result, its epidemiology remains unknown 16. There have been few cases described with a definite diagnosis of CC due to GS. In some patients with CPPD deposition disease secondary to hypomagnesemia, the stabilization of magnesium and potassium levels can reduce the deposition of CPPD crystals in the synovium and synovial fluid, reducing the frequency of attacks of articular pain 14.

## Conclusion

GS is a hereditary disease characterized by defective tubular reabsorption of magnesium and potassium, mostly caused by mutations in the *SLC12A3* gene. Sometimes GS patients, as in our case, might come with a CC diagnosis. We identified the genetic cause for GS in a proband with secondary early onset CC. Further studies are needed in order to enlighten the pathophysiology and prevalence of CC in patients with GS.

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