## Supplementary Material

**Table S1 – Studied patients' clinical profiles.**

| Patient | Gender | Age (years) | Age at onset (years) | Nº episodes/ site | Drugs | Tolerance | Treatment | Family history | Comorbidities |
|---|---|---|---|---|---|---|---|---|---|
| 1 | M | 23 | 19 | >5 E<br>2 L | Dipyrone sodium 300 paracetamol 400 mg Ibuprofen | Paracetamol 500 mg Etoricoxib 90 mg | Antihistamines Oral corticosteroids | No | Rhinitis Aorta root dilation |
| 2 | M | 13 | 7 | 4 E<br>4 L | Dipyrone Ibuprofen Flurbiprofen | Paracetamol 500 mg | Antihistamines Oral corticosteroids | No | Rhinitis |
| 3 | F | 45 | 24 | 4 E | Topical Diclofenac Dipyrone ASA Paracetamol 750 mg | Paracetamol 500 mg Etoricoxib 90 mg | Antihistamines | No | Rhinitis<br>Hypothyroidism Dyslipidemia |
| 4 | M | 44 | 10 | >5 E | Topical Diclofenac ASA Paracetamol 1000 mg | Paracetamol 500 mg Etoricoxib 90 mg Celecoxib 200 mg | Antihistamines | Yes | Rhinitis Nephrolithiasis |

NSAIDs: nonsteroidal anti-inflamatory drugs; ASA: acetylsalicylic acid; E: eyelid; L: lips.

**Table S2. Quality parameters obtained from NGS data.**

| Subjects ID | Reads on target (%) | Mean base coverage | 20x coverage | Aligned reads |
|---|---|---|---|---|
| **1-P** | 93,47% | 130,1 | 95,80% | 8.068.458.298 |
| **1-M** | 93,46% | 136,6 | 96,15% | 8.457.634.816 |
| **1-F** | 93,40% | 139,5 | 96,40% | 8.661.388.162 |
| **2-P** | 95,23% | 122,1 | 92,19% | 7.455.565.365 |
| **2-F** | 93,97% | 108,4 | 91,49% | 6.664.218.291 |
| **2-M** | 93,27% | 113,5 | 92,67% | 7.010.023.254 |
| **3-P** | 92,84% | 111,8 | 94,47% | 6.353.454.869 |
| **3-F** | 94,06% | 116,4 | 88,73% | 6.042.789.030 |
| **3-M** | 93,10% | 127,1 | 95,63% | 7.912.164.638 |
| **4-P** | 95,26% | 210,8 | 94,68% | 12.174.100.407 |
| **4-F** | 94,48% | 122,1 | 92,38% | 7.478.588.384 |
| **4-M** | 93,91% | 108,2 | 90,85% | 6.654.532.405 |

Subject ID according to data presented on clinical profiles (Table 1).
P – proband; F – father; M – mother.

**Table S3. LOF variants found in each mode of inheritance combined for family 1.**

| Gene | Function | cDNA | Protein | ExAC Global | Genotype | OMIM Phenotype | MH | RVIS | ClinVar | ACMG |
|---|---|---|---|---|---|---|---|---|---|---|
| **ACSL6** | FD | c.29delG | p.G10fs | - | hom | Myelodysplastic syndrome | - | 16.63 | - | VUS |
| **CBFB** | FD | c.205delT | p.F69fs | 6.789e-05 | het | Myeloid leukemia | - | 52.85 | - | VUS |
| **CHIT1** | SG | c.1015_1016insAGGGACTG GGCGGGGCCATGGTCT | p.W339delinsX | - | hom | Chitotriosidase deficiency | AR | 91.32 | - | VUS |
| **DGUOK** | FD | c.464delT | p.L155fs | - | hom | Mitochondrial DNA depletion syndrome 3 (hepatocerebral type) | AR | 35.99 | - | VUS |
| **FREM2** | FI | c.6976_6977insT | p.T2326fs | - | hom | Fraser syndrome | AR | 16.77 | - | VUS |
| **HTRA2** | FD | c.60delG | p.L20fs | 0.0005 | het | 3-methylglutaconic aciduria | AR | 71.27 | - | VUS |
| **IL17RC** | FD | c.1422delG | p.S474fs | - | het | Candidiasis | AR | 97.87 | - | VUS |
| **LRP1** | FD | c.9927_9928del | p.P3309fs | - | hom | Keratosis pilaris atrophicans | AR | 0.02 | - | VUS |
| **MAGEL2** | FD | c.563delC | p.P188fs | - | het | Schaaf-Yang syndrome | AD | 68.13 | - | VUS |
| **MUC5B** | FD | c.13157_13158del | p.P4386fs | - | hom | Pulmonary fibrosis | AD | 99.98 | - | VUS |
| **PRX** | FD | c.1482delA | p.V494fs | - | het | Charcot-Marie-Tooth disease | AD | 40.17 | - | VUS |
| **RYR1** | FD | c.4089delG | p.A1363fs | - | het | Central core disease | AD | 0.01 | - | VUS |
| **SIK1** | FD | c.1551delC | p.P517fs | - | hom | Epileptic encephalopathy | AD | 34.93 | - | VUS |
| **SRCAP** | FD | c.7225delG | p.A2409fs | - | het | Floating-Harbor syndrome | AD | 0.15 | - | VUS |

Function – exonic function according to RefGene assembly; MH – mode of inheritance according to OMIM; RVIS – residual variation intolerance score; ACMG – Variant classification according to the American College of Medical Genetics and Genomics; FD – frameshift deletion; FI – frameshift insertion; SG – stop codon gain; del – deletion; ins – insertion; het – heterozygous; hom – homozygous; hem – hemizygous; AD – autosome dominant; AR – autosome recessive; XLD – X-linked dominat; XLR – X-linked recessive X; VUS – variant with uncertain significance; B – benign; fs – frame-shift; dup – duplication. ExAC (Exome Aggregation Consortium - http://exac.broadinstitute.org/)





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**Table S4. LOF Variants found in each mode of inheritance combined for family 2.**

| Gene | Function | cDNA | Protein | ExAC Global | Genotype | OMIM Phenotype | MH | RVIS | ClinVar | ACMG |
|---|---|---|---|---|---|---|---|---|---|---|
| **AXIN2** | FD | c.1994delG | p.G665fs | - | het | Colorectal cancer | AD | 72.85 | - | VUS |
| **CACNA1D** | FD | c.22delA | p.K8fs | - | hom | Primary aldosteronism | AD | 0.32 | - | VUS |
| **CC2D2A** | FI | c.4517dupA | p.E1506fs | 1.632e-05 | het | COACH syndrome | AR | 9.83 | - | VUS |
| **COL9A2** | FI | c.1231dupC | p.Q411fs | - | het | Stickler syndrome | AD | 96.41 | - | VUS |
| **GATA1** | FD | c.3delG | p.M1fs | - | hem | Anemia | XLR | 17.75 | - | VUS |
| **MAD2L2** | FI | c.425dupC | p.P142fs | - | het | Fanconi anemia | AR | 58.26 | - | VUS |
| **MAGEL2** | FD | c.563delC | p.P188fs | - | het | Schaaf-Yang syndrome | AD | 68.13 | - | VUS |
| **MMP3** | FI | c.132_133insG | p.K45fs | - | het | Coronary heart disease | - | 15.91 | - | VUS |
| **MUC5B** | FI | c.13245_13246insC | p.P4415fs | - | het | Pulmonary fibrosis | AD | 99.98 | - | VUS |
| **PDP1** | FD | c.27delA | p.R9fs | - | het | Pyruvate dehydrogenase phosphatase deficiency | AR | 13.33 | - | VUS |
| **PLCZ1** | FD | c.1589delA | p.N530fs | - | hom | Spermatogenic failure 17 | AR | 23.51 | - | VUS |
| **RB1** | FD | c.10delA | p.K4fs | - | het | Bladder cancer | AD | 15.12 | - | VUS |
| **RNF212** | FD | c.713delC | p.P238fs | - | het | Recombination rate QTL 1 | - | - | - | VUS |
| **SIK1** | FD | c.1551delC | p.P517fs | - | hom | Epileptic encephalopathy | AD | 34.93 | - | VUS |
| **SYN1** | SG | c.C1423T | p.Q475X | - | hem | Epilepsy | XLD | - | - | VUS |
| **TCF3** | FD | c.1474delG | p.A492fs | - | het | Agammaglobulinemia 8 | AD | 47.26 | - | VUS |
| **TMPRSS15** | SG | c.1228delT | p.L410X | - | het | Enterokinase deficiency | AR | 97.45 | - | VUS |

Function – exonic function according to RefGene assembly; MH – mode of inheritance according to OMIM; RVIS – residual variation intolerance score; ACMG – Variant classification according to the American College of Medical Genetics and Genomics; FD – frameshift deletion; FI – frameshift insertion; SG – stop codon gain; del – deletion; ins – insertion; het – heterozygous; hom – homozygous; hem – hemizygous; AD – autosome dominant; AR – autosome recessive; XLD – X-linked dominat; XLR – X-linked recessive X; VUS – variant with uncertain significance; B – benign; fs – frame-shift; dup – duplication. ExAC (Exome Aggregation Consortium - http://exac.broadinstitute.org/)





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**Table S5. LOF Variants found in each mode of inheritance combined for family 3.**

| Gene | Function | cDNA | Protein | ExAC Global | Genotype | OMIM Phenotype | MH | RVIS | ClinVar | ACMG |
|---|---|---|---|---|---|---|---|---|---|---|
| **ABL2** | FD | c.2445delA | p.K815fs | - | het | Leukemia | - | 8.60 | - | VUS |
| **AR** | FD | c.250delC | p.P84fs | - | het | Androgen insensitivity | AD | 17.31 | - | VUS |
| **AVP** | FI | c.120_121insC | p.C41fs | - | hom | Diabetes insipidus | AD | - | - | VUS |
| **MUC5B** | FI | c.13154dupC | p.T4385fs | - | het | Pulmonary fibrosis | AD | 99.98 | - | VUS |
| **MUC7** | FI | c.922_923insC | p.I308fs | - | het | Asthma | AD | 98.58 | - | VUS |
| **SRCAP** | FD | c.7225delG | p.A2409fs | - | hom | Floating-Harbor syndrome | AD | 0.15 | - | VUS |
| **TTN** | FD | c.15296delC | p.P5099fs | - | het | Cardiomyopathy | AD | 98.04 | - | VUS |
| **WNK4** | FD | c.3297delC | p.S1099fs | - | hom | Pseudohypoaldosteronism | AD | 74.74 | - | VUS |
| **XYLT2** | FD | c.608delC | p.P203fs | - | het | Spondyloocular syndrome | AR | 22.80 | - | VUS |

Function – exonic function according to RefGene assembly; MH – mode of inheritance according to OMIM; RVIS – residual variation intolerance score; ACMG – Variant classification according to the American College of Medical Genetics and Genomics; FD – frameshift deletion; FI – frameshift insertion; SG – stop codon gain; del – deletion; ins – insertion; het – heterozygous; hom – homozygous; hem – hemizygous; AD – autosome dominant; AR – autosome recessive; XLD – X-linked dominat; XLR – X-linked recessive X; VUS – variant with uncertain significance; B – benign; fs – frame-shift; dup – duplication. ExAC (Exome Aggregation Consortium - http://exac.broadinstitute.org/)





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**Table S6. LOF Variants found in each mode of inheritance combined for family 4.**

| Gene | Function | cDNA | Protein | ExAC Global | Genotype | OMIM Phenotype | MH | RVIS | ClinVar | ACMG |
|---|---|---|---|---|---|---|---|---|---|---|
| **ABL2** | FD | c.2444_2445del | p.K815fs | - | het | Leukemia | - | 8.60 | - | VUS |
| **ABL2** | FD | c.2444delA | p.K815fs | - | het | Leukemia | - | 8.60 | - | VUS |
| **ATP2B3** | FD | c.1473delA | p.G491fs | - | hem | Spinocerebellar ataxia | XLR | 2.68 | - | VUS |
| **ATRX** | FD | c.3801delA | p.K1267fs | - | hem | Alpha-thalassemia myelodysplasia syndrome | XLD | 9.75 | - | VUS |
| **ATXN7** | FD | c.1898_1901del | p.G633fs | - | hom | Spinocerebellar ataxia 7 | AD | 67.50 | - | VUS |
| **AXIN2** | FD | c.1994delG | p.G665fs | - | hom | Colorectal cancer | AD | 72.85 | - | VUS |
| **CFH** | FD | c.2929_2930del | p.K977fs | - | het | Basal laminar drusen | AD | 80.37 | - | VUS |
| **CNTN2** | FD | c.1297delG | p.G433fs | - | het | Epilepsy | AR | 39.31 | - | VUS |
| **COL18A1** | FD | c.3365_3366del | p.G1122fs | - | hom | Knobloch syndrome | AR | 86.36 | - | VUS |
| **DDHD1** | FD | c.2484delT | p.F828fs | - | het | Spastic paraplegia 28 | AR | 48.78 | - | VUS |
| **DST** | FD | c.5609delA | p.K1870fs | - | het | Neuropathy | AR | 20.71 | - | VUS |
| **FBLN1** | FD | c.1839_1840del | p.P613fs | - | het | Synpolydactyly | AD | 29.61 | - | VUS |
| **FRZB** | FD | c.84_85del | p.P28fs | - | het | Osteoarthritis susceptibility 1 | M | 77.80 | - | VUS |
| **GDI1** | FI | c.175_176insG | p.L59fs | - | hem | Mental retardation | XLD | 25.15 | - | VUS |
| **H6PD** | FD | c.1804delG | p.G602fs | - | het | Cortisone reductase deficiency 1 | AR | 10.19 | - | VUS |
| **INPP5E** | FD | c.367delG | p.A123fs | - | hom | Joubert syndrome 1 | AR | - | - | VUS |
| **ITPR2** | FD | c.5405delA | p.K1802fs | - | het | Anhidrosis | AR | 2.78 | - | VUS |
| **LHCGR** | FD | c.1764delT | p.F588fs | - | het | Leydig cell adenoma | AD | 74.63 | - | VUS |
| **LIAS** | FD | c.107delA | p.K36fs | - | het | Hyperglycinemia | AR | 27.69 | - | VUS |
| **NRG1** | FD | c.266delA | p.Q89fs | - | het | Schizophrenia | - | 91.71 | - | VUS |
| **PALB2** | SG | c.886delA | p.M296X | - | het | Fanconi anemia | AD | 72.85 | - | VUS |
| **PIKFYVE** | FD | c.787delA | p.K263fs | - | het | Corneal fleck dystrophy | AD | 4.16 | - | VUS |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| **RIN2** | FD | c.1192delG | p.G398fs | - | hom | Macrocephaly | AR | 80.40 | - | VUS |
| **RP1L1** | FI | c.3955dupG | p.A1319fs | - | het | Occult macular dystrophy | AD | 99.90 | B | VUS |
| **SERPINA3** | FI | c.659_660insCCCCAAGATA | p.P220fs | - | het | Alpha-1-antichymotrypsin deficiency | - | 25.73 | - | VUS |
| **SIK1** | FD | c.1551delC | p.P517fs | - | hom | Epileptic encephalopathy | AD | 34.93 | - | VUS |
| **SPRTN** | FD | c.1257delT | p.N419fs | - | het | Ruijs-Aalfs syndrome | AR | 18.72 | - | VUS |
| **TBCK** | FD | c.1181delA | p.N394fs | - | het | Hypotonia | AR | 50.50 | - | VUS |
| **TPCN2** | FD | c.348delT | p.A116fs | 1.649e-05 | het | Skin/hair/eye pigmentation 10 | - | 29.62 | - | VUS |
| **UGT1A3** | FD | c.511delT | p.F171fs | 8.244e-06 | hom | Crigler-Najjar syndrome | AR | 19.73 | - | VUS |
| **WAS** | FD | c.1349delC | p.A450fs | - | hem | Neutropenia | XLR | 80.01 | - | VUS |
| **ZFAT** | FD | c.1607delT | p.L536fs | - | het | Autoimmune thyroid disease | - | 27.08 | - | VUS |
| **ZFHX3** | FD | c.6847delC | p.Q2283fs | - | het | Prostate cancer | - | 0.12 | - | VUS |
| **ZNF513** | FD | c.867_868del | p.G289fs | - | hom | Retinitis pigmentosa 58 | AR | 24.53 | - | VUS |

Function – exonic function according to RefGene assembly; MH – mode of inheritance according to OMIM; RVIS – residual variation intolerance score; ACMG – Variant classification according to the American College of Medical Genetics and Genomics; FD – frameshift deletion; FI – frameshift insertion; SG – stop codon gain; del – deletion; ins – insertion; het – heterozygous; hom – homozygous; hem – hemizygous; AD – autosome dominant; AR – autosome recessive; XLD – X-linked dominat; XLR – X-linked recessive X; VUS – variant with uncertain significance; B – benign; fs – frame-shift; dup – duplication. ExAC (Exome Aggregation Consortium - http://exac.broadinstitute.org/)





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**Table S7 - Number of variants found in the 10 genes (*PTGS1, PTGS2, ALOX5AP, ALOX5, ALOX12, ALOX15, LTC4S, PTGFR, PTGDR, PTGER1, PTGER2, PTGER3, PTGER4, CYSLTR1 e CYSLTR2*) related to COX signaling pathway.**

| Family | Subject | Variants | Total | Real* | Rare** |
|---|---|---|---|---|---|
| | | | COX pathway genes variants (genes) | | |
| **1** | 1 | 52913 | 8 (5) | 2 (1) | - |
| | 3 | 53363 | 9 (5) | 3 (3) | - |
| | 2 | 52814 | 8 (6) | 2 (2) | - |
| **2** | 1 | 54210 | 8 (4) | 3 (3) | 1 |
| | 2 | 52022 | 11 (4) | 7 (3) | 1 |
| | 3 | 53545 | 9 (6) | 4 (4) | 2 |
| **3** | 3 | 53104 | 9 (5) | 3 (2) | 1 |
| | 1 | 53650 | 9 (6) | 3 (3) | - |
| | 2 | 52934 | 10 (6) | 5 (4) | - |
| **4** | 2 | 52730 | 8 (5) | 2 (1) | 1 |
| | 3 | 52500 | 10 (6) | 4 (4) | - |
| | 1 | 53173 | 12 (6) | 3 (3) | 1 |

*Real variants determined by analysis on IGV software (*Integrative Genomics Viewer, Broad Institute*). **Variants with frequency lower than 1% in ExAC (Exome Aggregation Consortium - http://exac.broadinstitute.org/).





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