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 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 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 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.

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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.

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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

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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

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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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