Novel human pathological mutations. Gene symbol: HBA1. Disease: haemoglobin variant

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HUMAN GENE MUTATIONS

Novel human pathological mutations

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Gene symbol: HEXA

Disease: Tay-Sachs disease

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Input for Missense/Nonsense Mutations (*single base-pair substitutions*)

Accession	Codon number	Nucleotide substitution	Amino acid substitution
HM080090	497	TAT-TGT	Tyr-Cys

Gene symbol: SLC3A1

Disease: Cystinuria

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Input for Missense/Nonsense Mutations (*single base-pair substitutions*)

Accession	Codon number	Nucleotide substitution	Amino acid substitution
HM080091	397	TAT-TGT	Tyr-Cys

Gene symbol: SLC3A1

Disease: Cystinuria

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Input for Missense/Nonsense Mutations (*single base-pair substitutions*)

Accession	Codon number	Nucleotide substitution	Amino acid substitution
HM080092	584	aAGA-TGA	Arg-Term

Gene symbol: SLC7A9

Disease: Cystinuria

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Input for small deletions (*<21 bp*)

Accession	Deletion	Codon number/location
HD080027	CCAAGGA^AACacAAAGAATTTT	203

Gene symbol: ABCA4

Disease: Macular dystrophy

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Input for Missense/Nonsense Mutations (*single base-pair substitutions*)

Accession	Codon number	Nucleotide substitution	Amino acid substitution
HM080093	187	CGT-CAT	Arg-His

Gene symbol: UBE3A

Disease: Angelman Syndrome

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Input for small insertions (*<21 bp*)

Accession	Insertion	Codon number/location
HI080014	GCTGAG^GCATgTGGTACAGAG	139

Comments: The mutation was detected by ECMA (Enzymatic Cleavage Mismatch Analysis) and characterized by direct sequencing (performed twice).The proband is a 27 months boy with microcephaly and presents a typical for Angelman EEG. Mutation analysis for both parents revealed normal sequences. Sequencing results available upon request.

Gene symbol: JAG1

Disease: Allagille syndrome

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Input for small insertions (*<21 bp*)

Accession	Insertion	Codon number/location
HI080015	TCCTCCAG_I16E17_GTt^GACAGTCAGT	706; c.2115dupT; p.Asp706Stop

Comments: cacgt(T)gaca T is the inserted base.

Gene symbol: COL4A5

Disease: Alport syndrome

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Input for small deletions (*<21 bp*)

Accession	Deletion	Codon number/location
HD080028	CTTACTG^GCCctGAGTCTTTGG	17

Comments: Female with asymptomatic hematuria and proteinuria. c.49_50delCT/p.Leu17GlufsX22.

Gene symbol: F9

Disease: Haemophilia B

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Input for small insertions (*<21 bp*)

Accession	Insertion	Codon number/location
HI080016	GTGGTT^TGCTcctgctCCTGTACTGA	109

Comments: Novel insertion in Pakistani patient.

Gene symbol: F8

Disease: Haemophilia A

Gulzar Niazi, Zeeshan Shaukat, Khalid Masood, Rashid Hussain
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Input for small deletions (*<21 bp*)

Accession	Deletion	Codon number/location
HD080029	GCTCAA^ACACtCTTGATGGAC	298

Comments: Novel deletion in a Pakistani patient.

Gene symbol: RHD

Disease: Rhesus negative blood group

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Input for complex rearrangements

Accession	Description
HP080001	Hybrid with ex. 4-9 RHCE

Comments: Haplotype—cdE.

Gene symbol: ALAS2

Disease: Sideroblastic anaemia

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Input for Missense/Nonsense Mutations (*single base-pair substitutions*)

Accession	Codon number	Nucleotide substitution	Amino acid substitution
HM080094	503	GCC-GTC	Ala-Val

Comments: Mutation found in the propositus and his mother.

Gene symbol: SRY

Disease: XY sex reversal

Celia Ravel, B. Lakhal, H. Elghezal, R. Braham, A. Saad, A. Bashamboo, J.P. Siffroi, K. McElreavey, S. Christin-Maitre
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Input for regulatory mutations

Accession	Nucleotide substitution	Location relative to
HR080003	TGGTTGGGCGGGGTTGAGGGGGTGTTGAGG(G-C) CGGAGAAATGCAAGTTTCATTACAAAAGTT	Initiator methionine

Comments: A 34 year-old phenotypically normal female was referred to our attention for primary amenorrhea. The vagina was present but reduced in length. The weight was 69 kg; the height 1 m 69. FSH, LH, estradiol, prolactin and testosterone levels reached 110 mUI/ml, 24.3 mUI/ml, 12 pg/ml, 12.6 ng/ml and 0.3 ng/ml, respectively. Karyotype was 46,XY. At ultrasound examination, gonads could not be identified. However, a small uterus was present. The two kidneys were normal. SRY mutational analysis revealed a single base-pair substitution. c. -130G > C located in a highly conserved Sp1A motif that has previously been shown experimentally to be involved in regulation of SRY expression. tgttgagg(g-c)cggagaaa.

Gene symbol: APC

Disease: Adenomatous polyposis coli

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Input for splicing mutations (*single base-pair substitution*)

Accession	Intron designation, number or letter	Donor/Acceptor	Relative location	Nucleotide substitution
HS080016	14	Donor	+1	G–C

Comments: Familial case, multiple polyps and colorectal cancer. HGVS notation: c.1958 + 1G > C. Reference sequence: NM_000038.

Gene symbol: F8

Disease: Hemophilia A

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Input for Missense/Nonsense Mutations (*single base-pair substitutions*)

Accession	Codon number	Nucleotide substitution	Amino acid substitution
HM080095	1888	AGC-ATC	Ser-Ile

Comments: Novel missense mutation in a Pakistani patient.

Gene symbol: COL7A1

Disease: Epidermolysis bullosa dystrophica

Natividad Cuadrado-Corrales, M. Garcia, M.J. Escamez, A. Carrillo, M.J. Trujillo-Tiebas, C. Ayuso, M. Del Rio
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Input for Missense/Nonsense Mutations (*single base-pair substitutions*)

Accession	Codon number	Nucleotide substitution	Amino acid substitution
HM080096	2434	aGGA-AGA	Gly-Arg

Comments: This mutation was found in two members of a spanish family. The proband (children) presented typical clinical features of DEB whereas the mother was asymptomatic.

Gene symbol: COL7A1

Disease: Epidermolysis bullosa dystrophica

Marta Garcia, M.J. Escamez, N. Cuadrado-Corrales, A. Carrillo, M.J. Trujillo-Tiebas, C. Ayuso, M. Del Rio
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Input for Missense/Nonsense Mutations (*single base-pair substitutions*)

Accession	Codon number	Nucleotide substitution	Amino acid substitution
HM080097	1332	GGC-GAC	Gly-Asp

Comments: Mutation identified in a 8 year-old-female patient from Spain, with recessive distrophic epidermolysis bullosa. This mutation has been identified in exon 33 of the COL7A1 gene.

Gene symbol: COL7A1

Disease: Epidermolysis bullosa dystrophica

Natividad Cuadrado-Corrales, M. Garcia, M.J. Escamez, A. Carrillo, M.J. Trujillo-Tiebas, C. Ayuso, M. Del Rio
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Input for splicing mutations (*single base-pair substitution*)

Accession	Intron designation, number or letter	Donor/Acceptor	Relative location	Nucleotide substitution
HS080017	96	Donor	+2	T–C

Comments: Mutation identifed in a year-old- male from Spain, with recessive distrophic epidermolysis bullosa. This mutation has been identified in intron 96 of the COL7A1 gene.

Gene symbol: SLC3A1

Disease: Cystinuria

Anthoula Chatzikyriakidou, K.D. Kollios, I. Georgiou
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Input for Missense/Nonsense Mutations (*single base-pair substitutions*)

Accession	Codon number	Nucleotide substitution	Amino acid substitution
HM080098	264	TGGc-TGA	Trp-Term

Comments: The novel described SLC3A1 mutation W264X (c.792G > A) was found in one cystinuria patient from Macedonia (North Greece) in heterozygosity with the common SLC3A1 mutation T216 M.

Gene symbol: ABCD1

Disease: Adrenoleukodystrophy

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Input for Missense/Nonsense Mutations (*single base-pair substitutions*)

Accession	Codon number	Nucleotide substitution	Amino acid substitution
HM080099	132	TGG-TAG	Trp-Term

Comments: It is a nonsense mutation found in exon 1 of ABCD1 gene in an X-ALD patient from India. c.395G > A.

Gene symbol: RHO

Disease: Retinitis pigmentosa

Juhua Yang
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Input for Missense/Nonsense Mutations (*single base-pair substitutions*)

Accession	Codon number	Nucleotide substitution	Amino acid substitution
HM080100	343	gAGC-TGC	Ser-Cys

Comments: This mutation was heteroplasmic missense (Ser343Cys) and was found in an isolated Chinese retinitis pigmentosa (RP) patient (designated as RP0101201), who originated from Fujian province, China.

Gene symbol: ECM1

Disease: Lipoid Proteinosis

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Input for gross insertions and duplications

Accession	Description
HN080001	Insertion 62 bp nt 1209_1210

Comments: A homozygous insertion, 1209_1210insTAGGAAGCCAATTGATATCATAGCTCAGACCATACCTATG TATCCAATGGTTCTTTTTTTCC in exon 8.

Gene symbol: PROC

Disease: Protein C deficiency

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Input for splicing mutations (*single base-pair substitution*)

Accession	Intron designation, number or letter	Donor/Acceptor	Relative location	Nucleotide substitution
HS080021	IVS8	Acceptor	−2	A–G

Comments: This acceptor splice-site mutation (IVS 8, −2 A–G) results in a frameshift with a stop codon at codon 274[TAG].

Gene symbol: SCN1A

Disease: Severe Myoclonic Epilepsy of Infancy

Giovanni Provenzano, E. Mannarino, F. Annesi, E.V. De Marco, F.E. Rocca, V. Greco, V. Scornaienchi, P. Tarantino, D. Civitelli, A. Quattrone, G. Tortorella, G. Annesi
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Input for small deletions (*<21 bp*)

Accession	Deletion	Codon number/location
HD080030	AT^GCAGG_E7I7_GTAaGTCAATAATT	342

Comments: E7I7 IVS7 + 4delA. The gene SCN1A coding for the alpha1 subunit of the neuronal sodium channel, has been found mutated in various types of epilepsy. The associated phenotypes range from benign febrile seizures to extremely serious conditions, such as severe myoclonic epilepsy of infancy (SMEI). We have identified in a SMEI patient coming from the Southern Italy a novel mutation. This variation was found in the splicing donor site of intron 7, consisting in a deletion of a single nucleotide (IVS7 + 4delA). The IVS7 + 4delA was not present in 100 healthy controls with a negative family history from Southern Italy.

Gene symbol: NR3C1

Disease: Glucocorticoid receptor deficiency

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Input for small deletions (*<21 bp*)

Accession	Deletion	Codon number/location
HD080031	AAAAAA^CTTCtgTTTCATCAAA	772

Comments: We detected a homozygous TG deletion (c. 2318-2319delTG) in a child with severe glucocorticoid resistance. The predicted effect on the glucocorticoid receptor protein is a frame shift mutation with a read-through of the stop codon and a 24 non-sense amino acid tail (p. F774S fs X24).

Gene symbol: DMD

Disease: Muscular dystrophy, Duchenne

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Input for small insertions (*<21 bp*)

Accession	Insertion	Codon number/location
HI080017	CTTACAG_I31E32_^AAAaAAATTACAAG	1449

Gene symbol: DMD

Disease: Muscular dystrophy, Duchenne

Javier Garcia-Planells,[1] Manoli Torres-Puente,[1] Juan J. Vilchez,[2] Manuel Pérez-Alonso[1]
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Input for Missense/Nonsense Mutations (*single base-pair substitutions*)

Accession	Codon number	Nucleotide substitution	Amino acid substitution
HM080102	1362	gCAA-TAA	Gln-Term

Comments: Unpublished.

Gene symbol: DMD

Disease: Muscular dystrophy, Duchenne

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Input for Missense/Nonsense Mutations (*single base-pair substitutions*)

Accession	Codon number	Nucleotide substitution	Amino acid substitution
HM080103	35	gCAG-TAG	Gln-Term

Comments: Unpublished.

Gene symbol: HMBS

Disease: Porphyria, acute intermittent

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Input for small insertions (*<21 bp*)

Accession	Insertion	Codon number/location
HI080018	GCAGT^GTGCCcAGTAGCCGTG	263

Comments: The C duplication at position 791 (c.791dupC) dose not change the aminoacid at codon 264 but it causes a frameshift with a stop after 2 codons. p.Pro264ProfsX2.

Gene symbol: SCN5A

Disease: Brugada Syndrome

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Input for Missense/Nonsense Mutations (*single base-pair substitutions*)

Accession	Codon number	Nucleotide substitution	Amino acid substitution
HM080101	43	cCGA-TGA	Arg-Term

Comments: A 21-year-old Caucasian male, asymptomatic for syncopal events, with a positive family history for sudden cardiac death (father died suddenly at age 42) and a diagnosis of Brugada Syndrome, was referred to our attention for molecular screening. The basal ECG showed incomplete bundle-branch block and coved-type ST-segment elevation in the right precordial leads (V1–V2), highly suggestive for Brugada Syndrome (BrS). The Flecainide test was positive, ventricular fibrillation was induced during electrophysiological study, and an implantable cardioverter defribillator (ICD) was implanted. His sister (18-year-old), asymptomatic for cardiac events, showed first-degree atrio-ventricular block, borderline interventricular conduction time and phases of diurnal sino-atrial blocks. The Flecanide test was interrupted prematurely for the occurrence of a stable sino-atrial block. SCN5A was screened through DHPLC and sequence analysis. A novel C127T transversion causing the nonsense mutation R43X and the premature truncation of the sodium channel protein was identified. The same mutation, not identified in 300 controls, was detected in the proband's sister. She performed an electrophysiological study that induced ventricular fibrillation and therefore an ICD was implanted. The father, who died suddenly, was an obligate mutation-carrier as the mother was negative at the molecular screening. Accordingly, the sodium channel mutation identified was related to BrS, conduction defects and sudden cardiac death.

Gene symbol: CYP17A1

Disease: 17α-Hydroxylase/17,20-Lyase Deficiency

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Input for Missense/Nonsense Mutations (*single base-pair substitutions*)

Accession	Codon number	Nucleotide substitution	Amino acid substitution
HM080104	209	CTG-CCG	Leu-Pro

Gene symbol: VHL

Disease: Von Hippel–Lindau syndrome

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Input for Missense/Nonsense Mutations (*single base-pair substitutions*)

Accession	Codon number	Nucleotide substitution	Amino acid substitution
HM080105	112	cTAC-TGC	Tyr-Cys

Gene symbol: SPG4

Disease: Spastic paraplegia, autosomal dominant

Antonella Fogli, Roberta Battini, Fulvia Baldinotti, Maria Elena Conidi, Angela Michelucci, Paolo Simi
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Input for Missense/Nonsense Mutations (*single base-pair substitutions*)

Accession	Codon number	Nucleotide substitution	Amino acid substitution
HM080106	454	gGAG-AAG	Glu-Lys

Comments: Male patient with moderate spasticity and moderate disability.

Gene symbol: SPG4

Disease: Spastic paraplegia, autosomal dominant

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Input for Missense/Nonsense Mutations (*single base-pair substitutions*)

Accession	Codon number	Nucleotide substitution	Amino acid substitution
HM080107	413	TCA-TTA	Ser-Leu

Comments: Female patient with mild spasticity and moderate disability.

Gene symbol: ABCA4

Disease: Stargardt disease

Jana Aguirre-Lamban, R. Riveiro-Alvarez, M. Garcia-Hoyos, D. Cantalapiedra, M. Martinez-Garcia, E. Vallespin, A. Avila-Fernandez, C. Villaverde-Montero, M.J. Trujillo-Tiebas, C. Ayuso
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Input for Missense/Nonsense Mutations (*single base-pair substitutions*)

Accession	Codon number	Nucleotide substitution	Amino acid substitution
HM080108	841	gCAG-AAG	Gln-Lys

Gene symbol: ASS1

Disease: Citrullinaemia

David Dimmock, Pamela Trapane, Annette Feigenbaum, Catherine E. Keegan, Stephen Cederbaum, James Gibson, Michael J. Gambello, Keith Vaux, Patricia Ward, Gregory M. Rice, Jon A. Wolff, William E. O'Brien, Ping Fang
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Input for Missense/Nonsense Mutations (*single base-pair substitutions*)

Accession	Codon number	Nucleotide substitution	Amino acid substitution
HM080109	272	CGC-CAC	Arg-His

Comments: c.815G > A.

Gene symbol: ASS1

Disease: Citrullinaemia

David Dimmock, Pamela Trapane, Annette Feigenbaum, Catherine E. Keegan, Stephen Cederbaum, James Gibson, Michael J. Gambello, Keith Vaux, Patricia Ward, Gregory M. Rice, Jon A. Wolff, William E. O'Brien, Ping Fang
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Input for Missense/Nonsense Mutations (*single base-pair substitutions*)

Accession	Codon number	Nucleotide substitution	Amino acid substitution
HM080110	72	TTCa-TTG	Phe-Leu

Comments: c.216C > G.

Gene symbol: HBA2

Disease: Thalassemia alpha

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Input for splicing mutations (*single base-pair substitution*)

Accession	Intron designation, number or letter	Donor/Acceptor	Relative location	Nucleotide substitution
HS080018	IVS1	Acceptor	+1	G-A

Comments: The mutation HBA2 c.96 G > A was found in an Ecuadorian patient with alpha Thalassemia type 2.

Gene symbol: CPOX

Disease: Coproporphyria

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Input for Missense/Nonsense Mutations (*single base-pair substitutions*)

Accession	Codon number	Nucleotide substitution	Amino acid substitution
HM080111	205	gGTG-TTG	Val-Leu

Comments: c.613 G > T.

Gene symbol: HBB

Disease: Haemoglobin variant

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Input for Missense/Nonsense Mutations (*single base-pair substitutions*)

Accession	Codon number	Nucleotide substitution	Amino acid substitution
HM080112	3	cCTG-ATG	Leu-Met

Comments: HBB c.10 C > A.

Gene symbol: HBB

Disease: Haemoglobin variant

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Input for Missense/Nonsense Mutations (*single base-pair substitutions*)

Accession	Codon number	Nucleotide substitution	Amino acid substitution
HM080113	103	cTTC-CTC	Phe > Leu

Comments: The mutation HBB c.310 T > C was found in a heterozygous Italian patient with polycythemia.

Gene symbol: HBA1

Disease: Haemoglobin variant

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Input for Missense/Nonsense Mutations (*single base-pair substitutions*)

Accession	Codon number	Nucleotide substitution	Amino acid substitution
HM080114	90	cAAG-GAG	Lys-Glu

Comments: HBA1 c.271A > G.

Gene symbol: ABCD1

Disease: Adrenoleukodystrophy

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Input for Missense/Nonsense Mutations (*single base-pair substitutions*)

Accession	Codon number	Nucleotide substitution	Amino acid substitution
HM080121	617	cCGC-AGC	Arg-Ser

Comments: We have submitted this mutation recently in the X-ald database (http://www.x-ald.nl). Other mutations also found at this position in the ABCD1 gene that results into the substitution of other amino acids. But this novel mutation results substitution of arginine to serine identified by our group first time.

Gene symbol: JAG1

Disease: Alagille syndrome

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Input for Missense/Nonsense Mutations (*single base-pair substitutions*)

Accession	Codon number	Nucleotide substitution	Amino acid substitution
HM080115	702	TGCc-TGA	Cys-Term

Comments: JAG1 gene were analyzed by sequencing of entire coding region. This transversion in exon 16 was found in one Italian patient in an heterozygous state. This nonsense mutation was de novo and it truncates the protein at codon 702, which is 517 amino acids from the end of the protein. Clinical phenotype: the age at diagnosis was 7 years old. She is a female patient with typical features of Alagille syndrome. The histological analysis revealed bile ducts paucity. c.2106C > A.

Gene symbol: JAG1

Disease: Alagille syndrome

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Input for Missense/Nonsense Mutations (*single base-pair substitutions*)

Accession	Codon number	Nucleotide substitution	Amino acid substitution
HM080116	885	TGCc > TGA	Cys-Term

Comments: JAG1 gene were analyzed by sequencing of entire coding region. This transversion in exon 22 was found in one Italian patient in an heterozygous state. This nonsense mutation was de novo and it truncates the protein at codon 885, which is 334 amino acids from the end of the protein. Clinical phenotype: The age at diagnosis was 1 year. She is a female patient with typical features of Alagille syndrome. Liver transplantation was performed when she was 1 year old. The histological analysis revealed bile ducts paucity. c.2655C > A.

Gene symbol: JAG1

Disease: Alagille syndrome

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Input for Missense/Nonsense Mutations (*single base-pair substitutions*)

Accession	Codon number	Nucleotide substitution	Amino acid substitution
HM080117	1097	gCGG-TGG	Arg-Trp

Comments: JAG1 gene were analyzed by sequencing of entire coding region. This transition in exon 26 was found in one Italian patient in an heterozygous state. The mutation occurs 122 amino acids from the end of the protein. This missense mutation was not found in 480 alleles (healthy blood donors). This variant is predicted to be probably damaging (PolyPhen informatic tool) and intolerant (SIFT informatic tool). The aminoacid is conserved during evolution. The same mutation was found in the mother in heterozygous state. Clinical phenotype: The age at diagnosis was 4 years. She is a female patient with typical features of Alagille syndrome. The mother shows a very mild phenotype. c.3289C > T.

Gene symbol: JAG1

Disease: Alagille syndrome

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Input for Missense/Nonsense Mutations (*single base-pair substitutions*)

Accession	Codon number	Nucleotide substitution	Amino acid substitution
HM080118	880	TGTa-TGA	Cys-Term

Comments: JAG1 gene were analyzed by sequencing of entire coding region. This transversion in exon 22 was found in one Italian patient in an heterozygous state. This nonsense mutation truncates the protein at codon 880, which is 339 amino acids from the end of the protein. The same mutation was found in the father in heterozygous state. Clinical phenotype: The age at diagnosis was 2 years. She is a female patient with typical features of Alagille syndrome. Liver transplantation was

performed when she was 2 years old. The histological analysis revealed bile ducts paucity. The father shows a very mild phenotype. c.2640T > A.

Gene symbol: JAG1

Disease: Alagille syndrome

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Input for splicing mutations (*single base-pair substitution*)

Accession	Intron designation, number or letter	Donor/Acceptor	Relative location	Nucleotide substitution
HS080019	IVS 13	Acceptor	−1	G–A

Comments: JAG1 gene were analyzed by sequencing of entire coding region.This transition affects the invariant AG on 3′ (acceptor) splice site of intron 13 and it was found in one Italian patient in an heterozygous state. This may affect RNA splicing, according to mutalyzer tool. Not found in 368 alleles (healthy blood donors).The parents were not available for analysis. Clinical phenotype: the age at diagnosis was 1 month old. He is a male patient with typical features of Alagille syndrome. Liver transplantation was performed when she was 11 year old. The histological analysis revealed bile ducts paucity. c.1721-1.

Gene symbol: JAG1

Disease: Alagille syndrome

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Input for splicing mutations (*single base-pair substitution*)

Accession	Intron designation, number or letter	Donor/Acceptor	Relative location	Nucleotide substitution
HS080020	IVS 2	Donor	+2	T–C

Comments: JAG1 gene were analyzed by sequencing of entire coding region. This transition affects the invariant GT on 5′ (donor) splice site of intron 2 and it was found in one Italian patient in an heterozygous state. This may affect RNA splicing, according to mutalyzer tool. Not found in 360 alleles (healthy blood donors).The parents were not available for analysis. Clinical phenotype: The age at diagnosis was 1 month. She is a female patient with typical features of Alagille syndrome. c.387 + 2 T > C.

Gene symbol: JAG1

Disease: Alagille syndrome

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Input for small insertions (*<21 bp*)

Accession	Insertion	Codon number/location
HI080019	ACAAA^TATCAaGTGTTCCTGC	320

Comments: JAG1 gene were analyzed by sequencing of entire coding region. This duplication in exon 7 was found in one Italian patient in an heterozygous state. It produces a frameshift from the aminoacid 322 generating a premature stop codon 5 amino acids after. The same mutation was found in the mother in heterozygous state. Not found in 100 alleles (healthy blood donors). Clinical phenotype: The age at diagnosis was 4 years old. She is a female patient with typical features of Alagille syndrome. Liver transplantation was performed when she was 4 years old. The histological analysis revealed bile ducts paucity. The mother shows a very mild phenotype. c.962dupA/p.Cys322Valfs*5.

Gene symbol: JAG1

Disease: Alagille syndrome

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Input for small insertions (*<21 bp*)

Accession	Insertion	Codon number/location
HI080020	ACTCAT^CAGCcCGTGTCTCAA	304

Comments: JAG1 gene were analyzed by sequencing of entire coding region. This duplication in exon 7 was found in one Italian patient in an heterozygous state. It produces a frameshift from the amino acids 306 generating a premature stop codon 8 amino acids after. It is a de novo mutation. This duplication was not found in 300 alleles (healthy blood donors). Clinical phenotype: the age at diagnosis was 2 months old. He is a male patient with typical features of Alagille syndrome. c.914dupC/p.Cys306Valfs*8.

Gene symbol: JAG1

Disease: Alagille syndrome

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Input for small insertions (*<21 bp*)

Accession	Insertion	Codon number/location
HI080021	GTGCTG^CCTTtTCAGTTTCGC	123

Comments: JAG1 gene were analyzed by sequencing of entire coding region. This duplication in exon 2 was found in one Italian patient in an heterozygous state. It produces a frameshift from the amino acids 125 generating a premature stop codon 19 amino acids after. It was de novo mutation. Clinical phenotype: The age at diagnosis was 10 years. He is a male patient with typical features of Alagille syndrome. c.371dupT/p.Ser125Glnfs*19.

Gene symbol: JAG1

Disease: Alagille syndrome

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Input for small deletions (*<21 bp*)

Accession	Deletion	Codon number/location
HD080032	CATCGCT^TGCgAGCCTTCCCC	1002

Comments: JAG1 gene were analyzed by sequencing of entire coding region. This duplication in exon 24 was found in one Italian patient in an heterozygous state. It produces a frameshift from the aminoacid 1003 generating a premature stop codon 33 amino acids after. This mutation was de novo. Not found in 308 alleles (healthy blood donors). Clinical phenotype: The age at diagnosis was 1 year old. She is a female patient with typical features of Alagille syndrome. The histological analysis revealed bile ducts paucity. c.3007delG/p.Glu1003Serfs*33.

Gene symbol: JAG1

Disease: Alagille syndrome

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Input for small deletions (*<21 bp*)

Accession	Deletion	Codon number/location
HD080033	CCTGAC^AAATatcAGTGTTCCTG	319

Comments: JAG1 gene were analyzed by sequencing of entire coding region. This three-bases deletion in exon 7 was found in one Italian patient in an heterozygous state. This nonsense mutation was de novo and it truncates the protein at codon 320, which is 899 amino acids from the end of the protein. Clinical phenotype: the age at diagnosis at birth. He is a male patient with typical features of Alagille syndrome. c.959_961del (ATC)/p.Tyr320X.

Gene symbol: JAG1

Disease: Alagille syndrome

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Input for small deletions (*<21 bp*)

Accession	Deletion	Codon number/location
HD080034	GGCATC^TGTAaTGAGCCCTGG	276

Comments: JAG1 gene were analyzed by sequencing of entire coding region. This deletion in exon 6 was found in one Italian patient in an heterozygous state. It produces a frameshift from the aminoacid 277 generating a premature stop codon 135 amino acids after. It is a de novo mutation. Clinical phenotype: the age at diagnosis was 1 year. She is a female patient with typical features of Alagille syndrome. c.830delA/p.Asn277Metfs*135.

Gene symbol: JAG1

Disease: Alagille syndrome

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Input for small deletions (*<21 bp*)

Accession	Deletion	Codon number/location
HD080035	ATCCTG^GACGaccagTGCTTCGTCC	922

Comments: JAG1 gene were analyzed by sequencing of entire coding region. This five-bases deletion in exon 23 was found in one Italian patient in an heterozygous state. It produces a frameshift from the aminoacid 923 generating a premature stop codon 27 amino acids after. The same mutation was found in the father in heterozygous state. Clinical phenotype: The age at diagnosis was 2 months. He is a male patient with typical features of Alagille syndrome. The father shows a very mild phenotype. c.2768_2772del (ACCAG)/p.Asp923Valfs*27.

Gene symbol: JAG1

Disease: Alagille syndrome

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Input for small deletions (*<21 bp*)

Accession	Deletion	Codon number/location
HD080036	GTCAC^AACAGagGCAGCTGTAA	347

Comments: JAG1 gene were analyzed by sequencing of entire coding region. This two-bases deletion in exon 8 was found in one Italian patient in an heterozygous state. It produces a frameshift from the aminoacid 349 generating a premature stop codon 3 amino acids after. The parents were not available for analysis. Clinical phenotype: the age at diagnosis was 2 years. She is a female patient with typical features of Alagille syndrome. c.1044_1045del (AG)/p.Gly349Glnfs*3.

Gene symbol: JAG1

Disease: Alagille syndrome

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Input for small deletions (*<21 bp*)

Accession	Deletion	Codon number/location
HD080037	GGAGGGG^CCCatctgtgctcaGA_E18I18_GTGAGTGT	777

Comments: JAG1 gene were analyzed by sequencing of entire coding region. This deletion in exon 18 was found in one Italian patient in an heterozygous state. It produces a frameshift from the aminoacid 778 generating a premature stop codon 4 amino acids after. The same mutation was found in the mother in heterozygous state. Clinical phenotype: The age at diagnosis was 7 years. He is a male patient with typical features of Alagille syndrome. The mother shows a very mild phenotype. c.2332_2342del (ATCTGTGCTCA)/p.Ile778Glufs*4.

Gene symbol: JAG1

Disease: Alagille syndrome

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Input for small deletions (*<21 bp*)

Accession	Deletion	Codon number/location
HD080038	CTGTGAC^AAAg_E6I6_GTATGGCCCT	295

Comments: JAG1 gene were analyzed by sequencing of entire coding region. The 1 bp deletion in exon 6 was found in one Italian patient in an heterozygous state. It produces a frameshift from the aminoacid 296 and generates a premature stop codon 116 amino acids after. The mutation was de novo. Clinical phenotype: the age at diagnosis was 2 months. He is

a male patient with typical features of Alagille syndrome. Liver transplantation was performed when he was 2 years old. The histological analysis revealed bile ducts paucity. c.886delG/p.Asp296Ilefs*116.

Gene symbol: MYBPC3

Disease: Cardiomyopathy, hypertrophic

Disease: Cardiomyopathy, hypertrophic
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Input for Missense/Nonsense Mutations (*single base-pair substitutions*)

Accession	Codon number	Nucleotide substitution	Amino acid substitution
HM080119	608	aCCT-TCT	Pro-Ser

Comments: Aminoacid substitution not conservative and conserved during evolution; not found in 384 alleles (healthy blood donors). SIFT and PolyPhen predict, respectively, that the substitution is tolerated and is possibly damaging. Clinical description: the age at onset was 16 years. She underwent cardiac transplantation at age 20 years. She is doing well. The family history was positive. c.1822C > T/p.Pro608Ser.

Gene symbol: MYBPC3

Disease: Cardiomyopathy, hypertrophic

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Input for small deletions (*<21 bp*)

Accession	Deletion	Codon number/location
HD080039	AG_I22E23_CTG^CTGTGtgAGACCGAGGG	718

Comments: The two-bases deletion produces the insertion of a stop codon and truncates the protein at codon 719, which is 556 amino acids from the end of the protein. The mutation was not found in 300 alleles (healthy blood donors); Clinical description: this mutation was found in two unrelated patients. The first one was 2 months old male baby. He underwent cardiac transplantation at age of 1 year. The family history was positive. The other patient was 43 years old male and he has obstructive type of hypertrophic cardiomyopathy that required a surgical myectomy. The family history was positive. c.2157_2158del (TG) NM_000256/p.Cys719ter.

Gene symbol: LDLR

Disease: Hypercholesterolemia

M.S. Katrina Kotzer, Linnea Baudhuin
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Input for Missense/Nonsense Mutations (*single base-pair substitutions*)

Accession	Codon number	Nucleotide substitution	Amino acid substitution
HM080120	317	TGCc-TGA	Cys-Term

Comments: The nomenclature we use is updated from what I see in the database. The nucleotide is c.1014C > A and changes the codon p.Cys338Term.

Gene symbol: GLA

Disease: Fabry disease

Susana Ferreira, Carmen Valbuena, Filipa Carvalho, João Paulo Oliveira
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Input for gross insertion and duplications

Accession	Description
HN080002	Tandem duplication of exons 2, 3 and 4

Comments: In a young adult male with the classic phenotype of Fabry disease, in whom sequencing of all GLA exons and exon-intron boundaries had been normal, a direct tandem duplication of exons 2–3–4 was found by cDNA analysis. This finding was confirmed by genomic DNA sequencing, which further showed that the duplicated segment most probably localized between exons 1 and 2. This interpretation is based on the demonstration of a normal intron 4 sequence, using a pair of primers in exons 4 (forward) and 5 (reverse), and an abnormal intron 4 sequence using a pair of primers in exons 4 (forward) and 2 (reverse). Both the 5′ and the 3′ ends of the duplicated segment localize to Alu repeats.

MLPA anaylsis confirmed the duplication of exons 2, 3 and 4. To the best of our knowledge this is the first duplication defect described in association with Fabry disease.