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HUMAN GENE MUTATIONS

Novel human pathological mutations

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Gene symbol: LAMP2

Disease: Danon Disease

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Missense/nonsense mutations (single base-pair substitutions)

Accession number	Codon number	Nucleotide substitution	Amino acid substitution
HM070116	293	cCGA-TGA	Arg293Term

Comments: This mutation was found in a young male patient. The mutant protein lacks the transmembrane domain, impairing the cellular autophagosomal pathway and leading to the vacuolar cardiomyopathy. Histological examination of left ventricle wall cardiac muscle specimens from explanted heart of our patient revealed hypertrophied myocardial cells, interstitial and replacement fibrosis and an extended sarcoplasmic vacuolization, more prominent in the inner layer of the myocardial wall than in the outer sub-epicardial layer. The vacuoles varied in size and most of them were empty but a few contained residues of PAS-positive diastase digestible material.

After the genetic analysis, we reviewed the clinical history of our patient because LAMP2 mutations are usually associated to Danon disease, characterised by cardiomyopathy, myopathy and variable mental retardation. In our patient, the age at diagnosis of HCM was 12 years. Two years later, he was transferred to our Hospital for an acute episode of heart failure. Echocardiography identify a concentric hypertrophy in a dilated left ventricle with a moderate systolic dysfunction. Neurological and electromyographic examinations prior to heart transplantation were normal. Laboratory investigations repeatedly revealed increased levels of serum creatine kinase (638 U/l). At the age of 15 years, he underwent successfully an orthotopic heart transplantation for persistent signs and symptoms of advanced heart failure. The mutation was de novo as the mother was not a carrier. NM_013995.1:c.877C>T and NM_02294.1:c877C>T.

Gene symbol: MTM1

Disease: Myotubular Myopathy

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Missense/nonsense mutations (single base-pair substitutions)

Accession number	Codon number	Nucleotide substitution	Amino acid substitution
HM070117	461	aCAA-TAA	Gln-Term

Gene symbol: GLA

Disease: Fabry Disease

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Small deletions (<21 bp)

Accession number	Deletion	Codon number/location
HD070025	CCCTG^GGTAAaggaGTGGCCTGTA	373

Comments: Detected in a family with classical variant of Fabry disease.

Gene symbol: UBE3A

Disease: Angelman Syndrome

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Missense/nonsense mutations (single base-pair substitutions)

Accession number	Codon number	Nucleotide substitution	Amino acid substitution
HM070118	20	GGC-GTC	Gly-Val

Comments: UBE3A Isoform 3.

Gene symbol: TBX19

Disease: ACTH deficiency, isolated?

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Missense/nonsense mutations (single base-pair substitutions)

Accession number	Codon number	Nucleotide substitution	Amino acid substitution
HM070119	159	TTGa-TTC	Leu-Phe

Comments: SIFT indicates this mutation is not tolerated.
Polyphen score idicates this mutation is probably damaging (score = 2.044).

Gene symbol: MTM1

Disease: Myotubular Myopathy?

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Missense/nonsense mutations (single base-pair substitutions)

Accession number	Codon number	Nucleotide substitution	Amino acid substitution
HM070120	409	aAAA-GAA	Lys-Glu

Comments: Heterozygous.

Gene symbol: VWF

Disease: Von Willebrand Disease?

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Missense/nonsense mutations (single base-pair substitutions)

Accession number	Codon number	Nucleotide substitution	Amino acid substitution
HM070121	1472	cCAC-GAC	His-Asp

Comments: Heterozygous.

Gene symbol: MTM1

Disease: Myotubular Myopathy

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Small deletions (<21 bp)

Accession	Deletion	Codon number/location
HI070013	TCACG^AGATAaCGCGTTTCCC	139

Comments: Stop codon introduced at insertion site.

Gene symbol: COL1A2

Disease: Ehlers-Danlos Syndrome Type VIIB

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Small deletions (<21 bp)

Accession	Deletion	Codon number/location
HD070026	ATATATATAAttttttttttttACTTCTCTAG	0

Comments: IVS5-22 to -11 deletion of 12 T nucleotides of the 3′ (acceptor) splice site consensus sequence, between T-22 and T-11. At the cDNA level the deletion causes skipping of exon 6 of COL1A2.

Gene symbol: ROBO3

Disease: Gaze Palsy, Horizontal, with Progressive Scoliosis

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Missense/nonsense mutations (single base-pair substitutions)

Accession number	Codon number	Nucleotide substitution	Amino acid substitution
HM070122	576	cTGG-CGG	Trp-Arg

Comments: 1726 T-C. Novel mutation found in Arab patient with HGPPS.

Gene symbol: KCNH2

Disease: Long QT Syndrome

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Missense/nonsense mutations (single base-pair substitutions)

Accession number	Codon number	Nucleotide substitution	Amino acid substitution
HM070123	72	CCG-CGG	Pro-Arg

Comments: A 15-year-old male was referred to our attention for a suspected Long QT Syndrome. The clinical and family history were negative for cardiac events and sudden death. Due to episodes of atypical chest pain, he performed an ECG that showed a prolonged QT interval (QTc 485 ms), with notched T waves in V3–V4. An MRI showed normal features. During the clinical investigation a 24-h Holter monitoring showed periods of marked QT interval prolongation (up to 600 ms) with notched and biphasic T waves in the precordial leads, suggesting a LQT2 genetic sub-type. Long QT Syndrome was diagnosed and beta-blocker therapy was started.

All LQTS genes were screened by DHPLC and sequence analysis. A novel C215G transversion predicting the missense mutation Pro72Arg was identified in the N-terminal region of KCNH2. This mutation is in a highly conserved amino acid and was not identified in 150 controls.

Gene symbol: KCNQ1

Disease: Long QT Syndrome

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Missense/nonsense mutations (single base-pair substitutions)

Accession number	Codon number	Nucleotide substitution	Amino acid substitution
HM070124	514	ATT-ACT	Ile-Thr

Comments: The proband of the family is a 14-year-old white female, asymptomatic for syncopal events, referred to our attention for a prolongation of the QT interval (QTc 514 ms), identified on an ECG performed for palpitations. The clinical history was negative for syncopal events; however, we were told that a cousin was affected by the Long QT Syndrome (LQTS). Exercise stress test showed a poor QT adaptation during exercise and a further prolongation during the recovery phase, strongly suggesting the LQT1 variant of LQTS. An echocardiogram was normal.

LQTS was diagnosed and beta-blocker therapy was started. The proband's brother was asymptomatic with periods of QT prolongation mainly during the recovery phase of exercise and the mother was asymptomatic with a slight QT prolongation (QTc 470 ms).

All LQTS genes were screened by DHPLC and sequence analysis. A novel T1541C transversion predicting the missense mutation Ile514Thr was identified in the C-terminal region of KCNQ1. The same mutation, located in a conserved region of the protein, was identified in the proband's mother and brother.

Gene symbol: KCNH2

Disease: Long QT Syndrome

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Missense/nonsense mutations (single base-pair substitutions)

Accession number	Codon number	Nucleotide substitution	Amino acid substitution
HM070126	50	cGAG-TAG	Glu-Stop

Comments: A 29-year-old white male, asymptomatic for syncopal events, was referred to our attention for a marked prolongation of the QT interval (QTc 500 ms), which was identified in an ECG performed during hospitalisation for orthopaedic surgery. The family history was negative for syncope or sudden cardiac death. The Long QT syndrome was diagnosed and beta-blocker therapy was started.

All LQTS genes were screened by DHPLC and sequence analysis. A novel G148T transversion predicting the nonsense mutation E50X was identified in the N-terminal region of KCNH2. The same mutation was not identified in his parents and in 150 Caucasian controls.

Gene symbol: SCN5A

Disease: Brugada Syndrome

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Missense/nonsense mutations (single base-pair substitutions)

Accession number	Codon number	Nucleotide substitution	Amino acid substitution
HM070127	1380	AACa-AAG	Asn-Lys

Comments: A 31-year-old male was referred to our attention for a syncopal event that occurred in resting conditions and that was associated with loss of urine. A basal ECG showed sinus rhythm, incomplete right bundle-branch block and coved type ST-segment elevation in the right precordial leads (V1–V2). The echocardiogram showed normal features; while a 12-lead 24-h Holter monitoring showed coved type ST-segment elevation, diagnostic for Brugada Syndrome, alternated with phases of saddle-back type ST-segment elevation. Flecanide test was positive and ventricular fibrillation was easily induced during electrophysiological study (EPS), therefore an implantable cardioverter defibrillator (ICD) was implanted.

SCN5A gene was screened through DHPLC and sequence analysis. A novel C4140G transversion predicting the missense Asn1380Lys was identified. The Asn 1380 is located between S5 and S6 in the third domain of the sodium channel and is highly conserved among different species. The mutation was not identified in proband's parents and in 150 Caucasian controls.

Gene symbol: SCN5A

Disease: Brugada Syndrome

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Missense/nonsense mutations (single base-pair substitutions)

Accession number	Codon number	Nucleotide substitution	Amino acid substitution
HM070128	878	tCGC-TGC	Arg-Cys

Comments: A 34-year-old male, asymptomatic for syncopal events, was referred to our attention for suspected Brugada Syndrome. Rest electrocardiogram showed sinus rhythm, incomplete right bundle-branch block and coved-type ST-segment elevation in the right precordial leads (V1–V2), diagnostic for Brugada Syndrome. Echocardiography showed a structurally normal heart. A 12-lead ECG Holter monitoring showed intermittently a coved and saddle-back type ST-segment elevation in the right precordial leads. Ventricular fibrillation was induced during electrophysiological study (EPS) and an implantable cardioverter defibrillator (ICD) was recommended.
The patient has a heterozygous twin without the Brugada pattern at the basal ECG and with a negative Flecainide test.

SCN5A gene was screened in the proband through DHPLC and sequence analysis. A novel C2632T transversion predicting the missense Arg878Cys was identified between S5 and S6 in the second domain of the sodium channel. The mutation was not identified in the proband's twin and in 150 Caucasian controls. The Arg 878 is highly conserved among different species.

Gene symbol: KCNQ1

Disease: Long QT Syndrome

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Small deletions (<21 bp)

Accession	Deletion	Codon number/location
HI070014	GGGGCAG^GTGtgTTTGCCACGT	221

Comments: The proband is a 52-year-old female, asymptomatic for syncopal events, with a clinical diagnosis of Long QT Syndrome. She was referred to our attention in order to perform molecular screening. All LQTS genes were screened by DHPLC and sequence analysis. A novel insertion of two nucleotides in the coding region of KCNQ1 was identified, causing a frameshift and a premature termination in the extra-cellular loop between S3 and S4 on KCNQ1. The same mutation was detected in the proband's sister and son, both asymptomatic with prolonged QTc.

Gene symbol: KCNH2

Disease: Long QT Syndrome

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Small deletions (<21 bp)

Accession	Deletion	Codon number/location
HD070027	CGACGCC^TCGgGCTCCAGCTG	261

Comments: A 23-year-old gypsy female was referred to our attention for multiple syncopal events and for an episode of cardiac arrest requiring DC shock. The ECG showed an important QTc prolongation (600 ms) with biphasic (V2–V3) and negative T waves (V4–V6, DI, DII, aVF). A Long QT syndrome was diagnosed, an ICD implanted and beta-blocker therapy started.

LQTS genes were screened through DHPLC and sequence analysis. A novel deletion of one nucleotide (784) in the coding region of KCNH2 was identified, causing a frameshift and a premature termination in the N-terminal segment of the protein.

The same mutation was identified in the proband's sister and in her three children, all with a clearly prolonged QTc.

Gene symbol: MAP2K2

Disease: Cardio-Facio-Cutaneous Syndrome

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Missense/nonsense mutations (single base-pair substitutions)

Accession number	Codon number	Nucleotide substitution	Amino acid substitution
HM070129	62	aGCC-CCC	Ala-Pro

Gene symbol: LAMC2

Disease: Epidermolysis Bullosa, Herlitz

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Missense/nonsense mutations (single base-pair substitutions)

Accession number	Codon number	Nucleotide substitution	Amino acid substitution
HM070130	1122	TTA-TGA	Leu-Stop

Comments: The patient, who was found to be homozygous for this mutation, showed the typical clinical symptoms of Herlitz disease and died at the age of three months. Immunofluorescence analysis of his skin revealed a complete absence of laminin-5 (laminin-332) in the epidermal basement membrane.

Gene symbol: ABCA4

Disease: Macular Dystrophy

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Small deletions (<21 bp)

Accession	Deletion	Codon number/location
HD070028	CCTCCCG^CCCcCCCAG_E30I30_GTACC	1512

Comments: The mutation was in the last codon of exon 30.

Gene symbol: ABCA4

Disease: Macular Dystrophy

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Missense/nonsense mutations (single base-pair substitutions)

Accession number	Codon number	Nucleotide substitution	Amino acid substitution
HM070131	2047	ATC-AAC	Ile-Asn

Gene symbol: AVP

Disease: Diabetes Insipidus, Neurohypophyseal

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Missense/nonsense mutations (single base-pair substitutions)

Accession number	Codon number	Nucleotide substitution	Amino acid substitution
HM070132	104	TGC-TAC	Cys-Tyr

Gene symbol: IDS

Disease: Mucopolysaccharidosis II

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Missense/nonsense mutations (single base-pair substitutions)

Accession number	Codon number	Nucleotide substitution	Amino acid substitution
HM070133	369	TCA-TAA	Ser-Term

Comments: The mutation was found in an argentinean hemizygote patient with arab descent. The substitution c.1106 C>A in exon 8 predicts a degradation post-transcriptional.

Gene symbol: IDS

Disease: Mucopolysaccharidosis II

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Splicing mutations (*single base-pair substitution*)

Accession	Intron designation, number or letter	Donor/acceptor	Relative location	Nucleotide substitution
HS070012	3	Donor	+3	A>T

Comments: The substitution c.418+3 A>T in the intron 3 was found in an argentinean hemizygote patient with phenotype Intermediate/Severe and Spanish–Chilean descent.

Gene symbol: ABCA4

Disease: Macular Dystrophy

Jana Aguirre-Lamban, R. Riveiro-Alvarez, D. Cantalapiedra, E. Vallespin, A. Avila-Fernandez, M. J. Trujillo-Tiebas, C. Villaverde-Montero, C. Ayuso
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Missense/nonsense mutations (single base-pair substitutions)

Accession number	Codon number	Nucleotide substitution	Amino acid substitution
HM070134	762	GCA-GAA	Ala-Glu

Gene symbol: IDS

Disease: Hunter Syndrome

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Small deletions (<21 bp)

Accession	Deletion	Codon number/location
HD070029	AATGCC^TTTGcGCAG_E2I2_GTATGT	78

Comments: The deletion c.236delC was found in an argentinean hemizygote patient with severe phenotype of Spanish–Chilean descent. Moreover, this patient was heterozygote for Sandhoff disease.

Gene symbol: ABCA4

Disease: Macular Dystrophy

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Missense/nonsense mutations (single base-pair substitutions)

Accession number	Codon number	Nucleotide substitution	Amino acid substitution
HM070135	1724	TGGg-TGT	Trp-Cys

Gene symbol: FECH

Disease: Porphyria, Erythropoietic

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Gross deletions
Description: 12566 bp incl. promoter + ex. 1 nt 1-9628 to 67+2871.

The breakpoints of this deletion are located in the upstream intergenic region and in the intron 1, respectively. The sequence at the first breakpoint is TGCCC/aggc, the sequence at the second breakpoint is tgccc/GGCCT. The deletion embraces a portion of 9628 bp of upstream intergenic region (including the entire FECH promoter), the exon 1 and a portion of 2871 bp of intron 1.
Comments: The lack of the entire promoter prevents the allele expression.
NC_000018: 53367797-53421484.
Accession number: HG070004

Gene symbol: ABCA4

Disease: Macular Dystrophy

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Splicing mutations (*single base-pair substitution*)

Accession	Intron designation, number or letter	Donor/acceptor	Relative location	Nucleotide substitution
HS070013	38	Donor	+5	G-A

Gene symbol: ABCA4

Disease: Macular Dystrophy

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Missense/nonsense mutations (single base-pair substitutions)

Accession number	Codon number	Nucleotide substitution	Amino acid substitution
HM070136	2137	TGT-TAT	Cys-Tyr

Gene symbol: EDA

Disease: Ectodermal Dysplasia

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Splicing mutations (*single base-pair substitution*)

Accession	Intron designation, number or letter	Donor/acceptor	Relative location	Nucleotide substitution
HS0700014	IVS6	Donor site	−1	G-A

Comments: The determination of mutation versus polymorphism was done by checking database (EDA1 mutation database http://chromium.liacs.nl/; HapMap Project Database http://www.hapmap.org; NCBI, http://www.ncbi.nlm.nih.gov/SNP), by searching for the alterations in 100 healthy Italian controls, and by checking the families similarly (mother not carried).

Gene symbol: EDA

Disease: Ectodermal Dysplasia

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Missense/nonsense mutations (single base-pair substitutions)

Accession number	Codon number	Nucleotide substitution	Amino acid substitution
HM070137	3	TACc-TAG	Tyr-Term

Gene symbol: EDA

Disease: Ectodermal Dysplasia

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Splicing mutations (*single base-pair substitution*)

Accession	Intron designation, number or letter	Donor/acceptor	Relative location	Nucleotide substitution
HS070015	IVS7	Donor	+4	A-T

Comments: This mutation was tested in 100 unaffected health subject, and it is not present in the main database (EDA1 mutation database http://chromium.liacs.nl/; HapMap Project Database http://www.hapmap.org; NCBI, http://www.ncbi.nlm.nih.gov/SNP).

Gene symbol: EDA

Disease: Ectodermal Dysplasia

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Gross deletions
Description: 10369 bp nt 406717-417085 incl. ex. 4-8
Comments: This gross deletion has been confirmed through PCR (ex4-ex8).
Accession: HG070005

Gene symbol: MEN1

Disease: Multiple Endocrine Neoplasia 1

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Missense/nonsense mutations (single base-pair substitutions)

Accession number	Codon number	Nucleotide substitution	Amino acid substitution
HM070138	141	cCAG-TAG	Gln-Term

Comments: This novel mutation was identified in a 10-year-old caucasian boy with an insulinoma and a family history of MEN1. His father died at 45 years of age due to complications related to a metastatic carcinoid tumor. The same mutation was found in another sister who developed an insulinoma at 15 years and a parathroid adenoma at 18 years of age. Another asymtomatic 15-year-old sister also carried the same mutation.

Gene symbol: ARX

Disease: Mental Retardation

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Missense/nonsense mutations (single base-pair substitutions)

Accession number	Codon number	Nucleotide substitution	Amino acid substitution
HM070139	539	gGCC-ACC	Ala-Thr

Comments: This novel mutation was identified in two brothers (11 and 9 years old) who presented with non-specific mental reatrdation, severe cognitive delay, microephaly, autism and history of infantile spasms that began during the first 2 months of life. The seizures were refractory to multiple anti-epileptic medictions. Family history was consistent with X-linked recessive inheritance. Brain MRI showed mild cerebral atrophy without neuro-migrational abnormalities. Symptomatic males in this family were concordant for this mutation.

Gene symbol: CHD7

Disease: CHARGE Syndrome

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Splicing mutations (*single base-pair substitution*)

Accession	Intron designation, number or letter	Donor/acceptor	Relative location	Nucleotide substitution
HS070016	24	Donor	+1	G-T

Comments: By RT-PCR and cDNA sequencing we observed that the mutation causes exon 24 skipping.

Gene symbol: CYP21A2

Disease: Adrenal Hyperplasia

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Missense/nonsense mutations (single base-pair substitutions)

Accession number	Codon number	Nucleotide substitution	Amino acid substitution
HM070140	407	tGAT-AAT	Asp-Asn

Comments: A 25-year-old white female, clinically diagnosed for the nonclassical form of adrenogenital syndrome, was addressed to our Laboratory for the molecular screening of CYP21A2 gene. The serum basal level of 17-OPH was 11.7 nmol/L, increasing to 32.1 nmol/L after ACTH loading. All the other serum hormonal levels were within the normal ranges. The complete direct sequencing on the entire gene showed a novel D407N missense mutations in heterozygous condition.

The D407N mutation has not been previously described until now and it has not been detected in 50 normal control samples tested in our Laboratory ($N = 100$ alleles).

Gene symbol: CYP21A2

Disease: Adrenal Hyperplasia

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Missense/nonsense mutations (single base-pair substitutions)

Accession number	Codon number	Nucleotide substitution	Amino acid substitution
HM070141	194	ATC-AAC	Ile-Asn

Comments: A 40-year-old white woman and his daughter, clinically diagnosed for the nonclassical form of adrenogenital syndrome, were addressed to our Laboratory for the molecular screening of CYP21A2 gene. The complete direct sequencing on the entire gene showed the following results: the woman resulted compound heterozygous for the V281L and the novel I194N missense mutations, while her daughter was heterozygous for the V281L mutations. The genetic analysis of CYP21A2 gene was extended to her parents: the mother resulted heterozygous for the I194N while the father for the V281L.

The novel I194N missense mutation, in exon 5 of CYP21A2 gene, has not been detected in 50 normal control subjects (100 alleles).

Gene symbol: CYP21A2

Disease: Adrenal Hyperplasia

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Missense/nonsense mutations (single base-pair substitutions)

Accession number	Codon number	Nucleotide substitution	Amino acid substitution
HM070142	119	CAC-CGC	His-Arg

Comments: A 20-year-old woman, affected by nonclassical form of adrenogenital syndrome, clinically diagnosed in an outside Hospital, was addressed to our Laboratory for the CYP21A2 genetic screening. The complete direct sequencing of CYP21A2 gene showed the presence of a novel H119R missense mutation in the exon3. The MLPA analysis confirmed the loss of wild-type allele. The mother of the girl carried the H119R mutation in heterozygous condition, with normal serum hormonal levels. Finally, the CYP21A2 molecular screening resulted wild-type on the father.

The novel H119R missense mutation has not been detected in 50 normal control subjects (100 alleles).

Gene symbol: MAP2K1

Disease: Cardio-Facio-Cutaneous Syndrome

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Missense/nonsense mutations (single base-pair substitutions)

Accession number	Codon number	Nucleotide substitution	Amino acid substitution
HM070143	55	tACC-CCC	Thr-Pro

Gene symbol: RS1

Disease: Retinoschisis, X-Linked juvenile

Rosa Riveiro-Alvarez, D. Cantalapiedra, E. Vallespin, J. Aguirre-Lamban, A. Avila-Fernandez, A. Gimenez-Pardo, M. J. Trujillo-Tiebas, C. Ayuso
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Missense/nonsense mutations (single base-pair substitutions)

Accession number	Codon number	Nucleotide substitution	Amino acid substitution
HM070144	207	gCAC-GAC	His-Asp

Gene symbol: RS1

Disease: Retinoschisis, X-Linked juvenile

Rosa Riveiro-Alvarez, D. Cantalapiedra, E. Vallespin, J. Aguirre-Lamban, A. Avila-Fernandez, A. Gimenez-Pardo, M. J. Trujillo-Tiebas, C. Ayuso
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Missense/nonsense mutations (single base-pair substitutions)

Accession number	Codon number	Nucleotide substitution	Amino acid substitution
HM070145	197	cCGC-AGC	Arg-Ser

Gene symbol: GCDH

Disease: Glutaricacidaemia I

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Missense/nonsense mutations (single base-pair substitutions)

Accession number	Codon number	Nucleotide substitution	Amino acid substitution
HM070146	178	GGG-GAG	Gly-Glu

Comments: Glutaric acidemia type I (GA-I, MIM#231670) is an inborn error of metabolism caused by the deficiency of glutaryl-CoA dehydrogenase (GCDH, EC1.33.99.7), the enzyme which catalyzes the conversion of glutaryl-CoA to crotonyl-CoA. In this study, we analyzed the GCDH gene of a female baby whose blood C5DC-carnitine was elevated detected by tandem mass spectrometry newborn screening and also revealed high amounts of glutaric acid and 3-hydroxy-glutaric acid in her urine. Direct sequencing of all exons and exon-intron boundaries revealed a G-to-A transition at nucleotide 533 in exon 6. This nucleotide variation converts a glycine at codon 178 to a glutamic acid (p.G178E). The other mutation was found in intron10 (IVS10-2 A-to-C), which caused a splicing variation in intron 10 and exon 11 and had been reported in previous articles. To identify whether the c.G533A is a polymorphism or not, a panel of 50 normal individual male was screened by direct sequencing and no one was present A base in this site. We purposed that this novel mutation would affect the GCDH activity.

Gene symbol: GNE

Disease: Inclusion Body Myopathy

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Missense/nonsense mutations (single base-pair substitutions)

Accession number	Codon number	Nucleotide substitution	Amino acid substitution
HM070147	179	cCTT-TTT	Leu-Phe

Comments: Missense mutation.

Gene symbol: CLN5

Disease: Neuronal Ceroid Lipofuscinosis, Finnish Variant

Romina Kohan, Natalia Cannelli, Chiara Aiello, Filippo M. Santorelli, Adriana I. Cismondi, Montserrat Milà, Ana M. Oller Ramírez, Inés Noher Halac
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Small deletions (<21 bp)

Accession	Deletion	Codon number/location
HD070030	ATTGTG^CACAaacaGTTCTATTTG	367

Comments: This 4-bp deletion in exon 4 was found in one Spanish patient in homozygous state. It produces frameshift from the 368 aminoacid and generates a premature stop codon 13 aminoacids after. The same mutation was found in heterozygous state in the mother and the father. The onset age was 7 years, and death at 15 years. The skin biopsy showed numerous membrane-bound lysosomal vacuoles with curvilinear bodies at electron microscopy level.

Gene symbol: TPP1

Disease: Neuronal Ceroid Lipofuscinosis, Late Infantile

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Missense/nonsense mutations (single base-pair substitutions)

Accession number	Codon number	Nucleotide substitution	Amino acid substitution
HM070148	104	cTTG-TAG	Leu-stop

Comments: This mutation was found in one Argentinean patient in heterozygous state. This substitution p.L104X (c.311T>A) in exon 4 predicts a post-transcriptional degradation. The patient showed TPP-I deficiency (value: 0.0, normal range = 110–368 nmol/h per mg prot).

Gene symbol: MEN1

Disease: Multiple Endocrine Neoplasia Type 1

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Missense/nonsense mutations (single base-pair substitutions)

Accession number	Codon number	Nucleotide substitution	Amino acid substitution
HM070154	417	TACg-TAG	Tyr-Term

Gene symbol: CYP21A2

Disease: Non-classic 21-Hydroxylase Deficiency

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Missense/nonsense mutations (single base-pair substitutions)

Accession number	Codon number	Nucleotide substitution	Amino acid substitution
HM070149	119	CAC-CGC	His-Arg

Comments: Paola Concolino, Angelo Minucci, Bruno Giardina, and Ettore Capoluongo.
A 20-year-old woman, affected by nonclassical form of adrenogenital syndrome, clinically diagnosed in an outside Hospital, was addressed to our Laboratory for the CYP21A2 genetic screening. The complete direct sequencing of CYP21A2 gene showed the presence of a novel H119R missense mutation in the exon 3. The MLPA analysis confirmed the loss of wild-type allele. The mother of the girl carried the H119R mutation in heterozygous condition, with normal serum hormonal levels. Finally, the CYP21A2 molecular screening resulted wild-type on the father.

The novel H119R missense mutation has not been detected in 50 normal control subjects (100 alleles).

Gene symbol: HBD

Disease: Thalassaemia Delta

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Small deletions (<21 bp)

Accession	Deletion	Codon number/location
HD070031	TGGTGTG^GCTggctAATGCCCTGG	138

Comments: The insertion of GGCT between codons 138 and 139 results in a frameshift with a new stop codon at codon 140 (TAA) and premature termination of translation. c.417_418insGGCT; p.Asn139GlyfsX2.

Gene symbol: CLN5

Disease: Neuronal Ceroid Lipofuscinosis, Finnish Variant

I. Adriana Cismondi, Natalia Cannelli, Chiara Aiello, Filippo M. Santorelli, Romina Kohan, Ana M. Oller Ramírez, Inés Noher Halac
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Small deletions (<21 bp)

Accession	Deletion	Codon number/location
HI070015	TCGGGC^ATCCcCCTCCCGGCG	96

Comments: This 1-bp insertion in exon 1 was found in one Argentinean patient in homozygous state. It produces a frameshift from the aminoacid 97 and probably generates a premature stop codon 12 aminoacids after. Clinical phenotype: onset age 4 months, current age 9 years. Morphological phenotype: electron microscopy of skin biopsy with granular osmiophilic deposits (GROD)-like bodies and cytosomes filled of fingerprint profiles.

Gene symbol: NOTCH3

Disease: CADASIL

Carmine Ungaro, Teresa Sprovieri, Francesca Luisa Conforti, Domenico Consoli, Luigi Citrigno, Maria Liguori, Aldo Quattrone, Rosalucia Mazzei
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Missense/nonsense mutations (single base-pair substitutions)

Accession number	Codon number	Nucleotide substitution	Amino acid substitution
HM070152	997	gTGC-GGC	Cys-Gly

Comments: The molecular screening of a CADASIL patient revealed a novel missense mutation within the exon 18 of the NOTCH3 gene, leading to the aminoacid change Cys-Gly at codon 997.

Gene symbol: NOTCH3

Disease: CADASIL

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Missense/nonsense mutations (single base-pair substitutions)

Accession number	Codon number	Nucleotide substitution	Amino acid substitution
HM070153	131	cGGT-TGT	Gly-Cys

Comments: We report a new missense mutation in the NOTCH3 gene in which a single substitution in exon 4 results in an aminoacid change at codon 131.

Gene symbol: MECP2

Disease: Rett Syndrome

Teresa Sprovieri, Rosalucia Mazzei, Carmine Ungaro, Luigi Citrigno, Aldo Quattrone, Francesca Luisa Conforti
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Gross deletions
Description: 26 bp nt 1167
Comments: A 26-bp deletion in exon 4 of the MeCP2 gene was found in a classical Rett patient. This novel mutation creates a frameshift with a resultant TGA stop codon.
Accession: HG070006

Gene symbol: ABCA4

Disease: Stargardt Disease

Susana Maia-Lopes, M. Castelo-Branco, E. Silva, J. Aguirre-Lamban, R. Riveiro-Alvarez, M. J. Trujillo-Tiebas, C. Ayuso
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Small deletions (<21 bp)

Accession	Deletion	Codon number/location
HD070032	GCAGCTC^AACacGGGGACACAG	1345

Comments: In this codon there is also a insCA. However, in our case we have found an 'AC' deletion in three subjects!