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HUMAN GENE MUTATIONS

Novel human pathological mutations

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Gene Symbol: MLH1

Disease: Colorectal cancer, non-polyposis

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Small Deletions (<21 bp)

Accession number:	**Codon number/location:**	**Deletion:**
hd0609	11/E1	CGG CGG∧C TGG ACG

Comments: L11X6

Gene Symbol: LMNA

Disease: Emery-Dreifuss muscular dystrophy (EMD)

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Small Deletions (<21 bp)

Accession number:	**Codon number/location:**	**Deletion:**
hd0610	68–69	GAGTCT∧GAA GaggtggTCAGCCGCG

Comments: A 37-year-old female clinically diagnosed with Emery-Dreifuss Muscular Distrophy (EDMD) was referred to our attention after a syncope episode. Rest electrocardiogram showed sinus rhythm and I°-atrio-ventricular block (AVB) (PQ interval 294 ms). Echocardiography showed normal left ventricular end-diastolic diameter and left ventricular ejection fraction (53%). A Holter monitoring showed episodes of paroxystic II° and III° AVB. Electrophysiological study was negative for induced ventricular arrhythmias and confirmed an advanced AVB. A dual-chamber pacemaker was implanted. In the family history the father of the proband (57 years of age) and a paternal aunt (42 years of age) were affected by EDMD plus advanced AVB; both underwent pacemaker implantation. Another paternal aunt (35 years of age) was affected by EDMD and paroxystic atrial

fibrillation. The candidate gene LMNA was screened by DHPLC and sequencing of heteroduplex amplicons. A novel 6 bp 203–208 aggtgg deletion (NM_170707) was identified in exon 1 in the proband and affected relatives. The deletion was absent in non-affected family members. The mutation predicts the in-frame deletion of codons Glu68 and Val69.

Gene Symbol: MUTYH

Disease : MUTYH-associated polyposis

S. Aretz et al.; Int J Cancer 2006; DOI 10.1002/ijc.21905
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Small Deletions (<21 bp)

Accession number:	Codon number/location:	Deletion:
hd0611	273	GAGCTAGGG∧GCCACAGTG

Comments: p.Ala273ProfsX32; allele frequency in 329 polyposis patients: 1/658 chromosomes.

Gene Symbol: ATP7B

Disease: Wilson's Disease

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Small Deletions (<21 bp)

Accession number:	Codon number/location:	Deletion:
hd0612	1009	GCATC∧CTCAtcaAGG

Comments: This is a novel deletion mutation located on exon13 of ATP7B gene, which was found in the Indian patients with Wilson's disease SSCP.

Gene Symbol: PRPF31

Disease: Retinitis Pigmentosa

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Small Deletions (<21 bp)

Accession number:	Codon number/location:	Deletion
hd0613	120	TAAGTACTCA∧aaGAGATTCCCT

Comments: Deletion of two nucleotides (AA) in codon 120 (AAG), PRPF31 gene in an Indian patient with isolated form of retinitis pigmentosa.

Gene Symbol: ATP7B

Disease: Wilson's Disease

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Gross Deletions (>20 bp)

Accession number:	Codon number	Deletion
Hg0602	899–908	ATTGTGAAACTGGTGGAAGAGGCTCAG

Gene Symbol: SRY

Disease: Swyer syndrome: complete gonadal dysgenesis with gonadoblastoma and dysgerminoma

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Small Insertions (<21 bp)

Accession number:	Codon number/location:	Insertion:
Hi0601	77	GCGATCAGAGGCGC∧CAAGATGGCTCT

Comments: This is a mutation shared by two XY sisters but not by their normal brother. The two sisters show complete sex reversal with pure gonadal dysgenesis, and both developed bilateral gonadoblastoma and dysgerminoma that arose from their streak gonads. The mutation consists of an insertion of a cytosine [c. 376 dupC] (NM_003140), in between position 3 of codon 76 and position 1 of codon 77 within the HMG box [p. Lys77GlnfsX26] (NP_003131). This insertion results in a change of the amino acid sequence from this point to a premature stop codon 26 amino acids downstream. Presumably, the mutation results in a truncated protein with most of the HMG box missing. Although the two sisters present the same mutation we were not able to detect it in genomic DNA extracted from peripheral blood of their normal father. This suggests a low frequency mosaicism absent in blood but possibly present in the father's germinal line.

Gene Symbol: ARSA

Disease: Metachromatic leukodystrophy

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Small Insertions (<21 bp)

Accession number:	Codon number/location:	Insertion:
Hi0602	78	CTCCTG∧ACCcGGCCGG

Comments: The proband is an American child diagnosed with late infantile metachromatic leukodystrophy (MLD). The parental ARSA gene mutations were identified by nucleotide sequencing. The mother was heterozygous for the p.Pro426Leu (c.1277C>T) mutation, whereas the father carried a novel frameshift mutation at codon 78 (c.234dupC).

Gene Symbol: BRCA1

Disease: Breast cancer

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Missense/nonsense mutations (single base-pair substitutions)

Accession number:	Codon number:	Nucleotide substitution:	Amino acid substitution:
Hm0632	275	GGC–GGT	Gly–Gly

Comments: Unreported variant, silent mutation, unknown pathogenicity, unknown effect on splicing.

Gene Symbol: LDB3

Disease: Dilated cardiomyopathy with left ventricular noncompaction (NCLV DCM)

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Missense/nonsense mutations (single base-pair substitutions)

Accession number:	Codon number:	Nucleotide substitution:	Amino acid substitution:
Hm0633	351	ACA–GCA	Thr–Ala

Comments: A 62-year-old male was referred for noncompaction dilated cardiomyopathy (NYHA class II–III) after a severe episode of dyspnoea. Rest electrocardiogram showed incomplete left bundle branch block and abnormal left ventricular repolarization. Echocardiography showed dilated left ventricle with low EF (25%) and increased mid-apical trabeculation. Coronary arteries were angiographically normal. The candidate gene LDB3 was screened by DHPLC and sequencing of heteroduplex amplicons. A novel c. A1072G (NM_007078) transversion predicting the missense p.Thr351Ala mutation was identified in exon 10.

Gene Symbol: LMNA

Disease: Dilated cardiomyopathy with conduction defect (CMD1A)

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Missense/nonsense mutations (single base-pair substitutions)

Accession number:	Codon number:	Nucleotide substitution:	Amino acid substitution:
Hm0634	219	AAG–AAC	Lys–Asn

Comments: A 39-year-old male was referred for palpitations and at exertion dyspnoea. Rest electrocardiogram showed sinus rhythm, I°-atrio-ventricular block (PQ interval 280 ms) and left bundle branch block. Echocardiography showed mild left ventricular dilation (left ventricular end-diastolic diameter 57 mm) and moderate reduced left ventricular ejection fraction (35%). Coronary angiography showed normal coronary arteries. Holter monitoring showed several episodes of non-sustained ventricular tachycardia and at electrophysiological study an episode of sustained ventricular flutter was induced. The patient underwent PM/ICD implantation. In the family history the father was affected with dilated cardiomyopathy (DCM) plus AVB and underwent PM implantation but he died suddenly at 56 years of age. A maternal aunt was diagnosed with DCM plus I°-AVB and she is in stable clinical conditions (NYHA functional class I). A paternal uncle was diagnosed with DCM plus AVB and underwent PM implantation but he died suddenly at 56 years of age. The candidate gene LMNA was screened by

DHPLC and sequencing of heteroduplex amplicons. A novel mutation (Lys219Asn) was identified in exon 4. The mutation was present in the paternal aunt and in the autopsy samples obtained from the father and the paternal uncle, and was absent in 150 healthy controls.

Gene Symbol: SCN1A

Disease: Generalized epilepsy with febrile seizures plus

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Missense/nonsense mutations (single base-pair substitutions)

Accession number:	Codon number:	Nucleotide substitution:	Amino acid substitution:
Hm0635	1916	cAGA–GGA	Arg–Gly

Comments: The mutation was found in heterozygosis in a GEFS+ proband as well as in his affected father, while it was absent in 100 control individuals. By an in silico prediction of the functional effect of this mutation,which was performed using the online PolyPhen tool (http://www.genetics.bwh.harvard.edu/pph/), it was suggested that the variant is probably damaging.

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:
Hm0636	978	GAG–TAG	Glu–Stop

Comments: A 13-year-old white male, asymptomatic for syncopal events, was referred to our attention for a slight prolongation of the QTc (465 ms) with notched and biphasic T waves in V2–V5, which was identified in a ECG performed during hospitalisation because of a sinus infection. A slight prolongation of the QTc, with abnormal T waves morphology, was identified also in this10-year-old brother and in her mother, both asymptomatic for syncopal events. Beta-blocker therapy was initiated and LQTS genes were screened through DHPLC and sequence analysis. A novel G2932T transversion predicting the nonsense E978X was identified in the C-terminal region of KCNH2.

Gene Symbol: SCN5A

Disease: Long QT syndrome

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Missense/nonsense mutations (single base-pair substitutions)

Accession number:	Codon number:	Nucleotide substitution:	Amino acid substitution:
Hm0637	1991	CGG–CAG	Arg–Gln

Comments: A 16-year-old white female, previously asymptomatic, was referred to our attention for recurrent episodes of Torsade de Pointes, suppressible only by keeping heart rate above 120 b/min with a temporary pacemaker. While in sinus rhythm, the resting electrocardiogram showed a QTc 680 ms. Long QT syndrome (LQTS) was diagnosed and beta-blocker therapy was started. While trying to reduce pacing rate from 120 to 90, the patients experienced two more episodes of Torsades-de-Pointes. The dosage of propranolol was increased up to 2,5 mg/kg/die and no more arrhythmic episodes happened thereafter. A bicameral ICD was implanted and programmed in DDD mode with initial minimal heart rate of 90 b/min and progressive subsequent heart rate reduction. LQTS genes were screened through DHPLC and sequence analysis. A novel G5972A transversion predicting the missense Arg1991Gln was identified in the C-terminal region of SCN5A.

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:
Hm0638	583	ATC–GTC	Ile–Val

Comments: A 14-year-old white male, affected by Gilles de La Tourette syndrome, was referred to our attention for a prolongation of the QT during therapy with risperidone. The patient was asymptomatic for cardiac events and also the family history was negative for syncope or sudden cardiac death. After 4 months of wash-out from risperidone the QT was at the upper limit of normal values at a basal ECG, with phases of marked QT prolongation during Holter recording (maximum QTc measured 500 ms). Echocardiography showed normal features. A Long QT syndrome was diagnosed and beta-blocker therapy started. LQTS genes were screened through DHPLC and sequence analysis. A novel A1747G transversion predicting the missense Ile583Val was identified between S5 and the pore region of KCNH2.

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:
Hm0639	367	CAG–CAT	Gln–His

Comments: A 12-year-old white female was referred to our attention for a suspected Long QT syndrome. The clinical history was negative for cardiac events; the girl simply referred episodes of palpitations. The family history was negative for syncope or sudden cardiac death; however also the mother's ECG showed a clear QTc prolongation (QTc 490 ms in D2). Echocardiography showed normal features. LQTS genes were screened through DHPLC and sequence analysis. A novel transversion predicting the missense Gln367His was identified in the C-terminal region of KCNQ1. The Gln 367 is highly conserved among different species. The same mutation was identified in the proband and in her mother and was not identified in 150 controls.

Gene Symbol: SCN5A

Disease: Long QT syndrome

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Missense/nonsense mutations (single base-pair substitutions)

Accession number:	Codon number:	Nucleotide substitution:	Amino acid substitution:
Hm0640	1175	CGC–TGC	Arg–Cys

Comments: A 8-year-old white female was referred to our attention for a suspected Long QT syndrome. The clinical history was negative for cardiac events. The prolongation of the QTc was initially observed after assumption of QT prolonging drugs (clarithromycin). However, even without those drugs and with normal potassium values, the QTc was still prolonged (QTc 490 ms in D2) and during the recovery phase of exercise a further prolongation of the QT, associated with the appearance of notched T waves in V2–V3, was observed. Echocardiography showed normal features. LQTS genes were screened through DHPLC and sequence analysis. A double mutation was identified, one on KCNQ1 (A372D), already described as a disease-causing mutation and a second novel one (R1175C) in the intra-cellular loop between D2 and D3 on SCN5A. This second mutation is in a highly conserved aminoacid and was not identified in 150 controls.

Gene Symbol: ARSA

Disease: Metachromatic leukodystrophy

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Missense/nonsense mutations (single base-pair substitutions)

Accession number:	Codon number:	Nucleotide substitution:	Amino acid substitution:
Hm0641	307	cGAG–cAAG	Glu–Lys

Comments: The proband is a 3-year-old American girl diagnosed with late infantile metachromatic leukodystrophy (MLD). Complete nucleotide sequence analysis of the ARSA gene demonstrated that she is a compound heterozygote for two missense mutations: p.Pro82Leu (c.245C>T) and p.Glu307Lys (c.919G>A). The novel p.Glu307Lys (c.919G>A) mutation was not detected in normal control samples ($N = 100$ alleles). Glu307 is a conserved residue in ARSA.

Gene Symbol: MUTYH

Disease: MUTYH-associated polyposis

S. Aretz et al.; Int J Cancer 2006; DOI 10.1002/ijc.21905
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Missense/nonsense mutations

Accession number:	Codon number:	Nucleotide substitution:	Amino acid substitution:
Hm0644	479	gGTT–TTT	Val–Phe

Comments: c.1435G>T; p.V479F.

Gene Symbol: MUTYH

Disease : MUTYH-associated polyposis

S. Aretz et al.; Int J Cancer 2006; DOI 10.1002/ijc.21905
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Missense/nonsense mutations

Assession number:	Codon number:	Nucleotide substitution:	Amino acid substitution:
Hm0645	377	gCAG–TAG	Gln–Term

Comments: c.1129C>T; pQ377X; allele frequency in 329 polyposis patients: 3/658 chromosomes.

Gene Symbol: MUTYH

Disease: MUTYH-associated polyposis

S. Aretz et al.; Int J Cancer 2006; DOI 10.1002/ijc.21905
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Missense/nonsense mutations

Accession number:	Codon number:	Nucleotide substitution:	Amino acid substitution:
Hm0646	281	CCA–CTA	Pro–Leu

Comments: c.842C>T; pP281L; allele frequency in 329 polyposis patients: 1/658 chromosomes.

Gene Symbol: MUTYH

Disease: MUTYH-associated polyposis

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Missense/nonsense mutations

Accession number:	Codon number:	Nucleotide substitution:	Amino acid substitution:
Hm0647	143	CCT–CTT	Pro–Leu

Comments: Allele frequency in 329 polyposis patients: 1/658 chromosomes.

Gene Symbol: CRB1

Disease: Leber congenital amaurosis

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Missense/nonsense mutations

Accession number:	Codon number:	Nucleotide substitution:	Amino acid substitution:
Hm0648	535	CTG–CCG	Leu–Pro

Gene Symbol: MYH7

Disease: Hypertrophic cardiomyopathy

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Missense/nonsense mutations

Accession number:	Codon number:	Nucleotide substitution:	Amino acid substitution:
Hm0649	932	gATG–AAG	Met–Lys

Comments: Nonconservative aminoacid substitution; not found in 100 alleles (healthy blood donors); aminoacid conserved during evolution. The age at onset was 14 years. She underwent cardiac transplantation at 16 years. Family history positive.

Gene Symbol: MYH7

Disease: hypertrophic cardiomyopathy

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Missense/nonsense mutations

Accession number:	Codon number:	Nucleotide substitution:	Amino acid substitution:
Hm0650	723	tCGC–CAC	Arg–His

Comments: Conservative aminoacid substitution; not found in 100 alleles (healthy blood donors); aminoacid conserved during evolution. The age at onset was 8 years. He is doing well. Family history positive.

Gene Symbol: MYH7

Disease: Hypertrophic cardiomyopathy

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Missense/nonsense mutations

Accession number:	Codon number:	Nucleotide substitution:	Amino acid substitution:
Hm0651	539	cATG–CTG	Met–Leu

Comments: Aminoacid substitution not conservative; not found in 100 alleles (healthy blood donors); aminoacid conserved during evolution. The age at onset was 16 years. She underwent cardiac tranplantation at age 20 years. Family history positve. The same mutation was found in an unrelated young patient.

Gene Symbol: MYH7

Disease: Hypertrophic cardiomyopathy

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Missense/nonsense mutations

Accession number:	Codon number:	Nucleotide substitution:	Amino acid substitution:
Hm0652	239	cGAC–AAC	Asp–Asn

Comments: Aminoacid charge change—aminoacid conserved during evolution—not found in 100 alleles (healthy blood donors)—found in one patient: age at onset 5 years, myectomy at 7 years; the mother is affected and she carried the same mutation. He has another novel mutation in MYBPC3.

Gene Symbol: SCN1A

Disease: Generalized epilepsy with febrile seizures plus (GEFS+)

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Missense/nonsense mutations

Accession number:	Codon number:	Nucleotide substitution:	Amino acid substitution:
Hm0654	1916	cAGA–GGA	Arg–Gly

Comments: The mutation was found in heterozygosis in a GEFS+ proband as well as in his affected father, while it was absent in 100 control individuals. By an in silico prediction of the functional effect of this mutation, which was performed using the online PolyPhen tool (http://www.genetics.bwh.harvard.edu/pph/), it was suggested that the variant is probably damaging.

Gene Symbol: LDB3

Disease: Dilated cardiomyopathy with left ventricular non compaction

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Missense/nonsense mutations

Accession number:	Codon number:	Nucleotide substitution:	Amino acid substitution:
Hm0654	358	aACA–GCA	Thr–Ala

Comments: A 62-year-old male was referred for non-compaction dilated cardiomyopathy with NYHA class II–III after a severe episode of dispnoea. Rest electrocardiogram showed incomplete left bundle branch block and abnormal left ventricular repolarisation. Echocardiography showed dilated left ventricle with low EF (25%) and evident signs of trabecolae at the medium-apical endocardium. Coronary arteries were angiographically normal. The patient was dignosed with MRI: NCLV. The family history was negative for sudden death, syncope and cardiomyopathies (but positive for CAD). The candidate gene LDB3 (MIM +605906) was screened by DHPLC and sequencing of heteroduplex amplicons. A novel c.A358G transversion predicting the missense p.Thr1358Ala mutation was identified in exon 10.

Gene Symbol: ATP7B

Disease: Wilson's Disease

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Missense/nonsense mutations

Accession number:	Codon number:	Nucleotide substitution:	Amino acid substitution:
Hm0655	876	gTCT–gTTT	Ser–Phe

Gene Symbol: FBN1

Disease: Bicuspid aortic valve

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Missense/nonsense mutations

Accession number:	Codon number:	Nucleotide substitution:	Amino acid substitution:
Hm0656	1148	CCC–GCC	Pro–Ala

Gene Symbol: NOTCH3

Disease: CADASIL

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Missense/nonsense mutations

Accession number:	Codon number:	Nucleotide substitution:	Amino acid substitution:
Hm0657	220	TAC–TGC	Tyr–Cys

Gene Symbol: LMNA

Disease: Dilated cardiomyopathy with conduction defect (CMD1A)

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Splicing mutations (single base-pair substitutions)

Accession number:	Intron designation:	Donor/acceptor:	Relative location:	Nucleotide substitution:
Hs0604	IVS5	Acceptor	+1	G–T

Comments: A 30-year-old male was referred for exertion dyspnoea. Rest electrocardiogram showed sinus rhythm, I°-atrio-ventricular block (AVB) (PQ interval 380 ms) and incomplete left bundle branch block. Echocardiography showed mild left ventricular dilation (left ventricular end-diastolic diameter 60 mm) and reduced left ventricular ejection fraction (30%). Coronary angiography showed normal coronary arteries. Holter monitoring documented 160 episodes of non-sustained ventricular tachycardia but electrophysiological study was negative for induced ventricular arrhythmias. In the family, the mother was affected by dilated cardiomyopathy plus advanced AVB and died suddenly at 36 years of age, after pacemaker (PM) implantation. The candidate LMNA gene was screened by DHPLC and sequencing of heteroduplex amplicons. A novel IVS5+1G>T mutation was identified. The proband underwent both PM and ICD implantation.

Gene Symbol: MUTYH

Disease: MUTYH

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Splicing mutations (single base-pair substitutions)

Accession number:	Intron designation, number or letter:	Donor/acceptor:	Nucleotide substitution:
Hs0605	IVS 15	Donor relative location: +2	T–C

Comments: c.1476+2T>C; allele frequency in 329 polyposis patients: 1/658 chromosomes.