NEXT GENERATION SEQUENCING (NGS) ANALYSIS OF PATIENTS WITH IDIOPATHIC EPILEPSY: DESIGN OF DIFFERENT GENETIC PANELS

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Objectives

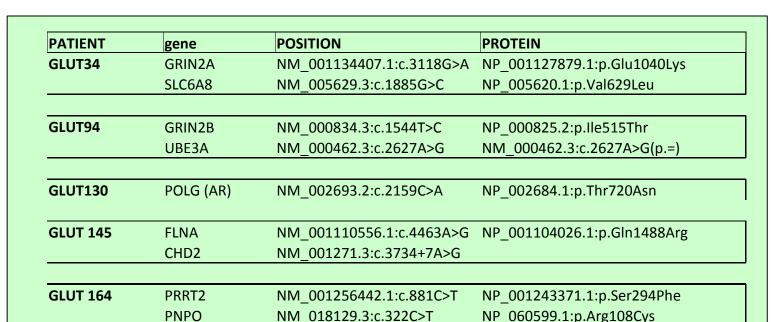
In order to analyze a large series of patients with different types of epilepsy, we designed a NGS genetic panel for the analysis of 46 disease genes. This genes were selected due to their involvement in different forms of epilepsy, such as treatable forms, epileptic encephalopathies, benign epilepsy, myoclonic epilepsy, progressive epilepsy, epilepsy with febrile seizures, neuronal migration disorders, subcortical dysplasia, bilateral perisylvian polymicrogyria, heterotopic periventricular nodular microcephaly.

Materials and methods

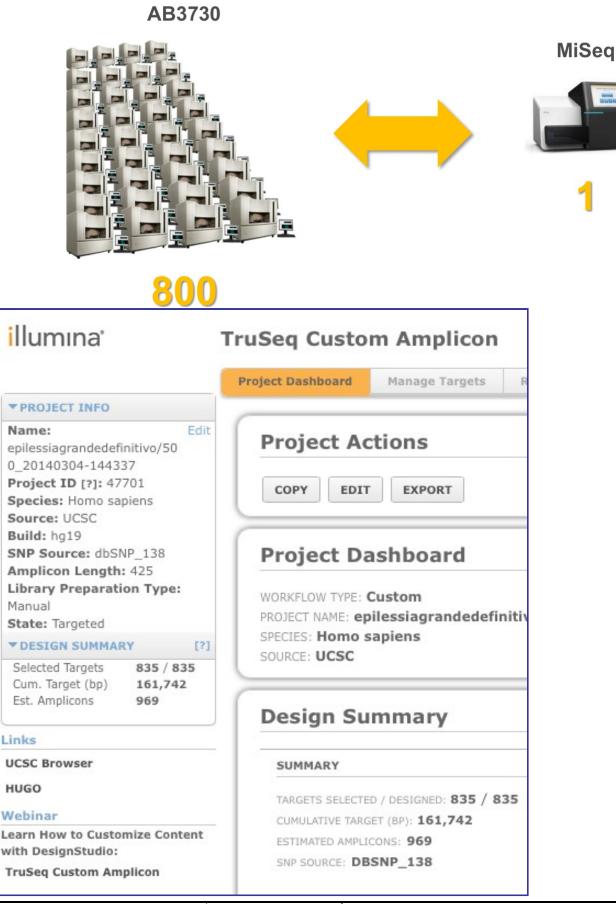
We conducted a preliminary study in 50 patients from 49 unrelated families. The analysis was carried out by a NGS method using the TruSeq Custom Amplicon Illumina technology and the MySeq Illumina apparatus.

Results The primary filtering process showed the presence of a total of 100 variants presenting a MAF<1% (on average 2 variants for patient). The secondary filtering process allowed us to extract about 63 exonic or splicing variants of possible pathogenic significance. In 41 patients (82%) we report at least one variant with unknown significance and in 12 patients (24%) we reported one mutation of possible pathological role. These variants were present in the following genes: GRIN2A, GRIN2B, POLG, SLC6A8, ATP1A3, PRRT2, TUBB8, PPT1, CDKL5, RELN, FOXG1, SLC2A1, KCNQ3 and COL4A1. Two mutations, one in the FOXG1 gene and one in the CDKL5 gene, are nonsense mutations, two other mutations, one in the ATP1A3 gene and one in the TUBB8, are intron splicing variants, while all the other variants are missense mutations. All mutations were novel and were confirmed by Sanger sequence analysis. **Discussion and conclusions**

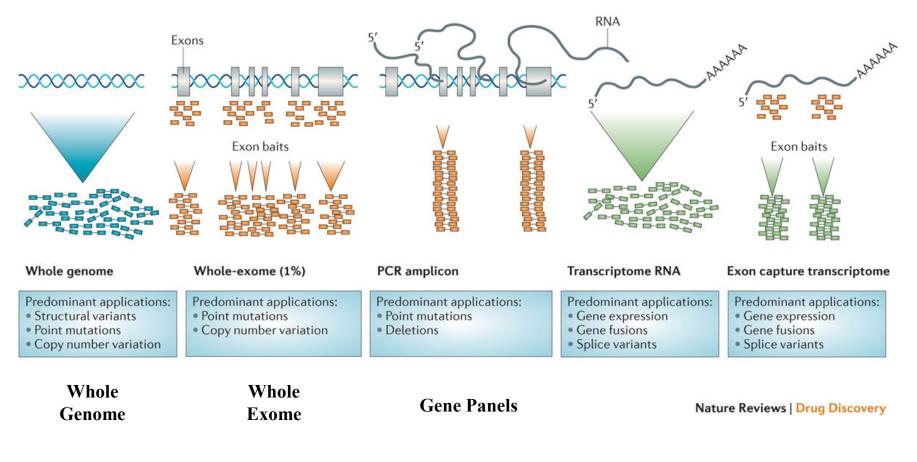
In order to extend the genetic analysis in a wide spectrum of diseases related to epilepsy, we are currently planning a second panel design using Nextera Rapid Capture technology. This panel contains also genes involved in other diseases presenting an epileptic phenotype such as Sialidosis, Lafora, Unverricht-Lundborg, Kufs, Niemann Pick and Gaucher. The platform will include the analysis of 93 genes. Our encouraging preliminary results suggest the usefulness of a NGS approach for large scale genetic investigation to increase the diagnostic score in the context of epilepsies.



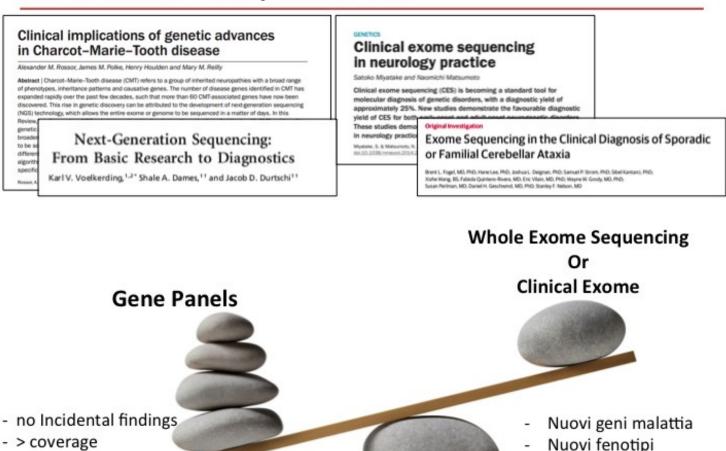




FORME TRATTABILI		
ALDH7A1-A16	5q23.2	Aldehyde Dehydrogenase 7 Family, Member A1
SLC2A1 PNPO	1p34.2	Solute Carrier Family 2 (Facilitated Glucose Transporter), Member 1
PHGDH	17q21.32 1p12	Pyridoxamine 5'-Phosphate Oxidase Phosphoglycerate Dehydrogenase
SLC6A8	Xq28	Solute Carrier Family 6 (Neurotransmitter Transporter), Member 8
epilessie		
precoci/encefalopatie epilettiche		
KCNT1	9q34.3	Potassium Channel, Subfamily T, Member 1
ARX	Xp21.3	Aristaless Related Homeobox Mental Retardation, X-Linked
STXBP1	9q34.1	Syntaxin Binding Protein
CDKL5	Xp22.13	Cyclin-Dependent Kinase-Like 5
FOXG1	14q13	Forkhead Box G1
MECP2	Xq28	Methyl CpG Binding Protein 2 (Rett Syndrome)
UBE3A KCNQ2	15q11.2 20q13.33	Ubiquitin Protein Ligase E3A (Angelman) Potassium Voltage-Gated Channel, KQT-Like Subfamily, Member 2
KCNQ3	8q24	Potassium Voltage-Gated Channel, KQT-Like Subfamily, Member 2
GRIN2A	16p13.2	Glutamate Receptor, Ionotropic, N-Methyl D-Aspartate 2A
GRIN2B	12p12	Glutamate Receptor, Ionotropic, N-Methyl D-Aspartate 2B
GABRB3	15q12	Gamma-Aminobutyric Acid (GABA) A Receptor, Beta 3
HCN1	5p12	Hyperpolarization Activated Cyclic Nucleotide-Gated Potassium Char
BENIGNE		
KCNQ2	20q13.33	Potassium Voltage-Gated Channel, KQT-Like Subfamily, Member 2
KCNQ3 SCN2A	8q24.22 2q24.3	Potassium Voltage-Gated Channel, KQT-Like Subfamily, Member 3 Sodium Channel, Voltage-Gated, Type II, Alpha Subunit
PRRT2	16p11.2	Proline-Rich Transmembrane Protein 2
ATP1A2-A12	1q23.2	ATPase, Na+/K+ Transporting, Alpha 2 Polypeptide
MIOCLONICA MALIGNA		
SYNGAP1	6p21.32	Synaptic Ras GTPase Activating Protein 1
CHD2	15q26.1	Chromodomain Helicase DNA Binding Protein 2
MIGRANTI		Forma clinica grave dell'infanzia
KCNT1	9q34.3	Potassium Channel, Subfamily T, Member 1
SCN2A	2q24.3	Sodium Channel, Voltage-Gated, Type II, Alpha Subunit
PLCB1	20p12.3	Phospholipase C, Beta 1
SCN1A	2q24.3	Sodium Channel, Voltage-Gated, Type I, Alpha Subunit
PROGRESSIVE CTSD	11p15.5	Cathepsin D Ceroid-Lipofuscinosis, Neuronal 10
POLG	15q26.1	Polymerase (DNA Directed), Gamma
TWINCKLE C100RF2	10q24.31	Chromosome 10 Open Reading Frame 2
PPT1 (CLN1)	1p34.2	Palmitoyl-Protein Thioesterase 1
CONVULSIONI FEBBRILI		
CONVOLSIONI FEBBRILI		
SCN1A	2q24.3	Sodium Channel, Voltage-Gated, Type I, Alpha Subunit
SCN2A	2q24.3	Sodium Channel, Voltage-Gated, Type II, Alpha Subunit
SCN1B	19q13.12	Sodium Channel, Voltage-Gated, Type I, Beta Subunit
SCN8A GABRG2	12q13.13	Sodium Channel, Voltage Gated, Type VIII, Alpha Subunit
PCDH19	5q34 Xq22.1	Gamma-Aminobutyric Acid (GABA) A Receptor, Gamma 2 Protocadherin 19
CHD2	15q26.1	Chromodomain Helicase DNA Binding Protein 2
CACNA1A	19p13.2	Calcium Channel, Voltage-Dependent, P/Q Type, Alpha 1A Subunit
DISORDINI MIGRAZIONE		
NEURONALE		
DCX	Xq23	doublecortin
PAFAH1B1/LIS1 FLNA	17p13.3	Platelet-Activating Factor Acetylhydrolase 1b, Regulatory Subunit 1 Filamin A
TUBA1A	Xq28 12q13.12	Filamin A Tubulin, Alpha 1a
TUBB2B	6p25.2	Tubulin, Beta 2B Class IIb
TUBB3	16q24.3	Tubulin, Beta 2 Class III
TUBB8	10p15.3	Tubulin, Beta 8 Class VIII
DISPLASIA SOTTOCORTICALI		
HESX1	3p14.3	Homeobox 1
COL4A1	13q34	Collagen, Type IV, Alpha 1
COL4A2	13q34	Collagen, Type IV, Alpha 2
POLIMICROGIRIE BILATERALI		
FRONTO-TEMPORALI		
GPR56	16q13	G Protein-Coupled Receptor 56
POLIMICROGIRIE BILATERALI		
PERISILVANE SRPX2	Xq21.33-q23	Sushi-Repeat Containing Protein, X-Linked 2
EMX2	10q26.11	Empty Spiracles Homeobox 2
EIVIA7		
MICROCEFALIA ETEROTOPICA		
	1021-022	Rho/Rac Guanine Nucleotide Exchange Factor (GEE) 2

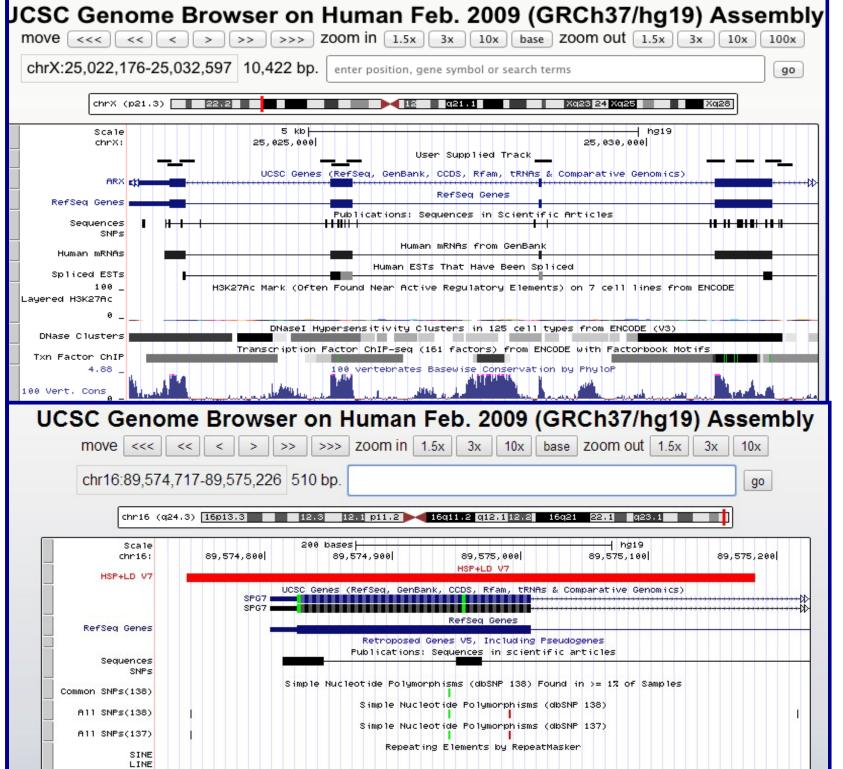


NGS in Clinica: Gene panel vs WES



TruSeq Custom Amplicon design

Heat OPIES NM_005882.5:::1693C>T NP_005673.3::p.Arg5651*p H52 TUBBS :::534A>G p.His71Arg p.Lix213Arg H533 COLALI NM_001854.5::2125*F NP_0013510.1::p.Arg1325C/v PL/9213Arg H1225 TUBBS :::534A>G NP_001350.1::p.Arg1347*r PL/9213Arg H1225 CDKL5 NM_001359.2::0.400C>T NP_000301.1:p.Arg1347*r P11522 CDKL5 NM_00210.3::0.5263C> NP_003501.1:p.Arg1347*r P11522 CDKL5 NM_002003.3::0.6436> NP_003501.1:p.Arg1347*r P12370 MAGI2 NM_002003.3::0.6436> NP_003561.2:p.Arg1346*r P12370 MAGI2 NM_0020931.3::C436> NP_003561.2:p.Arg5685h NMD376 GNIN28 NM_0026931.3::C436> NP_00356.2:p.Arg5685h NMD377 FOXG1 NM_0026931.3::C436> NP_00356.2:p.Arg5685h NM0 0378 COLAA1 NM_001256.2:r.Arg60C NP_000856.2:p.Arg5685h NM0 0378 FOXG1 NM_001256.2:r.Arg60C> NP_000856.2:p.Arg5685h NM0 0378 COLAA1 NM_001256.2:r.Arg60C> NP_0		PNPO RELN	NM_018129.3:c.322C>T NM_005045.3:c.5717T>C	NP_060599.1:p.Arg108Cys NP_005036.2:p.lle1906Thr
Size Classics pHis71 arg Size COLALI MV (20145) 4:C. 3712C-Y NP (201352) 2:A. 3712C-Y Size COLALI MV (20145) 4:C. 3712C-Y NP (201352) 2:A. 3712C-Y Size COLALI MV (20145) 4:C. 3712C-Y NP (201352) 1:A. 471347; Size COLALI MV (20145) 2:C. 106-44A-C NP (20135) 1:A. 471347; Fred MV (2021) 3:C. 330-CA NP (20135) 1:A. 471347; MAGIZ NV (2021) 3:C. 330-CA NP (20143) 2:D. Axp1314(i) NV (2021) 3:C. 330-CA NP (20143) 2:D. Axp1314(i) NV (2015) 1:D. 400313 3:C. 436-CA NP (20143) 2:D. Axp1314(i) NV (2020) 2:C. 7360-CA NP (20143) 2:D. 4706524) 4:C. 336-CA NV (2020) 3:C. 7360-CT NP (20143) 2:D. 4706524) 4:C. 336-CA NV (2020) 3:C. 7360-CT NP (20143) 2:D. 4706724) NV (2014) 1:M. 40. 001263 4:C. 336-CA NP (20143) 2:D. 4706724) Size COLAL1 NM (2025) 2:C. 7360-CA NP (20143) 2:D. 4706724) Size COLAL1 NM (2015) 2:C. 7360-CA NP (20143) 2:D. 4706724) Size COLAL1 NM (2015) 2:C. 7360-CA NP (20143) 2:D. 4706734)	GLUT 183	COL4A2	NM_001846.2:c.3326G>A	NP_001837.2:p.Arg1109Gln
TUBBE C638A-5G [Ly-2134/g] H533 COLAL NM 001451-5X 3712C-T NP 0015252 Avg1223C/y H533 TUBBE C638A-5G PL/213A/g H1235 TUBBE C638A-5G NPL 001525 PL/213A/g H1471A/g PL/213A/g PL/213A/g H1525 TUBBE NM_001250 2x.000C-T NP_003150 1p.Ag1317fr PPT NM_002501 3x.030C-A NP_003613 2p.Ag13160 REVN NM_002501 3x.030C-A NP_005812 2p.Ag113160 REVN NM_002502 2p.330C-A NP_005812 2p.Ag12160 NM0 376 GRIN2B NM_001855 2p.2793C-A NP_000825 2p.Ag126167 NM0 377 FOXG NM_001845 4p.2030C-A NP_000825 2p.Ag026167 NM0 378 FOXG NM_001845 4p.2030C-A NP_000582 1p.Pro245747 NM0 374 COUALI NM_001845 4p.2030C-A NP_001825 2p.Ag026567 NM0 374 COUALI NM_001845 4p.2030C-A NP_001825 2p.Pro24587 S1445 KCNQ2 NM_001845 4p.2030C-A NP_001825 2p.Pro24587 S1447 FINA NM_001845 2p.2050C-T NP_0	H443	GPR56	NM_005682.5:c.1693C>T	NP_005673.3:p.Arg565Trp
H533 COLA1 NMI 001845 4/c 3712C>T NPI 001836 2; µArg1238Cy6 H1235 TUBBS c.638A-6 p.1y213Arg H1235 TUBBS NMI_077967.2/c:166-4A>C H1622 CDRLS NMI_003159.2/c:400C-T NPI_003150.1;p. Arg134Ter H1622 CDRLS NMI_003310.3/c.6286>C NPI_003430.1;p. 6(y210Arg H13270 NMAC02 NMI_00545.3/c.64740AA NPI_00545.2/c.670054.2/c.67140 H142370 NMAC02 NMI_00545.3/c.64740AA NPI_00545.2/c.670054.2/c.67140 H143 NMI_005453.6/c.23036>A NPI_00545.2/c.67140 NPI_00545.2/c.67140 H143 NMI_001256214.1/c.396C>T NPI_00264.1/p.1723116 NMD 378 FOXG1 NMI_002633.2/c.7760C>T NPI_00264.1/p.1723116 NMD 378 FOXG1 NMI_002633.2/c.7760C>T NPI_002634.1/p.1723116 S1441 ATP1A3 NMI_002633.2/c.7726C>T NPI_002634.1/p.1723116 S1441 ATP1A3 NMI_002633.2/c.7726C>T NPI_002635.2/p.167640 NMI_003545.2/p.014363/ser NPI_0003512.2/p.1676140 NPI_0003512.2/p.1676140 S1447 CDLA11	H532			
TUBBS c. 324A-5 p.His/21Arg TUBBS C. 324A-5 p.Liy/213Arg H1225 TUBBS NM_177987.21:166-4A-C Frei				· · · · · · · · · · · · · · · · · · ·
TUBBR c.638A>G p.1ys213Arg H1235 TUBBR NM_177987.2)::16644A>C Fred NM_0003163.2::628G>C NP_0003511:p./dp131fr/ NP_000301:p./dp121d1;r H1622 CDKIS NM_002301.3:::598C>A NP_005067::2,:6(y1158er PPT1 NM_005634.3:::633G>A NP_005641::5::6553Ann NMD366 GRIN28 NM_005249.4::7::68253Ann NMD366 GRIN28 NM_005249.4::7::68253Ann NMD366 GRIN28 NM_005249.4::7::682541 NMD376 COLA1 NM_005249.2::052C1 NMD384 COLA1 NM_00263.2::0750C-T NP_0002641::p.595274:reg NMD384 COLA1 NM_00263.2::0750C-T NM_002623::p.0760630 NM_00263::2::0750C-T NP_00125214::1::396C-T NP_000852::p.0760630 S1447 ATP1A3 NM_001359.2::C52C-T NM_001252::p.1::07015300; S1447 FINA NM_001359.2::C55C-T NP_001363::2::0701582; S1447 FINA NM_001359.2::C55C-T NP_001363::2::071552; S1447 FINA NM_001359.2::C55C-T NP_001352::2::071552; <	H533			
Free				
PT1 NM_000310.3:::6.268-c NP_000301.1:p.Gip210.4rg H2370 MAG12 NM_0102501.3:::303C-A NP_005633.2::App131G/u PKX5 NM_0105591.2::758C-A NP_005630.2:::05921155cr NMD360 GRIN28 NM_005249.4::C738C-A NP_005743.1::05672.4: NMD376 FOXG1 NM_005249.4::C738C-A NP_005240.3::0::1726677 NMD376 COLA1 NM_005249.4::C738C-A NP_000588.1::p.Pro587Leii NMD378 COLA1 NM_002693.2::1726C-T NP_000584.1::p.Pro587Leii POLG NM_002523.2::1726C-T NP_000258.2:::p.Pro587Leii S1441 ATP1A3 NM_000513.2::1726C-T NP_000258.2:::p.Pro587Leii S1445 KCNQ2 NM_1001555.1:::238C-T NP_000135.2:::p.Gip3105er S1447 FLNA NM_001355.2:::255C-T NP_001350.1::p.Gip22Vai S1447 COLA1 NM_001355.2:::255C-T NP_001350.1::p.Gip22Vai S1447 COLA1 NM_001363.2:::2132C-A NP_001350.1::p.Gip22Vai S1447 COLA1 NM_001363.2:::1736C-A NP_0001350.1::p.Gip22Vai S1487 SIC21 NM_001363.2:	H1235 Freri	TUBB8	NM_177987.2:c.166+4A>C	
H2370 MAG12 NM 012301.3:r.293C-A NO 00.06433.2; n.4913G.u H2370 RELN NM 016539.2; r.758C-A NP 0.06938.2; p.6233Acn NM0.9560 GRIN28 NM 000834.3; r.633C-A NP 0.00825.2; p.val15Met NM0.9766 GRIN28 NM 0.00834.3; r.633C-A NP 0.00825.2; p.val15Met NM0.976 FOXG1 NM 0.00263.2; r.756C-A NP 0.00824.1; p.763787.4; w. NMD.976 COLA1 NM 0.002633.2; r.756C-A NP 0.0084.1; p.763787.4; w. S1441 ATP1A3 MM 0.002633.4; r.2082C-F NP 0.00183.2; p.Prob80Ab S1445 COLA1 NM 0.002522.4; r.750C-T NP 0.00183.2; p.Prob80Ab S1447 FLNA NM 0.01256214.1; r.336C-T NP 0.01183.2; p.Pro14585er S1447 COLA1 NM 0.01256214.1; r.0352C-F NP 0.01183.2; p.Pro14585er S1447 FLNA NM 0.011345.4; G29026-A NP 0.01187.2; r.752Va S1447 </td <td>H1622</td> <td>CDKL5</td> <td>NM_003159.2:c.400C>T</td> <td>NP_003150.1:p.Arg134Ter</td>	H1622	CDKL5	NM_003159.2:c.400C>T	NP_003150.1:p.Arg134Ter
RFLM NMI 005043 3r.6343(G-A) NPI 005036 2;p. cbj21155er NMD360 GRIN28 NMI 00639.4;;C38G-A NPI 00525.2;p.Val15Met NMD 378 FOXG1 NMI 005249.4;C738C-G NPI 00525.2;p.Val15Met NMD 394 COLA11 NMI 001545.4;C2903G-A NPI 005263.1;p.FOS7E1eu POLG NMI 001265.2;C.752C-T NPI 002684.1;p.T052871eu NPI 002684.1;p.T052871eu POLG NMI 001256214.1;r.396C-T NPI 000285.2;p.Pr0680Ala NPI 0002851.2;c.752C-T S1441 ATP1A3 NMI 001256214.1;r.396C-T NPI 0003825.2;p.Pr0680Ala GRIN28 NMI 001256214.1;r.396C-T NPI 001380.2;p.Pr0680Ala KCNQ3 NMI 001385.4;r.2038C-G NPI 001380.2;p.T05875er S1445 KCINQ3 NMI 001385.4;r.2038C-C NPI 001380.2;p.T0585er S1447 FLNA NMI 001385.4;r.2038C-R NPI 001380.2;p.T075185er S1447 COLA1 NMI 001385.4;r.2037C-R NPI 001387.2;p.T075125er S1447 COLA1 NMI 00126214.1;r.393.5C-G NPI 001387.2;p.Arg5186in S1447 COLA1 NMI 00126214.1;r.393.5C-G NPI 00137.2;p.Arg518cin		PPT1	NM_000310.3:c.628G>C	NP_000301.1:p.Gly210Arg
PEXSL NM_016559.2c.758G>A NP_057643.1;p.5cr253Asn NMD360 GRIN28 NM_000834.3;c.43G>A NP_000825.2;p.Val15Met NMD 378 FOXG1 NM_001845.4;c.2903G>A NP_001835.2;p.Arg968Gin NM_002693.2;c.752C>T NP_002864.1;p.Pro587Leu NP_002864.1;p.Pro587Leu POLG NM_002593.2;c.752C>T NP_002864.1;p.Pro587Leu POLG NM_002593.2;c.752C>T NP_002864.1;p.Pro587Leu POLG NM_002593.2;c.752C>T NP_002864.1;p.Pro587Leu S1441 ATP1A3 NM_001256214.1;c.396C>T NM_0002563.2;p.Pro680Ala KNN03 NM_001256214.1;c.130C>T NP_004510.1;p.For97Aser S1445 COLA1 NM_00112551.2;c.4585PC NP_00110256.1;p.Gly3105er S1447 FLNA NM_001130551.2;c.4585PC NP_001836.2;p.Arg586Gin COLA1 NM_00113059.2;c.656C>A NP_001836.2;p.Arg586Gin S1447 FLNA NM_00125612.4;c.139.5CC NP_001836.2;p.Arg586Gin COLA1 NM_00125612.4;c.139.5CC NP_001836.2;p.Arg586Gin S1449 COLA1 NM_0013619.2;c.1526AS NP_001837.2;p.Arg51His KCN03 <td>H2370</td> <td></td> <td>—</td> <td></td>	H2370		—	
NMD 378 FOXG1 NM_002249.4:::738C>6 NP_005240.3:p.Tyr246Ter NMD 394 COLA11 NM_002693.2::752C>1 NP_001836.2:p.Arg668Gin POLG NM_002693.2::752C>1 NP_002684.1:p.Thr251Ie S1441 ATP1A3 NM_002693.2::752C>1 NP_002852.2:p.Pro680Aia S1441 ATP1A3 NM_002853.3::1720C>1 NP_002825.2:p.Pro680Aia S1445 KCNQ3 NM_00455.1::238C>6 NP_001862.2:p.Pro680Aia S1445 KCNQ2 NM_10215621.4::4387C> NP_001836.2:p.Arg688Gin S1445 KCNQ2 NM_10215651.2::4387C NP_0013150.1:p.Giy310Ser S1445 COLA1 NM_001356.1::2.4387C NP_0013150.1:p.Giy22Val S1447 FUNA NM_001365.1::2.4387C NP_001332.2:p.Pro14358er S1449 COLA1 NM_001366.2::1526>A NP_001332.2:p.Pro51359.2: S1449 COLA1 NM_0013616.2::1526>A NP_001332.2:p.Pro51359.2: S1449 COLA1 NM_004519.3::16240>A NP_005137.2:p.Arg518is S147 SLC2A1 NM_0013161.2::036>A NP_005573.3:p.Ser2141ee S1487 SLC2				
NMD 394 COL4A1 NM_001845.4:: 2903G>A NP_001836.2: Arg668Gin NMD 394 COL4A1 NM_002693.2:: 1750C>T NP_002694.1: p.Thr251le S1441 ATP1A3 NM_002693.2:: 752C>T NP_000825.2:: p.Pro680Ala S1441 ATP1A3 NM_001256214.1::: 396C>T NM_001256214.1::: 396C>T S1445 KCN02 NM_001851.3::: 1720C>T NP_000825.2:: p.Pro680Ala S1445 KCN02 NM_001855.1::: 4396C>T NP_001310.1: p.Vro5745er S1445 KCN02 NM_00155.1::: 4396C>T NP_001310.1: p.Vro5745er S1447 FLNA NM_001510.5: 1::: 4397C>C NP_001310.1: p.Vro5745er S1447 COL4A1 NM_00156.1:::: 4397C>C NP_001310.1: p.Vro51230Ala MU_00145.2::: 615C>T NP_001310.1: p.Vro51230Ala NP_001310.1: p.Vro51230Ala MU_00145.2:: 615C>T NP_0013130.1: p.Vro51230Ala NP_001310.1: p.Vro51230Ala MU_00145.2:: 615C>T NP_0013130.1: p.Vro51230Ala NP_0013130.1: p.Vro51230Ala MU_00145.2:: 615C>A NP_001330.2: p.Vro5130.3: p.Vro5130Ala NP_001310.1: p.Vro52428 S1487 SLC2A1 NM_00104142.1::: 25G>A NP_0013523.2: p	NMD360	GRIN2B	NM_000834.3:c.43G>A	NP_000825.2:p.Val15Met
POLG NM_002693.2:: 750C>T NP_002684.1:p. Thr251Ile S1441 ATP1A3 NM_0002493.2:: 752C>T NP_002584.1:p. Thr251Ile S1441 ATP1A3 NM_000343.3:: C132C>T NP_00255.2:p. Pro680Ala S1445 KCN02 NM_000319.3:: T172C>T NP_000525.2:p. Pro680Ala S1445 KCN02 NM_001845.4:: C338C>T NP_001856.2:p. Pro1458Ser S1445 KCN02 NM_001845.4:: C338C>T NP_001836.2:p. Pro1458Ser S1447 FLNA NM_0011845.4:: C3903C>A NP_001836.2:p. Pro1458Ser S1447 FLNA NM_0011845.4:: C393C>T NP_001836.2:p. Pro1458Ser S1447 FLNA NM_0011845.4:: C393C>T NP_001836.2:p. Pro1458Ser S1447 FLNA NM_001845.4:: C393C>T NP_001837.2:p. Thr552Lys S1449 C0L4A1 NM_001845.2:: T52C>A NP_001837.2:p. Thr552Lys S1449 C0L4A1 NM_001519.3:: L172C> NP_001510.1:p. Naj552Lys S1487 SLC2A1 NM_001519.3:: L172C> NP_001510.1:p. Naj552Lys S1487 SLC2A1 NM_00519.3:: L172C> NP_001510.1:p. Naj552Lys <td< td=""><td>NMD 378</td><td>FOXG1</td><td>NM_005249.4:c.738C>G</td><td>NP_005240.3:p.Tyr246Ter</td></td<>	NMD 378	FOXG1	NM_005249.4:c.738C>G	NP_005240.3:p.Tyr246Ter
POLG NM_002693.2:: 750C>T NP_002684.1:p. Thr251Ile S1441 ATP1A3 NM_0002493.2:: 752C>T NP_002584.1:p. Thr251Ile S1441 ATP1A3 NM_000343.3:: C132C>T NP_00255.2:p. Pro680Ala S1445 KCN02 NM_000319.3:: T172C>T NP_000525.2:p. Pro680Ala S1445 KCN02 NM_001845.4:: C338C>T NP_001856.2:p. Pro1458Ser S1445 KCN02 NM_001845.4:: C338C>T NP_001836.2:p. Pro1458Ser S1447 FLNA NM_0011845.4:: C3903C>A NP_001836.2:p. Pro1458Ser S1447 FLNA NM_0011845.4:: C393C>T NP_001836.2:p. Pro1458Ser S1447 FLNA NM_0011845.4:: C393C>T NP_001836.2:p. Pro1458Ser S1447 FLNA NM_001845.4:: C393C>T NP_001837.2:p. Thr552Lys S1449 C0L4A1 NM_001845.2:: T52C>A NP_001837.2:p. Thr552Lys S1449 C0L4A1 NM_001519.3:: L172C> NP_001510.1:p. Naj552Lys S1487 SLC2A1 NM_001519.3:: L172C> NP_001510.1:p. Naj552Lys S1487 SLC2A1 NM_00519.3:: L172C> NP_001510.1:p. Naj552Lys <td< td=""><td></td><td>COL441</td><td></td><td></td></td<>		COL441		
POLG NM 002693.2:c,752C>T NP 002684.1:p,Thr251IIe S1441 ATP1A3 NM 001256214.1:c.396C>T NM 001256214.1:c.396C>T NP 000825.2:p,Pro580Ais S1441 ATP1A3 NM 001256214.1:c.396C>T NP 000825.2:p,Pro580Ais S1445 KCNQ2 NM 12107.2:c.928G>A NP 742105.1:p,Gly3105er S1445 COL4A1 NM 00110556.1:c.488T>C NP 001836.2:p,Pro5458er S1447 FLNA NM 0011845.4:c.2903G>A NP 001836.2:p,Arg968Gin S1449 COL4A1 NM 001845.2:c.152G>A NP 001836.2:p,Arg968Gin S1449 COL4A1 NM 001845.2:c.152G>A NP 004510.1:p,Arg542Asn S1487 SLC2A1 NM 005516.2:c.152G>A NP 004510.1:p,Arg542Asn S1487 SLC2A1 NM 005612.2:n.52G>A NP 004510.1:p,Arg542Asn S1656 SCN2A NM 001040142.1:c.256A> NP 001572:p,Arg51His S1656	141410 394		—	
GRIN2B NM_0003154.3:::.038C-6 NP_000825.2:::070680Ala S1445 KCNQ2 NM_172107.2:::928G>A NP_742105.1::0193105er S1445 KCNQ2 NM_001845.4::4372C>T NP_001836.2::0193105er S1447 FLNA NM_00110556.1::5897C NP_00104026.1::0458897C S1447 FLNA NM_0011455.4::2903G>A NP_001836.2::041530Ala COL4A1 NM_001845.4::1935C>A NP_001837.2:07569KB S1449 COL4A1 NM_006516.2::152C>A NP_006507.2::4799686In CU14A2 NM_004519.3::152G>A NP_006507.2::479542Asn NM_004519.3::1075G>T NP_006510.1::9.49542Asn NM_004519.3::1075G>T NP_006510.1::9.49542Asn NM_00518.2:1075G>T NP_005871.3::9.5672141eu S1650 SCN2A NM_00114407.1::2268>C NP_00127879.1::68104 S1635 GRIN2A NM_0013407.1::2765C>T NP_00127879.1::6810761ys S1652 MAGI2 NM_00134407.1::2765C>T NP_00127879.1::64126y H3170 GRIN2A NM_00134407.1::2765C>T NP_001127879.1::61761ys			—	
GRIN2B NM_0003154.3:::.038C-6 NP_000825.2:::070680Ala S1445 KCNQ2 NM_172107.2:::928G>A NP_742105.1::0193105er S1445 KCNQ2 NM_001845.4::4372C>T NP_001836.2::0193105er S1447 FLNA NM_00110556.1::5897C NP_00104026.1::0458897C S1447 FLNA NM_0011455.4::2903G>A NP_001836.2::041530Ala COL4A1 NM_001845.4::1935C>A NP_001837.2:07569KB S1449 COL4A1 NM_006516.2::152C>A NP_006507.2::4799686In CU14A2 NM_004519.3::152G>A NP_006507.2::479542Asn NM_004519.3::1075G>T NP_006510.1::9.49542Asn NM_004519.3::1075G>T NP_006510.1::9.49542Asn NM_00518.2:1075G>T NP_005871.3::9.5672141eu S1650 SCN2A NM_00114407.1::2268>C NP_00127879.1::68104 S1635 GRIN2A NM_0013407.1::2765C>T NP_00127879.1::6810761ys S1652 MAGI2 NM_00134407.1::2765C>T NP_00127879.1::64126y H3170 GRIN2A NM_00134407.1::2765C>T NP_001127879.1::61761ys				
KCNQ3 NM_004519.3r.:1720C>T NP_004510.1:p.Pro574Ser S1445 KCNQ2 NM_0127107.2:: 928G>A NP_742105.1:p.Gly310Ser S1447 FLNA NM_001140556.1:: 4589T>C NP_0011805.2:: p.Pro14585er S1447 FLNA NM_001110556.1:: 4589T>C NP_001104026.1:p.Val1530Ala CDI4A1 NM_001845.4:: 2903G>A NP_001836.2: p.Arg968Gln CD14A2 NM_001562.2: 152G>A NP_001836.2: p.Arg968Gln CD14A2 NM_0015561.2: 152G>A NP_00101.0: p. Arg95124s S1487 SLC2A1 NM_006519.3: 0: 159G-X NP_004510.1: p. Arg95124s KCN03 NM_004519.3: 0: 152G-X NP_006571.2: p.Arg91His KCN03 NM_004519.3: 0: 152G-X NP_004510.1: p. Arg914s S1550 SCN2A NM_001040142.1: c.256A>G NP_00135232.1: p.He8111le S1565 GRIN2A NM_0013407.1: c.3228C>A NP_0013233.2: p.Fro711Thr S1635 GPR56 NM_005623.3: c.425A>G NP_00127879.1: p.Asi10761yS S1652 MAGI2 NM_01134407.1: c.2765C>T NP_001127879.1: p.Asi10761yS S1654 KCNE2 NM_01134407.1: c.2266A>G	S1441		—	
S1445 KCNQ2 COL4A1 NM_172107.2:::23265A NP_742105.1::p.Gly3105er S1447 FLNA CDKLS NM_001845.4::4372C>T NP_001836.2::p.Pro14585er S1447 FLNA CDKLS NM_00116556.1::C4589T>C NP_0013150.1::p.Gly22Val S1449 COL4A1 NM_001845.4::29036>A NP_001836.2::p.Arg968Gln COL4A2 NM_001256214.1::033-5C>G NP_001836.2::p.Arg968Gln S1487 SLC2A1 NM_006151.2::C152G>A NP_006570.2::p.Arg968Gln KCNQ3 NM_004519.3::C1075G>T NP_006571.1::p.Arg968Gln KCNQ3 NM_0012412.4::2933G>T NP_006571.2::p.Arg91His KCNQ3 NM_00112.4::2933G>T NP_006571.2::p.Arg91His S1560 SCN2A NM_001142.1:::256A> NP_006571.2::p.Arg91His S1635 GPR56 NM_00114407.1:::256A>G NP_006573.3::p.Ser214Leu S1636 GRIN2A NM_001134407.1:::226C>C NP_001127879.1::p.Ais91076Lys S1652 MAGI2 NM_001134407.1:::2765C>T NP_001127879.1::p.Ais922Val S1654 KCNE2 NM_172201.1:::1707C NP_751951.1::p.Ile571hr S1654 KCNE2 <t< td=""><td></td><td></td><td>—</td><td></td></t<>			—	
COL4A1 NM_001845.4:c.4372C>T NP_001836.2:p.Pro1458Ser 51447 FLNA CDKL5 NM_003159.2:c.65G>T NP_001104026.1:p.Val1530Ala NP_003150.1:p.Ghy22Val 51449 COL4A1 COL4A2 NM_001845.4:c.2903G>A NM_001256214.1:c.193-5C>G NP_001837.2:p.Arg968Gin NP_001837.2:p.Arg968Gin NP_004510.1:p.Asp542Asn NM_004519.3:c.1624G>A NP_004510.1:p.Asp542Asn KCNQ3 NM_006519.3:c.1624G>A NP_004510.1:p.Asp542Asn NM_004519.3:c.1075G>T NP_006507.2:p.Arg51His NP_004510.1:p.Val359Leu GABRB3 51487 SLC2A1 NM_004519.3:c.1075G>T NP_006507.2:p.Arg51His NM_001912.4:c.933G>T NP_004510.1:p.Val359Leu GABRB3 51560 SCN2A NM_00104142.1:c.256A>G NP_001035232.1:p.He86Val 51651 GPR56 NM_00134407.1:c.3228C>A NP_00127879.1:p.Asn1076Lys 51652 MAGI2 NM_00134407.1:c.2765C>T NP_006613.2:p.Glu12Giy 51654 KCNE2 NM_00134407.1:c.2765C>T NP_00127879.1:p.Ala922Val 51654 KCNE2 NM_00134407.1:c.2765C>T NP_001837.2:p.Arg6His 51720 GRIN2A NM_001846.2:c.17G>A NP_001837.2:p.Arg6His 51721 MGDH NM_001846.2:c.126C>T NP_001837.2:p.Arg6His 51723 RELN NM_001846.			WW_004313.3.C.1/20C>1	M004310.1.p.F10374381
S1447 FLNA NM_001110556.1:::.4589T>C NP_001104026.1::p.Val1530Ala S1447 FLNA NM_003159.2:::.6565T NP_0013150.1::p.Gh/22Val S1449 C0L4A1 NM_001846.2:::1655C-A NP_001836.2::p.Arg968Gln C0L4A2 NM_001846.2::1655C-A NP_001837.2:p.Thr552Lys S1487 SLC2A1 NM_006516.2::152G>A NP_006507.2:p.Arg51His KCN03 NM_004519.3::.1626C-A NP_006507.2:p.Arg51His KCN03 NM_004519.3::.1626C-A NP_006871.0:p.Val59Lu GABRB3 NM_001040142.1:::C256A>G NP_006871.0:p.Val59Lu S1635 GPR56 NM_005682.5::.641C>T NP_001035232.1:p.He86Val S1635 GRIN2A NM_00113407.1:::C3228C>A NP_006614.2:p.Glu142Gly S1636 GRIN2A NM_0013407.1:::C3276C>T NP_006614.2:p.Glu142Gly S1652 MAGI2 NM_00134407.1:::C2765C>T NP_006132.2:p.Frp.1:p.Asg6His S1654 KCNE2 NM_172201.1::C170T>C NP_751951.1:p.He57Thr S1687 C0L4A2 NM_001846.2::C175C>T NP_001837.2:p.Arg6His S1722 SCN2A NM_001846.2::C176C>T </td <td>S1445</td> <td></td> <td></td> <td></td>	S1445			
CDKL5 NM_003159.2:c.65G>T NP_003150.1:p.Gly22Val S1449 COL4A1 NM_001845.4:c.2903G>A NP_001836.2:p.Arg968Gin S1487 SLC2A1 NM_001256214.1:c.133-5C>G NP_006507.2:p.Arg51His S1487 SLC2A1 NM_004519.3:c.126467.N NP_004510.1:p.Asg52Asn KCNQ3 NM_004519.3:c.1267657 NP_004510.1:p.Asg52Asn KCNQ3 NM_004519.3:c.1267657 NP_004510.1:p.Asg52Asn S1650 SCN2A NM_00140142.1:c.256A>G NP_004510.1:p.Asg52Asn S1635 GPR56 NM_005682.5:c.641C>T NP_005673.3:p.Ser214Leu S1636 GRIN2A NM_00134407.1:c.3228C>A NP_005643.2:p.Fro711Thr GLUT57 PHGDH NM_006623.3:c.425A>G NP_001127879.1:p.Asn10761ys S1652 MAGi2 NM_01134407.1:c.2765C>T NP_006142.1:p.Glu142Giy H3170 GRIN2A NM_001134407.1:c.2765C>T NP_001127879.1:p.Ala922Val S1654 KCNE2 NM_01014407.1:c.2765C>T NP_001127879.1:p.Ala922Val S1654 KCNE2 NM_001040142.1:c.34466>C NP_001127879.1:p.Ala922Val S1722 SCN2A		COL4A1	NM_001845.4:c.4372C>T	NP_001836.2:p.Pro1458Ser
S1449 COL4A1 COL4A2 NM_001845.4:c.2903G>A NM_001836.2:c.1655C>A NM_001837.2:p.Thr552Lys S1487 SLC2A1 NM_001516.2:c.152G>A NM_004519.3:c.1624G>A NM_004519.3:c.1624G>A NM_004510.1:p.Asp542Asn NM_004519.3:c.1624G>A NM_004510.1:p.Val59Leu GABRB3 NP_006507.2:p.Arg51His NP_004510.1:p.Asp542Asn NP_004510.1:p.Val59Leu GABRB3 S1560 SCN2A NM_00140142.1:c.256A>G NP_001035232.1:p.ile86Val S1563 GPR56 NM_00134407.1:c.3228C>A NP_005673.3:p.Ser214Leu S1635 GRIN2A NM_00134407.1:c.3228C>A NP_001127879.1:p.Asn1076Lys S1652 MAGI2 NM_012301.3:c.2131C>A NP_006614.2:p.Glu142Giy H3170 GRIN2A NM_001134407.1:c.2765C>T NP_001127879.1:p.Ala922Val S1654 KCNE2 NM_172201.1:c.170T>C NP_751951.1:p.ile57Thr S1657 COL4A2 NM_00140142.1:c.236G>C NP_0011837.2:p.Arg6His S1723 RELN MM_0016454.5:c.5156C>T NP_0011837.2:p.Jrg6His S1724 HESX1 NM_00164407.1:c.2365A NP_001385.2:p.Ser1719Leu NM_00134407.1:c.239G>C S1731 CHD2 NM_0014442.1:c.3446G>C NP_001137479.1:p.Val967Leu S1724 HESX1 NM_0016454.5:c.156C>T <td>S1447</td> <td></td> <td></td> <td></td>	S1447			
COL4A2 ATP1A3 NM_001846.2:c.1655C-A NM_001256214.1:c.193-5C-G NP_006307.2:p.Arg51His NP_004510.1:p.Asp542Asn NP_004510.1:p.Asp542Asn NP_004510.1:p.Asp542Asn NP_004510.1:p.Asp542Asn NP_004510.1:p.Asp542Asn NP_004510.1:p.Asp542Asn NP_006510.1:p.Asp542Asn NP_006510.1:p.Asp542Asn NP_006712.1:p.Met311Ile 51560 SCN2A NM_001040142.1:c.256A>G NP_006573.3:p.Ser214Leu 51635 GPR56 NM_001040142.1:c.256A>G NP_005673.3:p.Ser214Leu 51636 GRIN2A NM_001134407.1:c.3228C>A NP_005673.3:p.Ser214Leu 51652 MAGI2 NM_012301.3:c.2131C>A NP_006614.2:p.Glu142Gly 51652 MAGI2 NM_00134407.1:c.2765C>T NP_001127879.1:p.Asp1076Lys 51654 KCNE2 NM_172201.1:c.170T>C NP_751951.1:p.Ile57Thr 51654 KCNE2 NM_001040142.1:c.3446G>C NP_00103523.2:p.Ser1719Leu 51722 SCN2A NM_001040142.1:c.3446G>C NP_00103523.2:p.Ser1719Leu S1723 RELN NM_00134407.1:c.299G>C NP_001127879.1:p.Val967Leu 51724 HESX1 NM_00134407.1:c.299G>C NP_001385.2:p.Ser1719Leu NM_00134407.1:c.2885C>A NP_00103523.2:p.Gly1149Ala S1723 S1724 HESX1		CDKL5	NM_003159.2:c.65G>T	NP_003150.1:p.Gly22Val
ATP1A3 NM_001256214.1:c.193-5C>G \$ 1487 SLC2A1 NM_006516.2:c.152G>A NP_006507.2:p.Arg51His KCNQ3 NM_004519.3:c.1624G>A NP_004510.1:p.Asp542Asn S 1487 SLC2A1 NM_004519.3:c.1075G>T NP_004510.1:p.Asp542Asn SGABRB3 NM_021912.4:c.933G>T NP_006712.1:p.Met311He S1560 SCN2A NM_001040142.1:c.256A>G NP_001055232.1:p.Het311He S1635 GPR56 NM_001134407.1:c.3228C>A NP_005673.3:p.Ser214Leu S1636 GRIN2A NM_001134407.1:c.3228C>A NP_006614.2:p.Glu142Gly S1652 MAGI2 NM_001301.3:c.2131C>A NP_006614.2:p.Glu142Gly H3170 GRIN2A NM_001134407.1:c.2765C>T NP_001127879.1:p.Ala922Val S1654 KCNE2 NM_172201.1:c.170T>C NP_001127879.1:p.Ala922Val S1687 C0L4A2 NM_001040142.1:c.34466>C NP_00135232.1:p.Gly1149Ala S1722 SCN2A NM_001040142.1:c.34466>C NP_00132723.1:p.Gly1149Ala S1723 RELN NM_00134407.1:c.240G>A NP_0003856.1:p.Val129He NM_0013454.5:c.162C>T NP_0013856.2:p.For033er<	S1449		—	
SIL22A1 NM_006516.2:c:.152G>A NM_004519.3:c:.1624G>A NM_004519.3:c:.1075G>T NP_004510.1:p.Asp542Asn NM_004519.3:c:.1075G>T NP_004510.1:p.Val359Leu NP_004510.1:p.Val359Leu NP_004510.1:p.Val359Leu S1560 SCN2A NM_001040142.1:c.256A>G NP_001035232.1:p.Ile86Val S1635 GPR56 NM_00134407.1:c.3228C>A NP_005673.3:p.Ser214Leu S1636 GRIN2A NM_00134407.1:c.3228C>A NP_006614.2:p.Glu142Gly S1652 MAGI2 NM_00134407.1:c.2765C>T NP_00127879.1:p.Asn1076Lys S1654 KCNE2 NM_00134407.1:c.2765C>T NP_00127879.1:p.Asn1076Lys S1654 KCNE2 NM_00134407.1:c.2765C>T NP_00127879.1:p.Ala922Val S1657 C014A2 NM_001846.2:c.17G>A NP_0013837.2:p.Arg6His S1722 SCN2A NM_001846.2:c.17G>A NP_001035232.1:p.Gly1149Ala S1723 RELN NM_00134407.1:c.2899G>C NP_00127879.1:p.Val967Leu S1724 HESX1 NM_00134407.1:c.289G>C NP_0013232.2:p.Fr06035er NM_00134407.1:c.2310G>A111ins NP_001278.1:p.Val129He S1731 CHD2 NM_001845.4:c.1807C>T NP_001836.2:p.Gly474Arg S1732 CH42 NM				
KCNQ3 NM_004519.3:c.1624G>A NP_004510.1:p.Asp542Asn KCNQ3 NM_0021912.4:c.933G>T NP_004510.1:p.Val359Leu S1560 SCN2A NM_001040142.1:c.256A>G NP_0068712.1:p.Met311Ile S1560 SCN2A NM_001040142.1:c.256A>G NP_001055232.1:p.Ile86Val S1635 GPR56 NM_001134407.1:c.3228C>A NP_00127879.1:p.Asn1076Lys S1636 GRIN2A NM_001134407.1:c.3228C>A NP_006614.2:p.Glu142Gly S1652 MAGI2 NM_001134407.1:c.2765C>T NP_006614.2:p.Glu142Gly S1654 KCNE2 NM_010114407.1:c.2765C>T NP_001127879.1:p.Ala922Val S1654 KCNE2 NM_001134407.1:c.2765C>T NP_001337.2:p.Arg6His S1723 RELN NM_001040142.1:c.170F>C NP_0013523.2:p.GrJ119Leu S1723 RELN NM_001040142.1:c.28496>C NP_001035232.1:p.Gly1149Ala S1724 HESX1 NM_003865.2:c.385G>A NP_003856.2:p.Ser1719Leu NM_001845.4:c.1807C>T NP_001836.2:p.F0603ser NP_0056850.2:p.Val414Met NM_001845.4:c.1807C>T NP_001836.2:p.Gly474Arg S1734 GRIN2A NM_00134			<u>NM_001230214.1.0.193 3070</u>	J
KCNQ3 GABRB3 NM_004519.3:c.1075G>T NM_001912.4:c:933G>T NP_004510.1:p.Val359Leu NP_068712.1:p.Met311lle S1550 SCN2A NM_001040142.1:c.256A>G NP_001035232.1:p.lle86Val S1635 GPR56 NM_001134407.1:c.3228C>A NP_00127879.1:p.Asn1076Lys S1636 GRIN2A NM_001134407.1:c.3228C>A NP_001127879.1:p.Asn1076Lys S1652 MAGI2 NM_001134407.1:c.2765C>T NP_001127879.1:p.Asn1076Lys GLUTS7 PHGDH NM_001134407.1:c.2765C>T NP_001127879.1:p.Ala922Val S1654 KCNE2 NM_001134407.1:c.2765C>T NP_001127879.1:p.Ala922Val S1654 KCNE2 NM_001134407.1:c.2765C>T NP_001127879.1:p.Ala922Val S1654 KCNE2 NM_001846.2:c.17G>A NP_001337.2:p.Arg6His S1722 SCN2A NM_001040142.1:c.3446G>C NP_00135232.1:p.Gly1149Ala S1723 RELN NM_00134407.1:c.289G>C NP_0013565.2:p.Ser1719Leu GRIN2A NM_00134407.1:c.289G>C NP_00127879.1:p.Val967Leu S1724 HESX1 NM_003865.2:c.385G>A NP_00127879.1:p.Val967Leu S1724 HESX1 NM_0015682.5:c.844G>C	S 1487		—	
GABRB3 NM_021912.4:c;933G>T NP_068712.1:p.Met311Ile \$1560 SCN2A NM_001040142.1:c.256A>G NP_001035232.1:p.Ile86Val \$1635 GPR56 NM_00134407.1:c.3228C>A NP_001127879.1:p.Asn1076Lys \$1636 GRIN2A NM_012301.3:c.2131C>A NP_006673.3:p.Ser214Leu \$1636 GRIN2A NM_012301.3:c.2131C>A NP_006614.2:p.Glu142Gly \$1652 MAGI2 NM_001134407.1:c.2765C>T NP_001127879.1:p.Ala922Val \$1654 KCNE2 NM_001134407.1:c.2765C>T NP_001127879.1:p.Ala922Val \$1654 KCNE2 NM_001846.2:c:17G>A NP_001837.2:p.Arg6His \$1722 SCN2A NM_001846.2:c:17G>A NP_001837.2:p.Arg6His \$1723 RELN NM_001846.2:c:385G>C NP_001837.2:p.Arg6His \$1724 HESX1 NM_003665.2:c:385G>A NP_003563.2:p.Ser1719Leu NM_01134407.1:c.2899G>C NP_003836.1:p.Val129lie NM_001134407.1:c.289G>C NP_003826.1:p.Val129lie \$1724 HESX1 NM_0013865.2:c:385G>A NP_003826.2:p.Cer033:p.Glu1037_Arg1038in \$1734 GRIN2A NM_00134407.1:c.422C>T			—	
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S1636 GRIN2A NM_001134407.1:c.3228C>A NP_001127879.1:p.Asn1076Lys S1652 MAGI2 NM_012301.3:c.2131C>A NP_036433.2:p.Pro711Thr GLUT57 PHGDH NM_006623.3:c.425A>G NP_006614.2:p.Glu142Gly H3170 GRIN2A NM_001134407.1:c.2765C>T NP_001127879.1:p.Ala922Val S1654 KCNE2 NM_172201.1:c.170T>C NP_751951.1:p.He57Thr S1657 C0L4A2 NM_001040142.1:c.3446G>C NP_001035232.1:p.Gly1149Ala S1722 SCN2A NM_001040142.1:c.3446G>C NP_001035232.1:p.Gly1149Ala S1723 RELN NM_005045.3:c.5156C>T NP_001035232.1:p.Val967Leu GRIN2A NM_00134407.1:c.2899G>C NP_001127879.1:p.Val967Leu S1724 HESX1 NM_003865.2:c.385G>A NP_003856.1:p.Val129Ile HCN1 NM_0012072.3:c.1240G>A NP_001836.2:p.For603Ser GPR56 NM_001271.3:c.3110_3111ins NP_001836.2:p.Gly474Arg S1732 C0L4A1 NM_00134407.1:c.422C>T NP_00136.2:p.Gly474Arg S1734 GRIN2A NM_00134407.1:c.422C>T NP_00136.2:p.Arg732Lys S1734 <t< td=""><td>S1635</td><td>GPR56</td><td>NM 005682.5:c.641C>T</td><td>NP 005673.3:p.Ser214Leu</td></t<>	S1635	GPR56	NM 005682.5:c.641C>T	NP 005673.3:p.Ser214Leu
S1652 MAGI2 NM_012301.3:c.2131C>A NP_036433.2:p.Pro711Thr GLUT57 PHGDH NM_006623.3:c.425A>G NP_006614.2:p.Glu142Gly H3170 GRIN2A NM_001134407.1:c.2765C>T NP_001127879.1:p.Ala922Val S1654 KCNE2 NM_172201.1:c.170T>C NP_751951.1:p.Ile57Thr S1687 C0L4A2 NM_001846.2:c.17G>A NP_001837.2:p.Arg6His S1722 SCN2A NM_001040142.1:c.34466>C NP_001035232.1:p.Gly1149Ala S1723 RELN NM_005045.3:c.5156C>T NP_005036.2:p.Ser1719Leu GRIN2A NM_001134407.1:c.2899G>C NP_001127879.1:p.Val967Leu S1724 HESX1 NM_002865.2:c.385G>A NP_003856.1:p.Val129lle MC014A1 NM_001845.4:c.1807C>T NP_001836.2:p.Pro603Ser GPR56 NM_005682.5:c.844G>C NP_001836.2:p.Fro603Ser S1731 GCG g S1732 C0L4A1 NM_001845.4:c.1420G>A NP_001836.2:p.Gly474Arg S1734 GRIN2A NM_001845.4:c.1420G>A NP_001127879.1:p.Thr141Met S1734 GRIN2A NM_0006772.2:c.2195G>A NP_006763.2:p.Arg				
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S1654 KCNE2 NM_172201.1:c.170T>C NP_751951.1:p.lle57Thr S1687 C0L4A2 NM_001846.2:c.17G>A NP_001837.2:p.Arg6His S1722 SCN2A NM_001040142.1:c.3446G>C NP_001035232.1:p.Gly1149Ala S1723 RELN NM_005045.3:c.5156C>T NP_005036.2:p.Ser1719Leu GRIN2A NM_001134407.1:c.2899G>C NP_001127879.1:p.Val967Leu S1724 HESX1 NM_003865.2:c.385G>A NP_006356.1:p.Val129lle HCN1 NM_021072.3:c.1240G>A NP_006550.2:p.Val414Met C0L4A1 NM_001845.4:c.1807C>T NP_001865.2:p.Pro603Ser GPR56 NM_005682.5:c.844G>C NP_001636.2:p.Gly1282Arg S1731 CHD2 NM_001271.3:c.3110_3111ins NP_001262.3:p.Glu1037_Arg1038in GCG g S S1732 C0L4A1 NM_001845.4:c.1420G>A NP_00127879.1:p.Thr141Met S1734 GRIN2A NM_00134407.1:c.422C>T NP_001127879.1:p.Thr141Met S1774 PEX5L NM_005045.3:c.5618C>T NP_005036.2:p.Thr1873ille	GLUT57	PHGDH	NM_006623.3:c.425A>G	NP_006614.2:p.Glu142Gly
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S1723 RELN GRINZA NM_005045.3:c.5156C>T NM_001134407.1:c.2899G>C NP_005036.2:p.Ser1719Leu NP_001127879.1:p.Val967Leu S1724 HESX1 NM_003865.2:c.385G>A NP_003856.1:p.Val129Ile HCN1 NM_021072.3:c.1240G>A NP_066550.2:p.Val414Met COL4A1 NM_001845.4:c.1807C>T NP_001836.2:p.For603Ser GPR56 NM_005682.5:c.844G>C NP_001262.3:p.Gly282Arg S1731 CHD2 NM_001271.3:c.3110_3111ins NP_001262.3:p.Glu1037_Arg1038in GCG g S1732 COL4A1 NM_001134407.1:c.422C>T NP_001836.2:p.Gly474Arg S1734 GRIN2A SYNGAP1 NM_005045.3:c.5618C>T NP_005036.2:p.Thr141Met NP_005036.2:p.Thr1873Ile S1772 RELN NM_005045.3:c.2146G>C NP_004510.1:p.Asp716His S1773 KCNQ3 NM_016559.2:c.85C>T NP_057643.1:p.Gln29Ter	S1687	COL4A2	NM_001846.2:c.17G>A	NP_001837.2:p.Arg6His
GRIN2A NM_001134407.1:c.2899G>C NP_001127879.1:p.Val967Leu S1724 HESX1 NM_003865.2:c.385G>A NP_003856.1:p.Val129Ile HCN1 NM_021072.3:c.1240G>A NP_066550.2:p.Val414Met COL4A1 NM_001845.4:c.1807C>T NP_001836.2:p.Pro603Ser GPR56 NM_005682.5:c.844G>C NP_001836.2:p.Gly282Arg CHD2 NM_001271.3:c.3110_3111ins NP_001262.3:p.Glu1037_Arg1038in GCG g S1732 COL4A1 NM_001845.4:c.1420G>A NP_001836.2:p.Gly474Arg S1734 GRIN2A NM_001134407.1:c.422C>T NP_001127879.1:p.Thr141Met NM_006772.2:c.2195G>A NP_006763.2:p.Arg732Lys S1772 RELN NM_005045.3:c.5618C>T NP_005036.2:p.Thr1873Ile S1773 KCNQ3 NM_004519.3:c.2146G>C NP_004510.1:p.Asp716His S1774 PEX5L NM_016559.2:c.85C>T NP_057643.1:p.Gln29Ter	S1722	SCN2A	NM_001040142.1:c.3446G>C	NP_001035232.1:p.Gly1149Ala
S1724 HESX1 HCN1 NM_003865.2:c.385G>A NM_021072.3:c.1240G>A NP_003856.1:p.Val129lle NP_06550.2:p.Val414Met COL4A1 NM_001845.4:c.1807C>T GPR56 NP_001836.2:p.Pro603Ser MM_005682.5:c.844G>C NP_0005673.3:p.Gly282Arg CHD2 NM_001271.3:c.3110_3111ins NP_001262.3:p.Glu1037_Arg1038in g S1731 CCl4A1 NM_001845.4:c.1420G>A NP_001836.2:p.Gly474Arg S1732 COL4A1 NM_001134407.1:c.422C>T NP_001127879.1:p.Thr141Met SYNGAP1 NM_006772.2:c.2195G>A NP_006763.2:p.Arg732Lys S1772 RELN NM_005045.3:c.5618C>T NP_005036.2:p.Thr1873lle S1773 KCNQ3 NM_004519.3:c.2146G>C NP_0057643.1:p.Gln29Ter	S1723		—	
HCN1 NM_021072.3:c.1240G>A NP_066550.2:p.Val414Met COL4A1 NM_001845.4:c.1807C>T NP_001836.2:p.Pro603Ser GPR56 NM_005682.5:c.844G>C NP_005673.3:p.Gly282Arg CHD2 NM_001271.3:c.3110_3111ins NP_001262.3:p.Glu1037_Arg1038in S1731 GCG g S1732 COL4A1 NM_001845.4:c.1420G>A NP_001836.2:p.Gly474Arg S1734 GRIN2A NM_001134407.1:c.422C>T NP_001127879.1:p.Thr141Met SYNGAP1 NM_006772.2:c.2195G>A NP_006763.2:p.Arg732Lys S1772 RELN NM_005045.3:c.5618C>T NP_005036.2:p.Thr1873ile S1773 KCNQ3 NM_004519.3:c.2146G>C NP_004510.1:p.Asp716His	[i
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SYNGAP1 NM_006772.2:c.2195G>A NP_006763.2:p.Arg732Lys \$1772 RELN NM_005045.3:c.5618C>T NP_005036.2:p.Thr1873Ile \$1773 KCNQ3 NM_004519.3:c.2146G>C NP_004510.1:p.Asp716His \$1774 PEX5L NM_016559.2:c.85C>T NP_057643.1:p.Gln29Ter		00000		
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S1774 PEX5L NM_016559.2:c.85C>T NP_057643.1:p.Gln29Ter	S1772	RELN	NM_005045.3:c.5618C>T	NP_005036.2:p.Thr1873lle
S1774 PEX5L NM_016559.2:c.85C>T NP_057643.1:p.Gln29Ter	S1773	KCNQ3	NM_004519.3:c.2146G>C	NP_004510.1:p.Asp716His
S1//S SCN2A NM_001040142.1:c.2119A>T NP_001035232.1:p.lle707Leu				
	S1775	SCN2A	NM_001040142.1:c.2119A>T	NP_001035232.1:p.lle707Leu



RESULTS

Data validation

- < costo</p>

> facilità interpretazione

Number of patients:	50
Patients with variants:	41 (82%)
Patients with mutations with pathological effect:	12 (24%)
Patients with variants of unknown significance (VUS)	29 (58%)
No variants	9 (18%)

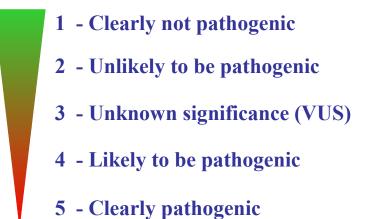
Data analysis

Silico prediction: [SIFT; PolyPhen-2; PMUT; MutationTaster]

Sanger sequencing validation

Clearly pathogenic (10 mutations in 6 patients) Unknown significance (VUS) (31 variants in 22 patients) Unlikely to be pathogenic (2 variants in 2 patients) **no variants in 10 patients**

Classification



DISORDINI DI RELINA		
RELN	7q22	reelin
VLDLR	9p24	Very Low Density Lipoprotein Receptor

1q21-q22

ARHGEF2





Rho/Rac Guanine Nucleotide Exchange Factor (GEF) 2



