# Supplementary Online Content

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This supplementary material has been provided by the authors to give readers additional information about their work.

# eMethods

## Mitochondrial Genome Sequencing

Beginning with samples received on 10/15/2012, our clinical WES test also included mitochondrial genome (mtDNA) sequencing. The mitochondrial genome was amplified by a single long-range PCR with TakaRa LA Hot Start Taq enzyme and the products subjected to paired-end library construction as described[1]. Libraries were then made from the 16Kb long-range PCR product using the same protocols as for WES library construction in a parallel process. To achieve co-processing in the sequencing step, the WES/mitochondrial library mixtures from each sample were labeled with different sequencing indexes (DNA barcodes) and analyzed in the same lane (1:30 ratio) on an Illumina NGS flowcell for sequencing on the Illumina HiSeq 2000 or 2500 platforms. Our procedures usually result in a mean depth of sequencing coverage of >100X with more than 95% of the targeted bases covered at least 20X for the WES, and a minimum average of >10,000X with 100% covered at least 40X for the mitochondrial genome. Mercury and Cassandra data annotation pipelines were employed for WES analysis as previously describped [2,3]. For the mitochondrial genome analysis the Revised Cambridge Reference Sequence (RCRS) was used as a reference.

## SNP Array Analysis

A separate aliquot of each individual's DNA was also analyzed by a cSNP-array (Illumina HumanExome-12 v1 array) for quality control assessment. The cSNP array allows a 'low resolution' genome-wide scan to detect copy number variants (CNV) and regions of absence of heterozygosity (AOH). Suspected AOH by cSNP array data were independently evaluated using the exome data in the same region.

## De novo Mutation Detection

WES variants were first analyzed as described in the "Molecular Diagnosis" section of Methods. Variants in loci known to be associated with Mendelian disease related to their clinical phenotypes were independently validated via PCR and Sanger fluorescent dideoxy DNA sequencing in the proband sample and also tested for segregation in DNA samples from parents, when available. Sanger confirmation studies in the proband and parental samples, data analysis and variant annotation were as previously described[2]. Absence of a mutant allele in the parental blood samples and presence in the proband by Sanger sequencing was reported as a de novo event. For each case, several rare variants were usually studied thus verifying parentage.

## Statistical Analysis

Confidence intervals of estimated proportions in a binomial distribution[4] were calculated using R software version 3.1.1, which was downloaded from http://www.r-project.org/.

**eTable 1.** Prior workup and cost for WES case # 218 [a]

| **Work up** | **Cost ($)** |
|---|---|
| **Prior workup**<br>(Listed individually below) | **20,097.00 (Total)**<br>(Listed individually below) |
| Fragile X | 420.00 |
| Creatine/Guanidinoacetate | 150.00 |
| Plasma amino acids | 185.00 |
| Oligo microarray | 3190.00 |
| Urine Organic acids | 300.00 |
| Lactate | 100.00 |
| Homocysteine panel | 100.00 |
| PWS methylation | 500.00 |
| Acylcarnitine | 185.00 |
| CK | 100.00 |
| CDKL5 | 2800.00 |
| FOXG1 | 580.00 |
| Thymidine | 190.00 |
| CSF neurotransmitters | 190.00 |
| Myotonic dystrophy | 350.00 |
| MRI Brain | 4715.00 |
| CT brain | 3042.00 |
| Lumbar puncture | 3000.00 |
| **Physician Consultations** | **Cost ($)** |
| Genetics consult | 287.00 |
| Neurology consult | 378.00 |
| Developmental Pediatrics consult | 275.00 |
| Gastroenterology consult | 225.00 |

[a] Presented as an example of a typical prior evaluation for patients referred for WES testing. Verification was provided by the referring physician and genetic counselor that no other studies (such as ordered by other physicians or institutions) were performed for this patient.

**eTable 2.** Percentage of patients (n=2000) demonstrating specific phenotypic features, overall and by different phenotype groups

| Phenotype | Overall No. | Overall Percentage | Neurologic group No. | Neurologic group Percentage | Neurologic plus other organ system No. | Neurologic plus other organ system Percentage | Specific neurologic group No. | Specific neurologic group Percentage | Non neurologic group No. | Non neurologic group Percentage |
|---|---|---|---|---|---|---|---|---|---|---|
| Developmental delay | 1249 | 62.5% | 389 | 73.8% | 848 | 73.9% | 5 | 6.0% | 3 | 1.2% |
| Abnormal muscle tone | 903 | 45.2% | 243 | 46.1% | 625 | 54.5% | 20 | 24.1% | 0 | 0.0% |
| Dysmorphic facial features | 693 | 34.7% | 69 | 13.1% | 572 | 49.9% | 2 | 2.4% | 50 | 20.6% |
| Seizure | 665 | 33.3% | 247 | 46.9% | 397 | 34.6% | 15 | 18.1% | 6 | 2.5% |
| Intellectual disability | 602 | 30.1% | 205 | 38.9% | 394 | 34.4% | 2 | 2.4% | 0 | 0.0% |
| Skeletal | 538 | 26.9% | 57 | 10.8% | 413 | 36.0% | 12 | 14.5% | 56 | 23.0% |
| Hearing loss, vision | 512 | 25.6% | 101 | 19.2% | 382 | 33.3% | 6 | 7.2% | 23 | 9.5% |
| Microcephaly | 339 | 17.0% | 87 | 16.5% | 241 | 21.0% | 2 | 2.4% | 9 | 3.7% |
| Failure to thrive | 331 | 16.6% | 49 | 9.3% | 260 | 22.7% | 1 | 1.2% | 21 | 8.6% |
| Brain malformation | 298 | 14.9% | 99 | 18.8% | 189 | 16.5% | 7 | 8.4% | 0 | 0.0% |
| Autism | 273 | 13.7% | 108 | 20.5% | 159 | 13.9% | 5 | 6.0% | 0 | 0.0% |
| Congenital heart disorder/Cardiovascular | 268 | 13.4% | 6 | 1.1% | 194 | 16.9% | 0 | 0.0% | 68 | 28.0% |
| Short stature | 263 | 13.2% | 37 | 7.0% | 199 | 17.3% | 2 | 2.4% | 25 | 10.3% |
| Regression | 252 | 12.6% | 118 | 22.4% | 132 | 11.5% | 1 | 1.2% | 0 | 0.0% |
| Abnormal movement, tremor | 234 | 11.7% | 79 | 15.0% | 143 | 12.5% | 11 | 13.3% | 0 | 0.0% |
| Speech delay | 215 | 10.8% | 72 | 13.7% | 141 | 12.3% | 1 | 1.2% | 0 | 0.0% |
| Ataxia | 169 | 8.5% | 63 | 12.0% | 99 | 8.6% | 7 | 8.4% | 0 | 0.0% |
| Connective tissue disorder | 163 | 8.2% | 8 | 1.5% | 130 | 11.3% | 2 | 2.4% | 23 | 9.5% |
| Macrocephaly | 131 | 6.6% | 32 | 6.1% | 91 | 7.9% | 0 | 0.0% | 8 | 3.3% |
| Muscle weakness | 108 | 5.4% | 28 | 5.3% | 60 | 5.2% | 13 | 15.7% | 0 | 0.0% |
| Respiratory | 106 | 5.3% | 11 | 2.1% | 77 | 6.7% | 5 | 6.0% | 13 | 5.3% |
| Genitourinary | 105 | 5.3% | 2 | 0.4% | 88 | 7.7% | 2 | 2.4% | 13 | 5.3% |
| Abnormal gait | 88 | 4.4% | 26 | 4.9% | 53 | 4.6% | 8 | 9.6% | 0 | 0.0% |
| Gastrointestinal | 86 | 4.3% | 6 | 1.1% | 60 | 5.2% | 0 | 0.0% | 20 | 8.2% |
| Skin | 75 | 3.8% | 5 | 0.9% | 62 | 5.4% | 0 | 0.0% | 8 | 3.3% |
| Liver | 70 | 3.5% | 3 | 0.6% | 38 | 3.3% | 0 | 0.0% | 29 | 11.9% |
| Myopathy | 41 | 2.1% | 10 | 1.9% | 21 | 1.8% | 10 | 12.0% | 0 | 0.0% |
| Neuropathy | 37 | 1.9% | 11 | 2.1% | 16 | 1.4% | 8 | 9.6% | 0 | 0.0% |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Cancer | 35 | 1.8% | 0 | 0.0% | 16 | 1.4% | 0 | 0.0% | 14 | 5.8% |
| Demyelinating disorder | 29 | 1.5% | 12 | 2.3% | 16 | 1.4% | 1 | 1.2% | 0 | 0.0% |
| Spastic paraplegia/quadriplegia/triplegia/diplegia | 19 | 1.0% | 4 | 0.8% | 12 | 1.0% | 2 | 2.4% | 0 | 0.0% |
| Parkinson-like movement | 8 | 0.4% | 3 | 0.6% | 3 | 0.3% | 2 | 2.4% | 0 | 0.0% |
| Muscular atrophy | 7 | 0.4% | 0 | 0.0% | 2 | 0.2% | 4 | 4.8% | 0 | 0.0% |
| Fetal dyskinesia | 1 | 0.1% | 0 | 0.0% | 0 | 0.0% | 1 | 1.2% | 0 | 0.0% |

The table was sorted by the overall rate from the highest percentage to the lowest percentage.

**eTable 3.** Variant interpretation criteria [a]

| Variant Type | Disease Inheritance | Reported Strong or Moderate Evidence (functional, population or segregation) available? [b] | Familial Evidence for Dominant Disorders in the Proband (*de novo* in the proband or inherited from a symptomatic parent) Available? | Familial Evidence for Recessive Disorders in the Proband (In trans with another variant in the proband) Available? | Variant Classification |
|---|---|---|---|---|---|
| Truncating | Dominant | Yes | Yes or No | Not applicable | Pathogenic |
| | | No | Yes | | Pathogenic |
| | | No | No | | Likely Pathogenic |
| | Recessive | Yes | Not applicable | Yes or No | Pathogenic |
| | | No | | Yes | Pathogenic |
| | | No | | No | Likely Pathogenic |
| Non-truncating | Dominant | Yes, strong evidence | Yes or No | Not applicable | Pathogenic |
| | | Yes, moderate evidence | Yes | | Pathogenic |
| | | Yes, moderate evidence | No, but the change is predicted to be damaging or possibly damaging by multiple *in silico* predications | | Likely Pathogenic |
| | | No | Yes, and the change is predicted to be damaging or possibly damaging by multiple *in silico* predications | | Likely Pathogenic |
| | Recessive | Yes, strong evidence | Not applicable | Yes or No | Pathogenic |
| | | Yes, moderate evidence | | Yes | Pathogenic |
| | | Yes, moderate evidence | | No, but the change is predicted to be damaging or possibly damaging by multiple *in silico* predications | Likely Pathogenic |
| | | No | | Yes, and the change is predicted to be damaging or possibly | Likely Pathogenic |

| | | | | | |
|---|---|---|---|---|---|
| | | | | damaging by multiple *in silico* predications | |

[a] The starting variants should be absent (for high-penetrance dominant disorders) or have allele frequencies lower than expected for the disease (for recessive disorders or dominant disorders with incomplete penetrance) in controls from Exome Sequencing Project (ESP) or the 1000 Genomes Project (TG). Criteria for pathogenic and likely pathogenic variants are listed in this table. Variants that do not meet these criteria were usually classified as variants of unknown clinical significance (VUS).

[b] Strong evidence includes well established functional studies strongly supporting the damaging effect of a variant, segregations in at least two families, or previously reported in at least two unrelated probands without other contradicting evidence. Moderate evidence includes well established functional studies supporting the damaging effect of a variant, segregations in one family, or previously reported once in an unrelated proband with no other contradicting evidence.

**eTable 4. Information on the causative mutations in the molecularly diagnosed cases**

| Group I: Patients with Neurologic (developmental delay, speech delay, autism, or intellectual disability) Disease Phenotype | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| **Patient #** | **Age (yr)** | **Gender** | **Inheritance** | **Gene** | **MIM Gene # [a]** | **Zygosity** | **Parental Origin** | **Mutation Type** | **Novel or Reported** | **Two diagnoses** |
| 1 | 3 | F | AD | *ACTA2* | 102620 | Het | de novo, recurrent | Missense | Reported in patients | |
| 2 | 7.3 | F | AD | *ADCY5* | 600293 | Het | de novo | Missense | Novel | |
| 3 | 4.3 | F | AD | *ANKRD11* | 611192 | Het | de novo | Frameshift | Novel | |
| 4 | 3.1 | M | AR | *AP4B1* | 607245 | Het | Inherited from mother, father not studied | Missense | Reported in controls | |
| | | | | *AP4B1* | 607245 | Het | did not Inherited from mother, father not studied | Frameshift | Reported in controls | |
| 5 | 10.4 | M | AR | *AP4M1* | 602296 | Het | Inherited, in trans with the other allele | Nonsense | Reported in controls | x |
| | | | AR | *ATM* | 607585 | Het | Inherited, in trans with the other allele | Nonsense | Reported in patients | x |
| | | | AR | *ATM* | 607585 | Het | Inherited, in trans with the other allele | Missense | Novel | x |
| | | | AR | *AP4M1* | 602296 | Het | Inherited, in trans with the other allele | Missense | Novel | x |
| 6 | 14.3 | M | X-linked | *ARHGEF6* | 300267 | Hem | Inherited from mother | Splice | Reported in patients | |
| 7 | 14.7 | F | AR | *ASAH1* | 613468 | Het | Inherited, in trans with the other allele | Missense | Novel | |
| | | | | *ASAH1* | 613468 | Het | Inherited, in trans with the other allele | Missense | Novel | |
| 8 | 54.3 | M | AR | *ATP13A2* | 610513 | Het | parents not studied | Missense | Reported in controls | |
| | | | | *ATP13A2* | 610513 | Het | parents not studied | Splice | Novel | |
| 9 | 2.8 | M | AD | *ATP1A2* | 182340 | Het | de novo | Missense | Novel | |
| 10 | 5.4 | M | X-linked | *ATP2B3* | 300014 | Het | de novo | Missense | Novel | |
| 11 | 15.4 | M | AR | *BBS1* | 209901 | Hom | Inherited, in trans with the other allele | Missense | Reported in patients | |

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|---|---|---|---|---|---|---|---|---|---|---|
| 12 | 13.3 | F | AR | *C12orf57* | 615140 | Hom | Inherited, in trans with the other allele | Start codon | Reported in patients | |
| **Group I: Patients with Neurologic (developmental delay, speech delay, autism, or intellectual disability) Disease Phenotype** | | | | | | | | | | |
| **Patient #** | **Age (yr)** | **Gender** | **Inheritance** | **Gene** | **MIM Gene # [a]** | **Zygosity** | **Parental Origin** | **Mutation Type** | **Novel or Reported** | **Two diagnoses** |
| 13 | 15 | M | AR | *C12orf65* | 613541 | Hom | Inherited, in trans with the other allele | Frameshift | Reported in patients | |
| 14 | 9.7 | M | AD | *CACNA1A* | 601011 | Het | de novo | Missense | Novel | |
| 15 | 3.5 | F | AD | *CACNA1A* | 601011 | Het | de novo | Missense | Reported in patients | |
| 16 | 0.1 | M | X-linked | *CASK* | 300172 | Hem | de novo | Nonsense | Reported in patients | |
| 17 | 2.3 | F | X-linked | *CDKL5* | 300203 | Het | mother is negative, father not studied | Nonsense | Novel | |
| 18 | 11.9 | M | X-linked | *CDKL5* | 300203 | Hem | de novo | Missense | Novel | |
| 19 | 3.9 | F | X-linked | *CDKL5* | 300203 | Het | de novo | Missense | Novel | |
| 20 | 4.4 | F | AD | *CHD2* | 602119 | Het | Inherited from symptomatic father | Nonsense | Novel | |
| 21 | 8.4 | F | AD | *CHD2* | 602119 | Het | de novo | Missense | Novel | x |
| | | | AD | *PRRT2* | 614386 | Het | Inherited from father | Frameshift | Novel | x |
| 22 | 13.2 | M | AR | *CHKB* | 612395 | Hom | Inherited, in trans with the other allele | Splice | Novel | |
| 23 | 6.8 | F | AD | *CHRNA7* | 118511 | Het | Inherited from symptomatic father | Splice | Novel | |
| 24 | 15.4 | F | AR/AD | *CHRNE* | 100725 | Hom | parents not studied | Frameshift | Reported in patients | |
| 25 | 1.9 | M | AR | *CPT2* | 600650 | Het | Inherited, in trans with the other allele | Frameshift | Reported in patients | |
| | | | | *CPT2* | 600650 | Het | Inherited, in trans with the other allele | Missense | Reported in patients | |
| 26 | 20.8 | F | AD | *CREBBP* | 600140 | Het | de novo | Missense | Novel | x |
| | | | AD | *PRICKLE2* | 608501 | Het | de novo | Frameshift | Novel | x |

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|---|---|---|---|---|---|---|---|---|---|---|
| 27 | 6.8 | M | AD | *CTNNB1* | 116806 | Het | de novo | Missense | Novel | |
| 28 | 4 | F | AD | *CTNNB1* | 116806 | Het | de novo | Nonsense | Novel | |
| 29 | 2.6 | M | AD | *CTNNB1* | 116806 | Het | de novo | Splice | Novel | |
| **Group I: Patients with Neurologic (developmental delay, speech delay, autism, or intellectual disability) Disease Phenotype** | | | | | | | | | | |
| **Patient #** | **Age (yr)** | **Gender** | **Inheritance** | **Gene** | **MIM Gene # [a]** | **Zygosity** | **Parental Origin** | **Mutation Type** | **Novel or Reported** | **Two diagnoses** |
| 30 | 2.1 | M | AR | *DHCR24* | 606418 | Het | Inherited, in trans with the other allele | Missense | Novel | |
| | | | | *DHCR24* | 606418 | Het | Inherited, in trans with the other allele | Missense | Reported in patients | |
| 31 | 3.9 | M | AD | *DNM1L* | 603850 | Het | Inherited from mother, mother mosaic | Missense | Novel | |
| 32 | 13.1 | F | AR | *DOK7* | 610285 | Het | Inherited, in trans with the other allele | Splice | Reported in patients | |
| | | | | *DOK7* | 610285 | Het | Inherited, in trans with the other allele | Frameshift | Reported in patients | |
| 33 | 5.1 | M | AD | *DYRK1A* | 600855 | Het | de novo | Nonsense | Novel | |
| 34 | 13.8 | F | AD | *DYRK1A* | 600855 | Het | de novo | Nonsense | Novel | |
| 35 | 1.8 | F | AR | *DYSF* | 603009 | Het | Inherited, in trans with the other allele | Frameshift | Novel | |
| | | | | *DYSF* | 603009 | Het | Inherited, in trans with the other allele | Missense | Reported in controls | |
| 36 | 15.2 | F | AD | *EFHC1* | 608815 | Het | Inherited from father | Nonsense | Reported in controls | x |
| | | | X-linked | *SMC1A* | 300040 | Het | de novo | Missense | Novel | x |
| 37 | 2.5 | M | AD | *EHMT1* | 607001 | Het | Mother is negative, father not studied | Nonsense | Reported in patients | |
| 38 | < 1 mo | M | AR | *EIF2B3* | 606273 | Hom | Inherited, in trans with the other allele | Missense | Novel | |
| 39 | 2.6 | M | AR | *EIF2B5* | 603945 | Hom | Inherited, in trans with the other allele | Missense | Novel | |

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|---|---|---|---|---|---|---|---|---|---|---|
| 40 | 4.2 | M | AR | *EIF2B5* | 603945 | Hom | Inherited, in trans with the other allele | Missense | Reported in patients | |
| 41 | 3.9 | M | AD | *EPB41L1* | 602879 | Het | de novo | Missense | Novel | |
| 42 | 7.9 | M | AR | *EXOSC3* | 606489 | Hom | Inherited, in trans with the other allele | Missense | Reported in patients | |
| 43 | 13.9 | M | AR | *FASTKD2* | 612322 | Hom | Inherited, in trans with the other allele | Nonsense | Novel | |
| **Group I: Patients with Neurologic (developmental delay, speech delay, autism, or intellectual disability) Disease Phenotype** | | | | | | | | | | |
| **Patient #** | **Age (yr)** | **Gender** | **Inheritance** | **Gene** | **MIM Gene # [a]** | **Zygosity** | **Parental Origin** | **Mutation Type** | **Novel or Reported** | **Two diagnoses** |
| 44 | 0.8 | M | AD | *FBN2* | 612570 | Het | inherited from mother | Splice | Novel | x |
| | | | X-linked | *PQBP1* | 300428 | Hem | inherited from mother | Missense | Novel | x |
| 45 | 2.3 | F | AD | *FOXG1* | 164874 | Het | de novo | Missense | Novel | |
| 46 | 12.3 | M | AR | *GAN* | 605379 | Het | Inherited, in trans with the other allele | Inframe deletion | Novel | |
| | | | | *GAN* | 605379 | Het | Inherited, in trans with the other allele | Missense | Novel | |
| 47 | 4 | M | AR | *GJC2* | 608803 | Het | Inherited, in trans with the other allele | Frameshift | Novel | |
| | | | | *GJC2* | 608803 | Het | Inherited, in trans with the other allele | Nonsense | Reported in patients | |
| 48 | 16.7 | M | AD | *GRIN1* | 138249 | Het | de novo | Missense | Novel | |
| 49 | 6.6 | M | AD | *GRIN2A* | 138253 | Het | de novo | Missense | Novel | |
| 50 | 7.1 | F | AD | *GRIN2B* | 138252 | Het | de novo | Inframe deletion | Novel | |
| 51 | 9 | M | AD | *GRIN2B* | 138252 | Het | de novo | Missense | Novel | |
| 52 | 1.4 | F | AD | *GRIN2B* | 138252 | Het | de novo | Inframe deletion | Novel | |
| 53 | 4.6 | F | AD | *GRIN2B* | 138252 | Het | de novo | Missense | Novel | |
| 54 | 7 | F | AD | *HNRNPU* | 602869 | Het | Mother is negative, father not studied | Nonsense | Novel | |
| 55 | 2.4 | M | AD | *IDH2* | 147650 | Mosaic | de novo | Missense | Reported in patients | |

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|---|---|---|---|---|---|---|---|---|---|---|
| 56 | 12.9 | F | AD | *ITPR1* | 147265 | Het | de novo | Missense | Novel | |
| 57 | 4.9 | F | AD | *KATNAL2* | 614697 | Het | Mother is negative, father not studied | Frameshift | Novel | |
| 58 | 5.1 | M | AD | *KCNT1* | 608167 | Het | de novo | Missense | Novel | |
| 59 | 3.3 | F | AD | *KCNT1* | 608167 | Het | de novo | Missense | Novel | |
| 60 | 11 | M | AD | *KCNT1* | 608167 | Het | de novo | Missense | Reported in patients | |
| **Group I: Patients with Neurologic (developmental delay, speech delay, autism, or intellectual disability) Disease Phenotype** | | | | | | | | | | |
| **Patient #** | **Age (yr)** | **Gender** | **Inheritance** | **Gene** | **MIM Gene # [a]** | **Zygosity** | **Parental Origin** | **Mutation Type** | **Novel or Reported** | **Two diagnoses** |
| 61 | 6.8 | M | AD | *KCNT1* | 608167 | Het | de novo | Missense | Reported in patients | |
| 62 | 2.4 | F | AR | *KCTD7* | 611725 | Hom | Inherited, in trans with the other allele | Missense | Novel | |
| 63 | 12.3 | F | X-linked | *KIAA2022* | 300524 | Het | mother is negative, father not studied | Framshift | Novel | |
| 64 | 6.3 | M | AD | *KIF5C* | 604593 | Het | de novo | Missense | Novel | x |
| | | | AR | *NRXN1* | 600565 | Hom | inherited, in trans with the other allele | Missense | Novel | x |
| | | | AR | *NRXN1* | 600565 | Hom | Inherited, in trans with the other allele | Missense | Novel | x |
| 65 | 5.7 | M | AR | *LAMB1* | 150240 | Het | Inherited, in trans with the other allele | Missense | Reported in controls | |
| | | | | *LAMB1* | 150240 | Het | Inherited, in trans with the other allele | Missense | Reported in controls | |
| 66 | 15.2 | F | AR | *LAMC3* | 604349 | Hom | Inherited, in trans with the other allele | Splice | Novel | |
| 67 | 9.3 | F | AD/AR | *LMNA* | 150330 | Het | de novo | Missense | Novel | |
| 68 | 1.9 | F | X-linked | *MECP2* | 300005 | Het | de novo | Nonsense | Reported in patients | |
| 69 | 6.8 | M | X-linked | *MECP2* | 300005 | Hem | Inherited from mother | Missense | Reported in patients | |

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|---|---|---|---|---|---|---|---|---|---|---|
| 70 | 7 | F | X-linked | *MECP2* | 300005 | Het | mother is negative, father not studied | Missense | Novel | |
| 71 | 2.2 | F | X-linked | *MECP2* | 300005 | Het | de novo | Missense | Reported in patients | |
| 72 | 7.4 | F | X-linked | *MECP2* | 300005 | Het | de novo | Nonsense | Novel | |
| 73 | 19.9 | M | AD | *MFN2* | 608507 | Het | parents not studied | Missense | Reported in patients | |
| 74 | 18.6 | F | AR | *MFRP* | 606227 | Hom | Inherited, in trans with the other allele | Nonsense | Novel | |
| **Group I: Patients with Neurologic (developmental delay, speech delay, autism, or intellectual disability) Disease Phenotype** | | | | | | | | | | |
| **Patient #** | **Age (yr)** | **Gender** | **Inheritance** | **Gene** | **MIM Gene #** [a] | **Zygosity** | **Parental Origin** | **Mutation Type** | **Novel or Reported** | **Two diagnoses** |
| 75 | 19.4 | M | AR | *MTFMT* | 611766 | Hom | Inherited, in trans with the other allele | Missense | Reported in patients | |
| 76 | 2.5 | F | AR | *MYO5A* | 160777 | Hom | mother is heterozygous, father not studied | Splice | Novel | |
| 77 | 2.1 | M | AD | N/A [b] | 176270 [b] | Het | Deletion affects maternal chromosome 15 in the proband | Large deletion | Reported in patients | |
| 78 | 1.3 | M | AR | *NDE1* | 609449 | App Hom | Inherited, in trans with the other allele | Missense | Reported in controls | |
| | | | | *NDE1* | 609449 | Het | Inherited, in trans with the other allele | Large deletion | Novel | |
| 79 | 0.4 | F | AR | *NDUFAF2* | 609653 | Hom | Inherited, in trans with the other allele | Nonsense | Reported in patients | |
| 80 | 0.8 | F | AR | *NDUFS1* | 157655 | Het | inherited, in trans with the other allele | Missense | Novel | |
| | | | | *NDUFS1* | 157655 | Het | inherited, in trans with the other allele | Missense | Reported in controls | |
| 81 | 14.1 | M | AR | *NPC2* | 601015 | Hom | Inherited, in trans with the other allele | Splice | Reported in patients | |

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|---|---|---|---|---|---|---|---|---|---|---|
| 82 | 5.7 | M | AD | *PACS1* | 607492 | Het | de novo, recurrent | Missense | Reported in patients | |
| 83 | 19.8 | F | AD | *PAFAH1B1* | 601545 | Het | de novo | Nonsense | Reported in patients | |
| 84 | 14.7 | M | X-linked | *PCDH19* | 300460 | Mosaic | de novo | Missense | Novel | |
| 85 | 10.1 | F | X-linked | *PCDH19* | 300460 | Het | Inherited from father | Frameshift | Novel | |
| 86 | 6.2 | F | X-linked | *PDHA1* | 300502 | Het | mother is negative, father not studied | Missense | Reported in patients | |
| 87 | 0.4 | M | X-linked | *PDHA1* | 300502 | Hem | Inherited from mother | Missense | Novel | |
| 88 | 2.9 | F | X-linked | *PDHA1* | 300502 | Het | de novo | Frameshift | Reported in patients | |
| **Group I: Patients with Neurologic (developmental delay, speech delay, autism, or intellectual disability) Disease Phenotype** | | | | | | | | | | |
| **Patient #** | **Age (yr)** | **Gender** | **Inheritance** | **Gene** | **MIM Gene # [a]** | **Zygosity** | **Parental Origin** | **Mutation Type** | **Novel or Reported** | **Two diagnoses** |
| 89 | 12.8 | M | X-linked | *PDHA1* | 300502 | Mosaic | de novo | Missense | Reported in patients | |
| 90 | 11.5 | F | X-linked | *PDHA1* | 300502 | Het | mother is negative, father not studied | Missense | Reported in patients | |
| 91 | 1.4 | M | AR | *PDHX* | 608769 | Hom | Inherited, in trans with the other allele | Missense | Reported in controls | |
| 92 | 20.7 | F | AR | *PEX16* | 603360 | Hom | Inherited, in trans with the other allele | Inframe deletion | Novel | |
| 93 | 14.5 | M | X-linked | *PIGA* | 311770 | Hem | de novo | Missense | Novel | |
| 94 | 4.3 | F | AR | *PLA2G6* | 603604 | Het | Inherited, in trans with the other allele | Nonsense | Reported in patients | |
| | | | | *PLA2G6* | 603604 | Het | Inherited, in trans with the other allele | Missense | Reported in patients | |
| 95 | 5.4 | F | AR | *PLA2G6* | 603604 | Het | parents not studied | Nonsense | Reported in patients | |
| | | | | *PLA2G6* | 603604 | Het | parents not studied | Nonsense | Reported in patients | |
| 96 | 5.4 | F | AR | *PLA2G6* | 603604 | Het | Inherited, in trans with | Nonsense | Reported | |

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|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | the other allele | | in patients | |
| | | | | *PLA2G6* | 603604 | Het | Inherited, in trans with the other allele | Splice | Novel | |
| 97 | 4 | M | AR | *PLA2G6* | 603604 | Hom UPD | Inherited from mother, maternal UPD 22 | Frameshift | Reported in patients | |
| 98 | 3.5 | M | AR | PLA2G6 | 603604 | Het | inherited, in trans with the other allele | Missense | Reported in patients | |
| | 3.5 | M | AR | PLA2G6 | 603604 | Het | inherited, in trans with the other allele | Missense | Reported in patients | |
| 99 | 4.2 | M | AR | *PNPT1* | 610316 | Het | Inherited, in trans with the other allele | Missense | Reported in controls | |
| | | | | *PNPT1* | 610316 | Het | Inherited, in trans with the other allele | Missense | Reported in controls | |
| 100 | 1.4 | M | AR | *POMT1* | 607423 | Hom | Inherited, in trans with the other allele | Missense | Reported in patients | |
| **Group I: Patients with Neurologic (developmental delay, speech delay, autism, or intellectual disability) Disease Phenotype** | | | | | | | | | | |
| **Patient #** | **Age (yr)** | **Gender** | **Inheritance** | **Gene** | **MIM Gene #** [a] | **Zygosity** | **Parental Origin** | **Mutation Type** | **Novel or Reported** | **Two diagnoses** |
| 101 | 7.1 | F | AR | *RMND1* | 614917 | Hom-App Hom | Inherited from mother, father is negative indicating carrier for a large deletion | Missense | Reported in controls | |
| 102 | 5.4 | F | AR/AD | *RYR1* | 180901 | Het | did not Inherited from mother, father not studied | Nonsense | Novel | |
| | | | | *RYR1* | 180901 | Het | Inherited from mother, father not studied | Missense | Reported in controls | |
| 103 | 0.7 | F | AD | *SCN1A* | 182389 | Het | de novo | Missense | Novel | |
| 104 | 0.9 | F | AD | *SCN1A* | 182389 | Het | de novo | Nonsense | Reported in patients | |
| 105 | 13.8 | F | AD | *SCN2A* | 182390 | Het | de novo | Missense | Novel | |
| 106 | 6.7 | F | AD | *SCN8A* | 600702 | Het | de novo | Missense | Novel | |
| 107 | 8.3 | M | AR | *SETX* | 608465 | Het | Inherited, in trans with the other allele | Frameshift | Novel | |
| | | | | *SETX* | 608465 | Het | Inherited, in trans with | Missense | Novel | |

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|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | the other allele | | | |
| 108 | 51.3 | M | AR | *SETX* | 608465 | Het | Inherited from father, mother not studied | Frameshift | Novel | |
| | | | | *SETX* | 608465 | Het | did not Inherited from father, mother not studied | Missense | Novel | |
| 109 | 17.4 | F | AD | *SHANK3* | 606230 | Het | de novo | Nonsense | Novel | |
| 110 | 11.3 | F | AD | *SHANK3* | 606230 | Het | de novo | Frameshift | Reported in patients | |
| 111 | 5 | F | AD | *SHANK3* | 606230 | Het | de novo | Frameshift | Novel | |
| 112 | 3.3 | F | AD | *SLC2A1* | 138140 | Het | de novo | Missense | Reported in patients | |
| 113 | 13.3 | F | AD | *SLC2A1* | 138140 | Het | Mother is negative, father not studied | Nonsense | Reported in patients | |
| 113 | 13.3 | F | AD | SLC2A1 | 138140 | Het | Mother is negative, father not studied | Nonsense | Reported in patients | |
| 114 | 7.6 | M | X-linked | SLC6A8 | 300036 | Hem | Mother not studied, confirmed by Biochem. | Missense | Novel | |
| 115 | 11.7 | M | AD | SMARCA2 | 600014 | Het | de novo | Missense | Novel | |
| **Group I: Patients with Neurologic (developmental delay, speech delay, autism, or intellectual disability) Disease Phenotype** | | | | | | | | | | |
| **Patient #** | **Age (yr)** | **Gender** | **Inheritance** | **Gene** | **MIM Gene #** [a] | **Zygosity** | **Parental Origin** | **Mutation Type** | **Novel or Reported** | **Two diagnoses** |
| 116 | 5.4 | F | AD | *SPAST* | 604277 | Het | de novo | Missense | Novel | |
| 117 | 4.9 | F | AD | *STXBP1* | 602926 | Het | de novo | Missense | Novel | |
| 118 | 9.5 | F | AD | *STXBP1* | 602926 | Het | de novo | Splice | Novel | |
| 119 | 16.3 | M | AD/AR | *STXBP1* | 602926 | Het | de novo | Nonsense | Novel | |
| 120 | 8.9 | M | AD | *STXBP1* | 602926 | Het | de novo | Splice | Novel | |
| 121 | 7.9 | F | AR | *SUCLG1* | 611224 | Het | Inherited from mother, father not studied | Missense | Reported in patients | |
| | | | | *SUCLG1* | 611224 | Het | did not Inherited from mother, father not studied | Missense | Novel | |
| 122 | 4.2 | M | AD | *SYNGAP1* | 603384 | Het | de novo | Nonsense | Novel | |
| 123 | 10.2 | F | AD | *SYNGAP1* | 603384 | Het | de novo | Frameshift | Novel | |
| 124 | 4.9 | F | AD | *SYNGAP1* | 603384 | Het | de novo | Frameshift | Reported in patients | |

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|---|---|---|---|---|---|---|---|---|---|---|
| 125 | 4.7 | M | AD | *SYNGAP1* | 603384 | Het | Mother is negative, father not studied | Frameshift | Novel | |
| 126 | 7.3 | M | AD | *SYNGAP1* | 603384 | Het | parents not studied | Nonsense | Novel | |
| 127 | 7.4 | F | AD | *SYNGAP1* | 603384 | Het | de novo | Frameshift | Novel | |
| 128 | 3.2 | M | AD | *SYNGAP1* | 603384 | Het | de novo | Nonsense | Novel | |
| 129 | 4.6 | M | AR | *TK2* | 188250 | Hom | Inherited, in trans with the other allele | Missense | Reported in patients | |
| 130 | 4.9 | M | X-linked | *TMLHE* | 300777 | Hem | Inherited from mother | Frameshift | Novel | |
| 131 | 3.7 | F | AD/AR | *TPM3* | 191030 | Het | de novo | Missense | Novel | |
| 132 | 7.4 | M | AR | *TPP1* | 607998 | Het | Inherited, in trans with the other allele | Nonsense | Novel | |
| | | | | *TPP1* | 607998 | Het | Inherited, in trans with the other allele | Missense | Reported in patients | |
| 133 | 1.3 | F | AR | *TRAPPC11* | 614138 | Hom | Inherited, in trans with the other allele | Missense | Reported in patients | |
| 134 | 6.5 | F | AD | *TSC1* | 605284 | Het | parents not studied | Frameshift | Reported in patients | |
| **Group I: Patients with Neurologic (developmental delay, speech delay, autism, or intellectual disability) Disease Phenotype** | | | | | | | | | | |
| **Patient #** | **Age (yr)** | **Gender** | **Inheritance** | **Gene** | **MIM Gene # [a]** | **Zygosity** | **Parental Origin** | **Mutation Type** | **Novel or Reported** | **Two diagnoses** |
| 135 | 1.5 | F | AR | TSEN54 | 608755 | Het | inherited, in trans with the other allele | Framshift | Novel | |
| | | | | TSEN54 | 608755 | Het | inherited, in trans with the other allele | Missense | Reported in patients | |
| 136 | 0.4 | F | AR | *TSEN54* | 608755 | Hom | Inherited, in trans with the other allele | Missense | Reported in patients | |
| 137 | 20 | M | AD | *TUBA1A* | 602529 | Het | parents not studied | Nonsense | Novel | |
| 138 | 0.2 | F | AD | *TUBA1A* | 602529 | Het | de novo | Missense | Novel | |
| 139 | 13.4 | M | AD | *TUBB4A* | 602662 | Het | de novo | Missense | Reported in patients | |
| 140 | 32.1 | F | AR | *USH2A* | 608400 | Het | parents not studied | Missense | Reported in controls | |
| | | | | *USH2A* | 608400 | Het | parents not studied | Missense | Reported | |

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|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | in patients | |
| 141 | 4 | F | X-linked | *WDR45* | 300526 | Het | de novo | Nonsense | Reported in patients | |
| 142 | 1.7 | M | AD | *WNT5A* | 164975 | Het | de novo | Missense | Novel | |
| 143 | 0.4 | M | AD | *ZFPM2* | 603693 | Het | Inherited from mother | Frameshift | Novel | |
| **Group II: Patients with Neurologic Plus Other Organ System Disease Phenotype** | | | | | | | | | | |
| **Patient #** | **Age (yr)** | **Gender** | **Inheritance** | **Gene** | **MIM Gene #** [a] | **Zygosity** | **Parental Origin** | **Mutation Type** | **Novel or Reported** | **Two diagnoses** |
| 144 | 7.3 | M | AD | *ABCC9* | 601439 | Het | de novo | Missense | Reported in patients | |
| 145 | 1.9 | M | AD | *ACTA1* | 102610 | Het | de novo | Missense | Reported in patients | |
| 146 | 0.1 | F | AD | *ACTA1* | 102610 | Het | de novo | Missense | Novel | |
| 147 | 0.8 | F | AD | *ACTA2* | 102620 | Het | de novo, recurrent | Missense | Reported in patients | |
| 148 | 17.2 | M | AD | *ADNP* | 611386 | Het | de novo | Frameshift | Novel | |
| 149 | 18.3 | M | AR | *AGK* | 610345 | Het | Inherited, in trans with the other allele | Splice | Reported in patients | |
| | | | | *AGK* | 610345 | Het | Inherited, in trans with the other allele | Nonsense | Novel | |
| **Group II: Patients with Neurologic Plus Other Organ System Disease Phenotype** | | | | | | | | | | |
| **Patient #** | **Age (yr)** | **Gender** | **Inheritance** | **Gene** | **MIM Gene #** [a] | **Zygosity** | **Parental Origin** | **Mutation Type** | **Novel or Reported** | **Two diagnoses** |
| 150 | fetus | U | AR | *ALG12* | 607144 | Het | Inherited, in trans with the other allele | Frameshift | Novel | |
| | | | | *ALG12* | 607144 | Het | Inherited, in trans with the other allele | Missense | Reported in patients | |
| 151 | 8 | F | AD | *ANKRD11* | 611192 | Het | Inherited from symptomatic mother | Frameshift | Novel | |

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|---|---|---|---|---|---|---|---|---|---|---|
| 152 | 4.7 | F | AD | *ANKRD11* | 611192 | Het | de novo | Frameshift | Novel | |
| 153 | 2.3 | F | AD | *ANKRD11* | 611192 | Het | de novo | Splice | Novel | |
| 154 | 2.4 | F | AD | *ANKRD11* | 611192 | Het | de novo | Frameshift | Novel | |
| 155 | 2.5 | M | AD | *ANKRD11* | 611192 | Het | Mother is negative, father not studied | Frameshift | Novel | |
| 156 | 1.2 | M | AD | *ANKRD11* | 611192 | Het | Inherited from symptomatic mother | Nonsense | Novel | |
| 157 | 0.9 | M | AD | *ANKRD11* | 611192 | Het | Inherited from mother | Frameshift | Novel | |
| 158 | 10.2 | M | AD | *ANKRD11* | 611192 | Het | de novo, recurrent | Frameshift | Novel | |
| 159 | 6.8 | F | AD | *ANKRD11* | 611192 | Het | de novo, recurrent | Frameshift | Novel | x |
| | | | AD | *ARID1B* | 614556 | Het | de novo | Frameshift | Novel | x |
| 160 | 14.4 | F | AD | *ANKRD11* | 611192 | Het | de novo | Nonsense | Novel | |
| 161 | 3.1 | F | AD | *ARID1A* | 603024 | Het | de novo | Frameshift | Novel | |
| 162 | 0.9 | F | AD | *ARID1A* | 603024 | Het | de novo | Nonsense | Novel | |
| 163 | 2.2 | M | AD | *ARID1A* | 603024 | Het | parents not studied | Frameshift | Novel | |
| 164 | 5.5 | M | AD | *ARID1B* | 614556 | Het | de novo | Nonsense | Novel | |
| 165 | 12 | F | AD | *ARID1B* | 614556 | Het | parents not studied | Nonsense | Novel | |
| 166 | 9.7 | F | AD | *ARID1B* | 614556 | Het | de novo | Frameshift | Novel | |
| 167 | 4.9 | F | AD | *ARID1B* | 614556 | Het | de novo | Nonsense | Novel | |
| 168 | 9.1 | M | AD | *ARID1B* | 614556 | Het | de novo | Nonsense | Novel | |
| 169 | 4.3 | F | AD | *ARID1B* | 614556 | Het | de novo | Nonsense | Reported in patients | |
| **Group II: Patients with Neurologic Plus Other Organ System Disease Phenotype** | | | | | | | | | | |
| **Patient #** | **Age (yr)** | **Gender** | **Inheritance** | **Gene** | **MIM Gene # [a]** | **Zygosity** | **Parental Origin** | **Mutation Type** | **Novel or Reported** | **Two diagnoses** |
| 170 | 5.6 | F | AD | *ARID1B* | 614556 | Het | de novo | Frameshift | Novel | |
| 171 | 2.6 | F | AD | *ARID1B* | 614556 | Het | de novo | Nonsense | Novel | |
| 172 | 12.1 | F | AD | *ARID1B* | 614556 | Het | Mother is negative, father not studied | Frameshift | Novel | |
| 173 | 1.9 | F | AD | *ARID1B* | 614556 | Het | de novo | Frameshift | Novel | |
| 174 | 10.4 | F | AD | *ARID1B* | 614556 | Het | de novo | Framshift | Novel | x |
| | | | X-linked | *GRIA3* | 305915 | Het | de novo | Missense | Novel | x |
| 175 | 9.1 | F | AD | *ARID1B* | 614556 | Het | de novo | Nonsense | Novel | |

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|---|---|---|---|---|---|---|---|---|---|---|
| 176 | 5.7 | M | AD | *ARID1B* | 614556 | Het | de novo | Frameshift | Novel | |
| 177 | 13.2 | F | AD | *ARID1B* | 614556 | Het | de novo | Nonsense | Novel | |
| 178 | 16.1 | M | AD | *ARID1B* | 614556 | Het | de novo | Frameshift | Novel | |
| 179 | 3.4 | M | AD | *ASXL1* | 612990 | Het | de novo | Nonsense | Novel | |
| 180 | 3.1 | F | AD | *ASXL3* | 615115 | Het | de novo | Nonsense | Novel | |
| 181 | 2.2 | F | AD | *ASXL3* | 615115 | Het | Mother is negative, father not studied | Nonsense | Novel | x |
| | | | AD | *ENG* | 131195 | Het | Inherited from mother, 2nd diagnoses | Splice | Reported in patients | x |
| 182 | 6.9 | U | AD | *ASXL3* | 615115 | Het | de novo | Nonsense | Novel | |
| 183 | 3.7 | M | AD | *ATL1* | 606439 | Het | de novo | Missense | Novel | |
| 184 | 12 | M | AR | *ATM* | 607585 | Het | Inherited, in trans with the other allele | Frameshift | Reported in patients | |
| | | | | *ATM* | 607585 | Het | Inherited, in trans with the other allele | Nonsense | Novel | |
| 185 | 3.4 | M | AR | *ATM* | 607585 | Het | Inherited, in trans with the other allele | Missense | Reported in patients | |
| | | | | *ATM* | 607585 | Het | Inherited, in trans with the other allele | Start codon | Novel | |
| **Group II: Patients with Neurologic Plus Other Organ System Disease Phenotype** | | | | | | | | | | |
| **Patient #** | **Age (yr)** | **Gender** | **Inheritance** | **Gene** | **MIM Gene # [a]** | **Zygosity** | **Parental Origin** | **Mutation Type** | **Novel or Reported** | **Two diagnoses** |
| 186 | 0.6 | F | AR | *ATM* | 607585 | Het | Inherited, in trans with the other allele | Splice | Novel | |
| | | | | *ATM* | 607585 | Het | Inherited, in trans with the other allele | Nonsense | Reported in patients | |
| 187 | 28.3 | F | AD | *ATP1A3* | 182350 | Het | de novo | Missense | Reported in patients | |
| 188 | 0.3 | M | X-linked | *ATP7A* | 300011 | Hem | Inherited from mother | Frameshift | Novel | |
| 189 | 9.2 | M | X-linked | *ATRX* | 300032 | Hem | Inherited from mother | Missense | Reported in patients | |
| 190 | 8.1 | M | X-linked | *ATRX* | 300032 | Hem | Inherited from mother | Nonsense | Reported | |

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| | | | | | | | | | in patients | |
| 191 | 2.8 | M | AR | *B3GALNT2* | 610194 | Het | Inherited, in trans with the other allele | Splice | Novel | |
| | | | | *B3GALNT2* | 610194 | Het | Inherited, in trans with the other allele | Missense | Novel | |
| 192 | 4.9 | M | AR | *B3GAT3* | 606374 | Hom | Inherited, in trans with the other allele | Missense | Reported in patients | |
| 193 | 4.4 | M | AD | *BAG3* | 603883 | Het | Mother is negative, father not studied | Missense | Reported in patients | |
| 194 | 7.1 | F | AR | *BBS1* | 209901 | Hom | Inherited, in trans with the other allele | Missense | Reported in patients | |
| 195 | 3 | F | AR | *BBS10* | 610148 | Het | Inherited, in trans with the other allele | Frameshift | Reported in patients | x |
| | | | | *BBS10* | 610148 | Het | Inherited, in trans with the other allele | Missense | Reported in controls | x |
| | | | X-linked | *PDHA1* | 300502 | Het | de novo | Frameshift | Novel | x |
| 196 | < 1 mo | F | AD | *BICD2* | 609797 | Het | de novo | Missense | Novel | |
| 197 | 24.3 | F | AD | *BRAF* | 164757 | Het | de novo | Missense | Reported in patients | |
| 198 | 8.1 | M | AD | *BRWD1* | NM_ 018963 | Het | de novo | Missense | Novel | |
| 199 | 3.9 | M | AD | *CACNA1A* | 601011 | Het | de novo | Missense | Novel | |
| 200 | 9.7 | M | AD/AR | *CASR* | 601199 | Het | de novo | Missense | Novel | |
| 201 | 3.1 | M | X-linked | *CDKL5* | 300203 | Hem | Mother not studied | Frameshift | Novel | |
| **Group II: Patients with Neurologic Plus Other Organ System Disease Phenotype** | | | | | | | | | | |
| **Patient #** | **Age (yr)** | **Gender** | **Inheritance** | **Gene** | **MIM Gene #** [a] | **Zygosity** | **Parental Origin** | **Mutation Type** | **Novel or Reported** | **Two diagnoses** |
| 202 | 14 | M | AR | *CFTR* | 602421 | Hom | Inherited, in trans with the other allele | Missense | Reported in patients | |
| 203 | 10.9 | M | AD | *CHD2* | 602119 | Het | de novo | Missense | Novel | |
| 204 | 0.6 | M | AD | *CHD7* | 608892 | Het | de novo | Missense | Reported in patients | |
| 205 | 0.2 | F | AD | *CHD7* | 608892 | Het | de novo | Frameshift | Reported | |

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| | | | | | | | | | in patients | |
| 206 | 5.5 | F | AD | *CHD8* | 610528 | Het | de novo | Frameshift | Novel | |
| 207 | 14 | M | AD | *CHD8* | 610528 | Het | de novo | Frameshift | Novel | |
| 208 | 46.6 | M | AR/AD | *CLCN1* | 118425 | Het | Parents not studied | Missense | Novel | x |
| | | | | *CLCN1* | 118425 | Het | Parents not studied | Missense | Reported in patients | x |
| | | | AD/AR | *DES* | 125660 | Het | Parents not studied | Missense | Reported in patients | x |
| 209 | < 1 mo | M | AR | *CNTNAP1* | 602346 | Hom | Inherited, in trans with the other allele | Nonsense | Novel | |
| 210 | 2.5 | F | AD | *COL4A1* | 120130 | Het | de novo | Missense | Novel | |
| 211 | 5.1 | M | AD | *COL4A2* | 120090 | Het | parents not studied | Splice | Novel | |
| 212 | 1.3 | F | AD/AR | *COL6A3* | 120250 | Het | de novo | Splice | Reported in patients | |
| 213 | 1.5 | M | AD | *CREBBP* | 600140 | Het | de novo | Frameshift | Novel | |
| 214 | 10.9 | M | AD | *CTNNB1* | 116806 | Het | de novo | Frameshift | Novel | |
| 215 | 0.4 | M | X-linked | *CYBB* | 300481 | Hem | Mother not studied | Frameshift | Reported in controls | |
| 216 | 11.4 | M | AR | *CYP7B1* | 603711 | Hom | Inherited, in trans with the other allele | Nonsense | Reported in patients | |
| 217 | 12 | F | X-linked | *DCX* | 300121 | Het | de novo | Missense | Reported in patients | |
| 218 | 11.8 | F | AD | *DEAF1* | 602635 | Het | de novo | Missense | Reported in patients | |
| 219 | 12 | M | X-linked | *DKC1* | 300126 | Hem | Inherited from mother | Promoter | Reported in patients | |
| 220 | 1.6 | F | X-linked | *DMD* | 300377 | Het | Inherited | Splice | Reported in controls | x |
| | | | AD | *TPM1* | 191010 | Het | de novo | Missense | Novel | x |
| 221 | 1 | F | AD | *DNM2* | 602378 | Het | de novo | Missense | Novel | |
| **Group II: Patients with Neurologic Plus Other Organ System Disease Phenotype** | | | | | | | | | | |
| **Patient #** | **Age (yr)** | **Gender** | **Inheritance** | **Gene** | **MIM Gene # [a]** | **Zygosity** | **Parental Origin** | **Mutation Type** | **Novel or Reported** | **Two diagnoses** |

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|---|---|---|---|---|---|---|---|---|---|---|
| 222 | 0.2 | F | AR | *DOLK* | 610746 | Het | Inherited, in trans with the other allele | Missense | Reported in patients | |
| | | | | *DOLK* | 610746 | Het | Inherited, in trans with the other allele | Missense | Novel | |
| 223 | 0.1 | F | AR | *DPAGT1* | 191350 | Hom | Inherited, in trans with the other allele | Missense | Novel | |
| 224 | 13.6 | F | AD | *DYNC1H1* | 600112 | Het | de novo | Missense | Novel | |
| 225 | 6.2 | M | AD | *DYNC1H1* | 600112 | Het | de novo | Missense | Novel | |
| 226 | 13.7 | F | AD | *DYNC1H1* | 600112 | Het | de novo | Missense | Novel | |
| 227 | 3.3 | M | AD | *DYRK1A* | 600855 | Het | de novo | Frameshift | Novel | |
| 228 | 7.9 | M | AD | *DYRK1A* | 600855 | Het | Inherited from father | Splice | Novel | x |
| | | | AD | *KAT6B* | 605880 | Het | de novo | Frameshift | Novel | x |
| 229 | 27.2 | M | AD | *DYRK1A* | 600855 | Het | Inherited from father, father is mosaic | Frameshift | Novel | |
| 230 | 7 | F | AD | *DYRK1A* | 600855 | Het | de novo | Missense | Novel | |
| 231 | 1.1 | F | AD | *EEF1A2* | 602959 | Het | de novo | Missense | Reported in patients | |
| 232 | 2.5 | M | AD | *EFTUD2* | 603892 | Het | de novo | Nonsense | Novel | |
| 233 | 2.2 | F | AD | *EFTUD2* | 603892 | Het | de novo | Missense | Novel | |
| 234 | 1.6 | F | AD | *EFTUD2* | 603892 | Het | de novo | Frameshift | Novel | |
| 235 | 8.5 | M | AD | *EHMT1* | 607001 | Het | de novo | Frameshift | Novel | |
| 236 | 1.3 | M | AD | *EHMT1* | 607001 | Het | de novo | Nonsense | Reported in patients | |
| 237 | 6.8 | M | AD | *EHMT1* | 607001 | Het | de novo | Frameshift | Novel | |
| 238 | 1.5 | M | AR | *ELAC2* | 605367 | Het | Inherited, in trans with the other allele | Frameshift | Novel | |
| | | | | *ELAC2* | 605367 | Het | Inherited, in trans with the other allele | Missense | Reported in patients | |
| 239 | 2.5 | F | AR/AD | *ELOVL4* | 605512 | Het | Inherited, in trans with the other allele | Splice | Novel | |
| | | | | *ELOVL4* | 605512 | Het | | Frameshift | Novel | |
| **Group II: Patients with Neurologic Plus Other Organ System Disease Phenotype** | | | | | | | | | | |
| **Patient #** | **Age (yr)** | **Gender** | **Inheritance** | **Gene** | **MIM Gene #** [a] | **Zygosity** | **Parental Origin** | **Mutation Type** | **Novel or Reported** | **Two diagnoses** |
| 240 | 1.6 | M | AR | *ENPP1* | 173335 | Het | Inherited, in trans with | Missense | Novel | |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | the other allele | | | |
| | | | | *ENPP1* | 173335 | Het | Inherited, in trans with the other allele | Missense | Reported in patients | |
| 241 | 2.8 | M | AD | *EP300* | 602700 | Het | de novo | Missense | Novel | |
| 242 | 3.4 | F | AR | *EPCAM* | 185535 | Hom | Inherited, in trans with the other allele | Frameshift | Reported in patients | |
| 243 | 1.9 | F | AR | *ERCC6* | 609413 | Het | Inherited, in trans with the other allele | Splice | Reported in patients | |
| | | | | *ERCC6* | 609413 | Het | Inherited, in trans with the other allele | Nonsense | Reported in patients | |
| 244 | 0.7 | F | AR | *ERCC6* | 609413 | Het | Inherited, in trans with the other allele | Nonsense | Reported in patients | |
| | | | | *ERCC6* | 609413 | Het | Inherited, in trans with the other allele | Frameshift | Reported in patients | |
| 245 | 5.2 | F | AD | *FBN1* | 134797 | Het | de novo | Frameshift | Reported in controls | |
| 246 | 2.6 | F | AD | *FBN1* | 134797 | Het | Inherited from mother | Missense | Reported in patients | |
| 247 | 3.9 | F | AR | *FBXL4* | 605654 | Het | Inherited, in trans with the other allele | Missense | Reported in patients | |
| | | | | *FBXL4* | 605654 | Het | Inherited, in trans with the other allele | Frameshift | Reported in patients | |
| 248 | 6 | M | AD/AR | *FGFR1* | 136350 | Het | de novo | Missense | Novel | |
| 249 | 3.3 | F | X-linked | *FLNA* | 300017 | Het | de novo | Missense | Novel | |
| 250 | 1.8 | F | AD | *FOXP1* | 605515 | Het | de novo | Splice | Novel | |
| 251 | 2.7 | F | AD | *FOXP1* | 605515 | Het | de novo | Frameshift | Novel | |
| 252 | 1.4 | M | AD | *FOXP1* | 605515 | Het | de novo | Missense | Novel | |
| 253 | 54.1 | M | AR | *FTCD* | 606806 | Het | Inherited, in trans with the other allele | Frameshift | Reported in patients | |
| | | | | *FTCD* | 606806 | Het | Inherited, in trans with the other allele | Missense | Reported in controls | |
| **Group II: Patients with Neurologic Plus Other Organ System Disease Phenotype** | | | | | | | | | | |
| **Patient** | **Age** | **Gender** | **Inheritance** | **Gene** | **MIM** | **Zygosity** | **Parental Origin** | **Mutation** | **Novel or** | **Two** |

| # | (yr) | | | | Gene # [a] | | | Type | Reported | diagnoses |
|---|---|---|---|---|---|---|---|---|---|---|
| 254 | 9.4 | M | AR | *G6PC3* | 611045 | Het | Inherited, in trans with the other allele | Frameshift | Novel | |
| | | | | *G6PC3* | 611045 | Het | Inherited, in trans with the other allele | Missense | Reported in patients | |
| 255 | 1 | F | AR | *GAA* | 606800 | Het | Inherited, in trans with the other allele | Missense | Reported in patients | |
| | | | | *GAA* | 606800 | Het | Inherited, in trans with the other allele | Missense | Reported in patients | |
| 256 | 16.9 | F | AR | *GALNT3* | 601756 | Hom | Inherited, in trans with the other allele | Nonsense | Reported in controls | x |
| | | | AD | *NF1* | 613113 | Het | de novo | Missense | Novel | x |
| 257 | 19.9 | M | AD | *GARS* | 600287 | Het | Inherited from symptomatic mother | Missense | Reported in patients | |
| 258 | 14.9 | F | AD | *GATA3* | 131320 | Het | de novo | Frameshift | Reported in patients | |
| 259 | 13.4 | M | AR | *GFER* | 600924 | Het | Inherited, in trans with the other allele | Frameshift | Novel | |
| | | | | *GFER* | 600924 | Het | Inherited, in trans with the other allele | Missense | Reported in patients | |
| 260 | 0.5 | M | AR | *GLB1* | 611458 | Hom | Inherited, in trans with the other allele | Missense | Reported in patients | |
| 261 | 15 | F | AR | *GLB1* | 611458 | Hom | Inherited, in trans with the other allele | Missense | Reported in patients | |
| 262 | 10.4 | M | AD | *GLI2* | 165230 | Het | Parents not studied | Frameshift | Novel | x |
| | | | AD | *IRF6* | 607199 | Het | Parents not studied | Nonsense | Reported in patients | x |
| 263 | 0.5 | M | X-linked | *GRIA3* | 305915 | Hem | de novo | Missense | Novel | |
| 264 | 12.4 | F | X-linked | *GRIA3* | 305915 | Het | de novo | Missense | Novel | |
| 265 | 2.6 | M | AD | *GRIN1* | 138249 | Het | de novo | Missense | Novel | |
| 266 | 3.4 | F | AD | *GRIN2B* | 138252 | Het | de novo | Missense | Novel | |
| 267 | 4.5 | M | AD | *GRIN2B* | 138252 | Het | de novo | Missense | Novel | |
| 268 | 5.9 | F | AD | *GRIN2B* | 138252 | Het | de novo | Missense | Novel | |

| Group II: Patients with Neurologic Plus Other Organ System Disease Phenotype | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| **Patient #** | **Age (yr)** | **Gender** | **Inheritance** | **Gene** | **MIM Gene #** [a] | **Zygosity** | **Parental Origin** | **Mutation Type** | **Novel or Reported** | **Two diagnoses** |
| 269 | 1.5 | F | AR | *HAX1* | 605998 | Het | Inherited, in trans with the other allele | Nonsense | Reported in controls | |
| | | | | *HAX1* | 605998 | Het | Inherited, in trans with the other allele | Missense | Reported in controls | |
| 270 | 3 | F | X-linked | *HDAC8* | 300269 | Het | de novo | Missense | Novel | |
| 271 | 6 | F | AR | *HEXA* | 606869 | Hom | Inherited, in trans with the other allele | Start codon | Reported in patients | |
| 272 | 8.9 | F | AR | *HGSNAT* | 610453 | Hom | Inherited, in trans with the other allele | Missense | Novel | |
| 273 | 11 | M | AD | *HNRNPU* | 602869 | Het | de novo | Frameshift | Novel | |
| 274 | 5.2 | M | AD | *HNRNPU* | 602869 | Het | de novo | Frameshift | Novel | |
| 275 | < 1 mo | F | AD | *HRAS* | 190020 | Het | de novo | Missense | Reported in patients | |
| 276 | 1.7 | F | X-linked | *HUWE1* | 300697 | Het | de novo | Splice | Novel | |
| 277 | 1.2 | M | AR | *IGHMBP2* | 600502 | Hom | Inherited, in trans with the other allele | Nonsense | Reported in patients | |
| 278 | < 1 mo | F | AR | *ISPD* | 614631 | Het | Inherited, in trans with the other allele | Nonsense | Reported in patients | |
| | | | | *ISPD* | 614631 | Het | Inherited, in trans with the other allele | Nonsense | Novel | |
| 279 | 3 | F | AD | *KANSL1* | 612452 | Het | parents not studied | Frameshift | Novel | |
| 280 | 5.1 | F | AD | *KANSL1* | 612452 | Het | Mother is negative, father not studied | Frameshift | Novel | |
| 281 | < 1 mo | M | AD | *KAT6B* | 605880 | Het | de novo | Frameshift | Novel | |
| 282 | 6.5 | M | AD | *KCNK9* | 605874 | Het | de novo | Missense | Novel | |
| 283 | 15.1 | F | AD | *KCNMA1* | 600150 | Het | Inherited from mother | Missense | Novel | |
| 284 | 0.5 | F | AD | *KCNQ2* | 602235 | Het | de novo | Missense | Novel | |
| 285 | 5.4 | F | AD | *KCNQ2* | 602235 | Het | de novo | Missense | Novel | |

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|---|---|---|---|---|---|---|---|---|---|---|
| **Group II: Patients with Neurologic Plus Other Organ System Disease Phenotype** | | | | | | | | | | |
| **Patient #** | **Age (yr)** | **Gender** | **Inheritance** | **Gene** | **MIM Gene #** [a] | **Zygosity** | **Parental Origin** | **Mutation Type** | **Novel or Reported** | **Two diagnoses** |
| 286 | 14.3 | F | AD | *KCNT1* | 608167 | Het | de novo, recurrent | Missense | Reported in patients | x |
| | | | AR/AD | *TTN* | 188840 | Het | Inherited, in trans with the other allele | Nonsense | Novel | x |
| | | | | *TTN* | 188840 | Het | | Missense | Novel | x |
| 287 | 3.3 | M | X-linked | *KDM6A* | 300128 | Hem | de novo | Missense | Novel | |
| 288 | 6.5 | F | X-linked | *KDM6A* | 300128 | Het | de novo | Frameshift | Novel | |
| 289 | 7.5 | F | AD | *KIF11* | 148760 | Het | de novo | Frameshift | Novel | |
| 290 | 7.9 | M | AD/AR | *KIF1A* | 601255 | Het | de novo | Missense | Novel | |
| 291 | 3.3 | F | AD/AR | *KIF1A* | 601255 | Het | de novo | Missense | Novel | |
| 292 | 4 | F | AD | *KMT2A* | 159555 | Het | de novo | Frameshift | Novel | |
| 293 | 13.1 | M | AD | *KMT2A* | 159555 | Het | Parents not studied | Frameshift | Novel | x |
| | | | AR | *TCIRG1* | 604592 | Het | Parents not studied | Missense | Novel | x |
| | | | | *TCIRG1* | 604592 | Het | Parents not studied | Nonsense | Reported in patients | x |
| 294 | 19.4 | F | AD | *KMT2A* | 159555 | Het | de novo | Missense | Novel | |
| 295 | 1.5 | F | AD | *KMT2A* | 159555 | Het | de novo | Missense | Novel | |
| 296 | 4.8 | M | AD | *KMT2C* | 606833 | Het | de novo | Nonsense | Novel | |
| 297 | 7.1 | M | AD | *KMT2C* | 606833 | Het | de novo | Missense | Novel | |
| 298 | 3 | M | AD | *KMT2D* | 602113 | Mosaic | de novo | Missense | Novel | |
| 299 | 1.7 | M | AD | *KMT2D* | 602113 | Het | de novo | Frameshift | Novel | |
| 300 | fetus | U | AD | *KMT2D* | 602113 | Het | de novo | Frameshift | Novel | |
| 301 | 8 | F | AD | *KRAS* | 190070 | Het | de novo | Missense | Novel | |
| 302 | 1.3 | F | AR | *LAMC3* | 604349 | Het | Inherited, in trans | Missense | Novel | |
| | | | | *LAMC3* | 604349 | Het | | Missense | Reported in controls | |
| 303 | 4.2 | F | X-linked | *LAMP2* | 309060 | Het | de novo | Nonsense | Reported in patients | |
| 304 | 2 | F | AR | *LARS* | 151350 | Het | Inherited, in trans with the other allele | Missense | Novel | |

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|---|---|---|---|---|---|---|---|---|---|---|
| | | | | *LARS* | 151350 | Het | | Missense | Reported in controls | |
| **Group II: Patients with Neurologic Plus Other Organ System Disease Phenotype** | | | | | | | | | | |
| **Patient #** | **Age (yr)** | **Gender** | **Inheritance** | **Gene** | **MIM Gene #** [a] | **Zygosity** | **Parental Origin** | **Mutation Type** | **Novel or Reported** | **Two diagnoses** |
| 305 | 16 | M | AR | *LIFR* | 151443 | Het | Inherited, in trans with the other allele | Nonsense | Novel | |
| | | | | *LIFR* | 151443 | Het | Inherited, in trans with the other allele | Missense | Novel | |
| 306 | 8.2 | F | AR | *LIPT1* | 610284 | Het | Inherited, in trans with the other allele | Nonsense | Reported in controls | |
| | | | | *LIPT1* | 610284 | Het | Inherited, in trans with the other allele | Missense | Novel | |
| 307 | 9.5 | F | AD/AR | *LMNA* | 150330 | Het | de novo | Missense | Novel | |
| 308 | 1.9 | M | AR | *LRP2* | 600073 | Het | Inherited, in trans with the other allele | Missense | Reported in controls | |
| | | | | *LRP2* | 600073 | Het | Inherited, in trans with the other allele | Missense | Reported in controls | |
| 309 | 19 | M | AD | *MAGEL2* | 605283 | Het | de novo | Nonsense | Novel | |
| 310 | 5.1 | M | AD | *MAGEL2* | 605283 | Het | de novo | Frameshift | Novel | |
| 311 | 8 | M | AD | *MAGEL2* | 605283 | Het | Mother is negative, father not studied | Frameshift | Novel | |
| 312 | 12.7 | M | AD | *MAGEL2* | 605283 | Het | Inherited from father, paternally imprinted | Frameshift | Novel | |
| 313 | 13.1 | F | AD | *MAP2K1* | 176872 | Het | de novo | Missense | Reported in patients | |
| 314 | 5.6 | M | AD | *MAP2K1* | 176872 | Het | de novo | Missense | Novel | |
| 315 | 11 | F | AD | *MBD5* | 611472 | Het | de novo | Nonsense | Novel | |
| 316 | 5.7 | M | X-linked | *MED12* | 300188 | Hem | de novo | Missense | Reported in patients | |
| 317 | 1.3 | M | AR | *MEGF8* | 604267 | Het | Inherited, in trans with the other allele | Missense | Novel | x |
| | | | | *MEGF8* | 604267 | Het | Inherited, in trans with the other allele | Missense | Novel | x |

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|---|---|---|---|---|---|---|---|---|---|---|
| | | | AD | *NF1* | 613113 | Mosaic | de novo | Frameshift | Novel | x |
| 318 | 11.3 | F | AR | *MEGF8* | 604267 | Hom | mother is heterozygous, father not studied | Splice | Novel | |
| **Group II: Patients with Neurologic Plus Other Organ System Disease Phenotype** | | | | | | | | | | |
| **Patient #** | **Age (yr)** | **Gender** | **Inheritance** | **Gene** | **MIM Gene #** [a] | **Zygosity** | **Parental Origin** | **Mutation Type** | **Novel or Reported** | **Two diagnoses** |
| 319 | 11.9 | F | AR | *MTFMT* | 611766 | Het | Inherited, in trans with the other allele | Missense | Reported in patients | x |
| | | | | *MTFMT* | 611766 | Het | Inherited, in trans with the other allele | Missense | Reported in patients | x |
| | | | AD | *SYNGAP1* | 603384 | Het | de novo | Nonsense | Novel | x |
| 320 | 32.8 | F | AD | N/A [b] | 176270 [b] | Het | Deletion affects maternal chromosome 15 in the proband | large deletion | Reported in patients | |
| 321 | 1.8 | M | X-linked | *NAA10* | 300013 | Hem | de novo | Frameshift | Novel | |
| 322 | 0.7 | M | Mitochondrial | *ND5* | 516005 | Heteroplasmy | de novo | Mito Missense | Reported in patients | |
| 323 | 13.2 | F | AR | *NDUFAF5* | 612360 | Hom | Inherited, in trans with the other allele | Missense | Novel | |
| 324 | 4.5 | M | AD | *NFIX* | 164005 | Het | de novo | Missense | Novel | |
| 325 | 30.1 | F | AD | *NFIX* | 164005 | Het | parents not studied | Frameshift | Novel | |
| 326 | 19.8 | F | AR | *NGLY1* | 610661 | Hom | Inherited, in trans with the other allele | Frameshift | Novel | |
| 327 | 5.1 | M | AD | *NKX2-1* | 600635 | Het | de novo | Nonsense | Novel | |
| 328 | 6.6 | F | X-linked | *NLGN4X* | 300427 | Het | de novo | Missense | Novel | |
| 329 | 1.6 | F | AD | *NOTCH2* | 600275 | Het | Mother is negative, father not studied | Frameshift | Novel | |
| 330 | 15.8 | F | AR | *NPC1* | 607623 | Het | Inherited, in trans with the other allele | Missense | Novel | |
| | | | | *NPC1* | 607623 | Het | Inherited, in trans with the other allele | Missense | Reported in patients | |
| 331 | 1.7 | M | AD | *NSD1* | 606681 | Het | de novo | Nonsense | Reported in patients | |

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|---|---|---|---|---|---|---|---|---|---|---|
| 332 | 0.2 | M | AD | *NSD1* | 606681 | Het | de novo | Frameshift | Novel | |
| 333 | 1.7 | F | AD | *NSD1* | 606681 | Het | de novo | Nonsense | Reported in patients | |
| 334 | 1 | M | AD | *NSD1* | 606681 | Het | Inherited from mother | Frameshift | Novel | |
| **Group II: Patients with Neurologic Plus Other Organ System Disease Phenotype** | | | | | | | | | | |
| **Patient #** | **Age (yr)** | **Gender** | **Inheritance** | **Gene** | **MIM Gene # [a]** | **Zygosity** | **Parental Origin** | **Mutation Type** | **Novel or Reported** | **Two diagnoses** |
| 335 | 4.9 | F | AD | *NSD1* | 606681 | Het | Mother is negative, father not studied | Splice | Novel | |
| 336 | 18.9 | M | AR | *NUBPL* | 613621 | Het | Inherited from mother, father not studied | Splice | Reported in patients | |
| | | | | *NUBPL* | 613621 | Het | did not Inherited from mother, father not studied | Missense | Novel | |
| 337 | 2.8 | M | X-linked | *OCRL* | 300535 | Hem | Mother not studied | Nonsense | Reported in patients | |
| 338 | 0.9 | M | X-linked | *OPHN1* | 300127 | Hem | de novo | Frameshift | Novel | |
| 339 | 1 | M | AD | *OTX2* | 600037 | Het | de novo | Frameshift | Novel | |
| 340 | 2.7 | M | AD | *PACS1* | 607492 | Het | de novo, recurrent | Missense | Reported in patients | |
| 341 | 8.7 | M | AD | *PACS1* | 607492 | Het | de novo, recurrent | Missense | Reported in patients | |
| 342 | 3.5 | F | AD | *PAFAH1B1* | 601545 | Het | de novo | Nonsense | Novel | |
| 343 | 0.7 | F | X-linked | *PDHA1* | 300502 | Het | de novo | Frameshift | Reported in patients | |
| 344 | fetus | U | AR | *PEX1* | 602136 | Het | Inherited, in trans with the other allele | Nonsense | Novel | |
| | | | | *PEX1* | 602136 | Het | Inherited, in trans with the other allele | Frameshift | Reported in patients | |
| 345 | fetus | U | AR | *PEX12* | 601758 | Hom | Inherited, in trans with the other allele | Nonsense | Novel | |
| 346 | 8.4 | M | AR | *PEX16* | 603360 | Hom | Inherited, in trans with the other allele | Missense | Novel | |

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|---|---|---|---|---|---|---|---|---|---|---|
| 347 | 0.4 | F | AD | *PHOX2B* | 603851 | Het | de novo | Missense | Novel | |
| 348 | 0.5 | F | AR | *PIGB* | 604122 | Hom | Inherited, in trans with the other allele | Missense | Novel | |
| 349 | 0.7 | F | AD | *PIK3CA* | 171834 | Het | Mother is negative, father not studied | Missense | Reported in patients | |
| 350 | 4.4 | F | AR | *PLA2G6* | 603604 | Hom | Inherited, in trans with the other allele | Missense | Novel | |
| **Group II: Patients with Neurologic Plus Other Organ System Disease Phenotype** | | | | | | | | | | |
| **Patient #** | **Age (yr)** | **Gender** | **Inheritance** | **Gene** | **MIM Gene #** [a] | **Zygosity** | **Parental Origin** | **Mutation Type** | **Novel or Reported** | **Two diagnoses** |
| 351 | 4.4 | F | AR | *PLOD1* | 153454 | Het | Inherited, in trans with the other allele | Nonsense | Reported in patients | |
| | | | | *PLOD1* | 153454 | Het | Inherited, in trans with the other allele | Nonsense | Reported in patients | |
| 352 | 3.6 | F | AR | *PLOD1* | 153454 | Het | Inherited, in trans with the other allele | Missense | Reported in patients | |
| | | | | *PLOD1* | 153454 | Het | Inherited, in trans with the other allele | Frameshift | Novel | |
| 353 | 1.5 | M | X-linked | *PLP1* | 300401 | Hem | de novo | Missense | Novel | |
| 354 | 4.4 | M | X-linked | *PLP1* | 300401 | Hem | de novo | Nonsense | Novel | |
| 355 | 1.9 | M | X-linked | *PLP1* | 300401 | Hem | de novo | Missense | Novel | |
| 356 | 1.2 | F | AR | *PMM2* | 601785 | Het | Inherited, in trans with the other allele | Missense | Reported in patients | |
| | | | | *PMM2* | 601785 | Het | Inherited, in trans with the other allele | Missense | Reported in patients | |
| 357 | 18.9 | M | AR | *PNPT1* | 610316 | Het | Inherited, in trans with the other allele | Missense | Reported in controls | |
| | | | | *PNPT1* | 610316 | Het | Inherited, in trans with the other allele | Missense | Reported in controls | |
| 358 | 27.2 | M | AR | *POMGNT1* | 606822 | Het | Parents not studied | Missense | Novel | |
| | | | | *POMGNT1* | 606822 | Het | Parents not studied | Missense | Reported | |

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|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | in controls | |
| 359 | 40.6 | M | X-linked | *PQBP1* | 300428 | Hem | Inherited from mother | Frameshift | Reported in patients | |
| 360 | 0.8 | M | X-linked | *PQBP1* | 300428 | Hem | Inherited from mother | Nonsense | Reported in patients | |
| 361 | 2 | F | AD | *PRICKLE2* | 608501 | Het | Inherited from mother | Missense | Reported in patients | |
| 362 | 2.3 | F | AD | *PTEN* | 601728 | Het | Mother is negative, father not studied | Frameshift | Novel | |
| 363 | 6.8 | F | AD | *PTEN* | 601728 | Het | Inherited from mother | Nonsense | Reported in patients | |
| 364 | 0.2 | M | AD | *PTPN11* | 176876 | Het | Parents not studied | Missense | Reported in patients | |
| **Group II: Patients with Neurologic Plus Other Organ System Disease Phenotype** | | | | | | | | | | |
| **Patient #** | **Age (yr)** | **Gender** | **Inheritance** | **Gene** | **MIM Gene # [a]** | **Zygosity** | **Parental Origin** | **Mutation Type** | **Novel or Reported** | **Two diagnoses** |
| 365 | 8.6 | F | AR | *RAB3GAP1* | 602536 | Het | Inherited, in trans with the other allele | Nonsense | Novel | |
| | | | | *RAB3GAP1* | 602536 | Het | Inherited, in trans with the other allele | Nonsense | Novel | |
| 366 | 12.9 | F | AR | *RAB3GAP1* | 602536 | Hom | Inherited, in trans with the other allele | Missense | Novel | |
| 367 | 13.4 | M | AR | *RARS2* | 611524 | Het | Inherited from mother, father not studied | Missense | Reported in controls | |
| | | | | *RARS2* | 611524 | Het | did not Inherited from mother, father not studied | Missense | Novel | |
| 368 | 5.4 | F | AR | *RIPK4* | 605706 | Hom | Inherited, in trans with the other allele | Missense | Novel | |
| 369 | 1.1 | F | AR | *ROBO3* | 608630 | Het | Inherited, in trans with the other allele | Missense | Novel | |
| | | | | *ROBO3* | 608630 | Het | Inherited, in trans with the other allele | Frameshift | Novel | |
| 370 | 8.8 | M | X-linked | *RPS6KA3* | 300075 | Hem | de novo | Splice | Reported | |

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|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | in patients | |
| 371 | 0.3 | F | AR/AD | *RRM2B* | 604712 | Hom | Inherited, in trans with the other allele | Missense | Novel | |
| 372 | 3 | F | AR | *RTTN* | 610436 | Het | Inherited, in trans with the other allele | Missense | Reported in controls | |
| | | | | *RTTN* | 610436 | Het | Inherited, in trans with the other allele | Missense | Reported in controls | |
| 373 | 13.4 | F | AR/AD | *RYR1* | 180901 | Het | Inherited, in trans with the other allele | Frameshift | Novel | |
| | | | | *RYR1* | 180901 | Het | Inherited, in trans with the other allele | Missense | Novel | |
| 374 | 24.9 | F | AR/AD | *RYR1* | 180901 | Het | Inherited, in trans with the other allele | Missense | Reported in patients | |
| | | | | *RYR1* | 180901 | Het | Inherited, in trans with the other allele | Nonsense | Reported in controls | |
| 375 | 10.7 | M | AD | *SATB2* | 608148 | Het | de novo | Nonsense | Novel | |
| 376 | 5.5 | F | AD | *SATB2* | 608148 | Het | de novo | Frameshift | Novel | |
| **Group II: Patients with Neurologic Plus Other Organ System Disease Phenotype** | | | | | | | | | | |
| **Patient #** | **Age (yr)** | **Gender** | **Inheritance** | **Gene** | **MIM Gene # [a]** | **Zygosity** | **Parental Origin** | **Mutation Type** | **Novel or Reported** | **Two diagnoses** |
| 377 | 14 | M | AD | *SATB2* | 608148 | Het | de novo | Frameshift | Novel | |
| 378 | 14.8 | M | AD | *SATB2* | 608148 | Het | de novo | Frameshift | Novel | |
| 379 | 9.9 | F | AD | *SCN1A* | 182389 | Het | de novo | Missense | Novel | x |
| | | | AD | *SMARCA2* | 600014 | Het | de novo | Missense | Novel | x |
| 380 | 4.9 | F | AD | *SHANK3* | 606230 | Het | de novo | Frameshift | Novel | |
| 381 | 12.1 | M | AD | *SHANK3* | 606230 | Het | de novo | Frameshift | Novel | |
| 382 | 6.2 | F | AD | *SHOC2* | 602775 | Het | de novo | Missense | Reported in patients | |
| 383 | 3.3 | F | AD | *SKI* | 164780 | Het | de novo | Missense | Reported in patients | |
| 384 | 0.6 | F | AR | *SKIV2L* | 600478 | Het | Inherited, in trans with the other allele | Splice | Novel | |
| | | | | *SKIV2L* | 600478 | Het | Inherited, in trans with the other allele | Frameshift | Novel | |

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|---|---|---|---|---|---|---|---|---|---|---|
| 385 | 4.7 | M | AR | *SLC7A7* | 603593 | App Hom | Inherited, in trans with the other allele | Nonsense | Novel | |
| | | | | *SLC7A7* | 603593 | Het | Inherited, in trans with the other allele | large deletion | Novel | |
| 386 | 16.1 | F | AD | *SLC9A3R1* | 604990 | Het | Mother is negative, father not studied | Missense | Reported in controls | |
| 387 | 2.2 | M | AD | *SMARCA4* | 603254 | Het | de novo | Missense | Novel | |
| 388 | 2.6 | M | AD | *SMARCB1* | 601607 | Het | de novo | Missense | Novel | |
| 389 | 8.9 | F | AD | *SMARCB1* | 601607 | Het | de novo | Missense | Reported in patients | |
| 390 | 4.3 | F | X-linked | *SMC1A* | 300040 | Het | de novo | Frameshift | Novel | |
| 391 | 21.5 | F | X-linked | *SMC1A* | 300040 | Het | de novo | Frameshift | Novel | |
| 392 | 4.9 | F | X-linked | *SMC1A* | 300040 | Het | de novo | Frameshift | Novel | |
| 393 | 2.1 | F | X-linked | *SMC1A* | 300040 | Het | de novo | Missense | Novel | |
| **Group II: Patients with Neurologic Plus Other Organ System Disease Phenotype** | | | | | | | | | | |
| **Patient #** | **Age (yr)** | **Gender** | **Inheritance** | **Gene** | **MIM Gene #** [a] | **Zygosity** | **Parental Origin** | **Mutation Type** | **Novel or Reported** | **Two diagnoses** |
| 394 | 5.1 | M | AR | *SRD5A3* | 611715 | Hom | Inherited, in trans with the other allele | Nonsense | Reported in patients | |
| 395 | 11.1 | M | X-linked | *SSR4* | 300090 | Hem | de novo | Splice | Novel | |
| 396 | 0.1 | M | AR | *STAMBP* | 606247 | Het | Inherited, in trans with the other allele | Missense | Reported in patients | |
| | | | | *STAMBP* | 606247 | Het | Inherited, in trans with the other allele | Nonsense | Novel | |
| 397 | 3.7 | M | AR | *SUMF1* | 607939 | App Hom | Inherited, in trans with the other allele | Missense | Reported in patients | |
| | | | | *SUMF1* | 607939 | Het | large deletion, apparently in trans with the other allele | large deletion | Novel | |
| 398 | 10.7 | M | AD | *TAB2* | 605101 | Het | de novo | Nonsense | Novel | |
| 399 | 1.5 | M | AR | *TBX19* | 604614 | Hom | mother is heterozygous, father not studied | Nonsense | Novel | |

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|---|---|---|---|---|---|---|---|---|---|---|
| 400 | 17.4 | F | AD | *TCF4* | 602272 | Het | de novo | Frameshift | Novel | |
| 401 | 3.5 | F | AD | *TCF4* | 602272 | Het | de novo | Frameshift | Novel | |
| 402 | 17.1 | M | AD | *TCF4* | 602272 | Het | de novo | Frameshift | Novel | |
| 403 | 12.5 | M | AD | *TGFBR2* | 190182 | Het | de novo | Missense | Novel | |
| 404 | 7.6 | F | AR | *TMEM67* | 609884 | Het | Inherited, in trans with the other allele | Missense | Reported in patients | |
| | | | | *TMEM67* | 609884 | Het | Inherited, in trans with the other allele | Missense | Novel | |
| 405 | fetus | U | AR | *TMEM67* | 609884 | Het | Inherited, in trans with the other allele | Missense | Reported in patients | |
| | | | | *TMEM67* | 609884 | Het | Inherited, in trans with the other allele | Missense | Novel | |
| 406 | 0.8 | M | AR | *TTC37* | 614589 | Hom | Inherited, in trans with the other allele | Nonsense | Novel | |
| 407 | 0.1 | M | AR/AD | *TTN* | 188840 | Het | parents not studied | Splice | Novel | |
| | | | | *TTN* | 188840 | Het | parents not studied | Missense | Novel | |
| **Group II: Patients with Neurologic Plus Other Organ System Disease Phenotype** | | | | | | | | | | |
| **Patient #** | **Age (yr)** | **Gender** | **Inheritance** | **Gene** | **MIM Gene #** [a] | **Zygosity** | **Parental Origin** | **Mutation Type** | **Novel or Reported** | **Two diagnoses** |
| 408 | 11.5 | M | AR/AD | *TTN* | 188840 | Het | de novo in AR/AD | Frameshift | Novel | |
| | | | | *TTN* | 188840 | Het | Inherited from mother, father is negative for both alleles | Missense | Novel | |
| 409 | 0.1 | F | AD | *TUBA1A* | 602529 | Het | de novo | Missense | Novel | |
| 410 | 2.5 | M | AD | *UBE3A* | 601623 | Het | de novo | Frameshift | Reported in patients | |
| 411 | 14.7 | M | X-linked | *UPF3B* | 300298 | Hem | Inherited from mother | Frameshift | Reported in patients | |
| 412 | 5.6 | F | AR | *VPS13B* | 607817 | Het | Inherited, in trans with the other allele | Missense | Novel | |
| | | | | *VPS13B* | 607817 | Het | Inherited, in trans with the other allele | Nonsense | Reported in controls | |

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|---|---|---|---|---|---|---|---|---|---|---|
| 413 | 1.2 | F | AR | *VPS13B* | 607817 | Het | Inherited, in trans with the other allele | Frameshift | Reported in patients | |
| | | | | *VPS13B* | 607817 | Het | Inherited, in trans with the other allele | Splice | Reported in patients | |
| 414 | 5.5 | F | AR/AD | *VWF* | 613160 | Het | Inherited, in trans with the other allele | Missense | Reported in patients | |
| | | | | *VWF* | 613160 | Het | Inherited, in trans with the other allele | Missense | Reported in controls | |
| 415 | 2.5 | F | AR | *WDPCP* | 613580 | Het | Inherited, in trans with the other allele | Frameshift | Novel | |
| | | | | *WDPCP* | 613580 | Het | Inherited, in trans with the other allele | Missense | Reported in controls | |
| 416 | 0.5 | M | AR | *WDR35* | 613602 | Het | Inherited, in trans with the other allele | Missense | Novel | |
| | | | | *WDR35* | 613602 | Het | Inherited, in trans with the other allele | Missense | Novel | |
| 417 | 5.3 | M | X-linked | *WDR45* | 300526 | Hem | de novo | Splice | Novel | |
| 418 | 2.4 | M | X-linked | *WDR45* | 300526 | Hem | de novo | Inframe deletion | Novel | |
| **Group II: Patients with Neurologic Plus Other Organ System Disease Phenotype** | | | | | | | | | | |
| **Patient #** | **Age (yr)** | **Gender** | **Inherit -ance** | **Gene** | **MIM Gene # [a]** | **Zygosity** | **Parental Origin** | **Mutation Type** | **Novel or Reported** | **Two diagnoses** |
| 419 | 38.2 | F | AR/AD | *WFS1* | 606201 | Het | Inherited, in trans with the other allele | Missense | Novel | |
| | | | | *WFS1* | 606201 | Het | Inherited, in trans with the other allele | Frameshift | Reported in patients | |
| 420 | 9.8 | M | AR | *XPA* | 611153 | Hom | Inherited, in trans with the other allele | Missense | Novel | |
| 421 | 1.6 | M | AD | *ZEB2* | 605802 | Het | de novo | Frameshift | Novel | |
| 422 | 17.5 | M | AD | *ZEB2* | 605802 | Het | Parents not studied | Nonsense | Reported in patients | |
| 423 | < 1 | M | AD | *ZEB2* | 605802 | Het | de novo | Frameshift | Novel | |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | mo | | | | | | | | | |
| 424 | 7.4 | F | AD | *ZEB2* | 605802 | Het | de novo | Nonsense | Novel | |
| 425 | 3.3 | F | AR | *ZNF335* | 610827 | Het | Inherited, in trans with the other allele | Frameshift | Novel | |
| | | | | *ZNF335* | 610827 | Het | Inherited, in trans with the other allele | Inframe deletion | Novel | |
| **Group III: Patients with Specific Neurological Findings** | | | | | | | | | | |
| **Patient #** | **Age (yr)** | **Gender** | **Inheritance** | **Gene** | **MIM Gene #** | **Zygosity** | **Parental Origin** | **Mutation Type** | **Novel or Reported** | **Two diagnoses** |
| 426 | < 1 mo | F | AD | *ACTA1* | 102610 | Het | de novo | Missense | Reported in patients | |
| 427 | 0.1 | F | AD | *ACTA1* | 102610 | Het | de novo | Missense | Reported in patients | |
| 428 | 0.1 | M | AD | *ACTA1* | 102610 | Het | de novo | Missense | Novel | |
| 429 | 0.3 | M | AD | ACTG2 | 102545 | Het | Inherited from symptomatic father | Missense | N/R | |
| 430 | 12.4 | F | AD | *ATL1* | 606439 | Het | de novo | Missense | Novel | |
| **Group III: Patients with Specific Neurological Findings** | | | | | | | | | | |
| **Patient #** | **Age (yr)** | **Gender** | **Inheritance** | **Gene** | **MIM Gene #** [a] | **Zygosity** | **Parental Origin** | **Mutation Type** | **Novel or Reported** | **Two diagnoses** |
| 431 | < 1 mo | M | AR | *CHRNG* | 100730 | Het | Inherited, in trans with the other allele | Frameshift | Reported in patients | |
| | | | | *CHRNG* | 100730 | Het | Inherited, in trans with the other allele | Frameshift | Novel | |
| 432 | 9.6 | M | AR | *CHRNG* | 100730 | Hom UPD | Inherited from father, paternal UPD 2 | Frameshift | Reported in patients | |
| 433 | 42.7 | F | AD | *CSF1R* | 164770 | Het | Mother is negative, father | Missense | Reported | |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | not studied | | in patients | |
| 434 | 7 | M | AD | *DEPDC5* | 614191 | Het | Inherited from symptomatic mother | Frameshift | Novel | |
| 435 | 35.5 | M | AR | *DNAJB2* | 604139 | Hom | Inherited, in trans with the other allele | Nonsense | Reported in controls | |
| 436 | 43.7 | M | AD | *DNM2* | 602378 | Het | Parents not studied | Missense | Reported in patients | |
| 437 | 16.6 | F | AD | *DNM2* | 602378 | Het | de novo | Missense | Reported in patients | |
| 438 | fetus | F | AR | *DOK7* | 610285 | Het | Inherited, in trans with the other allele | Missense | Reported in patients | |
| | | | | *DOK7* | 610285 | Het | Inherited, in trans with the other allele | Missense | Reported in patients | |
| 439 | 17 | M | AR | *DOK7* | 610285 | Het | Did not inherit from father, mother not studied | Frameshift | Reported in patients | |
| | | | | *DOK7* | 610285 | Het | Inherited from father, mother not studied | Missense | Reported in patients | |
| 440 | 0.3 | F | AD | *KCNT1* | 608167 | Het | de novo, recurrent | Missense | Reported in patients | |
| 441 | 0.1 | M | AD | *KCNT1* | 608167 | Het | de novo | Missense | Novel | |
| 442 | 19.7 | F | AD/AR | *KIF1A* | 601255 | Het | de novo | Missense | Novel | |
| 443 | 5.4 | F | AR | *MRE11A* | 600814 | Hom | Mother is heterozygous, father not studied | Nonsense | Reported in patients | |
| 444 | 45.9 | M | AD | *NF2* | 607379 | Het | Mother is negative, father not studied | stoploss | Novel | |
| 445 | 14.1 | F | AR | *PRX* | 605725 | Hom | Inherited, in trans with the other allele | Nonsense | Reported in patients | |
| 446 | 0.2 | M | AD | *SCN2A* | 182390 | Het | de novo | Missense | Novel | |
| **Group IV: Patients with Non-Neurological Findings** | | | | | | | | | | |
| **Patient #** | **Age (yr)** | **Gender** | **Inheritance** | **Gene** | **MIM Gene #** [a] | **Zygosity** | **Parental Origin** | **Mutation Type** | **Novel or Reported** | **Two diagnoses** |
| 447 | 0.6 | F | AR/AD | *SCN4A* | 603967 | Het | Inherited, in trans with the other allele | Missense | Reported in patients | |
| | | | | *SCN4A* | 603967 | Het | Inherited, in trans with | Nonsense | Novel | |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | the other allele | | | |
| 448 | 1.5 | F | AR/AD | *SCN4A* | 603967 | Het | Inherited, in trans with the other allele | Missense | Reported in controls | |
| | | | | *SCN4A* | 603967 | Het | Inherited, in trans with the other allele | Missense | Novel | |
| 449 | 1.1 | M | AR | *SCN9A* | 603415 | Hom UPD | Inherited from mother, maternal UPD 2 | Frameshift | Novel | |
| 450 | 20.1 | F | AR | *SIGMAR1* | 601978 | Hom UPD | Inherited from father, paternal UPD 9 | Frameshift | Novel | |
| 451 | 5.2 | F | AD | *SIX1* | 601205 | Het | de novo | Missense | Reported in patients | |
| 452 | 10.6 | M | AR | *SPG11* | 610844 | Het | Inherited, in trans with the other allele | Nonsense | Reported in controls | |
| | | | | *SPG11* | 610844 | Het | Inherited, in trans with the other allele | Missense | Reported in controls | |
| 453 | 16.1 | F | AR | *TK2* | 188250 | Het | Inherited from mother, father not studied | Missense | Reported in patients | |
| | | | | *TK2* | 188250 | Het | Did not inherit from mother, father not studied | Missense | Reported in patients | |
| 454 | 8.4 | M | AR/AD | *TTN* | 188840 | Het | Inherited, in trans with the other allele | Frameshift | Novel | |
| | | | | *TTN* | 188840 | Het | Inherited, in trans with the other allele | Missense | Novel | |
| 455 | 33.9 | M | AR | *VRK1* | 602168 | Het | Inherited, in trans with the other allele | Missense | Novel | |
| | | | | *VRK1* | 602168 | Het | Inherited, in trans with the other allele | Missense | Novel | |
| **Group IV: Patients with Non-Neurological Findings** | | | | | | | | | | |
| **Patient** | **Age** | **Gender** | **Inheritance** | **Gene** | **MIM** | **Zygosity** | **Parental Origin** | **Mutation** | **Novel or** | **Two** |

| # | (yr) | | | | Gene # [a] | | | Type | Reported | diagnoses |
|---|---|---|---|---|---|---|---|---|---|---|
| 456 | 9.1 | M | AD | *ACVRL1* | 601284 | Het | Mother is negative, symptomatic father not studied | Missense | Reported in patients | |
| 457 | 2.5 | M | AR | *ADSL* | 608222 | Het | Inherited, in trans with the other allele | Nonsense | Novel | |
| | | | | *ADSL* | 608222 | Het | Inherited, in trans with the other allele | Splice | Reported in controls | |
| 458 | 21.2 | F | AR | *ANTXR2* | 608041 | Het | Inherited, in trans with the other allele | Frameshift | Novel | |
| | | | | *ANTXR2* | 608041 | Het | Inherited, in trans with the other allele | Missense | Novel | |
| 459 | 0.4 | F | AR | *BBS1* | 209901 | Het | Inherited, in trans with the other allele | Missense | Reported in patients | |
| | | | | *BBS1* | 209901 | Het | Inherited, in trans with the other allele | Missense | Reported in patients | |
| 460 | < 1 mo | M | AR | *BBS1* | 209901 | Hom | Inherited, in trans with the other allele | Missense | Reported in patients | |
| 461 | 0.5 | M | AR | *BBS10* | 610148 | Hom | Inherited, in trans with the other allele | Nonsense | Novel | |
| 462 | 0.7 | M | AR | *CCDC103* | 614677 | Hom | Inherited, in trans with the other allele | Missense | Reported in patients | |
| 463 | 6.6 | M | X-linked | *CLCN5* | 300008 | Hem | Inherited from mother, grandparents are negative, de novo in mother | Nonsense | Reported in patients | |
| 464 | 0.1 | M | AD/AR | *COL11A1* | 120280 | Het | Inherited from mother | Nonsense | Novel | |
| 465 | 4.4 | M | AD | *COL1A2* | 120160 | Het | de novo | Inframe insertion | Novel | |
| 466 | 5.3 | M | AD/AR | *COL2A1* | 120140 | Het | de novo | Splice | Novel | |
| 467 | 41.7 | F | X-linked | *COL4A5* | 303630 | Het | Parents not studied | Splice | Reported in patients | |
| 468 | 18.3 | F | AD | *COL5A1* | 120215 | Het | Inherited from symptomatic mother | Missense | Novel | |

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|---|---|---|---|---|---|---|---|---|---|---|
| **Group IV: Patients with Non-Neurological Findings** | | | | | | | | | | |
| **Patient #** | **Age (yr)** | **Gender** | **Inheritance** | **Gene** | **MIM Gene # [a]** | **Zygosity** | **Parental Origin** | **Mutation Type** | **Novel or Reported** | **Two diagnoses** |
| 469 | 5.8 | F | AR | *DGAT1* | 604900 | Hom | Inherited, in trans with the other allele | Splice | Reported in patients | x |
| | | | AD | *THRA* | 190120 | Het | Inherited from father | Splice | Novel | x |
| 470 | 14.3 | F | AR | *DNAH5* | 603335 | Het | Inherited, in trans with the other allele | Nonsense | Reported in patients | |
| | | | | *DNAH5* | 603335 | Het | Inherited, in trans with the other allele | Missense | Reported in controls | |
| 471 | < 1 mo | M | AR | *DYNC2H1* | 603297 | Het | Inherited, in trans with the other allele | Missense | Reported in patients | |
| | | | | *DYNC2H1* | 603297 | Het | Inherited, in trans with the other allele | Missense | Novel | |
| 472 | 0.8 | M | AR | *EPHX1* | 132810 | Hom | Inherited, in trans with the other allele | Missense | Reported in controls | |
| 473 | 3.1 | M | AR | *EVC2* | 607261 | Het | Inherited, in trans with the other allele | Missense | Novel | |
| | | | | *EVC2* | 607261 | Het | Inherited, in trans with the other allele | Missense | Reported in controls | |
| 474 | 44.3 | F | AR | *FANCD2* | 613984 | Het | Inherited, in trans with the other allele | Nonsense | Novel | |
| | | | | *FANCD2* | 613984 | Het | Inherited, in trans with the other allele | Missense | Reported in controls | |
| 475 | 3.4 | M | AD | *FBN1* | 134797 | Het | Mother is negative, father not studied | Missense | Reported in patients | |
| 476 | 2.2 | F | AD | *FGFR3* | 134934 | Het | de novo | Missense | Reported in patients | |
| 477 | 1.3 | F | AR | *IL7R* | 146661 | App Hom | Inherited, in trans with the other allele | Frameshift | Novel | |
| | | | | *IL7R* | 146661 | Het | Inherited, in trans with the other allele | Large deletion | Novel | |

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|---|---|---|---|---|---|---|---|---|---|---|
| 478 | 8 | F | AD/AR | *KIF1A* | 601255 | Het | de novo | Missense | Novel | |
| 479 | < 1 mo | F | AD | *KMT2D* | 602113 | Het | de novo | Nonsense | Novel | |
| 480 | 0.7 | M | AD/AR | *KRT14* | 148066 | Het | de novo | Missense | Reported in patients | |
| **Group IV: Patients with Non-Neurological Findings** | | | | | | | | | | |
| **Patient #** | **Age (yr)** | **Gender** | **Inheritance** | **Gene** | **MIM Gene #** [a] | **Zygosity** | **Parental Origin** | **Mutation Type** | **Novel or Reported** | **Two diagnoses** |
| 481 | 3 | F | AD | *KRT81* | 602153 | Het | Inherited from mother | Nonsense | Reported in controls | |
| 482 | 0.2 | F | AD | *MYH6* | 160710 | Het | Inherited from mother | Splice | Novel | |
| 483 | 6.1 | M | AD | *MYH7* | 160760 | Het | Inherited from symptomatic mother | Missense | Reported in patients | |
| 484 | 0.5 | F | AR | *NIPAL4* | 609383 | Hom | Inherited, in trans with the other allele | Missense | Reported in patients | |
| 485 | 7.4 | M | AR | *PAPSS2* | 603005 | Hom | Parents not studied | Nonsense | Reported in patients | x |
| | | | AR | *TRDN* | 603283 | Hom | Parents not studied | Splice | Novel | x |
| 486 | 4.9 | F | AR | *PCNT* | 605925 | Hom | Inherited, in trans with the other allele | Splice | Novel | |
| 487 | 1.4 | M | AD | *PKP2* | 602861 | Het | Inherited from mother | Nonsense | Reported in controls | |
| 488 | 0.1 | M | AR | *PRF1* | 170280 | Hom | Parents not studied | Frameshift | Reported in patients | |
| 489 | 0.3 | M | AR | *PRF1* | 170280 | Het | Inherited, in trans with the other allele | Nonsense | Novel | |
| | | | | *PRF1* | 170280 | Het | Inherited, in trans with the other allele | Frameshift | Reported in patients | |
| 490 | 1 | M | AD | *PTCH1* | 601309 | Het | Inherited from father | Splice | Novel | |
| 491 | 15.3 | F | AR | *RECQL4* | 603780 | Hom | Inherited, in trans with the other allele | Nonsense | Reported in patients | x |
| | | | AR | *XPC* | 613208 | Hom | Inherited, in trans with the other allele | Splice | Novel | x |
| 492 | < 1 | M | AD | *RPL11* | 604175 | Het | Inherited from | Nonsense | Reported | |

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|---|---|---|---|---|---|---|---|---|---|---|
| | mo | | | | | | symptomatic father | | in patients | |
| 493 | 15.4 | F | AR | *SLC25A38* | 610819 | Hom | Parents not studied, array data indicate UPD | Splice | Novel | |
| 494 | 8.4 | F | AR | *SLX4* | 613278 | Het | Inherited, in trans with the other allele | Missense | Reported in controls | |
| | | | | *SLX4* | 613278 | Het | Inherited, in trans with the other allele | Missense | Reported in controls | |
| 495 | 6.1 | F | AD | *TAB2* | 605101 | Het | de novo | Nonsense | Novel | |
| 496 | 4.3 | F | AD | *TAB2* | 605101 | Het | Parents not studied | Missense | Reported in controls | |
| **Group IV: Patients with Non-Neurological Findings** | | | | | | | | | | |
| **Patient #** | **Age (yr)** | **Gender** | **Inheritance** | **Gene** | **MIM Gene #** [a] | **Zygosity** | **Parental Origin** | **Mutation Type** | **Novel or Reported** | **Two diagnoses** |
| 497 | 4 | F | AD | *TAB2* | 605101 | Het | de novo | Missense | Novel | |
| 498 | 1.4 | M | AR | *TALDO1* | 602063 | Hom | Inherited, in trans with the other allele | Missense | Reported in patients | |
| 499 | 8.3 | F | AD | *TEK* | 600221 | Het | Inherited from symptomatic father | Missense | Novel | |
| 500 | 1.4 | F | AD | *TGFBR1* | 190181 | Het | Parents not studied | Missense | Novel | |
| 501 | 40.6 | F | AR | *TNXB* | 600985 | Het | Inherited, in trans with the other allele | Missense | Reported in controls | |
| | | | | *TNXB* | 600985 | Het | Inherited, in trans with the other allele | Missense | Reported in controls | |
| 502 | 0.2 | F | AR | *TRMU* | 610230 | Het | Parents not studied | Missense | Novel | |
| | | | | *TRMU* | 610230 | Het | Parents not studied | Missense | Novel | |
| 503 | 12.6 | F | AR | *TTC7A* | 609332 | Het | Inherited, in trans with the other allele | Splice | Reported in patients | |
| | | | | *TTC7A* | 609332 | Het | Inherited, in trans with the other allele | Missense | Reported in controls | |
| 504 | 3.9 | F | AR | *TYR* | 606933 | Het | Inherited, in trans with the other allele | Missense | Reported in patients | |
| | | | | *TYR* | 606933 | Het | Inherited, in trans with the other allele | Frameshift | Reported in patients | |

[a] MIM gene numbers from Online Mendelian Inheritance in Man (OMIM; www.omim.org) were shown in this column for all genes except the *BRWD1* gene, for which the MIM number is not available and Reference Sequence (RefSeq) accession number was included instead.

[b] Large deletion affecting the Angelman syndrome/ Prader-Willi syndrome (MIM disease ID 176270) region.

**eTable 5.** Selected contributing genes in cases with molecular diagnoses [a]

| Autosomal Dominant | Autosomal Dominant (cont.) | Autosomal Dominant (cont.) | Autosomal Dominant (cont.) | Autosomal Recessive | Autosomal Recessive (cont.) | Autosomal Recessive (cont.) | X-linked |
|---|---|---|---|---|---|---|---|
| *ACTA1 (5)* | ***CSF1R*** | ***KCNT1 (4)*** | *PTEN (2)* | ***AGK*** | *GLB1 (2)* | ***RMND1*** | ***ATP2B3*** |
| (102610) | (164770) | (608167) | (601728) | (610345) | (611458) | (614917) | (300014) |
| *ACTA2 (2)* | *CTNNB1 (3)* | *KCNT1 (3)* | *SATB2 (4)* | *ATM (4)* | ***HAX1*** | *RYR1 (3)* | *ATRX (2)* |
| (102620) | (116806) | (608167) | (608148) | (607585) | (605998) | (180901) | (300032) |
| ***ADCY5*** | ***DEAF1*** | *KIF1A (4)* | *SCN1A (3)* | ***B3GALNT2*** | ***LAMB1*** | *SCN4A (2)* | *CDKL5 (4)* |
| (600293) | (602635) | (601255) | (182389) | (610194) | (150240) | (603967) | (300203) |
| ***ADNP*** [b] | ***DEPDC5*** [b] | ***KIF5C*** | *SCN2A (2)* | ***B3GAT3*** | *LAMC3 (2)* | *SETX (2)* | *GRIA3 (3)* |
| (611386) | (614191) | (604593) | (182390) | (606374) | (604349) | (608465) | (305915) |
| *ANKRD11 (11)* | *DNM2 (3)* | *KMT2A (4)* | *SHANK3 (5)* | *BBS1 (4)* | ***LIPT1*** [b] | ***SKIV2L*** | *KDM6A (2)* |
| (611192) | (602378) | (159555) | (606230) | (209901) | (610284) | (600478) | (300128) |
| *ARID1A (3)* | *DYNC1H1 (3)* | ***KMT2C (2)*** | *SLC2A1 (2)* | *BBS10 (2)* | ***MEGF8 (2)*** | ***STAMBP*** | *MECP2 (5)* |
| (603024) | (600112) | (606833) | (138140) | (610148) | (604267) | (606247) | (300005) |
| *ARID1B (16)* | *DYRK1A (6)* | *KMT2D (4)* | ***SLC9A3R1*** | ***CCDC103*** | *MTFMT (2)* | *TK2 (2)* | *PCDH19 (2)* |
| (614556) | (600855) | (602113) | (604990) | (614677) | (611766) | (188250) | (300460) |
| ***ASXL1*** | ***EEF1A2*** | *LMNA (2)* | *SMARCA2 (2)* | *CHRNG (2)* | ***NGLY1*** | *TMEM67 (2)* | *PDHA1 (7)* |
| (612990) | (602959) | (150330) | (600014) | (100730) | (610661) | (609884) | (300502) |
| ***ASXL3*** [b] | *EFTUD2 (3)* | ***MAGEL2 (4)*** [b] | *SMARCB1 (2)* | ***CNTNAP1*** [b] | ***PAPSS2*** | ***TRAPPC11*** | *PLP1 (3)* |
| (615115) | (603892) | (605283) | (601607) | (602346) | (603005) | (614138) | (300401) |
| ***ASXL3 (2)*** | *EHMT1 (4)* | *MAP2K1 (2)* | *STXBP1 (4)* | ***DGAT1*** | *PEX16 (2)* | ***TRDN*** | *PQBP1 (3)* |
| (615115) | (607001) | (176872) | (602926) | (604900) | (603360) | (603283) | (300428) |
| *ATL1 (2)* | *FBN1 (3)* | *NF1 (2)* | *SYNGAP1 (8)* | ***DNAJB2*** | ***PIGB*** | *TSEN54 (2)* | *SMC1A (5)* |
| (606439) | (134797) | (613113) | (603384) | (604139) | (604122) | (608755) | (300040) |
| ***BRWD1*** | *FOXP1 (3)* | *NFIX (2)* | ***TAB2 (4)*** | *DOK7 (3)* | *PLA2G6 (6)* | ***TTC37*** | ***SSR4*** [b] |
| (NM_018963) [a] | (605515) | (164005) | (605101) | (610285) | (603604) | (614589) | (300090) |
| *CACNA1A (3)* | *GRIN1 (2)* | *NSD1 (5)* | *TCF4 (3)* | *EIF2B5 (2)* | *PLOD1 (2)* | ***TTC7A*** | *WDR45 (3)* |
| (601011) | (138249) | (606681) | (602272) | (603945) | (153454) | (609332) | (300526) |
| *CHD2 (3)* | *GRIN2B (7)* | *PACS1 (3)* | ***THRA*** | ***EPHX1*** | ***PNPT1 (2)*** | *TTN (4)* | |
| (602119) | (138252) | (607492) | (190120) | (132810) | (610316) | (188840) | |
| *CHD7 (2)* | ***HNRNPU (3)*** | *PAFAH1B1 (2)* | *TUBA1A (3)* | *ERCC6 (2)* | *PRF1 (2)* | *VPS13B (2)* | |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| (608892) | (602869) | (601545) | (602529) | (609413) | (170280) | (607817) | |
| ***CHD8 (2)*** [b] | ***KANSL1 (2)*** | ***PIK3CA*** | ***TUBB4A*** | ***FBXL4*** [b] | ***RIPK4*** | | |
| (610528) | (612452) | (171834) | (602662) | (605654) | (605706) | | |
| ***CHRNA7*** | *KAT6B (2)* | *PRICKLE2 (2)* | *ZEB2 (4)* | | | | |
| (118511) | (605880) | (608501) | (605802) | | | | |
| *CREBBP (2)* | *KCNQ2 (2)* | | | | | | |
| (600140) | (602235) | | | | | | |

[a] Shown in the table are genes leading to recurrent diagnoses (numbers of cases in parentheses) and genes which were not available as a single gene or sequencing panel clinical test according to the Genetic Test Registry (http://www.ncbi.nlm.nih.gov/gtr/) or other sources at the time the WES test was ordered (bold, 65 total). For the complete gene and disease list, see eTables 3 in the Supplement. MIM gene numbers from Online Mendelian Inheritance in Man (OMIM; www.omim.org) are shown in parentheses for all genes except BRWD1, for which the MIM number is not available. A Reference Sequence (RefSeq) accession number is included instead.

[b] Cases (13 total) for which the genes were identified by re-analyzing the WES data with newly published disease genes after the completion of the initial WES reports.

**eTable 6.** Patients and parents that demonstrated mosaicism

| Patient/Parent | Case # [a] | Disease | Inheritance | Gene | Tested by WES NGS? | NGS Reads (Mutant vs. Wild-type) | Mutation allele fraction from NGS Reads or Sanger [b] | Confirmed by Sanger? | Mutation Type |
|---|---|---|---|---|---|---|---|---|---|
| Male patient | 55 | D-2-hydrosyglutaric aciduria 2 [MIM:613657] | AD | *IDH2* | Yes | 28:115 | 20% of total NGS Reads | Yes | Missense |
| Male patient | 298 | Kabuki syndrome 1 [MIM:147920] | AD | *KMT2D* | Yes | 29:249 | 10% of total NGS Reads | Yes | Missense |
| Male patient | 317 | Neurofibromatosis, type 1 [MIM:162200]; Neurofibromatosis-Noonan syndrome [MIM:601321]; Leukemia, juvenile myelomonocytic [MIM:607785]; Neurofibromatosis, familial spinal [MIM:162210]; Watson syndrome [MIM:193520] | AD | *NF1* | Yes | 14:121 | 10% of total NGS Reads | Yes | Frameshift |
| Male patient | | Epileptic | X-linked | *PCDH19* | Yes | 123:39 | 76% of total NGS Reads | Yes | Missense |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | 84 | encephalopathy, early infantile, 9 [MIM:300088] | | | | | | | |
| Male patient | 89 | Leigh syndrome, X-linked [MIM:308930]; Pyruvate dehydrogenase E1-alpha deficiency [MIM:312170] | X-linked | *PDHA1* | Yes | 19:92 | 17% of total NGS Reads | Yes | Missense |
| Mother | 31 | Encephalopahty, lethal, due to defective mitochondrial peroxisomal fission [MIM:614388] | AD | *DNM1L* | No | n/a | Low level on both Sanger sequencing strands | Yes | Missense |
| Father | 229 | Mental retardation, autosomal dominant 7 [MIM:614104] | AD | *DYRK1A* | No | n/a | Low level on both Sanger sequencing strands | Yes | Frameshift |

[a] Case # as listed in eTables 4; [b]: While allele fractions can be quantified using next generation sequencing (NGS) reads for WES samples, allele fractions in the parents, which were tested by Sanger sequencing only, cannot be accurately quantified.

**eTable 7.** Contributing genes and inheritance patterns in the 23 cases with two diagnoses [a]

| Case # [b] | Autosomal Dominant | Autosomal Dominant | Autosomal Recessive | Autosomal Recessive | X-linked |
|---|---|---|---|---|---|
| | Diagnosis #1 | Diagnosis #2 | | | |
| 159 | *ANKRD11* (611192) | *ARID1B* (614556) | | | |
| 181 | *ASXL3* (615115) | *ENG* (131195) | | | |
| 21 | *CHD2* (602119) | *PRRT2* (614386) | | | |
| 26 | *CREBBP* (600140) | *PRICKLE2* (608501) | | | |
| 228 | *DYRK1A* (600855) | *KAT6B* (605880) | | | |
| 379 | *SCN1A* (182389) | *SMARCA2* (600014) | | | |
| 262 | *GLI2* (165230) | *IRF6* (607199) | | | |
| | Diagnosis #1 | | Diagnosis #2 | | |
| 208 | *DES* (125660) | | *CLCN1* (118425) | | |
| 286 | *KCNT1* (608167) | | *TTN* (188840) | | |
| 64 | *KIF5C* (604593) | | *NRXN1* (600565) | | |
| 293 | *KMT2A* (159555) | | *TCIRG1* (604592) | | |
| 256 | *NF1* (613113) | | *GALNT3* (601756) | | |
| 317 | *NF1* (613113) | | *MEGF8* (604267) | | |
| 319 | *SYNGAP1* (603384) | | *MTFMT* (611766) | | |
| 469 | *THRA* (190120) | | *DGAT1* (604900) | | |
| | Diagnosis #1 | | | | Diagnosis #2 |
| 174 | *ARID1B* (614556) | | | | *GRIA3* (305915) |
| 36 | *EFHC1* (608815) | | | | *SMC1A* (300040) |
| 44 | *FBN2* (612570) | | | | *PQBP1* (300428) |
| 220 | *TPM1* (191010) | | | | *DMD* (300377) |
| | | | Diagnosis #1 | Diagnosis #2 | |
| 5 | | | *AP4M1* (602296) | *ATM* (607585) | |
| 485 | | | *PAPSS2* (603005) | *TRDN* (603283) | |
| 491 | | | *RECQL4* (603780) | *XPC* (613208) | |
| 195 | | | *BBS10* (209901) | | *PDHA1* (300502) |

[a] MIM gene numbers from Online Mendelian Inheritance in Man are shown in parentheses. [b] Case # listed in eTables 4, which includes more details of the positive cases.

**eTable 8.** Uniparental disomy (UPD) cases contributing to the molecular diagnoses by unmasking mutations in recessive disorder genes

| | | | | | | | | Parental Age (yr) | |
|---|---|---|---|---|---|---|---|---|---|
| **Case #** [a] | **Age (yr)** | **Sex** | **Chromosome** | **Parental origin** | **Isodisomy type** | **Likely mechanism** [b] | **Genes** [c] | **Maternal** | **Paternal** |
| 449 | 1.1 | M | 2 | Maternal | Partial | Trisomy rescue | *SCN9A* (603415) | 36 | 41 |
| 432 | 9.6 | M | 2 | Paternal | Complete | Monosomy rescue | *CHRNG* (100730) | 19 | 18 |
| 450 | 20 | F | 9 | Paternal | Complete | Monosomy rescue | *SIGMAR1* (601978) | 32 | 28 |
| 97 | 4 | M | 22 | Maternal | Complete | Monosomy rescue | *PLA2G6* (603604) | 27 | 33 |
| 493 | 15 | F | 3 | Unknown[d] | Complete | Monosomy rescue | *SLC25A38* (610819) | n.a.[d] | n.a.[d] |

[a] Case # listed in eTables 3, which includes more details of the positive cases.

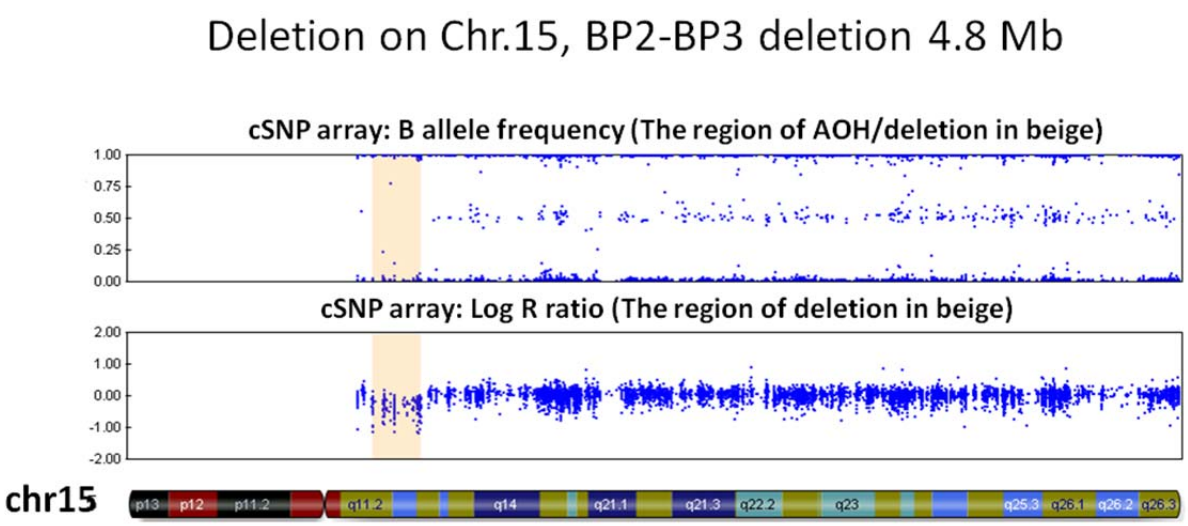
[b] Restoation of euploidy by loss of one chromosome in trisomy (trisomy rescue) or duplication of the chromosome in monosomy (monosomy rescue).

[c] MIM gene numbers from Online Mendelian Inheritance in Man (OMIM; www.omim.org) are shown in parentheses.

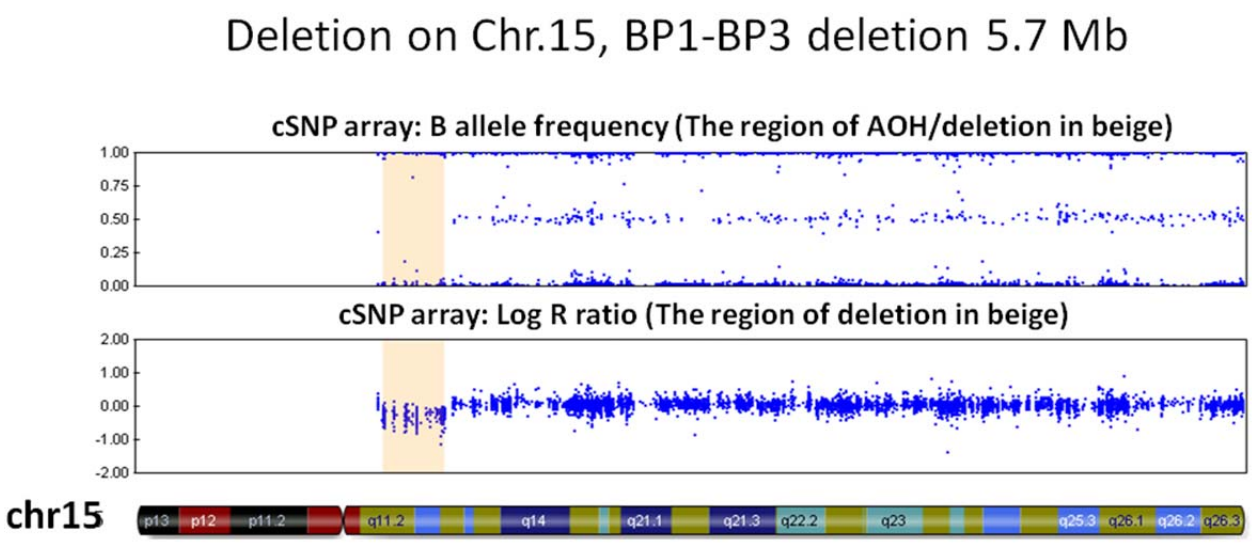
[d] Parental samples not available.

**eFigure 1**. Large deletions detected in WES cases

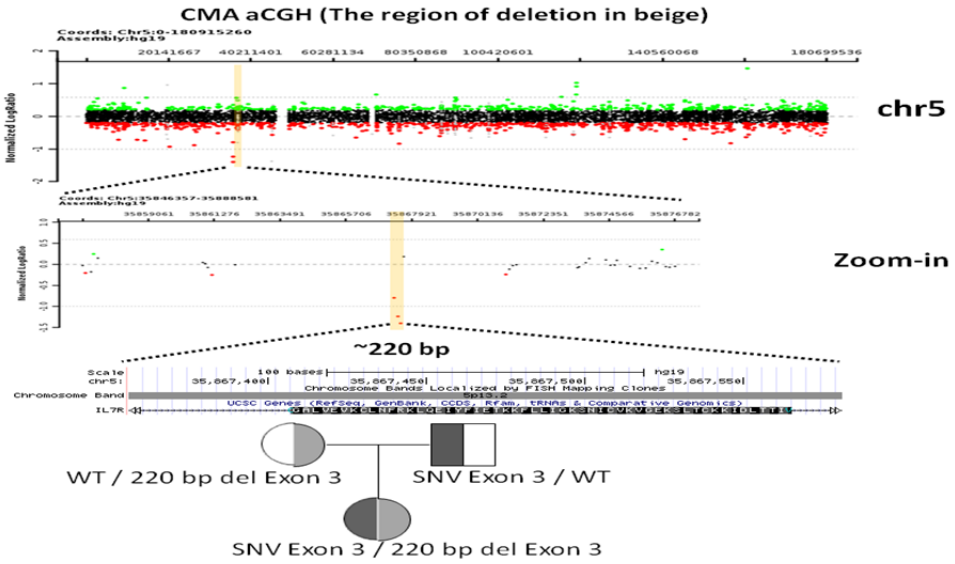
**Part A** (patient #77 in eTable 2)



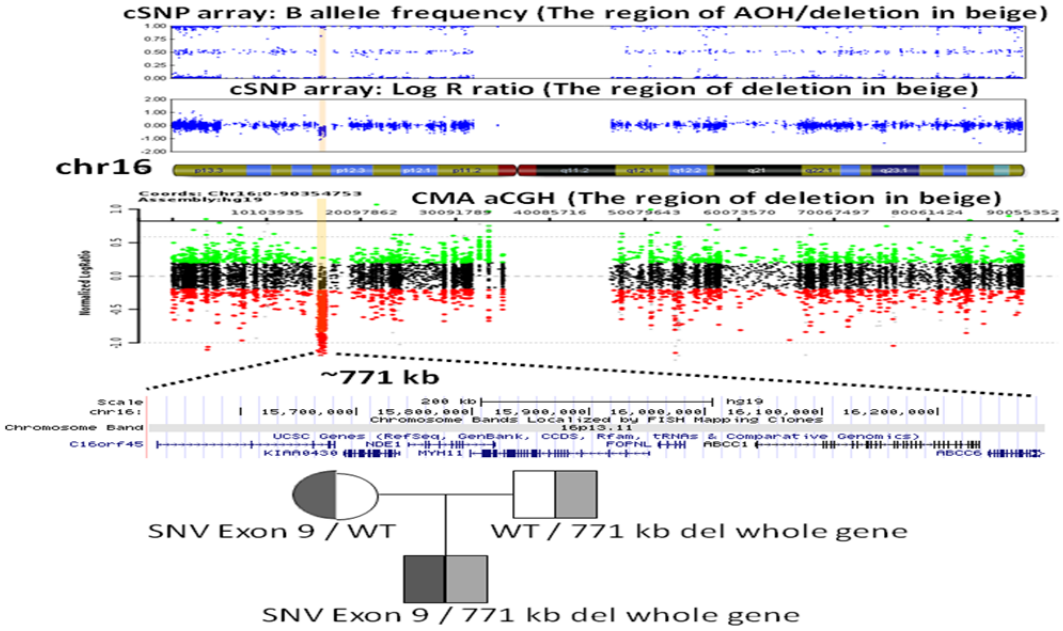
**Part B** (patient #320 in eTable 2)



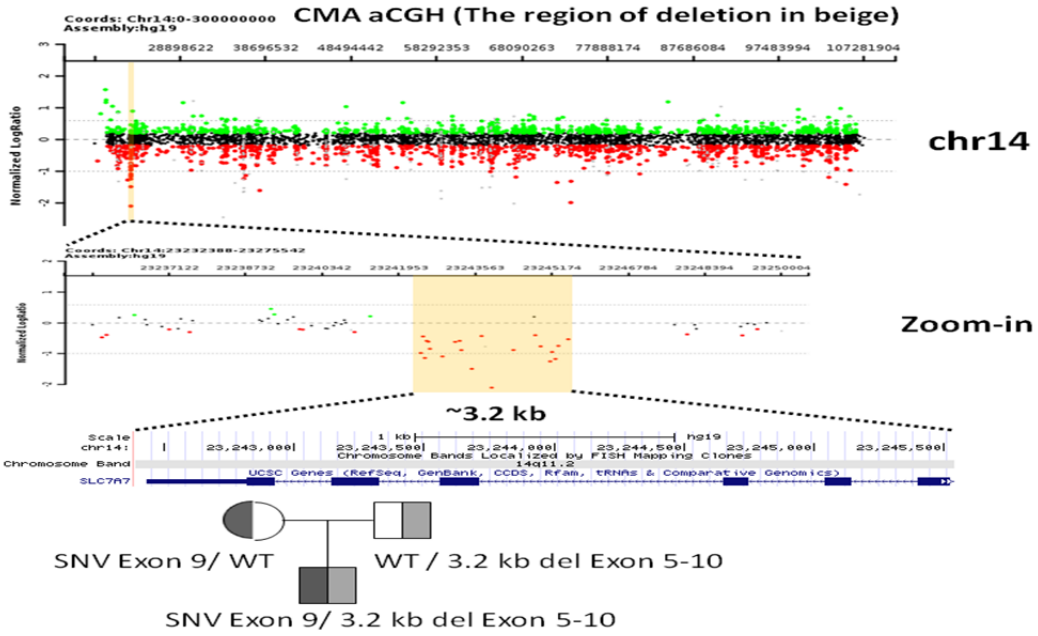
**Part C** (patient #477 in eTable 2)



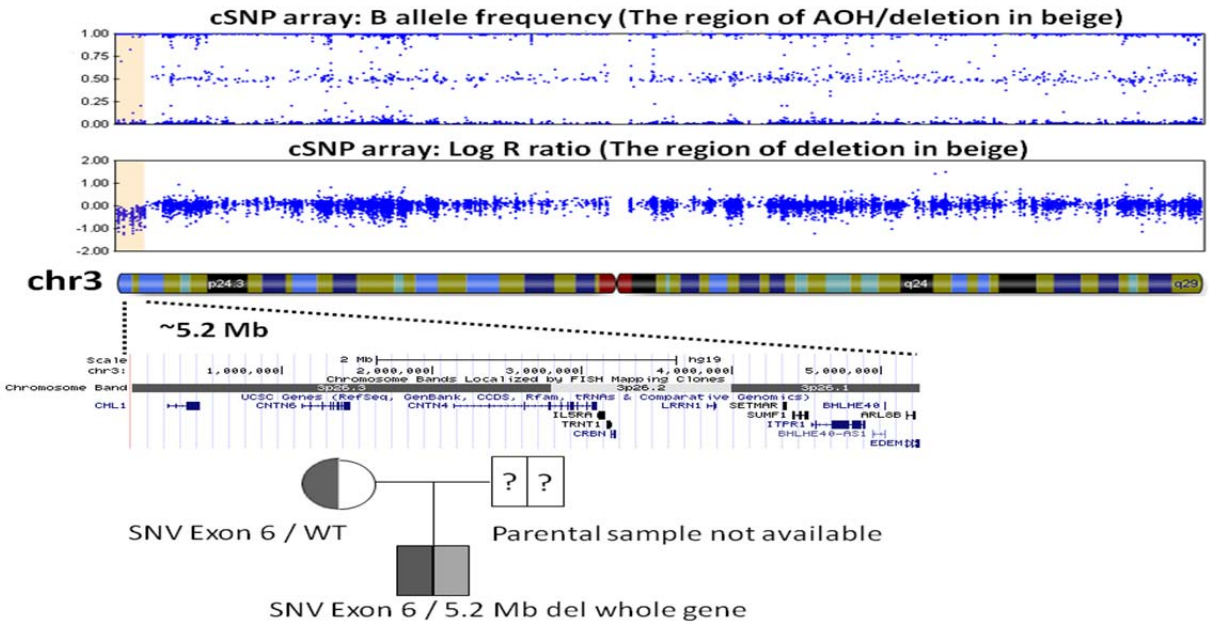
**Part D** (patient 78 in eTable 2)



**Part E** (patient #385 in eTable 2)



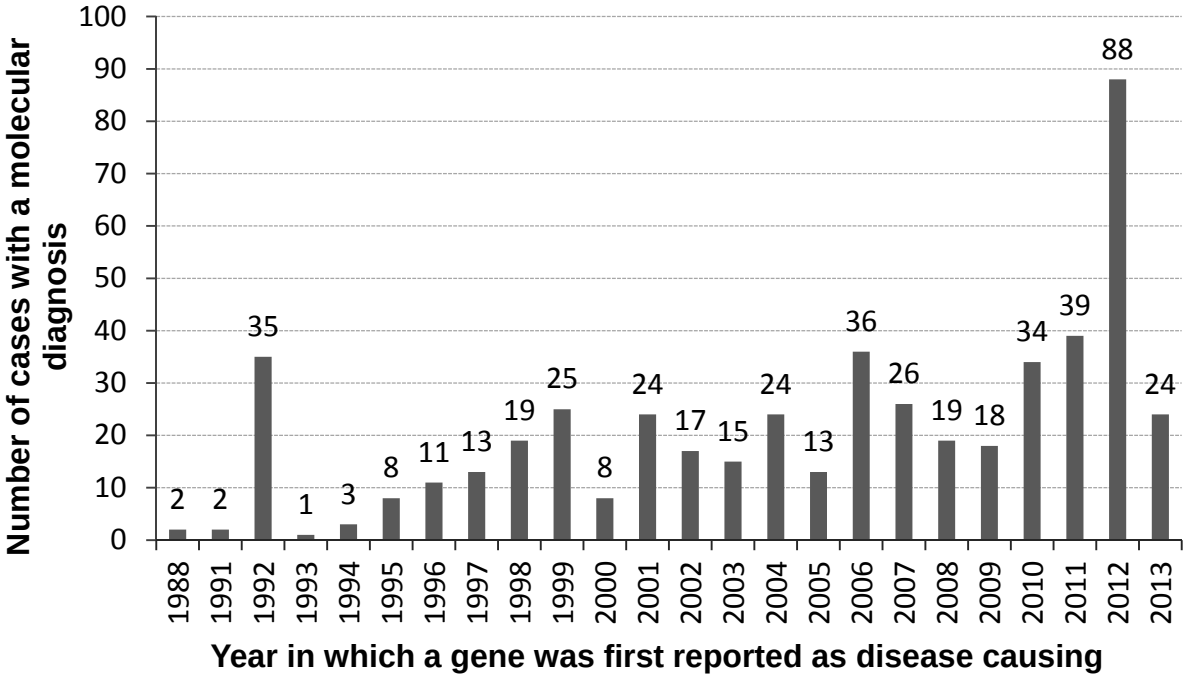
**Part F** (patient #397 in eTable 2)




Deletions are shaded in beige in the microarray array plots. The red, black and green dots in chromosomal microarray studies (CMA) plots, which were generated from software build in house[5], indicate that the corresponding oligo probes are in a potential region of copy number loss/gain/neutral, respectively. The cSNP array plots including B allele frequency panel, LogR ratio panel and chromosome ideogram were generated from the Illumina GenomeStudio software. B allele frequencies and LogR ratios are presented as Y-axis in the respective panels. The graphs illustrating locations of genes are taken from the UCSC genome browser (http://genome.ucsc.edu/). Panels A and B: two changes with large deletions encompassing the Prader-Willi/Angelman region on chromosome 15. The estimated coordinates for the deletion regions are chr15:23730704-28520072 (hg19 genomic coordinate intervals) and chr15:22816713-28530182 (hg19 genomic coordinate intervals) for A and B respectively. Panels C-F: cases with a point mutation on one allele of a recessive gene and a large deletion on the other allele as identified by chromosomal microarray studies (CMA) or cSNP arrays. The pedigrees are illustrated in order to show the

phases of the point mutations and the large deletions. Dark grey in the pedigree indicates the segregation of the point mutations in the family, whereas light grey indicates the segregation of the large deletion.

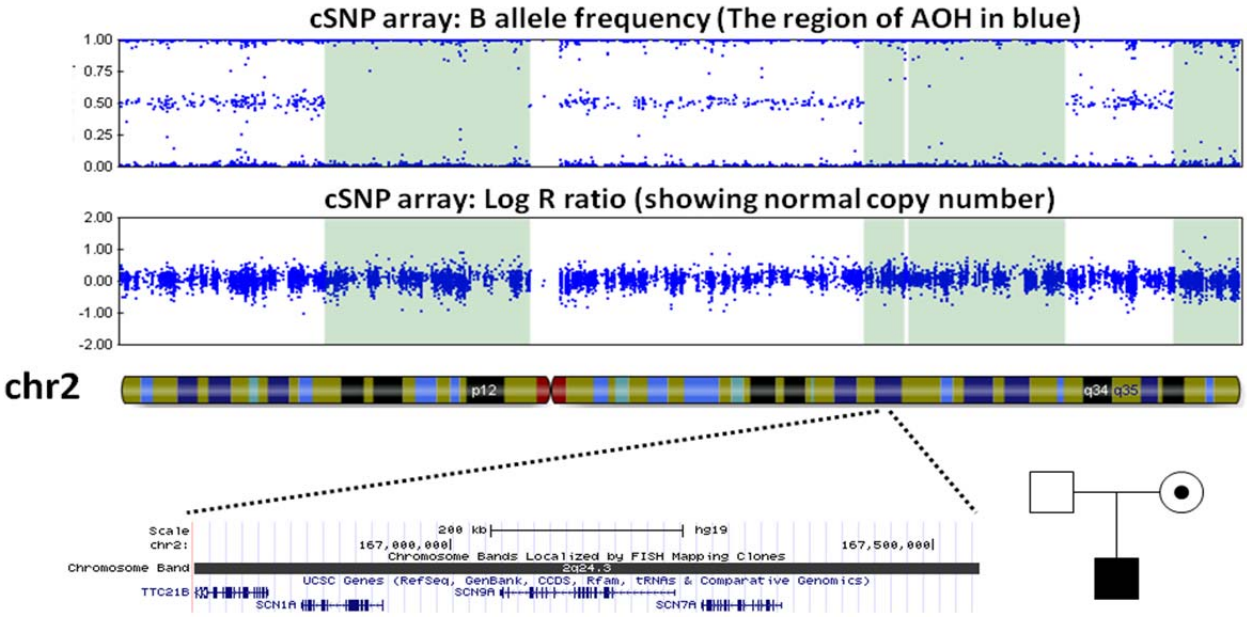
**eFigure 2.** Contribution of newly discovered disease genes to WES diagnosis



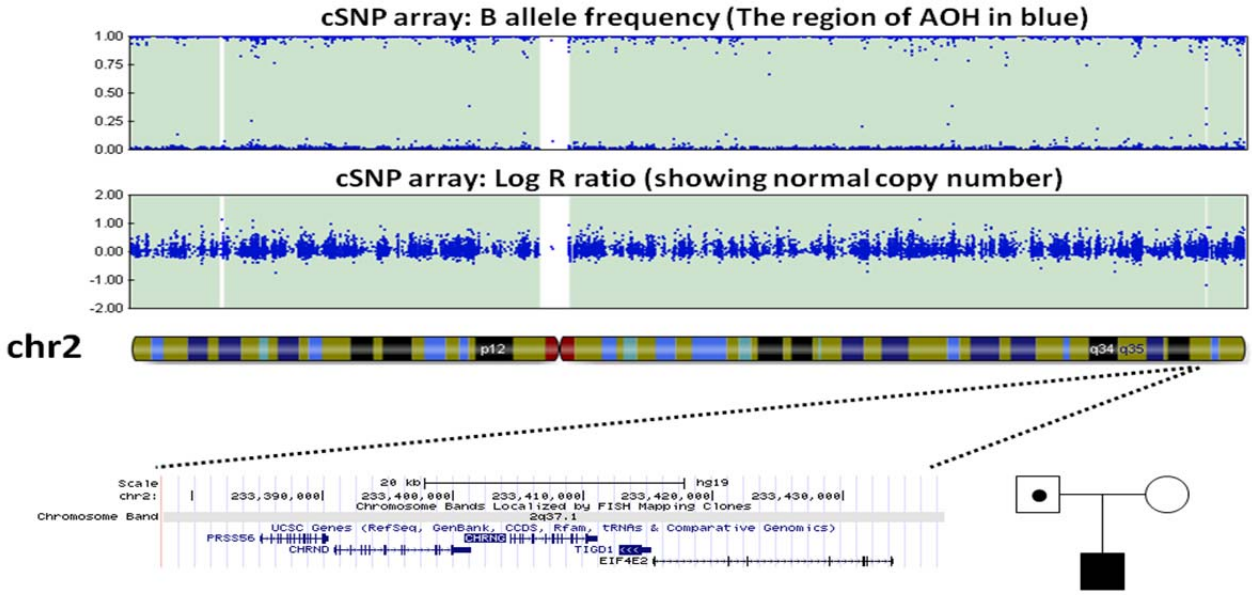

Number of molecularly diagnosed (positive) cases in this study per year that the disease gene was first reported. Cases with the same causal gene were counted separately. The high number of cases for 2012 is partly due to the high number of recurrent diagnoses of disorders caused by SWI/SNF complex genes including *ARID1A, ARID1B, SMARCA2, SMARCA4,* and *SMARCB1* (see Discussion).

**eFigure 3.** UPD unmasking mutations in recessive disorders

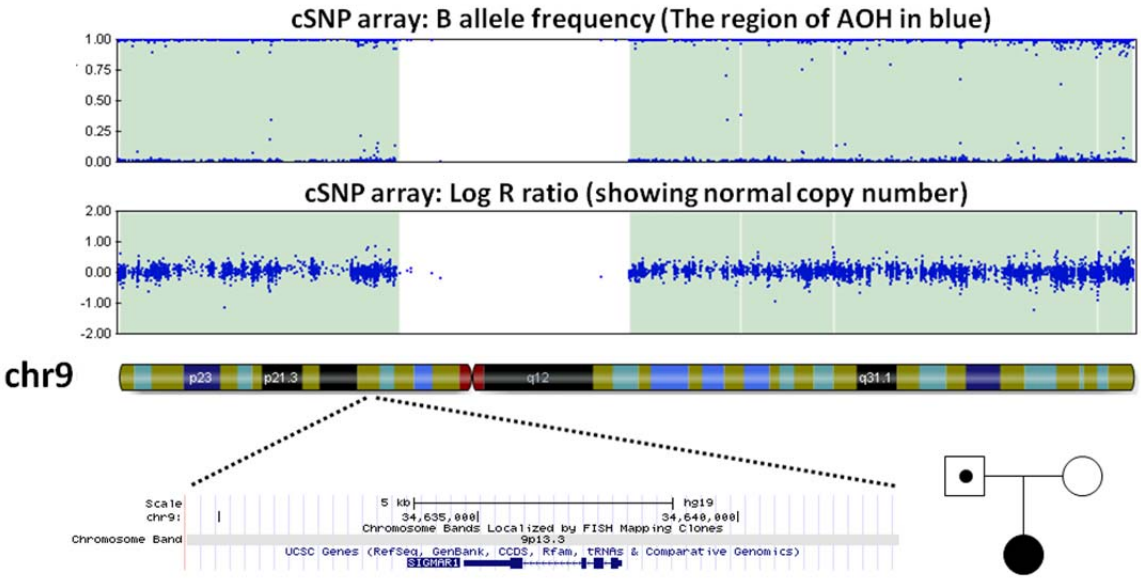
**Part A** (patient #449 in eTable 2)



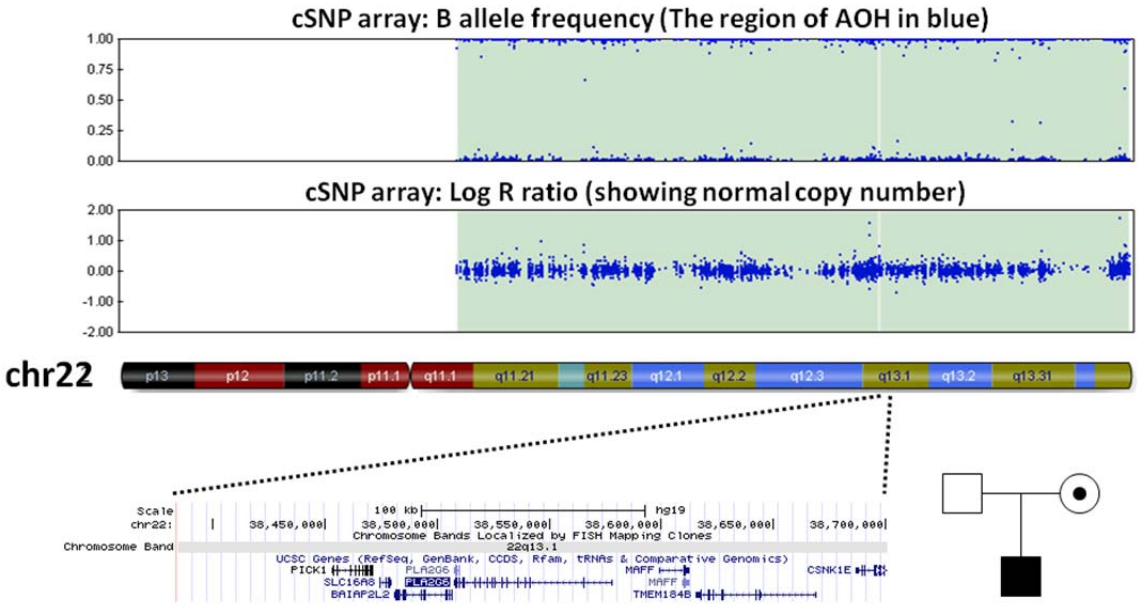
**Part B** (patient #432 in eTable 2)



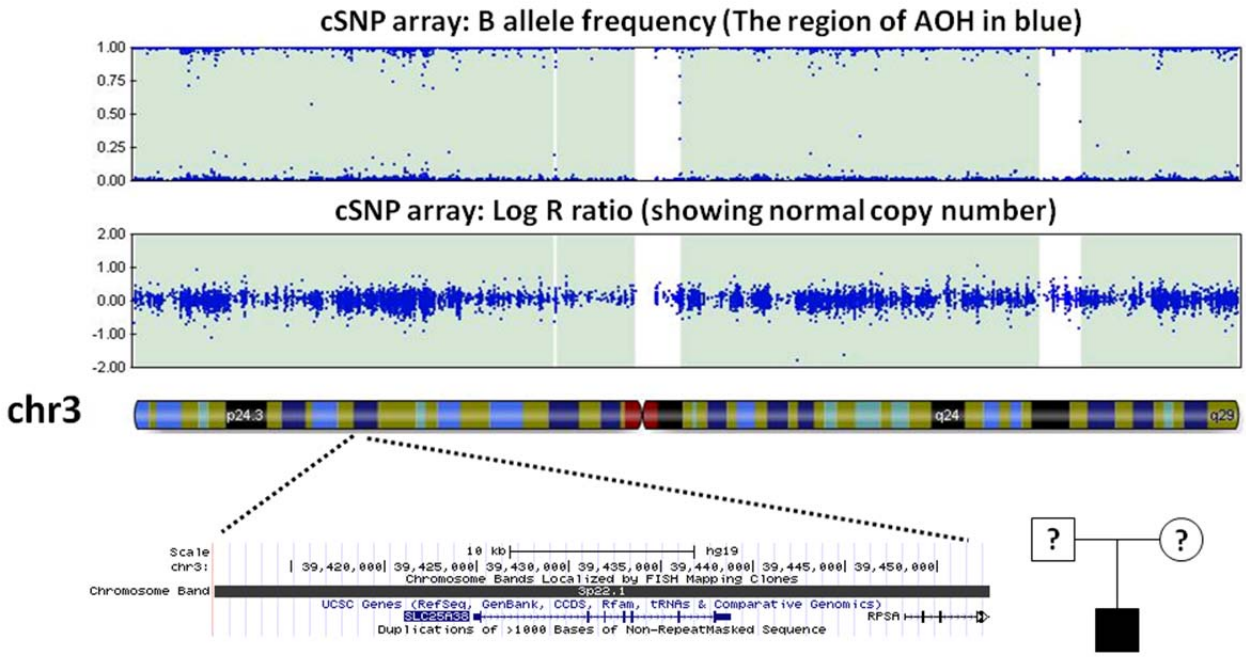
**Part C** (patient #450 in eTable 2)



**Part D** (patient #97 in eTable 2)



**Part E** (patient #493 in eTable 2)




The cSNP array plots including B allele frequency (Y-axis) panel, LogR ratio (Y-axis) panel and chromosome ideogram were generated from the Illumina GenomeStudio software. The graphs illustrating locations of genes are taken from the UCSC genome browser (http://genome.ucsc.edu/). Regions of absence of heterozygosity (AOH) are tinted in green in the "B Allele Freq" panel of the SNP genotyping array plots. The pedigrees are shown to illustrate the parental origin of the mutations (indicated by a dot in the pedigree). A: Maternal UPD 2, contributing gene: *SCN9A* (hg19 genomic coordinate intervals: chr2:167051697-167232497); B: Paternal UPD 2, contributing gene: *CHRNG* (chr2:233404437-233411113); C: Paternal UPD 9, contributing gene: *SIGMAR1* (chr9:34634719-34637768); D. Maternal UPD22, contributing gene: *PLA2G6* (chr22:38507502-38577761). E. UPD 3, parents not available for study, contributing gene: *SLC25A38* (chr3:39424815-39438819).

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