ORIGINAL ARTICLE

Joubert syndrome: a model for untangling recessive disorders with extreme genetic heterogeneity

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▶ Additional material is published online only. To view please visit the journal online (http://dx.doi.org/10.1136/jmedgenet-2015-103087).

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Received 23 February 2015
Revised 21 May 2015
Accepted 1 June 2015
Published Online First 19 June 2015

ABSTRACT

Background Joubert syndrome (JS) is a recessive neurodevelopmental disorder characterised by hypotonia, ataxia, cognitive impairment, abnormal eye movements, respiratory control disturbances and a distinctive mid-hindbrain malformation. JS demonstrates substantial phenotypic variability and genetic heterogeneity. This study provides a comprehensive view of the current genetic basis, phenotypic range and gene–phenotype associations in JS.

Methods We sequenced 27 JS-associated genes in 440 affected individuals (375 families) from a cohort of 532 individuals (440 families) with JS, using molecular inversion probe-based targeted capture and next-generation sequencing. Variant pathogenicity was defined using the Combined Annotation Dependent Depletion algorithm with an optimised score cut-off.

Results We identified presumed causal variants in 62% of pedigrees, including the first *B9D2* mutations associated with JS. 253 different mutations in 23 genes highlight the extreme genetic heterogeneity of JS. Phenotypic analysis revealed that only 34% of individuals have a 'pure JS' phenotype. Retinal disease is present in 30% of individuals, renal disease in 25%, coloboma in 17%, polydactyly in 15%, liver fibrosis in 14% and encephalocele in 8%. Loss of *CEP290* function is associated with retinal dystrophy, while loss of *TMEM67* function is associated with liver fibrosis and coloboma, but we observe no clear-cut distinction between JS subtypes.

Conclusions This work illustrates how combining advanced sequencing techniques with phenotypic data addresses extreme genetic heterogeneity to provide diagnostic and carrier testing, guide medical monitoring for progressive complications, facilitate interpretation of genome-wide sequencing results in individuals with a variety of phenotypes and enable gene-specific treatments in the future.

To cite: Bachmann-Gagescu R, Dempsey JC, Phelps IG, *et al*. *J Med Genet* 2015;**52**:514–522.

INTRODUCTION

Joubert syndrome (JS, OMIM 213300) is a recessive neurodevelopmental disorder characterised by abnormal eye movements, respiratory control disturbances, cognitive impairment, hypotonia and ataxia.[1–4] Diagnosis of JS relies on a pathognomonic combination of imaging findings on axial MRI: cerebellar vermis hypoplasia, thickened and horizontally oriented superior cerebellar peduncles and a deep interpeduncular fossa (the 'Molar Tooth Sign' (MTS)).[5] In addition to these core central nervous system (CNS) features, subsets of individuals with JS have ocular (chorioretinal coloboma and progressive retinal dystrophy), kidney (nephronophthisis), liver (spectrum of ductal plate malformation and fibrosis) and/or skeletal (dystrophy and polydactyly) involvement. JS overlaps genetically and phenotypically with the more severe Meckel syndrome, often defined by co-occurrence of occipital encephalocele, cystic-dysplastic kidney disease, liver fibrosis, and perinatal lethality.[6] Care of individuals with JS is complex, requiring surveillance for progressive complications and input from multiple medical subspecialists.

JS can be caused by recessive mutations in more than 27 genes, all of which encode proteins localising to the primary cilium or basal body.[3 7] Primary cilia are microtubule-based organelles projecting from the surface of most differentiated cells where they serve as environmental sensors, transducing sensory, chemical or mechanical input, as well as signalling pathways (such as hedgehog) during development and homeostasis.[8] Given the key role of this organelle in such a wide variety of processes, it is not surprising that its dysfunction leads to a number of human diseases collectively named 'ciliopathies'.[9] These disorders are unified not only by the underlying pathophysiology and shared genetic causes, but also by a wide array of overlapping phenotypes including cognitive dysfunction, CNS malformations, fibrocystic kidney disease, retinal degeneration, skeletal and craniofacial abnormalities, polydactyly and defects in left-right asymmetry.[10]

Ciliopathies, in general, and JS, in particular, display prominent genetic heterogeneity, that is, biallelic mutations in many different genes cause the same disorder, albeit with variable severity. Clinically, identifying the genetic causes and understanding gene–phenotype correlations are essential for providing diagnostic testing, prognostic information and treatment recommendations; however, until recently, it has not been possible to identify

the genetic cause in the majority of affected individuals. The advent of next-generation sequencing has revolutionised the study of Mendelian disorders by accelerating novel gene discovery.[11] Using JS as a paradigm, we highlight how next-generation sequencing combined with extensive phenotypic data can inform prognosis leading to improved medical monitoring in rare disorders, generate insights into the differential tolerance of genes to mutation and aid in interpreting genome-wide sequencing results in individuals with diverse phenotypes. Understanding the genetic architecture of Mendelian disorders is also leading to gene-specific treatments and improved patient care.

METHODS

Subject ascertainment and phenotypic data

Participants were referred to the University of Washington (UW) Joubert Syndrome Research Program by the Joubert Syndrome and Related Disorders Foundation and clinical collaborators internationally (see Acknowledgements). All participants have clinical findings of JS (intellectual impairment, hypotonia, ataxia and/or oculomotor apraxia) and diagnostic or supportive brain imaging findings (MTS or cerebellar vermis hypoplasia), or they have a sibling with JS. Clinical data were obtained by direct examination of participants, review of medical records and structured questionnaires. Neurologically Normal Caucasian Control Panels (Coriell panels NDPT020 and NDPT090—http://ccr.coriell.org) were sequenced as controls.

Mutation identification

Using Molecular Inversion Probes (MIPs),[12] all exons in genes associated with JS or the allelic disorder Meckel syndrome (*AHI1, ARL13B, B9D1, B9D2, C2CD3, C5ORF42, CC2D2A, CEP290, CEP41, CSPP1, IFT172, INPP5E, KIF7, MKS1, NPHP1, OFD1, RPGRIP1L, TCTN1, TCTN2, TCTN3, TMEM138, TMEM216, TMEM231, TMEM237, TMEM67, TTC12B* and *ZNF423*;[13–36] details in online supplementary table S1) were captured using 100 ng of genomic DNA isolated from blood or saliva. Captured DNA was PCR amplified and sequenced on either the Illumina HiSeq or MiSeq platform. Sequence reads were mapped using the Burrows-Wheeler Aligner (V.0.5.9). Variants were called using the Genome Analysis Toolkit (V.2.5–2) and annotated with SeattleSeq (http://snp.gs.washington.edu/SeattleSeqAnnotation138/). We also included data previously generated by Sanger sequencing of individual genes in subsets of samples. We used the Combined Annotation Dependent Depletion (CADD) algorithm to estimate the deleteriousness of variants (V.1.1),[37] and considered all nonsense, frameshift and canonical splice-site mutations to be deleterious, regardless of CADD score. We defined a cause as the presence of ≥2 rare deleterious variants (RDVs) or a homozygous RDV in one gene in an affected individual. RDVs that were of high quality (depth ≥25, quality by depth >5 and heterozygous allele balance <0.8) were not confirmed by Sanger sequencing based on the previously demonstrated high sensitivity and specificity of the MIPs method for well-covered variants[12]; however, in affected individuals with one high-quality RDV, we did perform Sanger sequencing to confirm second RDVs that did not meet the above-mentioned quality criteria.

Statistical analysis

We tested the significance of associations between clinical features, as well as between features and genetic causes, using the χ^2 or Fisher's exact tests (SAS, V.9.4; SAS Institute, Cary, North Carolina, USA). We present ORs and 95% CIs as measures of these correlations. The Bonferroni method was used to correct for multiple hypothesis testing.

RESULTS

UW JS cohort

The study cohort comprised 532 affected participants from 440 families, 79 families having >1 affected individual. Participants were recruited from 29 countries, the majority (59%) residing in North America. Nineteen per cent of the families reported consanguinity. The mean age of the affected participants at the time of the analysis was 13.1 years (SD 9.1), with 34% of individuals <10 years of age and 30% 10–20 years of age. Fifty-six per cent were male (table 1). The large size of the cohort and worldwide ascertainment based on brain imaging and neurological findings provide a relatively unbiased spectrum of the disorder.

Multiorgan involvement is common and the 'pure JS' phenotype occurs in a minority of individuals

In addition to the core diagnostic features for JS (MTS, hypotonia, ataxia, cognitive dysfunction, abnormal breathing pattern and oculomotor apraxia) that were part of the inclusion criteria, several extra-CNS features are commonly described in JS. Based on the presence of these features, various subtypes of JS have been proposed:[2] 'pure' JS (core diagnostic features only), JS plus retinal dystrophy, JS plus cystic kidney disease, JS plus retinal–renal involvement, JS plus liver fibrosis and JS plus oral-facial-digital features. Therefore, we systematically assessed the relevant features (see online supplementary table S2) in the cohort. As a consequence of the worldwide recruitment required to collect a large cohort for a rare disorder, the ascertainment of clinical features was variable. To be conservative in calculating the prevalence of each feature, we restricted our analysis to individuals for whom definite positive or negative information was

Table 1 Demographic characteristics of the University of Washington Joubert syndrome cohort

Characteristic	N	%*
Current age (years)		
0–9	178	33.5
10–19	157	29.5
20–29	65	12.2
30–39	24	4.5
≥40	6	1.1
Unknown age	42	7.9
Deceased		
Terminations of pregnancy	11	2.1
Other deaths†	49	9.2
Total	532	100
Continent of residence		
North America	316	59.4
Europe	51	9.6
Australia	23	4.3
South America	17	3.2
Asia (Middle East=88)	125	23.5
Families with known consanguinity*	84	19.1
Male	295	55.5
Families with ≥1 affected child*	79	17.9

*Percentages are calculated by individual for all variables except consanguinity and >1 affected child.
*†Includes one in utero demise.

available for a given feature; consequently, the denominator for calculating the frequency of individual features varies accordingly. Retinal dystrophy (n=99/329, 30%) and renal disease (n=102/407, 25%) were the most common associated features, followed by coloboma (n=56/330, 17%), polydactyly (n=56/387, 15%), liver fibrosis (n=50/362, 14%) and encephalocele (n=29/386, 8%) (figure 1A). When considering only the individuals for whom definite information was available for all six associated features (n=201), only 68 (33.8%) had the 'pure JS' phenotype (see online supplementary table S3).

We next evaluated whether any of the major features were associated with each other. Liver fibrosis and coloboma were strongly associated (OR 6.5; 95% CI 3.2–13.4), that is, the likelihood of having liver fibrosis in individuals with coloboma was 6.5 times the likelihood of having liver fibrosis in individuals without coloboma. Retinal dystrophy and kidney disease (OR 3.0; 95% CI 1.7 to 5.2), liver fibrosis and kidney disease (OR 3.0; 95% CI 1.6 to 5.5) and polydactyly and encephalocele (OR 2.8; 95% CI 1.03 to 7.8) were more weakly associated with each other (figure 1B and see online supplementary table S4). In addition, we observed multiple combinations of features in subsets of individuals, often precluding categorisation into one of the proposed subtypes (see online supplementary table S3). For example, individuals presenting with the combination of liver fibrosis and kidney disease could be categorised as either 'JS plus kidney disease' or 'JS plus liver disease'. While the most frequent associations of features are consistent with the proposed JS subtypes, the broad range of additional combinations observed indicates that no clear-cut distinction exists between subtypes.

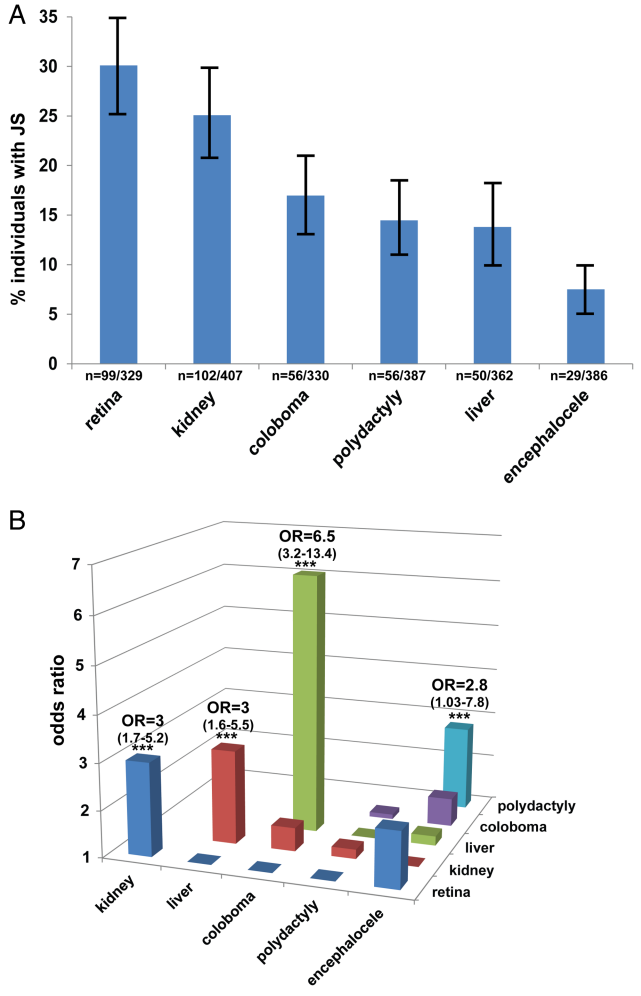

Figure 1 Phenotypic analysis of a large Joubert syndrome (JS) cohort. (A) Bar graph indicating the prevalence of major associated features. Absolute numbers are indicated below each bar and 95% CIs are presented. Information about each feature was not available in every subject, so the denominators are different for each variable. (B) ORs for the association between pairs of features. Hepatic disease and coloboma are highly associated with each other while encephalocele and polydactyly, retinal and renal disease, and hepatic and renal disease are less strongly associated with each other. Precise ORs with 95% CIs are indicated for the four statistically significant (***) associations. Detailed ORs and CIs for all pairwise possible associations are presented in online supplementary table S4.

Multiple additional clinical features

A variety of other clinically important features were documented in medical records and by families but were not systematically queried across the entire cohort (table 2). Additional brain abnormalities were identified in 91 individuals, most commonly

Table 2 Additional features observed in individuals with Joubert syndrome

Characteristic	N	Minimum prevalence (%)*
Nervous system		
Agenesis of the corpus callosum	16†	3.0
Heterotopia	15	2.8
Polymicrogyria	7	1.3
Ventriculomegaly	53	10.0
Seizures	55	10.3
Mouth		
Cleft palate		
Hard palate	13	2.4
Soft palate	7	1.3
Tongue tumours	17	3.2
Oral frenulae	9	1.7
Eye		
Strabismus	167	31.4
Ptosis	104	19.5
Other		
Hearing loss	16	3.0
G-Tube	43	8.1
Scoliosis	28	5.3
Heart	7‡	1.3
Endocrine		
Panhypopituitarism	5	0.9
Hypothyroidism	4	0.8
Micropenis	10	1.9
Other	11§	2.1
Laterality defects	3¶	0.8
Mental health issues	47**	8.8

*Assumes that the feature is absent when the feature is not documented to be present. Denominator=532 individuals.
†Includes complete (13) and partial (3) agenesis of the corpus callosum.
‡Includes atrial septal defect (3), coarctation of aorta (2), bicuspid aortic valve and aortic stenosis (1) and narrowing of aortic arch (1).
§Includes Hashimoto's disease (1), type I diabetes mellitus (2), unknown type diabetes (1), ovarian failure (1), polycystic ovarian syndrome (1), growth hormone deficiency (3), elevated parathyroid hormone (1) and absence of pituitary bright spot, premature puberty and borderline diabetes (1).
¶Includes dextrocardia (1) and situs inversus (2).
**Includes anxiety (6), ADHD/ADD (8), autism spectrum disorder (16), depression/bipolar disorder (5), aggression (2), obsessive compulsive disorder (2), borderline personality disorder (1), anorexia nervosa (1) and non-specified behavioural problems (6).

ventriculomegaly, and more rarely heterotopia, agenesis of the corpus callosum and polymicrogyria. This is likely an under-ascertainment compared with prior studies[38] since a detailed review of the brain imaging studies was not part of this study. Additional eye findings were also commonly reported in our cohort, including strabismus and ptosis in 167 and 104 individuals, respectively. Seizures were described in 55 individuals. Other, less common, features included scoliosis (n=28), cleft palate (n=20), hearing loss (n=16), tongue tumours (n=17), oral frenulae (n=9), heart defects (n=7) and a variety of mental health problems such as anxiety, aggression, depression and autism (total n=47). Since these features were not systematically assessed across the cohort, only minimum prevalence estimates can be calculated.

Comprehensive sequencing identifies the presumed genetic cause in 62% of JS families

We sequenced 27 JS-associated genes in 428 affected individuals from 363 families for whom DNA was available using MIP-targeted capture followed by next-generation sequencing. We previously demonstrated, using a subset of this cohort, that this method has 99.5% sensitivity and 98% positive predictive value for variant detection at covered basepairs compared with Sanger sequencing.[12] The MIP target included all coding positions and neighbouring intronic basepairs (see online supplementary table S1), and >89% of basepairs were adequately covered (≥8X) for all genes except *INPP5E* (75% covered) (see online supplementary figure S1). We also included previous Sanger sequencing data, as well as sequencing data from clinical testing when available (n=12), bringing the total number of affected individuals with sequencing data to 440 from 375 families. Based on the estimated prevalence of JS (~1/80 000 Northern Europeans[3]) and the genetic heterogeneity of the disease, we excluded variants with a minor allele frequency (MAF) >0.2% in the Exome Variant Server (http://evs.gs.washington.edu/EVS/). We considered all nonsense, frameshift and canonical splice-site mutations to be deleterious. We assessed the predicted deleteriousness of missense, synonymous and intronic variants using the CADD score algorithm,[37] which considers multiple available prediction techniques including conservation across species and protein function, and has the advantage of providing a score for all possible variants on a single scale. We selected the CADD score cut-off (11) for defining RDVs by maximising the number of affected individuals with genes harbouring two rare variants (or a homozygous rare variant), while minimising the number of controls with genes harbouring similar variants, an approach akin to generating a receiver operating characteristic curve (see online supplementary figure S2). For missense variants, using the CADD score identified more presumed causes in the JS cohort compared with Polyphen2 without increasing the false positive rate in controls (data not shown).

We defined a cause as the presence of ≥2 RDVs (or a homozygous RDV) in one gene in an affected individual. Using this definition and all available sequencing data, we identified the presumed genetic cause in 279 individuals from 232/375 families (62%) overall (figure 2), 77% in consanguineous families and 76% in families with >1 affected individual. The higher rate in the consanguineous families is likely due to the higher probability of calling a single homozygous variant compared with the probability of calling two different heterozygous variants in the non-consanguineous families. Similarly, in 9% of families for whom we were able to sequence >1 affected individual, we initially identified two RDVs in only one of the affected individuals. This likely accounts for the higher solve rate in multiplex families compared with families with only one affected child. In contrast to the results in affected individuals, 5/182 unrelated control individuals carried ≥2 RDVs in one of the known genes (see online supplementary table S5). In 68/70 (97%) families for which parental DNA was available, we confirmed that the identified compound heterozygous RDVs are in trans, excluding two samples from further analysis. We did not sequence parents of children with homozygous or hemizygous RDVs (90 families). Parental samples were not available for controls.

Despite satisfying our criteria (MAF<0.2%, CADD>11), the variants in 12 families did not meet the American College of Medical Genetics and Genomics variant interpretation categories 1, 2 or 3.[39] In 8 of these 12 families, one of the RDVs is a splice variant beyond±2 basepairs from the intron–exon junction, for which the functional effect on splicing has not been assessed. In 4/12 families, one RDV is a synonymous variant whose functional effect has not been evaluated. Therefore, we list these families separately in online supplementary table S5 and excluded them from gene–phenotype analyses.

In addition, we identified five families with pairs of RDVs in each of two genes (see online supplementary table S6). In 3/5, the variants in one gene appeared much more likely to be causal than the variants in the second gene (eg, a homozygous frameshift mutation in *C5ORF42* vs two missense variants in *CSPP1*,

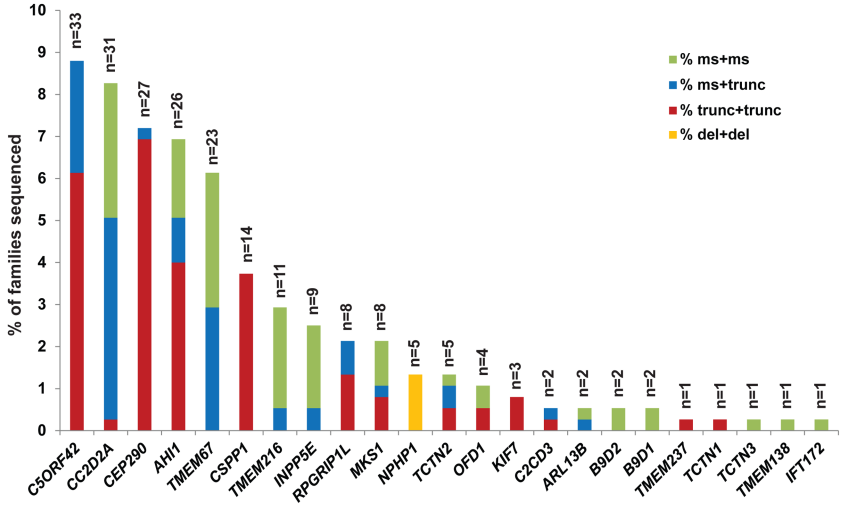

Figure 2 Genetic causes in a large Joubert syndrome cohort. Bar graph indicating the proportion of individuals with JS carrying two rare deleterious variants in each gene. Each bar is broken down to illustrate the relative frequency of the observed mutations in each gene: red indicates two truncating mutations (including nonsense, frameshift and canonical splice-site mutations), blue indicates one truncating and one missense mutation (including small in-frame indels), green indicates two missense mutations or small in-frame indels and orange represents larger deletions.

which harbours exclusively truncating mutations in our cohort). In these three families, the more likely cause was retained for the subsequent analyses. In the other two families, we could not determine the cause and excluded them from the subsequent genetic analyses. Of note, based on the clinical information available, the phenotypic severity in these five individuals was not substantially different from the rest of the cohort.

Including only the families with conservatively called genetic causes, five genes (*C5ORF42, CC2D2A, AHI1, CEP290* and *TMEM67*) each account for JS in ~6–9% of JS, three genes (*CSPP1, TMEM216* and *INPP5E*) for ~3% each and six genes for ~1–2%, while the remaining nine genes each account for JS in only 1–2 families. We also identified *B9D2* mutations as the genetic cause in two families, further extending the known genetic overlap between JS and the more severe Meckel syndrome. A detailed phenotypic description of the two individuals with *B9D2* mutations is presented in online supplementary table S7. *CEP41, TMEM138, TMEM231* and *ZNF423* do not harbour ≥2 or homozygous RDVs in any affected individuals. A single affected individual carries one synonymous and one missense variant in *TTC21B*; however, this individual also carries a homozygous nonsense variant in *C2CD3* that is predicted to truncate the protein near the N-terminus (see online supplementary table S6).

Further examination of the sequence data revealed variation in the types of mutations across the different genes. Considering all nonsense, frameshift and canonical splice-site mutations as truncating, we observed that *CEP290, CSPP1* and *C5ORF42* mostly harbour a combination of two truncating mutations, *CC2D2A* and *TMEM67* tend to have ≥1 missense mutation, and *TMEM216* and *INPP5E* have mainly two missense mutations. All individuals with JS caused by mutations in *NPHP1* (n=5) harbour the previously described deletion[24] in a homozygous state, and no causal point mutations were identified in this gene. The differences in mutation types across the genes were statistically significant (see online supplementary figure S3).

While the majority of RDVs were unique, we identified a subset of RDVs present in ≥3 families not known to be related (see online supplementary table S8). *TMEM216* R73L is common in families of Ashkenazi Jewish descent,[34] and accounts for most of the families with *TMEM216* mutations. Two *C5ORF42* RDVs (p.Gly2663Alafs*40 and W2593*) were found homozygous in six families of Saudi Arabian descent. The p.Gly2663Alafs*40 variant has been previously associated with both JS and Meckel syndrome in Saudi Arabian families.[40 41] One *CC2D2A* RDV (P1122S) was found homozygous in three families of Saudi Arabian descent. In three unrelated Brazilian families, the same combination of two *CSPP1* RDVs was identified, suggesting that they might in fact be related.[20] None of the other recurring RDVs appeared to be associated with specific ethnic groups, so they may represent mutation hotspots (such as *CEP290* G1890* identified in 10 unrelated families from 3 continents).

Gene–phenotype correlations

We next examined associations between the non-CNS features of JS and each genetic cause (figure 3, see online supplementary table S9) and observed several significant gene–phenotype correlations: *CEP290* mutations with retinal dystrophy (OR 22.9, 95% CI 6.7 to 78.4; p<0.0001) and cystic kidney disease (OR 3.3, 95% CI 1.6 to 7.1; p=0.001); *TMEM67* with liver fibrosis (OR 17.3, 95% CI 7.2 to 42.0; p<0.0001) and coloboma (OR 22.9, 95% CI 8.6 to 61.1; p<0.0001); *C5ORF42* with polydactyly (OR 2.7, 95% CI 1.2 to 5.9; p=0.01); *OFD1* with encephalocele (OR 13.1, 95% CI 1.8 to 97.0; p=0.03); *TCTN2*

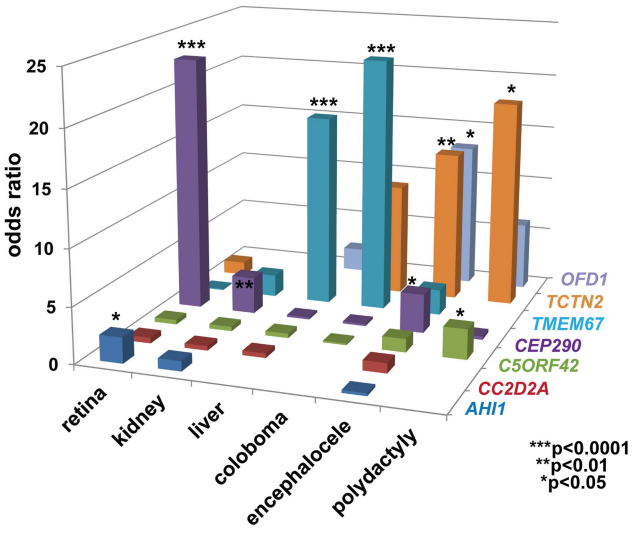

Figure 3 Gene–phenotype correlation in Joubert syndrome. Bar graph indicating for each of the more frequently involved genes, and for two genes with significant phenotypic associations, the OR for each of the six commonly associated features: retinal disease, renal disease, hepatic disease, coloboma, polydactyly and encephalocele. Statistically significant ORs (Fisher's exact test or χ^2 test) are marked with an asterisk (***). CIs are omitted for clarity but are listed in online supplementary table S9.

with encephalocele (OR 13.6, 95% CI 2.6 to 70.8; p=0.007) and polydactyly (OR 18.7, 95% CI 1.9 to 182.9; p=0.01). Even after Bonferroni correction for multiple hypothesis testing, the associations between *TMEM67* and liver disease and coloboma, and that between *CEP290* and retinal dystrophy remained statistically significant (p<0.0001). In addition, a negative correlation was observed between *TMEM67* mutations and retinal disease (OR 0.1, 95% CI 0.01 to 0.8; p=0.006), indicating that individuals with *TMEM67* mutations are less likely to be diagnosed with retinal disease than those without mutations in this gene. When counselling families, the absolute prevalence of clinical features may be more useful than ORs, so this information is provided in online supplementary figure S4.

Although we cannot test the statistical significance of genetic associations with non-systematically assessed clinical features, several possible associations are notable. Both individuals with *C2CD3* mutations had oral features including oral frenulae and/or cleft palate, suggesting *C2CD3* mutations may lead to an OFD-like phenotype.[2] However, among the individuals with oral features (n=46), the majority did not have mutations in *C2CD3* (or *OFD1*). Likewise, two of three individuals with *KIF7* mutations had agenesis of the corpus callosum (while the status of the corpus callosum in the third individual was unknown), consistent with a *KIF7*-related 'acro-callosal' subtype of JS. Again, however, the majority of individuals with agenesis of the corpus callosum (n=14) had mutations in other genes without a clear predominance of one genetic cause. None of the 55 individuals with seizures had causal *CEP290* mutations, despite *CEP290* loss of function being the third most common cause of JS, suggesting a negative association.

DISCUSSION

Presumed genetic cause of JS identified in 62% of families

Just over 10 years ago the first genetic causes of JS were identified.[13 24] Now, we can determine the presumed genetic cause in 62% of individuals with JS using the highly efficient MIP

capture technique, next-generation sequencing and an optimised CADD score cut-off to identify causal variants in 27 JS/Meckel genes. Five genes (*C5ORF42, CC2D2A, CEP290, AHI1* and *TMEM67)* account for the majority of affected individuals, while nine genes are mutated in <15 families, and nine more genes are mutated in only 1–2 families. In two families with JS, we identified causal mutations in the Meckel-associated gene *B9D2*, further expanding the allelism between JS and Meckel syndrome. Not surprisingly, B9D2 is part of a transition zone subcomplex (with MKS1 and B9D1) that regulates protein trafficking in and out of the cilium.[42]

These findings illustrate the extreme genetic heterogeneity of JS. Therefore, given that no single gene predominates as a cause for JS, the most efficient method for clinical diagnostic testing is next-generation sequencing of all known JS genes through targeted gene panels or whole-exome sequencing. The advantage of the MIP capture technique lies in its low cost and flexibility, allowing easy addition of newly identified JS genes to the target. For laboratories without a specific interest in JS, whole-exome sequencing might be more practical since it does not require any specialised set-up.

The genetic cause remains unidentified in 38% of families in our cohort. This may be due to mutations in genes not yet associated with JS, or variants in the known genes that were missed by our current techniques, either because they are inadequately covered in our data, located in non-coding regions, not called using our analysis pipeline, or not recognised as deleterious. Given the high coverage obtained for all but one gene (*INPP5E*) and the efficiency of MIP capture for identifying variants in the target regions,[12] it is likely that a sizeable fraction of the missed variants lie in non-coding regions that affect gene expression level, splicing or translation. Identifying these variants and understanding their significance will require integrating data from variant rating algorithms like CADD, global assessments of chromatin structure and regulatory elements from projects such as ENCODE[43] and targeted functional assays in affected cell lines, animal models or in vitro systems.

Clinical utility of gene–phenotype correlations and phenotypic associations

Gene–phenotype correlations in well-characterised, comprehensively sequenced cohorts translate directly into improved prognostic information and medical management for individuals with JS. For instance, results from this study indicate that individuals with JS harbouring causal mutations in *TMEM67* have a higher risk of developing liver fibrosis, necessitating closer monitoring to allow early diagnosis and treatment of portal hypertension. Likewise, individuals with causal mutations in *CEP290* require closer surveillance for retinal dystrophy. Our findings validate prior results from smaller cohorts focused on single genes[44 45 46] and also identify additional positive and negative correlations. For example, individuals with causal mutations in *TMEM67* appear less likely to develop retinal disease and may require less frequent monitoring for this complication. Even when the genetic cause is unknown, phenotypic associations can also guide management and surveillance; for example, individuals with JS and retinal dystrophy should be monitored more closely for renal dysfunction, and those with coloboma should be monitored more closely for liver fibrosis.

While the strongest phenotypic associations observed in this cohort are consistent with previously described JS-subtypes such as COACH syndrome,[45 46] and the retinal-renal form of JS,[44] we did not observe clear-cut distinctions between phenotypic subgroups corresponding to specific genetic causes. The MTS provides a unifying feature for all affected individuals in our cohort, but the distribution of associated phenotypes highlights the phenotypic variability and overlap with other ciliopathies. This is particularly well illustrated by the individuals with mutations in the OFD-associated genes *C2CD3* or *OFD1* who have oral features, consistent with an OFD-like JS subtype; however, most individuals with oral features in our cohort harbour mutations in other genes. Therefore, phenotypic subtyping is of limited clinical value for guiding molecular genetic testing. Fortuitously, next-generation sequencing panels now preclude the need for prioritising single gene tests. Nonetheless, grouping individuals by genetic cause or clinical phenotype retains value for determining their risk of developing progressive features and guiding clinical management as described above.

Gene-specific mutation patterns provide insights into gene function

The observed gene–phenotype correlations, along with the gene-specific mutation distributions, provide information about the function of the different genes. Genes associated preferentially with particular phenotypes suggest a specific or more important role for these genes in the affected organ systems. For instance, the association of *CEP290* mutations with retinal dystrophy in JS and Leber congenital amaurosis[44 47] confirms the importance of *CEP290* function in the human retina, as seen in animal models.

The distribution of mutation types harboured by each gene also reveals information about gene function. For instance, the near-absence of biallelic truncating mutations in some genes suggests that full loss of function for these genes is poorly tolerated in humans, leading to more severe phenotypes, such as Meckel syndrome or early fetal lethality. In support of this hypothesis, fetuses with Meckel syndrome tend to carry two truncating mutations in *CC2D2A* and *TMEM67* compared with individuals with JS who usually carry at least one missense mutation as previously described.[48–50] Likewise, biallelic truncating mutations in *TMEM216* and *INPP5E* have not been previously identified in individuals with JS and are not found in our cohort.[22 33 34 51] In contrast, virtually all individuals with JS due to mutations in *CSPP1* or *CEP290* harbour two truncating variants in these genes, indicating that severe loss of function is required to cause JS. This type of gene-specific information should be considered when interpreting the significance of newly identified sequence variants, in combination with allele frequency in controls, deleteriousness prediction algorithms and the phenotype of the affected individual. For example, missense mutations in *CEP290* or *CSPP1* detected by targeted or genome-wide clinical sequencing are less likely to be clinically significant than missense mutations in *TMEM216* or *INPP5E*. A further consequence of the gene-specific distribution of mutation types lies in the development of potential specific therapies: genes harbouring a majority of nonsense mutations such as *CEP290* may be amenable to read-through therapies,[52] while this therapeutic direction would be less valuable for genes harbouring mainly missense mutations.

Limitations

While larger than previously published studies, our analysis is still limited by the small number of individuals with two RDVs in several genes associated with JS, precluding statistically significant gene–phenotype correlations for these genetic causes. This is an inherent limitation to the study of rare disorders with prominent genetic heterogeneity. Similarly, the relative rarity of JS necessitates the worldwide enrolment of study participants;

consequently, phenotypic assessment is inhomogeneous and some features, especially neurodevelopmental outcome, are difficult to assess at a distance. This is currently a universal problem in the field of rare disorder genetics, where, for the first time, genetic data are more easily available than phenotypic data. In this study, we made every effort to use conservative assumptions for tests of statistical significance; however, until validated by other studies, these results should be translated into clinical practice with caution.

Impact of next-generation sequencing on diagnosis and treatment of Mendelian disorders

In summary, this work illustrates how applying advanced DNA sequencing technologies and improved functional prediction algorithms to large, well-characterised cohorts is enhancing our understanding of the genetic architecture and gene–phenotype correlations in rare Mendelian disorders. Identifying the genetic cause empowers individuals with JS and their families to make family planning decisions, and gene–phenotype correlations provide more reliable prognostic information leading to individually tailored, organ-specific surveillance, thereby improving the health and longevity of affected individuals while conserving healthcare costs. In parallel, identifying the genetic causes of Mendelian disorders is required for developing and applying gene-specific treatments. Similar to recent breakthroughs in cancer treatment based on genomic information (reviewed in Sameek and Chinnaiyan),[53] understanding the genetic causes of Mendelian disorders will inform future gene-specific treatments and is a major step towards personalised medicine for affected individuals.

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Acknowledgements We greatly appreciate the participation of all of the individuals with JS and their families. We also thank the Joubert Syndrome and Related Disorders Foundation and the innumerable clinicians who have referred participants to us over many years, including Jumana Al-Aama, Beth Allen, Ala'a Arafat, Mutluay Arslan, Louis Bartoshesky, Erawati Bawle, Anastashia Boli, Carsten Bönnemann, Sarah Bowdin, Steven Braddock, John Carey, Umran Cetincelik, Alicia Chan, David Chitayat, Juan Chemke, Krystyna Chrzanowska, Brian Chung, Robin Clark, Vida Culic, Duygu Cura, Cynthia Curry, Sumita Danda, Stephen Deputy, Charu Deshpande, William Dobyns, Emily Doherty, Lisa Ewans, Michael Gabbett, Özlem Giray, Himanshu Goel, Elaine Goh, Crystal Grimsley, Sachin Gupta, Jonathan Holt, Niels Illum, Olafur Indridason, A. Micheil Innes, Louise Izatt, Sujatha Jagadeesh, Usha Kini, Jarkko Kirjavainen, Edwin Kirk, Antonie Kline, Kristleifur Kristjannson, Mark Labinksy, Yves Lacassie, Amparo Lopez Lafuente, James Lemons, Richard Leventer, Jan Liebeit, Shawn Lipinski, Sally Lynch, Alan Ma, Richard Macias, Sahar Mansour, Bernard Maria, Isabelle Maystadt, Carole McKeown, Scott McLean, Nancy Mendelsohn, Markella Mikkelsen, Vinod Misra, Sheela Nampoothiri, Vinodh Narayanan, David Neubauer, Ann Olney, Wendy Osterling, Alex Paciorkowski, Shashidhar Pai, Ivan Pavkovic, Joan Pellegrino, Ruthann Pfau, Joseph Pinter, Kate Pope, Gerald Raymond, Miriam Regev, James Reggin, Janet Rennie, Anne Ronan, Alan Shanske, Lisa Sharf, Lori Skallerud, Diana Smith, Rhonda Spiro, Zornitza Stark, Lois Starr, Helen Stewart, Anne Summers, Krzysztof Szczaluba, David Tilstra, John Tolmie, Priya Verghese, Alain Verloes, Julie Vogt, Richard Webster, Kara Weisiger, Mark Wells, Kevin White, Sue White, Dorota Wicher, Robert Wildin, Denise Williams, Meredith Wilson, Barry Wolf, Lisa Worgan, Grace Yoon, Takehito Yokoi, Marc Yudkoff, Elaine Zackai. We thank Karen Barnett for help establishing the cohort, Elizabeth Blue for comments on the manuscript, and Stephan Neuhauss and Anita Rauch for their support for R.B.-G.

Contributors RB-G, JCD, IGP, PC, MAP, IG, JS, and DD participated in the design of the study. JCD, IGP, BJO, DMK, GEI, CRI, NG, JA, EAB, DO, AA, RRA, LL, CL, LM, AG-C, HO, GH, BT, MT, MAP, UWCMG and DD collected and/or generated the data. RB-G, JCD, IGP, BJO, TCR, EAB, NdL, UWCMG, and DD analysed and interpreted the data. RBG, JCD, IGP and DD drafted the manuscript. All coauthors read and approved the final manuscript.

Funding RB-G was supported by a Swiss NSF grant Ambizione-SCORE PZ00P3_142404/1. The following authors received support from the National Institutes of Health: M.A.P. K23NS45832, I.A.G. K24HD046712, D.D R01NS064077. D.D. also received funding from a March of Dimes Basil O'Connor Starter Scholar Research Award, The Arc of Washington Trust Fund, and private donations from families of children with Joubert syndrome. The work was also supported by the University of Washington Intellectual and Developmental Disabilities Research Center Genetics Core (National Institutes of Health U54HD083091). Sequencing was provided by the University of Washington Center for Mendelian Genomics (UW CMG) and was funded by the National Human Genome Research Institute and the National Heart, Lung and Blood Institute grant 1U54HG006493 to Drs Debbie Nickerson, JS and Michael Bamshad.

Competing interests None declared.

Patient consent Obtained.

Ethics approval Institutional Review Boards at University of Washington and Seattle Children's Hospital.

Provenance and peer review Not commissioned; externally peer reviewed.

Data sharing statement All data are included in the manuscript and online supplementary data.

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Supplementary Information

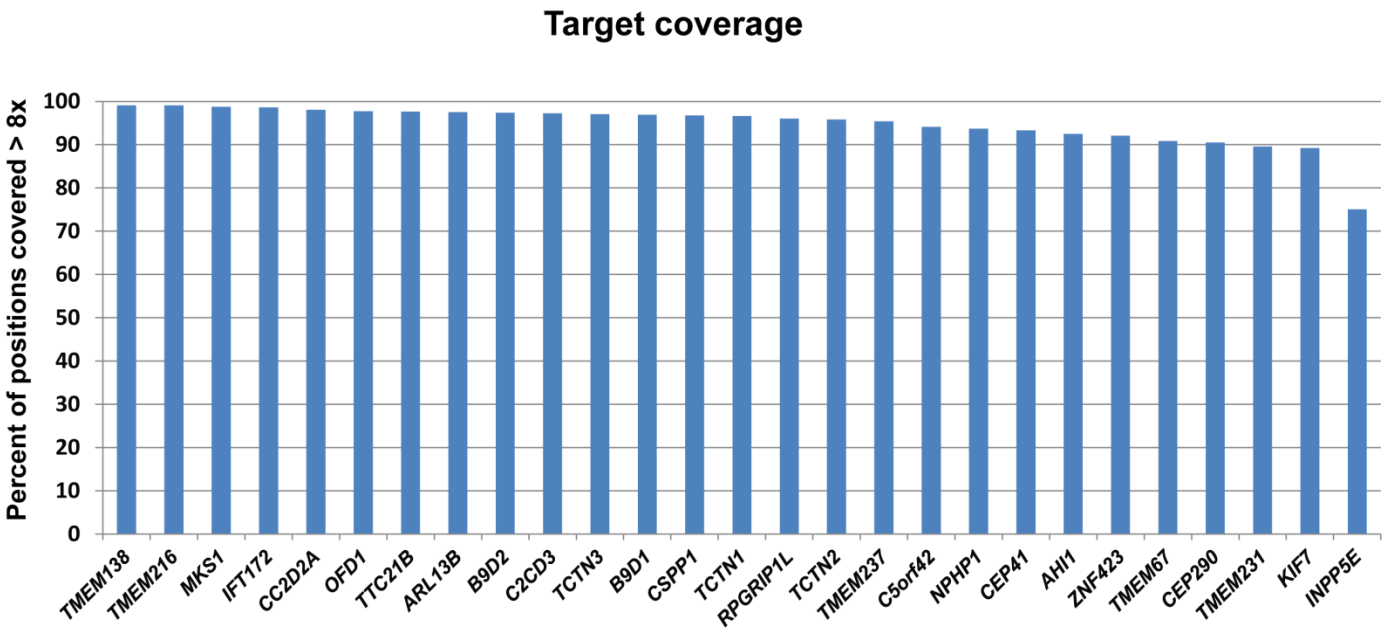
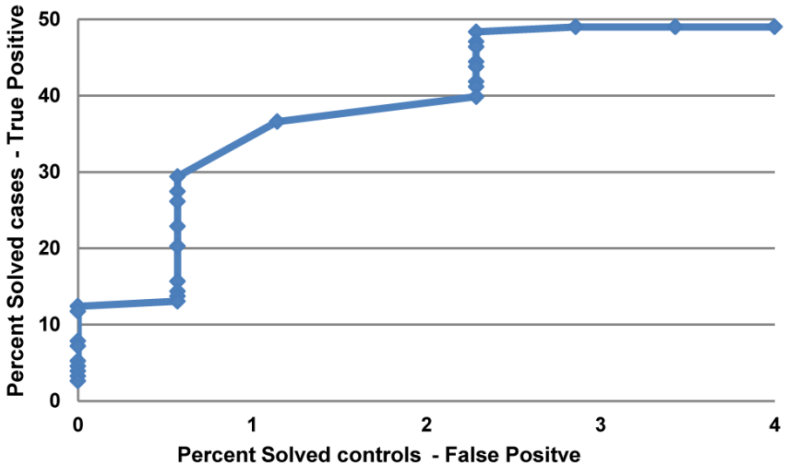


Figure S1: Coverage efficiency of the MIPs target by gene

A



CADD score cut-off	**Controls "solved"** (n)	**Cases "solved"** (n)	**False positive rate** (%)	**True positive rate** (%)	**solve rate (%)** (true positives-false positives)
0	7	75	4	49	45
11	5	75	2.9	49	46.1
12	4	74	2.9	48	45.1
13	4	72	2.9	47	44.1

B

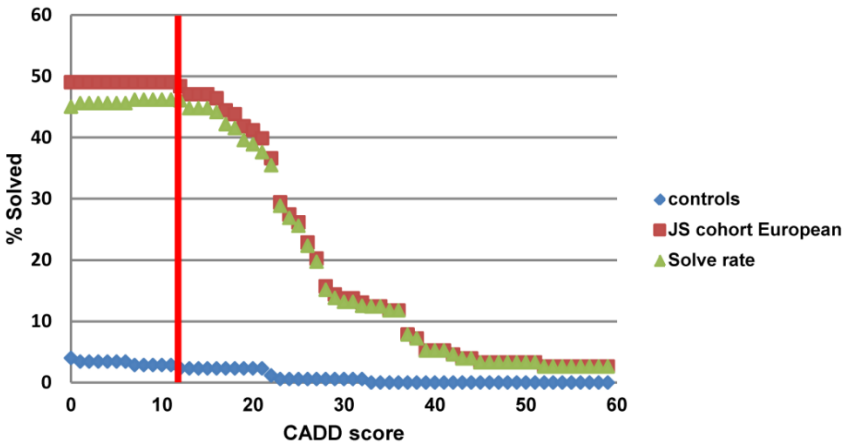


Figure S2. Receiver-Operating-Characteristic (ROC) curve method to determine CADD score cut off for causal mutations (A) ROC curve plotting the proportion of affected individuals with two RDVs against the proportion of control individuals with two RDVs. The table beneath the graph indicates the values for affected and control individuals at representative CADD score cutoffs, as well as the "solve rate" = proportion of affected individuals with two RDVs minus proportion of control individuals with two RDVs (presumed-false positives). Given that the control individuals are all European, the ROC curves were calculated using only the affected individuals of European descent. **(B)** Proportion of samples with two RDVs plotted against CADD score cutoff. The red curve represents affected individuals, the blue curve indicates the control individuals and the green curve indicates the solve rate. The vertical red bar indicates the CADD value of 11 that was used to define causal variants.

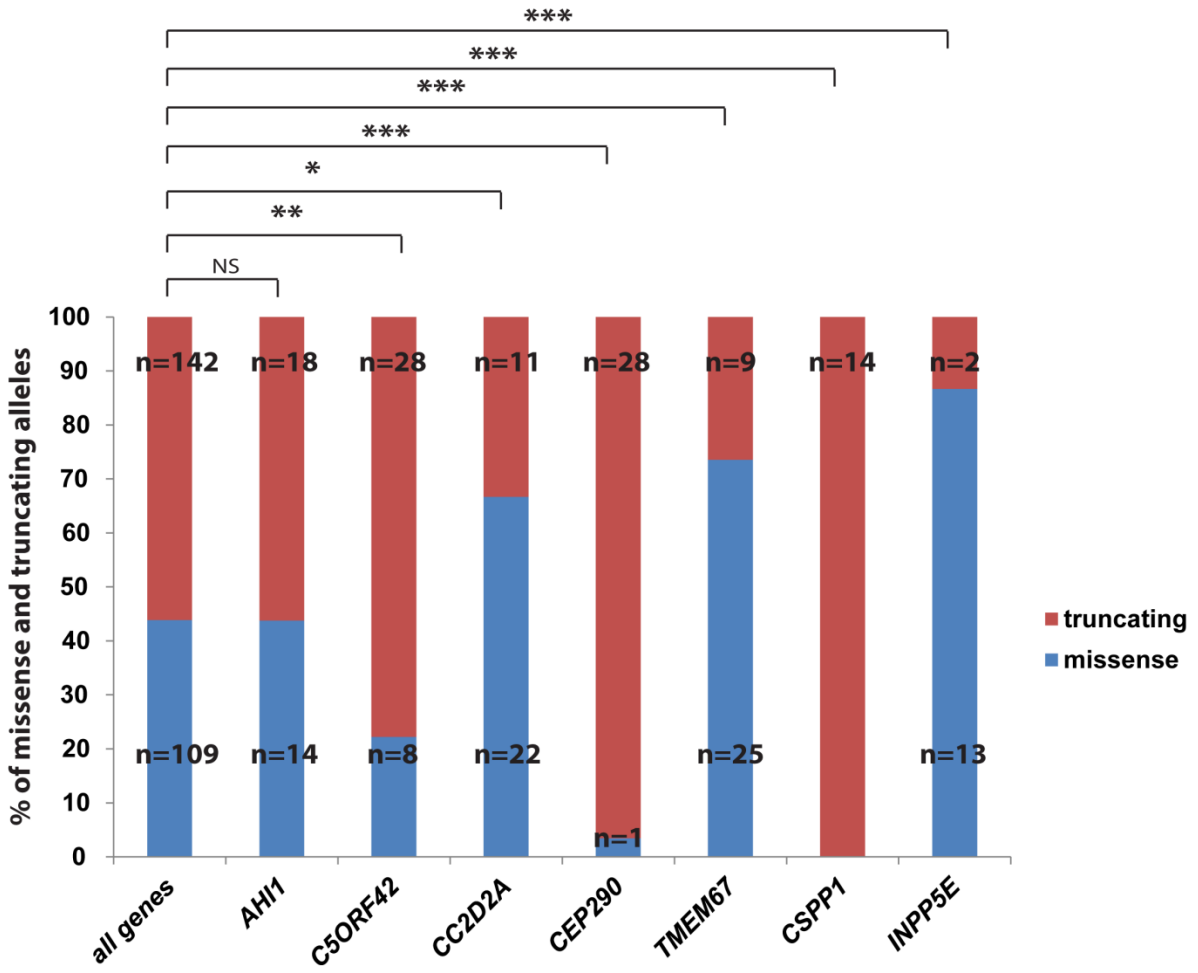


Figure S3: Differential distribution of mutation types (missense vs truncating) across the 7 genes most commonly associated with JS. The distribution of mutation types is not significantly different for *AHI1* compared with the entire cohort, but *C5ORF42*, *CEP290* and *CSPP1* have significantly fewer missense mutations than average while *CC2D2A*, *INPP5E* and *TMEM67* have significantly fewer truncating mutations (***$p<0.0001$, **$p<0.001$, *$p<0.01$; Fisher's exact test). Each mutation was only counted once, even if it occurred multiple times (homozygous or in >1 affected individual).

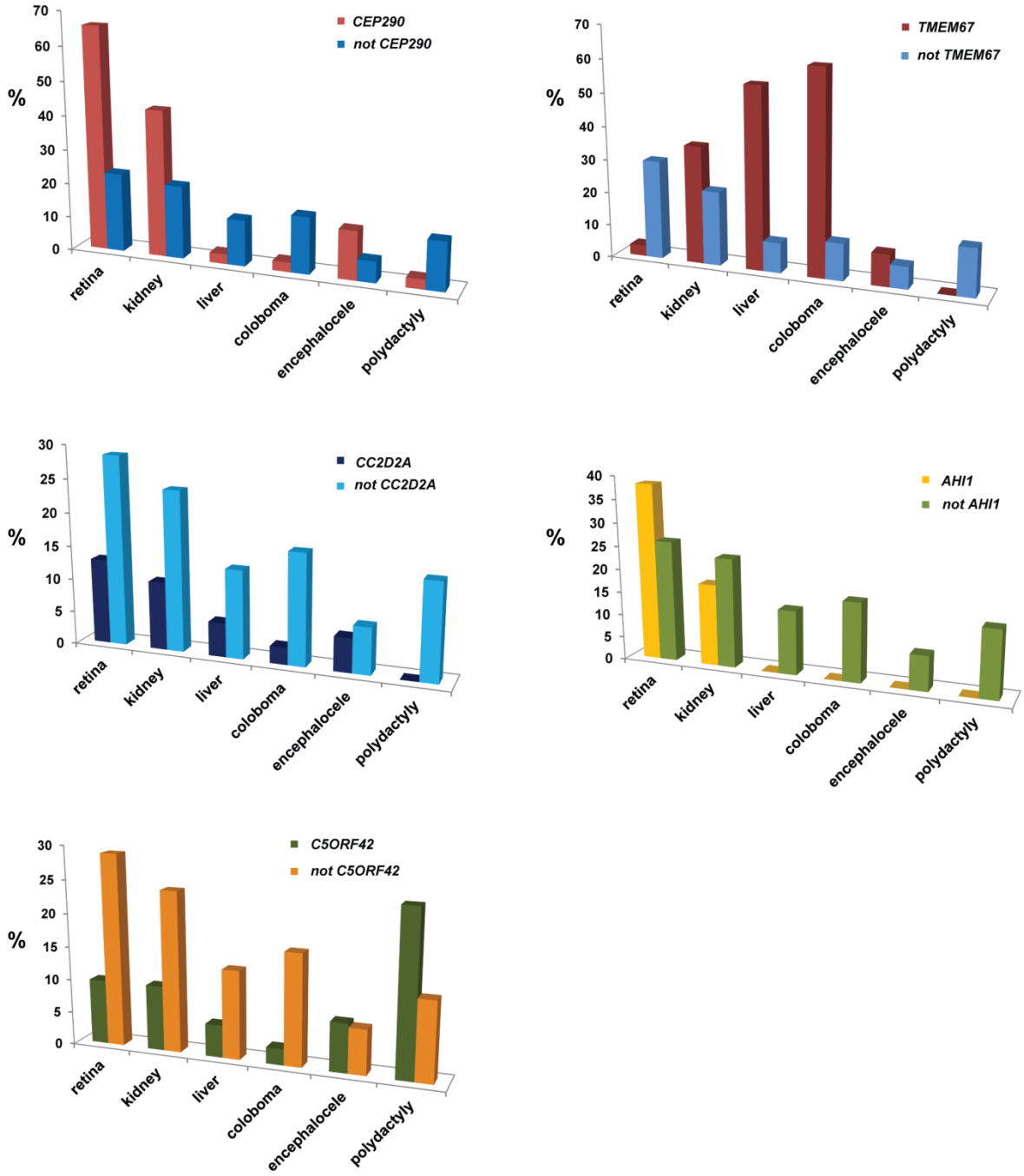


Figure S4. Frequency of variable clinical features in affected individuals with causal mutations in *CEP290*, *TMEM67*, *AHI1*, *CC2D2A*, or *C5ORF42* compared to the rest of the JS cohort.

Table S1. MIPS target

No	Gene	Gene name	Accession#	hg19 position	Exons	Additionally sequenced
1	***AHI1***	Abelson helper integration site 1	NM_001134831.1	chr6:135,285,296-135,497,776	29	chr6:135709110-135709181
2	***ARL13B***	ADP-ribosylation factor-like 13B	NM_182896.2	chr3: 93,980,155-94,054,069	11	
3	***B9D1***	B9 protein domain 1	NM_015681.3	chr17:19,343,170-19,362,713	7	
4	***B9D2***	B9 protein domain 2	NM_030578.3	chr19: 41,354,421-41,364,173	4	
5	***C2CD3***	C2 calcium-dependent domain containing 3	NM_001286577.1	chr11:74,012,714-74,171,019	33	chr11:73745633-73745663
6	***C5ORF42***	chromosome 5 open reading frame 42	NM_023073.3	chr5:37,106,228-37,249,428	52	chr5:37157405-37157532
7	***CC2D2A***	coiled-coil and C2 domain containing 2A	NM_001080522.2	chr4:15,469,930-15,601,557	38	
8	***CEP290***	centrosomal protein 290kDa	NM_025114.3	chr12:88,049,020-88,142,216	54	chr12:88509247-88509357
9	***CEP41***	centrosomal protein 41kDa	NM_018718.2	chr7:130,393,771-130,441,237	11	
10	***CSPP1***	centrosome and spindle pole associated protein 1	NM_024790.6	chr8:67,064,368-67,196,263	29	chr8:67999048-67999091; chr8:68004028-68004128
11	***IFT172***	intraflageller transport 172 homolog	NM_015662.2	chr2:27667240-27712678	48	
12	***INPP5E***	inositol polyphosphate-5-phosphatase, 72kDa	NM_019892.4	chr9:136,428,619-136,439,822	10	
13	***KIF7***	kinesin family member 7	NM_198525.2	chr15:89,627,977-89,655,451	19	
14	***MKS1***	Meckel syndrome, type 1	NM_017777.3	chr17:58,205,437-58,219,305	18	
15	***NPHP1***	nephrocystin-1 (juvenile)	NM_000272.3	chr2:110,122,311-110,205,042	20	
16	***OFD1***	oral-facial-digital syndrome 1	NM_003611.2	chrX:13,734,745-13,769,353	23	
17	***RPGRIP1L***	RPGRIP1-like / FTM	NM_015272.2	chr16:53,600,778-53,703,846	27	
18	***TCTN1***	tectonic family member 1	NM_001082538.2	chr12:110,614,164-110,649,128	15	chr12:111054109-111054167
19	***TCTN2***	tectonic family member 2	NM_024809.4	chr12:123,671,113-123,708,403	18	
20	***TCTN3***	tectonic family member 3	NM_015631.5	chr10:95,663,396-95,694,143	14	
21	***TMEM138***	transmembrane protein 138	NM_016464.4	chr11:61,362,001-61,369,509	5	
22	***TMEM216***	transmembrane protein 216	NM_001173990.2	chr11:11: 61,391,687-61,398,851	5	
23	***TMEM231***	transmembrane protein 231	NM_001077418.2	chr16:75,536,744-75,556,286	7	chr16:75,589,872-75,589,968
24	***TMEM237***	transmembrane protein 237	NM_001044385.2	chr2:201,620,184-201,643,517	13	chr2:202504975-202504998
25	***TMEM67***	transmembrane protein 67	NM_153704.5	chr8:93,754,857-93,818,057	28	chr8:94772079-94772231
26	***TTC21B***	tetratricopeptide repeat domain 21B	NM_024753.4	chr2:165,873,362-165,953,843	29	
27	***ZNF423***	zinc finger protein 423	NM_015069.3	chr16:49,490,605-49,822,738	8	

Table S2. Phenotypic assessment criteria

Major Feature	Positive criteria to determine the presence of this feature (one or more)
Retinal disease	Pigmentary abnormality on fundal examination, abnormal electroretinogram recording, retinal dystrophy, diagnosis of Leber congenital amaurosis or retinitis pigmentosa
Renal disease	Increased echogenicity or cystic kidneys on ultrasound, positive kidney biopsy (microcysts, fibrosis), diagnosis of nephronophthisis, chronic renal failure, dialysis, renal transplant
Liver disease	Persistently elevated transaminases or GGT, increased echogenicity on ultrasound, hepatomegaly, splenomegaly, upper gastrointestinal bleeding, positive liver biopsy (liver fibrosis, ductal plate malformation), portal hypertension, variceal bleeding, spleen removal, medication treatment of liver disease, liver transplant
Encephalocele	Based on clinical examination or head imaging
Coloboma	Based on clinical examination
Polydactyly	Single or multiple, pre-, meso-, or postaxial polydactyly

Supplementary Table S3: detailed phenotypic combinations

Phenotypes present	n	%	*AHI1*	*ARL13B*	*B9D1*	*C9D2*	*C2CD3*	*C5ORF42*	*CC2D2A*	*CEP290*	*CSPP1*	*IFT172*	*INPP5E*	*KIF7*	*MKS1*	*NPHP1*	*OFD1*	*RPGRIP1L*	*TCTN1*	*TCTN2*	*TCTN3*	*TMEM138*	*TMEM216*	*TMEM237*	*TMEM67*	*unkown*
pure JS	**68**	**33.83**	8	1	0	0	0	9	9	0	6	0	2	0	1	1	0	0	0	0	0	0	1	0	0	30
retina only	**26**	**12.93**	**4**	0	0	0	0	1	0	**3**	1	0	1	0	2	0	0	0	0	0	0	0	0	0	0	14
retina+kidney	**19**	**9.45**	**4**	0	0	0	0	0	1	**8**	0	0	2	0	0	0	0	0	0	0	0	0	0	0	0	4
kidney only	**12**	**5.97**	0	0	0	0	0	0	0	0	0	0	0	0	0	2	0	1	0	0	0	0	1	1	0	7
polydactyly only	**11**	**5.47**	0	0	0	0	0	**5**	0	0	0	0	0	1	0	0	0	1	0	0	0	0	1	0	0	3
coloboma only	**8**	**3.98**	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	**2**	4
liver only	**7**	**3.48**	0	0	0	0	0	1	0	0	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	4
coloboma+liver	**6**	**2.98**	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	**3**	3
retina+liver+kidney	**5**	**2.48**	0	0	0	0	0	0	0	1	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	3
encephalocele only	**5**	**2.48**	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	4
coloboma+liver+kidney	**5**	**2.48**	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	**5**	0
encephalocele+retina only	**4**	**1.99**	0	0	0	0	0	1	0	2	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
coloboma+retina	**4**	**1.99**	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	4
coloboma+retina+kidney	**3**	**1.49**	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	2
kidney+liver only	**2**	**0.99**	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	1
polydactyly+kidney only	**2**	**0.99**	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	1
coloboma+retina+liver	**2**	**0.99**	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1
coloboma+polydactyly	**2**	**0.99**	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	1
polydactyly+liver only	**1**	**0.49**	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
polydactyly+retina only	**1**	**0.49**	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
polydactyly+retina + kidney	**1**	**0.49**	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Polydactyly+retina+liver	**1**	**0.49**	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0
polydactyly+encephalocele	**1**	**0.49**	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0
polydactyly+encephalocele+retina+kidney	**1**	**0.49**	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0
coloboma+kidney	**1**	**0.49**	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1
coloboma+encephalocele+liver	**1**	**0.49**	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0
coloboma+encephalocele+retina	**1**	**0.49**	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0
coloboma+polydactyly+encephalocele+retina	**1**	**0.49**	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0
total	**201**	**100**	16	1	0	0	0	21	11	16	10	1	5	1	4	3	1	4	0	2	1	0	4	1	12	87

Only individuals for whom definite positive or negative information for all 6 major associated features was available (retinal disease, renal disease, liver disease, coloboma, polydactyly, encephalocele) were considered for this analysis (n=201).

Table S4. Correlations between common features seen in individuals with JS

Positive associations			
	Odds ratio	**95% CI**	**p-value**
Liver disease and coloboma	6.5	3.2, 13.4*	<0.0001
Kidney disease and retinal dystrophy	3.0	1.7, 5.2*	<0.0001
Liver disease and kidney disease	3.0	1.6, 5.5*	0.0004
Polydactyly and encephalocele	2.8	1.03, 7.8*	0.03
Retinal dystrophy and encephalocele	2.2	0.8, 5.5	0.1
Coloboma and encephalocele	1.6	0.5, 5.0	0.18
Coloboma and kidney disease	1.5	0.8, 2.9	0.22
Liver disease and encephalocele	1.2	0.3, 4.3	0.24
Kidney disease and polydactyly	1.2	0.6, 2.3	0.62
Polydactyly and coloboma	1.1	0.4, 2.9	0.87
Negative associations			
	Odds ratio	**95% CI**	**p-value**
Kidney disease and encephalocele	0.9	0.4, 2.5	0.91
Retinal dystrophy and liver disease	0.7	0.3, 1.6	0.39
Retinal dystrophy and polydactyly	0.7	0.3, 1.6	0.39
Retinal dystrophy and coloboma	0.6	0.3, 1.3	0.2
Polydactyly and liver disease	0.4	0.1, 1.5	0.08

CI = Confidence Interval, * statistically significant (p-value <0.05, Fisher's exact test if <5 observations are present in one category or Chi-Square test in all other situations)

Table S5. List of all presumed causal RDVs in JS families and false positive causal RDVs in control samples

UW ID	Gene	mutation1	cDNA1	genomic1	CADD	Polyphen2	GERP	maximum MAF	mutation2	cDNA2	genomic2	CADD	Polyphen2	GERP	maximum MAF
UW003-3	*AHI1*	splice	NM_001134831.1:c.2036+1G>T	chr6:g.135759512C>A	24.9	NA	5.79	0	splice	NM_001134831.1:c.2036+1G>T	chr6:g.135759512C>A	24.9	NA	5.79	0
UW003-4	*AHI1*	splice	NM_001134831.1:c.2036+1G>T	chr6:g.135759512C>A	24.9	NA	5.79	0	splice	NM_001134831.1:c.2036+1G>T	chr6:g.135759512C>A	24.9	NA	5.79	0
UW009-3	*AHI1*	p.Gln423*	NM_001134831.1:c.1267C>T	chr6:g.135776949G>A	40	NA	5.7	0	p.Gln423*	NM_001134831.1:c.1267C>T	chr6:g.135776949G>A	40	NA	5.7	0
UW012-3	*AHI1*	p.Leu832*	NM_001134831.1:c.2495T>G	chr6:g.135749895A>C	47	NA	5.55	0	p.Lys246*	NM_001134831.1:c.736A>T	chr6:g.135786965T>A	27.4	NA	-1.35	0
UW018-3	*AHI1*	p.Arg738*	NM_001134831.1:c.2212C>T	chr6:g.135754219G>A	37	NA	4.87	0.0122	p.Gln423*	NM_001134831.1:c.1267C>T	chr6:g.135776949G>A	40	NA	5.7	0
UW028-3	*AHI1*	p.Tyr634Aspfs*15	NM_001134831.1:c.1897_1898dupGG	chr6:g.135763734_135763735dupCC	36	NA	5.96	0	p.Ser221*	NM_001134831.1:c.662C>G	chr6:g.135787039G>C	36	NA	4.1	0
UW101-1	*AHI1*	splice	NM_001134831.1:c.1152-2a>g	chr6:g.135777066T>C	20.6	NA	5.7	unknown	p.Trp420*	NM_001134831.1:c.1260G>A	chr6:g.135776956C>T	43	NA	5.7	0
UW115-3	*AHI1*	p.Arg738*	NM_001134831.1:c.2212C>T	chr6:g.135754219G>A	37	NA	4.87	0.0122	p.Asp659Val	NM_001134831.1:c.1976A>T	chr6:g.135759573T>A	32	1	5.79	0
UW133-3	*AHI1*	p.Thr671Ile	NM_001134831.1:c.2012C>T	chr6:g.135759537G>A	29.8	0.986	5.79	0	p.Thr671Ile	NM_001134831.1:c.2012C>T	chr6:g.135759537G>A	29.8	0.986	5.79	0
UW187-3	*AHI1*	p.Asp372Gly	NM_001134831.1:c.1115A>G	chr6:g.135778668T>C	29.4	0.998	5.48	0	p.Trp725Arg	NM_001134831.1:c.2173T>C	chr6:g.135754258A>G	26.4	0.975	4.55	0
UW188-3	*AHI1*	p.Gln423*	NM_001134831.1:c.1267C>T	chr6:g.135776949G>A	40	NA	5.7	0	p.Gln423*	NM_001134831.1:c.1267C>T	chr6:g.135776949G>A	40	NA	5.7	0
UW200-3	*AHI1*	p.Asp719Gly	NM_001134831.1:c.2156A>G	chr6:g.135754275T>C	27	0.286	3.37	0	p.Asp719Gly	NM_001134831.1:c.2156A>G	chr6:g.135754275T>C	27	0.286	3.37	0
UW200-4	*AHI1*	p.Asp719Gly	NM_001134831.1:c.2156A>G	chr6:g.135754275T>C	27	0.286	3.37	0	p.Asp719Gly	NM_001134831.1:c.2156A>G	chr6:g.135754275T>C	27	0.286	3.37	0
UW205-3	*AHI1*	p.Arg723Gln	NM_001134831.1:c.2168G>A	chr6:g.135754263C>T	36	0.971	5.74	0	p.Arg723Gln	NM_001134831.1:c.2168G>A	chr6:g.135754263C>T	36	0.971	5.74	0
UW207-3	*AHI1*	p.Tyr639*	NM_001134831.1:c.1917T>A	chr6:g.135759632A>T	38	NA	-0.941	0	p.Tyr639*	NM_001134831.1:c.1917T>A	chr6:g.135759632A>T	38	NA	-0.941	0
UW209-3	*AHI1*	p.His896Arg	NM_001134831.1:c.2687A>G	chr6:g.135748382T>C	18.63	0.999	4.94	0	p.His896Arg	NM_001134831.1:c.2687A>G	chr6:g.135748382T>C	18.63	0.999	4.94	0
UW209-4	*AHI1*	p.His896Arg	NM_001134831.1:c.2687A>G	chr6:g.135748382T>C	18.63	0.999	4.94	0	p.His896Arg	NM_001134831.1:c.2687A>G	chr6:g.135748382T>C	18.63	0.999	4.94	0
UW213-3	*AHI1*	p.Tyr701Phefs*10	NM_001134831.1:c.2098_2099dupTG	chr6:g.135754332_135754333dupAC	35	NA	5.39	0	p.Trp725*	NM_001134831.1:c.2174G>A	chr6:g.135754257C>T	44	NA	5.74	0
UW218-3	*AHI1*	p.Arg506*	NM_001134831.1:c.1516C>T	chr6:g.135769538G>A	36	NA	2.74	0.0265	p.Asp675Asn	NM_001134831.1:c.2023G>A	chr6:g.135759526C>T	34	1	5.79	0
UW221-3	*AHI1*	splice	NM_001134831.1:c.1626+1G>A	chr6:g.135769427C>T	24.9	NA	5.86	0	p.Trp787Cys	NM_001134831.1:c.2361G>T	chr6:g.135752358C>A	29.2	0.996	5.1	0
UW226-3	*AHI1*	p.Thr304Asnfs*6	NM_001134831.1:c.910dupA	chr6:g.135784284dupT	17.91	NA	1.75	0	p.Thr304Asnfs*6	NM_001134831.1:c.910dupA	chr6:g.135784284dupT	17.91	NA	1.75	0
UW226-4	*AHI1*	p.Thr304Asnfs*6	NM_001134831.1:c.910dupA	chr6:g.135784284dupT	17.91	NA	1.75	0	p.Thr304Asnfs*6	NM_001134831.1:c.910dupA	chr6:g.135784284dupT	17.91	NA	1.75	0
UW226-5	*AHI1*	p.Thr304Asnfs*6	NM_001134831.1:c.910dupA	chr6:g.135784284dupT	17.91	NA	1.75	0	p.Thr304Asnfs*6	NM_001134831.1:c.910dupA	chr6:g.135784284dupT	17.91	NA	1.75	0
UW237-3	*AHI1*	p.Trp725Glyfs*5	NM_001134831.1:c.2172delA	chr6:g.135754259delT	33	NA	2.97	0	p.Trp725Glyfs*5	NM_001134831.1:c.2172delA	chr6:g.135754259delT	33	NA	2.97	0
UW248-3	*AHI1*	p.Arg351Leu	NM_001134831.1:c.1052G>T	chr6:g.135778731C>A	34	0.999	5.5	0	p.Arg351Leu	NM_001134831.1:c.1052G>T	chr6:g.135778731C>A	34	0.999	5.5	0
UW253-3	*AHI1*	p.Ser221*	NM_001134831.1:c.662C>G	chr6:g.135787039G>C	36	NA	4.1	0	exon 19 deletion						
UW253-4	*AHI1*	p.Ser221*	NM_001134831.1:c.662C>G	chr6:g.135787039G>C	36	NA	4.1	0	exon 19 deletion						
UW261-3	*AHI1*	p.Trp725Glyfs*5	NM_001134831.1:c.2172delA	chr6:g.135754259delT	33	NA	2.97	0	p.Trp725Glyfs*5	NM_001134831.1:c.2172delA	chr6:g.135754259delT	33	NA	2.97	0
UW261-4	*AHI1*	p.Trp725Glyfs*5	NM_001134831.1:c.2172delA	chr6:g.135754259delT	33	NA	2.97	0	p.Trp725Glyfs*5	NM_001134831.1:c.2172delA	chr6:g.135754259delT	33	NA	2.97	0
UW272-3	*AHI1*	p.Gly766Glu	NM_001134831.1:c.2297G>A	chr6:g.135752422C>T	33	1	5.1	0	p.Asp666Val	NM_001134831.1:c.1997A>T	chr6:g.135759552T>A	29.8	0.977	5.79	0
UW291-3	*AHI1*	p.Met729Ilefs*36	NM_001134831.1 hom c.2187_2196delGAGAG	chr6:g.135754235_135754244delATCTTC	34	NA	4.86	0	p.Met729Ilefs*36	NM_001134831.1 hom c.2187_2196del	chr6:g.135754235_135754244de	34	NA	4.86	0
UW292-3	*AHI1*	p.Val539Phefs*5	NM_001134831.1:c.1614delA	chr6:g.135769440delT	35	NA	5.86	0	p.Val902Asp	NM_001134831.1:c.2705T>A	chr6:g.135748364A>T	18.18	0.994	4.84	0
UW292-4	*AHI1*	p.Val539Phefs*5	NM_001134831.1:c.1614delA	chr6:g.135769440delT	35	NA	5.86	0	p.Val902Asp	NM_001134831.1:c.2705T>A	chr6:g.135748364A>T	18.18	0.994	4.84	0
UW306-3	*AHI1*	p.Thr304Asnfs*6	NM_001134831.1:c.910dupA	chr6:g.135784284dupT	17.91	NA	1.75	0	p.Thr304Asnfs*6	NM_001134831.1:c.910dupA	chr6:g.135784284dupT	17.91	NA	1.75	0
UW203-3	*ARL13B*	p.Val22Gly	NM_182896.2:c.65T>G	chr3:g.93714723T>G	27.9	0.93	5.64	0	p.Asn154Ser	NM_182896.2:c.461A>G	chr3:g.93754255A>G	25.7	0.997	5.78	0
UW277-3	*ARL13B*	p.Trp82*	NM_182896.2:c.246G>A	chr3:g.93722618G>A	38	NA	5.93	0	p.Arg200Cys	NM_182896.2:c.598C>T	chr3:g.93755507C>T	35	0.999	4.78	0
UW202-3	*B9D1*	p.Phe95Leu	NM_015681.3:c.285C>A	chr17:g.19251153G>T	22.5	0.156	-3.87	0	p.Phe95Leu	NM_015681.3:c.285C>A	chr17:g.19251153G>T	22.5	0.156	-3.87	0
UW232-3	*B9D1*	p.Arg156Trp	NM_015681.3:c.466C>T	chr17:g.19247109G>A	22.6	1	3.69	0.0116	p.Tyr32Cys	NM_015681.3:c.95A>G	chr17:g.19263670T>C	26.9	0.987	5.46	0
UW284-3	*B9D2*	p.Gly155Ser	NM_030578.3:c.463G>A	chr19:g.41860670C>T	20.3	0.451	2.98	0	p.Pro74Ser	NM_030578.3:c.220C>T	chr19:g.41860913G>A	21.7	1	4.04	0
UW309-3	*B9D2*	p.Leu36Pro	NM_030578.3:c.107T>C	chr19:g.41863909A>G	13.21	0.991	4.48	0	p.Leu36Pro	NM_030578.3:c.107T>C	chr19:g.41863909A>G	13.21	0.991	4.48	0
UW157-3	*C2CD3*	splice	NM_001286577.1:c.4951+1G>T	chr11:g.73785297C>A	25	NA	5.68	0	p.Gly1756Glu	NM_001286577.1:c.5267G>A	chr11:g.73760476C>T	32	1	5.58	0.0116
UW293-3	*C2CD3*	p.Arg62*	NM_001286577.1:c.184C>T	chr11:g.73879530G>A	33	NA	5.57	0	p.Arg62*	NM_001286577.1:c.184C>T	chr11:g.73879530G>A	33	NA	5.57	0
UW007-3	*C5orf42*	p.Ala2909Glnfs*4	NM_023073.3:c.8725delG	chr5:g.37125417delC	36	NA	4.29	0	p.Ile165Tyrfs*17	NM_023073.3:c.493delA	chr5:g.37244554delT	17.06	NA	0.513	0
UW033-3	*C5orf42*	p.Gln2723*	NM_023073.3:c.8167C>T	chr5:g.37153886G>A	38	NA	1.05	0	p.Leu595*	NM_023073.3:c.1784T>G	chr5:g.37226913A>C	36	NA	4.07	0
UW034-3	*C5orf42*	p.Ile165Tyrfs*17	NM_023073.3:c.493delA	chr5:g.37244554delT	17.06	NA	0.513	0	p.Arg1336Trp	NM_023073.3:c.4006C>T	chr5:g.37187590G>A	16.87	0.999	4.55	0.0116
UW039-3	*C5orf42*	p.Glu2906*	NM_023073.3:c.8716G>T	chr5:g.37125426C>A	51	NA	6.07	0	p.Glu1003*	NM_023073.3:c.3007G>T	chr5:g.37206441C>A	22.7	NA	5.24	0
UW119-3	*C5orf42*	splice	NM_023073.3:c.8855+1G>A	chr5:g.37122531C>T	25.1	NA	5.9	0	p.Trp1000Leu	NM_023073.3:c.2999G>T	chr5:g.37206449C>A	21.5	0.999	5.24	0
UW184-3	*C5orf42*	p.Arg2493*	NM_023073.3:c.7477C>T	chr5:g.37165697G>A	38	NA	4.43	0.0116	p.Arg1336Trp	NM_023073.3:c.4006C>T	chr5:g.37187590G>A	16.87	0.999	4.55	0.0227
UW184-4	*C5orf42*	p.Arg2493*	NM_023073.3:c.7477C>T	chr5:g.37165697G>A	38	NA	4.43	0.0116	p.Arg1336Trp	NM_023073.3:c.4006C>T	chr5:g.37187590G>A	16.87	0.999	4.55	0.0227
UW185-3	*C5orf42*	p.Thr2755Serfs*8	NM_023073.3:c.8263_8264insG	chr5:g.37148318_37148319insC	27	NA	-2.22	0	p.Leu595*	NM_023073.3:c.1784T>G	chr5:g.37226913A>C	36	NA	4.07	0
UW186-3	*C5orf42*	p.Thr2755Serfs*8	NM_023073.3:c.8263_8264insG	chr5:g.37148318_37148319insC	27	NA	-2.22	0	p.Leu595*	NM_023073.3:c.1784T>G	chr5:g.37226913A>C	36	NA	4.07	0
UW186-4	*C5orf42*	p.Thr2755Serfs*8	NM_023073.3:c.8263_8264insG	chr5:g.37148318_37148319insC	27	NA	-2.22	0	p.Leu595*	NM_023073.3:c.1784T>G	chr5:g.37226913A>C	36	NA	4.07	0
UW190-4	*C5orf42*	p.Arg2660*	NM_023073.3:c.7978C>T	chr5:g.37154075G>A	37	NA	5.21	0.0116	p.Gln793*	NM_023073.3:c.2377C>T	chr5:g.37224757G>A	25.7	NA	2.5	0
UW190-5	*C5orf42*	p.Arg2660*	NM_023073.3:c.7978C>T	chr5:g.37154075G>A	37	NA	5.21	0.0116	p.Gln793*	NM_023073.3:c.2377C>T	chr5:g.37224757G>A	25.7	NA	2.5	0
UW191-3	*C5orf42*	p.Glu2870*	NM_023073.3:c.8608G>T	chr5:g.37138844C>A	39	NA	3.77	0	p.Arg785*	NM_023073.3:c.2353C>T	chr5:g.37224781G>A	31	NA	3.56	0
UW194-3	*C5orf42*	p.Pro2397Glnfs*37	NM_023073.3:c.7190delC	chr5:g.37168936delG	29	NA	4.02	0	p.Arg2904*	NM_023073.3:c.8710C>T	chr5:g.37125432G>A	37	NA	1.65	0.0116
UW194-4	*C5orf42*	p.Pro2397Glnfs*37	NM_023073.3:c.7190delC	chr5:g.37168936delG	29	NA	4.02	0	p.Arg2904*	NM_023073.3:c.8710C>T	chr5:g.37125432G>A	37	NA	1.65	0.0116
UW195-3	*C5orf42*	p.Arg3020*	NM_023073.3:c.9058C>T	chr5:g.37120408G>A	36	NA	0.934	0.0681	p.Trp903*	NM_023073.3:c.2709G>A	chr5:g.37221463C>T	38	NA	3.83	0
UW196-3	*C5orf42*	p.Thr2755Asnfs*8	NM_023073.3:c.8263dupA	chr5:g.37148319dupT	27	NA	-2.22	0	p.Arg2493*	NM_023073.3:c.7477C>T	chr5:g.37165697G>A	38	NA	4.43	0.0116
UW197-3	*C5orf42*	p.Arg2904*	NM_023073.3:c.8710C>T	chr5:g.37125432G>A	37	NA	1.65	0.0116	p.Arg944His	NM_023073.3:c.2831G>A	chr5:g.37213750C>T	23.1	0.999	5.44	0
UW199-3	*C5orf42*	p.Arg2904*	NM_023073.3:c.8710C>T	chr5:g.37125432G>A	37	NA	1.65	0.0116	p.Gln975*	NM_023073.3:c.2923C>T	chr5:g.37206525G>A	11.25	NA	5.4	0
UW210-3	*C5orf42*	p.Leu1213Alafs*30	NM_023073.3:c.3636_3637delAT	chr5:g.37198839_37198840delAT	28.5	NA	1.28	0	splice	NM_023073.3:c.8855+1G>T	chr5:g.37122531C>A	25.1	NA	5.9	0
UW216-3	*C5orf42*	p.Ile165Tyrfs*17	NM_023073.3:c.493delA	chr5:g.37244554delT	17.06	NA	0.513	0	p.Thr323Met	NM_023073.3:c.968C>T	chr5:g.37231122G>A	26.8	0.668	4.48	0.0314
UW222-3	*C5orf42*	p.Gly2663Alafs*40	NM_023073.3:c.7988_7989delGA	chr5:g.37154064_37154065delTC	24.1	NA	-0.221	0	p.Gly2663Alafs*40	NM_023073.3:c.7988_7989delGA	chr5:g.37154064_37154065delT	24.1	NA	-0.221	0
UW231-3	*C5orf42*	p.Gln759*	NM_023073.3:c.2275C>T	chr5:g.37226422G>A	36	NA	5.22	0	p.Arg871Cys	NM_023073.3:c.2611C>T	chr5:g.37221561G>A	34	1	5.63	0
UW243-3	*C5orf42*	p.Trp2593*	NM_023073.3:c.7778G>A	chr5:g.37158360C>T	35	NA	2.39	0	p.Trp2593*	NM_023073.3:c.7778G>A	chr5:g.37158360C>T	35	NA	2.39	0

UW245-3	*C5orf42*	p.Trp2593*	NM_023073.3:c.7778G>A	chr5:g.37158360C>T	35	NA	2.39	0	p.Trp2593*	NM_023073.3:c.7778G>A	chr5:g.37158360C>T	35	NA	2.39	0
UW252-3	*C5orf42*	p.Arg2493*	NM_023073.3:c.7477C>T	chr5:g.37165697G>A	38	NA	4.43	0.0116	p.Arg2493*	NM_023073.3:c.7477C>T	chr5:g.37165697G>A	38	NA	4.43	0.0116
UW255-3	*C5orf42*	p.Leu2606*	NM_023073.3:c.7817T>A	chr5:g.37157912A>T	42	NA	4.24	0	p.Tyr607Thrfs*6	NM_023073.3:c.1819delT	chr5:g.37226878delA	25.8	NA	5.26	0
UW268-3	*C5orf42*	p.Gly2663Alafs*40	NM_023073.3:c.7988_7989delGA	chr5:g.37154064_37154065delTC	24.1	NA	-0.221	0	p.Gly2663Alafs*40	NM_023073.3:c.7988_7989delGA	chr5:g.37154064_37154065delT	24.1	NA	-0.221	0
UW273-3	*C5orf42*	p.Leu171Serfs*8	NM_023073.3:c.510dupT	chr5:g.37244537dupA	23.5	NA	2.16	0	p.Arg2904*	NM_023073.3:c.8710C>T	chr5:g.37125432G>A	37	NA	1.65	0.0116
UW276-3	*C5orf42*	p.Gly2663Alafs*40	NM_023073.3:c.7988_7989delGA	chr5:g.37154064_37154065delTC	24.1	NA	-0.221	0	p.Gly2663Alafs*40	NM_023073.3:c.7988_7989delGA	chr5:g.37154064_37154065delT	24.1	NA	-0.221	0
UW278-3	*C5orf42*	p.Gly2663Alafs*40	NM_023073.3:c.7988_7989delGA	chr5:g.37154064_37154065delTC	24.1	NA	-0.221	0	p.Gly2663Alafs*40	NM_023073.3:c.7988_7989delGA	chr5:g.37154064_37154065delT	24.1	NA	-0.221	0
UW283-3	*C5orf42*	p.Trp2593*	NM_023073.3:c.7778G>A	chr5:g.37158360C>T	35	NA	2.39	0	p.Trp2593*	NM_023073.3:c.7778G>A	chr5:g.37158360C>T	35	NA	2.39	0
UW295-3	*C5orf42*	p.Arg1044Glnfs*2	NM_023073.3:c.3130_3131insA	chr5:g.37206317_37206318insT	25.3	NA	2.79	0	p.Ala1200Val	NM_023073.3:c.3599C>T	chr5:g.37198877G>A	29.6	0.997	5.28	0.0116
UW297-3	*C5orf42*	p.Leu1213Alafs*30	NM_023073.3:c.3636_3637delAT	chr5:g.37198839_37198840delAT	28.5	NA	1.28	0	p.Glu142Lys	NM_023073.3:c.424G>A	chr5:g.37244623C>T	22.9	0.998	5.69	0
UW300-3	*C5orf42*	p.Leu171Serfs*11	NM_023073.3:c.510delT	chr5:g.37244537delA	23	NA	-1.66	0	p.Asn273His	NM_023073.3:c.817A>C	chr5:g.37239832T>G	27.1	0.999	5.46	0
UW304-4	*C5orf42*	p.Arg2904*	NM_023073.3:c.8710C>T	chr5:g.37125432G>A	37	NA	1.65	0.116	p.Gln759*	NM_023073.3:c.2275C>T	chr5:g.37226422G>A	36	NA	5.22	0
UW305-3	*C5orf42*	p.Val2090Alafs*15	NM_023073.3:c.6269_6270delTG	chr5:g.37170335_37170336delCA	29.5	NA	2.15	0	p.Glu142Lys	NM_023073.3:c.424G>A	chr5:g.37244623C>T	34	0.998	5.69	0
UW036-3	*CC2D2A*	p.Pro1122Ser	NM_001080522.2:c.3364C>T	chr4:g.15569375C>T	23.3	1	6.08	0	p.Pro1122Ser	NM_001080522.2:c.3364C>T	chr4:g.15569375C>T	23.3	1	6.08	0
UW041-3	*CC2D2A*	p.Arg950*	NM_001080522.2:c.2848C>T	chr4:g.15560806C>T	22.6	NA	5.37	0.0278	p.Arg950*	NM_001080522.2:c.2848C>T	chr4:g.15560806C>T	22.6	NA	5.37	0.0278
UW046-1	*CC2D2A*	p.Val1430Ala	NM_001080522.2:c.4289T>C	chr4:g.15591277T>C	27.5	0.977	5.42	0	Val1097Phefs*2	NM_001080522.2:c.3289delG	chr4:g.15569300delG	22.7	NA	6.08	0
UW046-2	*CC2D2A*	p.Val1430Ala	NM_001080522.2:c.4289T>C	chr4:g.15591277T>C	27.5	0.977	5.42	0	Val1097Phefs*2	NM_001080522.2:c.3289delG	chr4:g.15569300delG	22.7	NA	6.08	0
UW047-3	*CC2D2A*	p.Gln1096His	NM_001080522.2:c.3288G>C	chr4:g.15569105G>C	21.9	0.465	5.4	0	p.Arg1019*	NM_001080522.2:c.3055C>T	chr4:g.15565018C>T	22.9	NA	4.36	0.026
UW048-3	*CC2D2A*	p.Pro1122Ser	NM_001080522.2:c.3364C>T	chr4:g.15569375C>T	23.3	1	6.08	0	p.Pro1122Ser	NM_001080522.2:c.3364C>T	chr4:g.15569375C>T	23.3	1	6.08	0
UW049-3	*CC2D2A*	Val1097Phefs*2	NM_001080522.2:c.3289delG	chr4:g.15569300delG	22.7	NA	6.08	0	p.Arg1528Cys	NM_001080522.2:c.4582C>T	chr4:g.15601237C>T	20.3	0.995	5.75	0
UW050-3	*CC2D2A*	p.Arg1528Cys	NM_001080522.2:c.4582C>T	chr4:g.15601237C>T	20.3	0.995	5.75	0	p.Arg1528Cys	NM_001080522.2:c.4582C>T	chr4:g.15601237C>T	20.3	0.995	5.75	0
UW050-6	*CC2D2A*	p.Arg1528Cys	NM_001080522.2:c.4582C>T	chr4:g.15601237C>T	20.3	0.995	5.75	0	p.Arg1528Cys	NM_001080522.2:c.4582C>T	chr4:g.15601237C>T	20.3	0.995	5.75	0
UW075-3	*CC2D2A*	p.Val1298Phefs*17	NM_001080522.2:c.3891_3892delTG	chr4:g.15581710_15581711delTG	36	NA	5.35	0	p.Leu559Pro	NM_001080522.2:c.1676T>C	chr4:g.15538611T>C	24.3	0.998	5.58	0
UW076-3	*CC2D2A*	p.Arg1284Cys	NM_001080522.2:c.3850C>T	chr4:g.15581669C>T	35	1	5.16	0	p.Val1045Ala	NM_001080522.2:c.3134T>C	chr4:g.15565097T>C	21.1	0.848	5.41	0
UW079-3	*CC2D2A*	p.Val1151Ala	NM_001080522.2:c.3452T>C	chr4:g.15570969T>C	25.7	0.883	6.03	0	p.Phe421_Ser422insGlyMetPhe	NM_001080522.2:c.1263_1264insGGC	chr4:g.15529183_15529184insG	18.77	NA	5.78	0
UW079-4	*CC2D2A*	p.Val1151Ala	NM_001080522.2:c.3452T>C	chr4:g.15570969T>C	25.7	0.883	6.03	0	p.Phe421_Ser422insGlyMetPhe	NM_001080522.2:c.1263_1264insGGC	chr4:g.15529183_15529184insG	18.77	NA	5.78	0
UW080-3	*CC2D2A*	Val1097Phefs*2	NM_001080522.2:c.3289delG	chr4:g.15569300delG	22.7	NA	6.08	0	p.Thr1116Met	NM_001080522.2:c.3347C>T	chr4:g.15569358C>T	19.14	0.997	5.24	0.0244
UW081-3	*CC2D2A*	splice	NM_001080522.2:c.4179+1delG	chr4:g.15589553delG	15.53	NA	5.73	0	p.Asp1556Val	NM_001080522.2:c.4667A>T	chr4:g.15601322A>T	22.1	0.982	5.75	0.0266
UW088-3	*CC2D2A*	p.P1250Gfs*11	NM_001080522.2:c.3743_3746dupTGGT	chr4:g.15575921_15575924dupTGGT	36	NA	4.92	0	p.Arg1330Gln	NM_001080522.2:c.3989G>A	chr4:g.15587793G>A	29.1	0.973	3.38	0
UW088-4	*CC2D2A*	p.P1250Gfs*11	NM_001080522.2:c.3743_3746dupTGGT	chr4:g.15575921_15575924dupTGGT	36	NA	4.92	0	p.Arg1330Gln	NM_001080522.2:c.3989G>A	chr4:g.15587793G>A	29.1	0.973	3.38	0
UW102-3	*CC2D2A*	splice	NM_001080522.2:c.3772-1G>T	chr4:g.15581590G>T	24.6	NA	5.38	0	p.Arg1528Cys	NM_001080522.2:c.4582C>T	chr4:g.15601237C>T	20.3	0.995	5.75	0
UW104-3	*CC2D2A*	p.Val1045Ala	NM_001080522.2:c.3134T>C	chr4:g.15565097T>C	21.1	0.886	5.41	0	splice	NM_001080522.2:c.1017+1G>A	chr4:g.15517628G>A	22.3	NA	6.17	0
UW204-3	*CC2D2A*	p.Arg1019*	NM_001080522.2:c.3055C>T	chr4:g.15565018C>T	22.9	NA	4.36	0.026	p.Asp1556Val	NM_001080522.2:c.4667A>T	chr4:g.15601322A>T	22.1	0.982	5.75	0.0266
UW260-3	*CC2D2A*	Val1097Phefs*2	NM_001080522.2:c.3289delG	chr4:g.15569300delG	22.7	NA	6.08	0	p.Arg1330Gln	NM_001080522.2:c.3989G>A	chr4:g.15587793G>A	29.1	0.973	3.38	0
UW262-3	*CC2D2A*	p.Thr1581Ala	NM_001080522.2:c.4741A>G	chr4:g.15602926A>G	18.68	0.999	5.69	0	p.Thr1116Met	NM_001080522.2:c.3347C>T	chr4:g.15569358C>T	19.14	0.997	5.24	0.0244
UW265-3	*CC2D2A*	p.Glu1000Val	NM_001080522.2:c.2999A>T	chr4:g.15562230A>T	17.08	0.23	5.5	0	p.Glu1000Val	NM_001080522.2:c.2999A>T	chr4:g.15562230A>T	17.08	0.23	5.5	0
UW265-4	*CC2D2A*	p.Glu1000Val	NM_001080522.2:c.2999A>T	chr4:g.15562230A>T	17.08	0.23	5.5	0	p.Glu1000Val	NM_001080522.2:c.2999A>T	chr4:g.15562230A>T	17.08	0.23	5.5	0
UW267-3	*CC2D2A*	p.Pro1122Ser	NM_001080522.2:c.3364C>T	chr4:g.15569375C>T	23.3	1	6.08	0	p.Pro1122Ser	NM_001080522.2:c.3364C>T	chr4:g.15569375C>T	23.3	1	6.08	0
UW267-4	*CC2D2A*	p.Pro1122Ser	NM_001080522.2:c.3364C>T	chr4:g.15569375C>T	23.3	1	6.08	0	p.Pro1122Ser	NM_001080522.2:c.3364C>T	chr4:g.15569375C>T	23.3	1	6.08	0
UW271-3	*CC2D2A*	p.Ser875*	NM_001080522.2:c.2624C>A	chr4:g.15556832C>A	39	NA	1.89	0	p.Lys501_Asp502delinsAsn	NM_001080522.2:c.1503_1505delAGA	chr4:g.15534852_15534854delA	12.78	NA	5.18	0
UW275-3	*CC2D2A*	splice	NM_001080522.2:c.4179+1delG	chr4:g.15589553delG	15.53	NA	5.73	0	p.Asp1556Val	NM_001080522.2:c.4667A>T	chr4:g.15601322A>T	22.1	0.982	5.75	0.0266
UW287-3	*CC2D2A*	splice	NM_001080522.2:c.1017+1G>A	chr4:g.15517628G>A	22.3	NA	6.17	0.0255	p.Leu1534Val	NM_001080522.2:c.4600T>G	chr4:g.15601255T>G	14.55	0.999	-3.36	0
UW288-3	*CC2D2A*	Val1097Phefs*2	NM_001080522.2:c.3289delG	chr4:g.15569300delG	22.7	NA	6.08	0	p.Asp1556Val	NM_001080522.2:c.4667A>T	chr4:g.15601322A>T	22.1	0.982	5.75	0.0266
UW296-3	*CC2D2A*	p.Thr1116Met	NM_001080522.2:c.3347C>T	chr4:g.15569358C>T	19.14	0.997	5.24	0.0244	p.Thr1116Met	NM_001080522.2:c.3347C>T	chr4:g.15569358C>T	19.14	0.997	5.24	0.0244
UW296-4	*CC2D2A*	p.Thr1116Met	NM_001080522.2:c.3347C>T	chr4:g.15569358C>T	19.14	0.997	5.24	0.0244	p.Thr1116Met	NM_001080522.2:c.3347C>T	chr4:g.15569358C>T	19.14	0.997	5.24	0.0244
UW301-3	*CC2D2A*	p.Ser1615Leufs*16	NM_001080522.2:c.4843_4846delTCTC	chr4:g.15603028_15603031delTCTC	22.4	NA	5.69	0	p.Glu891Lys	NM_001080522.2:c.2671G>A	chr4:g.15558972G>A	32	0.978	4.79	0
UW302-3	*CC2D2A*	p.Asp1556Val	NM_001080522.2:c.4667A>T	chr4:g.15601322A>T	22.1	0.982	5.75	0	p.Thr1114Met	NM_001080522.2:c.3341C>T	chr4:g.15569352C>T	21.3	1	5.24	0
UW302-4	*CC2D2A*	p.Asp1556Val	NM_001080522.2:c.4667A>T	chr4:g.15601322A>T	22.1	0.982	5.75	0	p.Thr1114Met	NM_001080522.2:c.3341C>T	chr4:g.15569352C>T	21.3	1	5.24	0
UW307-3	*CC2D2A*	p.Ile1199Thr	NM_001080522.2:c.3596T>C	chr4:g.15575774T>C	28.7	0.989	5.18	0	p.Gln1497His	NM_001080522.2:c.4491A>C	chr4:g.15599083A>C	20.8	0.997	1.9	0
UW308-3	*CC2D2A*	p.Ile1409Thr	NM_001080522.2:c.4226T>C	chr4:g.15591214T>C	29.6	0.973	5.74	0	p.Ile1409Thr	NM_001080522.2:c.4226T>C	chr4:g.15591214T>C	29.6	0.973	5.74	0
UW312-3	*CC2D2A*	p.Glu1259*	NM_001080522.2:c.3774dupT	chr4:g.15581593dupT	38	NA	5.38	0	p.Arg1528Cys	NM_001080522.2:c.4582C>T	chr4:g.15601237C>T	20.6	0.995	5.75	0
UW315-3	*CC2D2A*	p.Glu1259*	NM_001080522.2:c.3774dupT	chr4:g.15581593dupT	38	NA	5.38	0	p.Asp1556Val	NM_001080522.2:c.4667A>T	chr4:g.15601322A>T	25.5	0.982	5.75	0.0266
UW002-3	*CEP290*	p.Gly1890*	NM_025114.3:c.5668G>T	chr12:g.88471040C>A	36	NA	2.73	0	p.Gln662*	NM_025114.3:c.1984C>T	chr12:g.88508265G>A	38	NA	5.87	0
UW008-3	*CEP290*	p.Val2093Serfs*4	NM_025114.3:c.6277delG	chr12:g.88456549delC	22.7	NA	5.93	0	p.Gln662*	NM_025114.3:c.1984C>T	chr12:g.88508265G>A	38	NA	5.87	0
UW013-3	*CEP290*	p.Ile556Phefs*17	NM_025114.3:c.1666delA	chr12:g.88512305delT	28.1	NA	4.38	0	p.Gln1302*	NM_025114.3:c.3904C>T	chr12:g.88482934G>A	37	NA	3.69	0
UW013-4	*CEP290*	p.Ile556Phefs*17	NM_025114.3:c.1666delA	chr12:g.88512305delT	28.1	NA	4.38	0	p.Gln1302*	NM_025114.3:c.3904C>T	chr12:g.88482934G>A	37	NA	3.69	0
UW016-1	*CEP290*	p.Gln1871Valfs*2	NM_025114.3:c.5611_5614delCAAA	chr12:g.88471094_88471097delTTTG	36	NA	4.59	0	p.Gln1628*	NM_025114.3:c.4882C>T	chr12:g.88476938G>A	47	NA	5.67	0.0244
UW020-3	*CEP290*	p.Ile556Asnfs*20	NM_025114.3:c.1666dupA	chr12:g.88512305dupT	32	NA	5.53	0	p.Arg1782*	NM_025114.3:c.5344C>T	chr12:g.88472889G>A	41	NA	3.06	0
UW029-3	*CEP290*	p.Lys1575*	NM_025114.3:c.4723A>T	chr12:g.88477713T>A	51	NA	5.43	0	p.Tyr218*	NM_025114.3:c.654T>G	chr12:g.88524060A>C	38	NA	3.94	0
UW032-3	*CEP290*	p.Thr55Serfs*3	NM_025114.3:c.164_167delCTCA	chr12:g.88534746_88534749delTGAG	22.9	NA	5.86	0	p.Arg1978*	NM_025114.3:c.5932C>T	chr12:g.88465150G>A	52	NA	5.23	0.0123
UW040-3	*CEP290*	p.Glu1462Argfs*5	NM_025114.3:c.4384delG	chr12:g.88479869delC	36	NA	5.78	0	p.Glu1462Argfs*5	NM_025114.3:c.4384delG	chr12:g.88479869delC	36	NA	5.78	0
UW045-3	*CEP290*	p.Arg1465*	NM_025114.3:c.4393C>T	chr12:g.88479860G>A	41	NA	4.89	0	p.Arg1465*	NM_025114.3:c.4393C>T	chr12:g.88479860G>A	41	NA	4.89	0
UW211-3	*CEP290*	p.Val705Leufs*11	NM_025114.3:c.2112delA	chr12:g.88505576delT	29	NA	4.61	0	p.Lys1575*	NM_025114.3:c.4723A>T	chr12:g.88477713T>A	51	NA	5.43	0
UW219-3	*CEP290*	p.Lys1484Asnfs*4	NM_025114.3:c.4452_4455delAGAA	chr12:g.88478612_88478615delTTCT	38	NA	5.24	0	p.Leu1062Argfs*3	NM_025114.3:c.3185delT	chr12:g.88487671delA	34	NA	5.66	0
UW220-3	*CEP290*	p.Gly1890*	NM_025114.3:c.5668G>T	chr12:g.88471040C>A	36	NA	2.73	0	p.Gly1890*	NM_025114.3:c.5668G>T	chr12:g.88471040C>A	36	NA	2.73	0
UW240-3	*CEP290*	p.Ile556Phefs*17	NM_025114.3:c.1666delA	chr12:g.88512305delT	28.1	NA	4.38	0	p.Ile556Phefs*17	NM_025114.3:c.1666delA	chr12:g.88512305delT	28.1	NA	4.38	0
UW241-3	*CEP290*	p.Ile1059Lysfs*6	NM_025114.3:c.3176delT	chr12:g.88487680delA	35	NA	5.66	0	p.Ile1059Lysfs*6	NM_025114.3:c.3176delT	chr12:g.88487680delA	35	5.66	0	0
UW241-6	*CEP290*	p.Ile1059Lysfs*6	NM_025114.3:c.3176delT	chr12:g.88487680delA	35	NA	5.66	0	p.Ile1059Lysfs*6	NM_025114.3:c.3176delT	chr12:g.88487680delA	35	5.66	0	0
UW241-7	*CEP290*	p.Ile1059Lysfs*6	NM_025114.3:c.3176delT	chr12:g.88487680delA	35	NA	5.66	0	p.Ile1059Lysfs*6	NM_025114.3:c.3176delT	chr12:g.88487680delA	35	5.66	0	0
UW244-3	*CEP290*	p.Gly1890*	NM_025114.3:c.5668G>T	chr12:g.88471040C>A	36	NA	2.73	0	p.Gly1890*	NM_025114.3:c.5668G>T	chr12:g.88471040C>A	36	NA	2.73	0

UW244-4	*CEP290*	p.Gly1890*	NM_025114.3:c.5668G>T	chr12:g.88471040C>A	45	NA	2.73	0	p.Gly1890*	NM_025114.3:c.5668G>T	chr12:g.88471040C>A	45	NA	2.73	0
UW246-3	*CEP290*	p.Tyr218*	NM_025114.3:c.654T>G	chr12:g.88524060A>C	38	NA	3.94	0	p.Gly1890*	NM_025114.3:c.5668G>T	chr12:g.88471040C>A	45	NA	2.73	0
UW250-3	*CEP290*	splice	NM_025114.3:c.1623+1G>A	chr12:g.88512419C>T	24.9	NA	5.53	0	p.Gly1890*	NM_025114.3:c.5668G>T	chr12:g.88471040C>A	36	NA	2.73	0
UW254-3	*CEP290*	p.Glu1656Asnfs*3	NM_025114.3:c.4966_4967delGA	chr12:g.88476853_88476854delTC	36	NA	5.55	0	p.Trp7Cys	NM_025114.3:c.21G>T	chr12:g.88535064C>A	23	0.999	5.03	0
UW259-3	*CEP290*	p.Gly1890*	NM_025114.3:c.5668G>T	chr12:g.88471040C>A	36	NA	2.73	0	p.Gly1890*	NM_025114.3:c.5668G>T	chr12:g.88471040C>A	36	NA	2.73	0
UW263-3	*CEP290*	p.Gly1890*	NM_025114.3:c.5668G>T	chr12:g.88471040C>A	36	NA	2.73	0	p.Gly1890*	NM_025114.3:c.5668G>T	chr12:g.88471040C>A	36	NA	2.73	0
UW269-3	*CEP290*	p.Glu1902*	NM_025114.3:c.5704G>T	chr12:g.88471004C>A	50	NA	5.27	0	p.Glu1902*	NM_025114.3:c.5704G>T	chr12:g.88471004C>A	50	NA	5.27	0
UW280-3	*CEP290*	p.Lys1575*	NM_025114.3:c.4723A>T	chr12:g.88477713T>A	51	NA	5.43	0	p.Arg1508*	NM_025114.3:c.4522C>T	chr12:g.88478545G>A	42	NA	4.64	0
UW281-3	*CEP290*	p.Tyr2313*	NM_025114.3:c.6939C>A	chr12:g.88449374G>T	10.19	NA	3.33	0	p.Met407Glufs*14	NM_025114.3:c.1219_1220delAT	chr12:g.88514913_88514914del	27.7	NA	5.84	0
UW282-3	*CEP290*	p.Gly1890*	NM_025114.3:c.5668G>T	chr12:g.88471040C>A	36	NA	2.73	0	p.Gly1890*	NM_025114.3:c.5668G>T	chr12:g.88471040C>A	36	NA	2.73	0
UW282-4	*CEP290*	p.Gly1890*	NM_025114.3:c.5668G>T	chr12:g.88471040C>A	36	NA	2.73	0	p.Gly1890*	NM_025114.3:c.5668G>T	chr12:g.88471040C>A	36	NA	2.73	0
UW286-3	*CEP290*	splice	NM_025114.3:c.103-1G>T	chr12:g.88534811C>A	23.2	NA	5.86	0	p.Gly1890*	NM_025114.3:c.5668G>T	chr12:g.88471040C>A	36	NA	2.73	0
UW303-3	*CEP290*	p.Ile556Phefs*17	NM_025114.3:c.1666delA	chr12:g.88512305delT	28.1	NA	5.53	0	p.Ile556Phefs*17	NM_025114.3:c.1666delA	chr12:g.88512305delT	28.1	NA	5.53	0
UW316-3	*CEP290*	p.Ile1059Asnfs*11	NM_025114.3:c.3175dupA	chr12:g.88487681dupT	34	NA	5.47	0	p.Gly1890*	NM_025114.3:c.5668G>T	chr12:g.88471040C>A	45	NA	2.73	0
UW035-3	*CSPP1*	p.N903Mfs*2	NM_024790.6:c.2708delA	chr8:g.68076638delA	35	NA	4.19	0	p.N903Mfs*2	NM_024790.6:c.2708delA	chr8:g.68076638delA	35	NA	4.19	0
UW097-3	*CSPP1*	p.Glu750Glyfs*30	NM_024790.6:c.2244_2245delAA	chr8:g.68070699_68070700delAA	35	NA	5.28	0	p.Glu761Lysfs*35	NM_024790.6:c.2280delA	chr8:g.68070735delA	23.3	NA	-2.38	0.0122
UW097-6	*CSPP1*	p.Glu750Glyfs*30	NM_024790.6:c.2244_2245delAA	chr8:g.68070699_68070700delAA	35	NA	5.28	0	p.Glu761Lysfs*35	NM_024790.6:c.2280delA	chr8:g.68070735delA	23.3	NA	-2.38	0.0122
UW123-3	*CSPP1*	p.Tyr1071*	NM_024790.6:c.3212dupA	chr8:g.68102891dupA	36	NA	4.31	0	splice	NM_024790.6:c.2953+1G>A	chr8:g.68084791G>A	22.8	NA	5.62	0
UW124-3	*CSPP1*	p.Tyr1071*	NM_024790.6:c.3212dupA	chr8:g.68102891dupA	36	NA	4.31	0	splice	NM_024790.6:c.2953+1G>A	chr8:g.68084791G>A	22.8	NA	5.62	0
UW127-3	*CSPP1*	p.Glu819Argfs*7	NM_024790.6:c.2448_2454dupAGAAGAA	chr8:g.68071297_68071303dupAGAAGAA	25.7	NA	5.06	0	p.Glu819Argfs*7	NM_024790.6:c.2448_2454dupAGAAG	chr8:g.68071297_68071303dup	25.7	NA	5.06	0
UW128-3	*CSPP1*	p.Arg153Glyfs*35	NM_024790.6:c.457delA	chr8:g.68005823delA	27.5	NA	5.14	0	p.Arg754*	NM_024790.6:c.2260C>T	chr8:g.68070715C>T	42	NA	5.28	0
UW129-3	*CSPP1*	p.Arg220*	NM_024790.6:c.658C>T	chr8:g.68007675C>T	22.1	NA	5.07	0.0253	p.Met843Glufs*25	NM_024790.6:c.2527_2528delAT	chr8:g.68074049_68074050delA	24.5	NA	2.8	0
UW129-4	*CSPP1*	p.Arg220*	NM_024790.6:c.658C>T	chr8:g.68007675C>T	22.1	NA	5.07	0.0253	p.Met843Glufs*25	NM_024790.6:c.2527_2528delAT	chr8:g.68074049_68074050delA	24.5	NA	2.8	0
UW130-3	*CSPP1*	p.Met843Glufs*25	NM_024790.6:c.2527_2528delAT	chr8:g.68074049_68074050delAT	24.5	NA	2.8	0	p.Met843Glufs*25	NM_024790.6:c.2527_2528delAT	chr8:g.68074049_68074050delA	24.5	NA	2.8	0
UW137-3	*CSPP1*	splice	NM_024790.6:c.3205+1G>A	chr8:g.68092162G>A	21.5	NA	5.56	0	splice	NM_024790.6:c.950+1G>C	chr8:g.68007968G>C	22	NA	6.06	0
UW143-3	*CSPP1*	p.Arg378*	NM_024790.6:c.1132C>T	chr8:g.68024218C>T	36	NA	1.2	0.027	p.Lys814Argfs*21	NM_024790.6:c.2433_2436delAGAA	chr8:g.68071282_68071285delA	35	NA	5.06	0
UW143-4	*CSPP1*	p.Arg378*	NM_024790.6:c.1132C>T	chr8:g.68024218C>T	36	NA	1.2	0.027	p.Lys814Argfs*21	NM_024790.6:c.2433_2436delAGAA	chr8:g.68071282_68071285delA	35	NA	5.06	0
UW147-3	*CSPP1*	p.Met843Glufs*25	NM_024790.6:c.2527_2528delAT	chr8:g.68074049_68074050delAT	24.5	NA	2.8	0	p.Met843Glufs*25	NM_024790.6:c.2527_2528delAT	chr8:g.68074049_68074050delA	24.5	NA	2.8	0
UW148-3	*CSPP1*	p.Tyr1071*	NM_024790.6:c.3212dupA	chr8:g.68102891dupA	36	NA	4.31	0	splice	NM_024790.6:c.2953+1G>A	chr8:g.68084791G>A	22.8	NA	5.62	0
UW151-3	*CSPP1*	p.Glu817Lysfs*17	NM_024790.6:c.2448_2454delAGAAGAA	chr8:g.68071297_68071303delAGAAGAA	33	NA	5.06	0	p.Glu817Lysfs*17	NM_024790.6:c.2448_2454delAGAAGA	chr8:g.68071297_68071303delA	33	NA	5.06	0
UW290-3	*CSPP1*	splice	NM_024790.6:c.1682+1G>T	chr8:g.68031057G>T	23.6	NA	5.19	0	p.His121Glnfs*22	NM_024790.6:c.362_363delAT	chr8:g.67998296_67998297delA	26.8	NA	4.45	0
UW112-3	*IFT172*	p.Arg1544Cys	NM_015662.1:c.4630C>T	chr2:g.27670411G>A	16.29	0.991	5.42	0	p.Arg1544Cys	NM_015662.1:c.4630C>T	chr2:g.27670411G>A	16.29	0.991	5.42	0
UW112-4	*IFT172*	p.Arg1544Cys	NM_015662.1:c.4630C>T	chr2:g.27670411G>A	16.29	0.991	5.42	0	p.Arg1544Cys	NM_015662.1:c.4630C>T	chr2:g.27670411G>A	16.29	0.991	5.42	0
UW011-3	*INPP5E*	p.Val303Met	NM_019892.4:c.907G>A	chr9:g.139329221C>T	29.7	0.382	3.55	0	p.Gly341Ser	NM_019892.4:c.1021G>A	chr9:g.139328502C>T	25.4	0.715	4.13	0
UW107-3	*INPP5E*	p.Ser562Gly	NM_019892.4:c.1684A>G	chr9:g.139324847T>C	25.2	0.393	5.15	0	p.Gly341Ser	NM_019892.4:c.1021G>A	chr9:g.139328502C>T	25.4	0.715	4.13	0
UW107-4	*INPP5E*	p.Ser562Gly	NM_019892.4:c.1684A>G	chr9:g.139324847T>C	25.2	0.393	5.15	0	p.Gly341Ser	NM_019892.4:c.1021G>A	chr9:g.139328502C>T	25.4	0.715	4.13	0
UW208-3	*INPP5E*	p.Thr355Met	NM_019892.4:c.1064C>T	chr9:g.139327702G>A	25.9	0.994	4.87	0	p.Pro315Leu	NM_019892.4:c.944C>T	chr9:g.139328579G>A	26.8	0.807	4.13	0
UW214-3	*INPP5E*	p.Val587Glyfs*7	NM_019892.4:c.1760delT	chr9:g.139324771delA	36	NA	5.55	0	p.Val388Leu	NM_019892.4:c.1162G>T	chr9:g.139327525C>A	23.1	0.043	4.82	0
UW214-4	*INPP5E*	p.Val587Glyfs*7	NM_019892.4:c.1760delT	chr9:g.139324771delA	36	NA	5.55	0	p.Val388Leu	NM_019892.4:c.1162G>T	chr9:g.139327525C>A	23.1	0.043	4.82	0
UW217-3	*INPP5E*	p.Arg585His	NM_019892.4:c.1754G>A	chr9:g.139324777C>T	36	0.999	5.55	0	p.Ser417Pro	NM_019892.4:c.1249T>C	chr9:g.139327438A>G	28.6	0.999	4.88	0
UW235-3	*INPP5E*	p.Gln633Glufs*64	NM_019892.4:c.1897_1898delCA	chr9:g.139324164_139324165delTG	26	NA	4.14	0	p.Arg435Gln	NM_019892.4:c.1304G>A	chr9:g.139327014C>T	36	1	5.28	0
UW238-3	*INPP5E*	p.Cys385Tyr	NM_019892.4:c.1154G>A	chr9:g.139327612C>T	32	0.989	5.13	0	p.Cys385Tyr	NM_019892.4:c.1154G>A	chr9:g.139327612C>T	32	0.989	5.13	0
UW289-3	*INPP5E*	p.Thr355Met	NM_019892.4:c.1064C>T	chr9:g.139327702G>A	32	0.994	4.87	0	p.Thr355Met	NM_019892.4:c.1064C>T	chr9:g.139327702G>A	32	0.994	4.87	0
UW294-3	*INPP5E*	p.Pro526Leu	NM_019892.4:c.1577C>T	chr9:g.139325542G>A	27.2	0.601	5.04	0	p.Asp490Tyr	NM_019892.4:c.1468G>T	chr9:g.139326357C>A	25.7	0.58	5.11	0
UW206-3	*KIF7*	p.Arg1111*	NM_198525.2:c.3331C>T	chr15:g.90172792G>A	21.2	NA	4.14	0	p.Arg1111*	NM_198525.2:c.3331C>T	chr15:g.90172792G>A	21.2	NA	4.14	0
UW230-3	*KIF7*	p.Arg973*	NM_198525.2:c.2917C>T	chr15:g.90174920G>A	21.5	NA	5.18	0.0684	p.Arg973*	NM_198525.2:c.2917C>T	chr15:g.90174920G>A	21.5	NA	5.18	0.0684
UW258-3	*KIF7*	p.Glu982*	NM_198525.2:c.2944G>T	chr15:g.90174893C>A	22.2	NA	5.18	0	p.Gln994Arg	NM_198525.2:c.2981A>G	chr15:g.90174856T>C	21.2	0.497	5.18	0
UW010-3	*MKS1*	p.Ser403Leu	NM_017777.3:c.1208C>T	chr17:g.56285320G>A	22.7	0.999	5.58	0	p.Phe88_Glu139del	NM_017777.3:c.417G>A	chr17:g.56293449C>T	23.3	NA	6.06	0.0242
UW031-3	*MKS1*	p.Arg510Profs*81	NM_017777.3:c.1528dupC	chr17:g.56283704dupG	32	NA	1.74	0.0247	p.Arg510Profs*81	NM_017777.3:c.1528dupC	chr17:g.56283704dupG	32	NA	1.74	0.0247
UW090-3	*MKS1*	p.Phe88_Glu139del	NM_017777.3:c.262-179_262-37del	chr17:g.56293641_56293783del	9.778	NA	NA	unknown	p.Phe88_Glu139del	NM_017777.3:c.262-179_262-37del	chr17:g.56293641_56293783del	9.778	NA	NA	unknown
UW091-3	*MKS1*	p.Asp19Tyr	NM_017777.3:c.55G>T	chr17:g.56296537C>A	22.8	0.996	4.88	0	p.Asp19Tyr	NM_017777.3:c.55G>T	chr17:g.56296537C>A	22.8	0.996	4.88	0
UW092-3	*MKS1*	p.Ser372del	NM_017777.3:c.1115_1117delCCT	chr17:g.56285514_56285516delAGG	22.9	NA	5.58	0	p.Tyr128Thrfs*17	NM_017777.3:c.381delC	chr17:g.56293485delG	21.3	NA	0.171	0
UW092-4	*MKS1*	p.Ser372del	NM_017777.3:c.1115_1117delCCT	chr17:g.56285514_56285516delAGG	22.9	NA	5.58	0	p.Tyr128Thrfs*17	NM_017777.3:c.381delC	chr17:g.56293485delG	21.3	NA	0.171	0
UW093-3	*MKS1*	p.Ser372del	NM_017777.3:c.1115_1117delCCT	chr17:g.56285514_56285516delAGG	22.9	NA	5.58	0	p.Ser372del	NM_017777.3:c.1115_1117delCCT	chr17:g.56285514_56285516del	22.9	NA	5.58	0
UW150-3	*MKS1*	splice	NM_017777.3:c.1589-2A>T	chr17:g.56283533T>A	22.6	NA	5.21	0	splice	NM_017777.3:c.1589-2A>T	chr17:g.56283533T>A	22.6	NA	5.21	0
UW153-3	*MKS1*	p.Gly317Glu	NM_017777.3:c.950G>A	chr17:g.56288349C>T	20.8	0.998	5.5	0	p.Ser372del	NM_017777.3:c.1115_1117delCCT	chr17:g.56285514_56285516del	22.9	NA	5.58	0
UW019-3	*NPHP1*	deletion							deletion						
UW023-1	*NPHP1*	deletion							deletion						
UW229-3	*NPHP1*	deletion							deletion						
UW247-3	*NPHP1*	deletion							deletion						
UW264-3	*NPHP1*	deletion							deletion						
UW087-3	*OFD1*	p.Glu923Lysfs*4	NM_003611.2:c.2767delG	chrX:g.13786182delG	32	NA	5.45	0	p.Glu923Lysfs*4	NM_003611.2:c.2767delG	chrX:g.13786182delG	32	NA	5.45	0
UW172-3	*OFD1*	p.Val93Phe	NM_003611.2:c.277G>T	chr23:g.13754762G>T	23.8	0.999	5.55	0	p.Val93Phe	NM_003611.2:c.277G>T	chr23:g.13754762G>T	23.8	0.999	5.55	0
UW172-4	*OFD1*	p.Val93Phe	NM_003611.2:c.277G>T	chr23:g.13754762G>T	23.8	0.999	5.55	0	p.Val93Phe	NM_003611.2:c.277G>T	chr23:g.13754762G>T	23.8	0.999	5.55	0
UW239-3	*OFD1*	p.Arg890*	NM_003611.2:c.2668C>T	chrX:g.13785314C>T	18.37	NA	3.92	0	p.Arg890*	NM_003611.2:c.2668C>T	chrX:g.13785314C>T	18.37	NA	3.92	0
UW274-3	*OFD1*	p.His50Arg	NM_003611.2:c.149A>G	chrX:g.13754634A>G	20.2	0.931	4.37	0	p.His50Arg	NM_003611.2:c.149A>G	chrX:g.13754634A>G	20.2	0.931	4.37	0
UW004-3	*RPGRIP1L*	p.Arg805*	NM_015272.2:c.2413C>T	chr16:g.53679807G>A	39	NA	3.28	0.0116	p.Ser659Pro	NM_015272.2:c.1975T>C	chr16:g.53686624A>G	26.9	0.999	5.45	0
UW004-4	*RPGRIP1L*	p.Arg805*	NM_015272.2:c.2413C>T	chr16:g.53679807G>A	39	NA	3.28	0.0116	p.Ser659Pro	NM_015272.2:c.1975T>C	chr16:g.53686624A>G	26.9	0.999	5.45	0
UW015-4	*RPGRIP1L*	p.Gln684*	NM_015272.2:c.2050C>T	chr16:g.53686549G>A	37	NA	4.75	0	p.Thr615Pro	NM_015272.2:c.1843A>C	chr16:g.53686756T>G	16.67	0.15	3.15	0
UW042-3	*RPGRIP1L*	splice	NM_015272.2:c.2305-1G>A	chr16:g.53679916C>T	23.4	NA	4.2	0	splice	NM_015272.2:c.2305-1G>A	chr16:g.53679916C>T	23.4	NA	4.2	0

UW043-3	*RPGRIP1L*	p.Tyr574Leufs*27	NM_015272.2:c.1721delA	chr16:g.53686878delT	32	NA	5.45	0	p.Tyr574Leufs*27	NM_015272.2:c.1721delA	chr16:g.53686878delT	32	NA	5.45	0
UW227-3	*RPGRIP1L*	p.Trp378Glyfs*3	NM_015272.2:c.1132delT	chr16:g.53698893delA	29.5	NA	5.36	0	p.Asp571Glyfs*12	NM_015272.2:c.1709dupA	chr16:g.53686890dupT	33	NA	5.45	0
UW242-3	*RPGRIP1L*	splice	NM_015272.2:c.2305-1G>A	chr16:g.53679916C>T	23.4	NA	4.2	0	splice	NM_015272.2:c.2305-1G>A	chr16:g.53679916C>T	23.4	NA	4.2	0
UW299-3	*RPGRIP1L*	splice	NM_015272.2:c.1243+1G>A	chr16:g.53698781C>T	16.56	NA	5.36	0	splice	NM_015272.2:c.3701+1G>T	chr16:g.53644878C>A	23.4	NA	5.26	0
UW314-3	*RPGRIP1L*	p.Arg1177*	NM_015272.2:c.3529C>T	chr16:g.53653024G>A	36	NA	2.65		p.Thr615Pro	NM_015272.2:c.1843A>C	chr16:g.53686756T>G	13.46	0.15	3.15	0
UW270-3	*TCTN1*	splice	NM_001082538.2:c.342-2A>G	chr12:g.111064165A>G	21.8	NA	5.17	0	splice	NM_001082538.2:c.342-2A>G	chr12:g.111064165A>G	21.8	NA	5.17	0
UW144-3	*TCTN2*	p.Gly373Arg	NM_024809.4:c.1117G>A	chr12:g.124179406G>A	12.35	0.67	3.3	0	p.Asp26Thrfs*27	NM_024809.4:c.71delG	chr12:g.124155858delG	24.6	NA		0
UW212-3	*TCTN2*	p.Asp543Ilefs*11	NM_024809.4:c.1626delT	chr12:g.124189092delT	24.9	NA	-1.64	0	p.Gly205Cys	NM_024809.4:c.613G>T	chr12:g.124171431G>T	27	0.998	5.65	0.116
UW225-3	*TCTN2*	p.Ile584Lys	NM_024809.4:c.1751T>A	chr12:g.124189217T>A	18.59	0.996	5.58	0	p.Ile584Lys	NM_024809.4:c.1751T>A	chr12:g.124189217T>A	18.59	0.996	5.58	0
UW225-4	*TCTN2*	p.Ile584Lys	NM_024809.4:c.1751T>A	chr12:g.124189217T>A	18.59	0.996	5.58	0	p.Ile584Lys	NM_024809.4:c.1751T>A	chr12:g.124189217T>A	18.59	0.996	5.58	0
UW225-8	*TCTN2*	p.Ile584Lys	NM_024809.4:c.1751T>A	chr12:g.124189217T>A	18.59	0.996	5.58	0	p.Ile584Lys	NM_024809.4:c.1751T>A	chr12:g.124189217T>A	18.59	0.996	5.58	0
UW228-3	*TCTN2*	p.Glu431*	NM_024809.4:c.1291G>T	chr12:g.124179823G>T	24.7	NA	-7.62	0	p.Glu431*	NM_024809.4:c.1291G>T	chr12:g.124179823G>T	24.7	NA	-7.62	0
UW266-3	*TCTN2*	p.Asp26Glyfs*52	NM_024809.4:c.76dupG	chr12:g.124155863dupG	24.6	NA	5.05	0	p.Asp26Glyfs*52	NM_024809.4:c.76dupG	chr12:g.124155863dupG	24.6	NA	5.05	0
UW215-3	*TCTN3*	p.Met1Ile	NM_015631.5:c.3G>A	chr10:g.97453654C>T	12.58	0.98	5.25	0	p.Met1Ile	NM_015631.5:c.3G>A	chr10:g.97453654C>T	12.58	0.98	5.25	0
UW256-3	*TMEM138*	p.Ala127Val	NM_016464.4:c.380C>T	chr11:g.61136072C>T	28.4	0.913	5.45	0	p.Ala127Val	NM_016464.4:c.380C>T	chr11:g.61136072C>T	28.4	0.913	5.45	0
UW040-5	*TMEM216*	p.Arg73Leu	NM_001173990.2:c.218G>T	chr11:g.61161437G>T	27.1	0.823	3.12	0	p.Arg73Leu	NM_001173990.2:c.218G>T	chr11:g.61161437G>T	27.1	0.823	3.12	0
UW066-3	*TMEM216*	p.Leu133*	NM_001173990.2:c.398T>G	chr11:g.61165414T>G	17.56	NA	4.93	0	p.Arg73Cys	NM_001173990.2:c.217C>T	chr11:g.61161436C>T	35	0.98	4.99	0
UW189-3	*TMEM216*	p.Arg73Leu	NM_001173990.2:c.218G>T	chr11:g.61161437G>T	27.1	0.823	3.12	0	p.Arg73Leu	NM_001173990.2:c.218G>T	chr11:g.61161437G>T	27.1	0.823	3.12	0
UW192-3	*TMEM216*	p.Arg73Leu	NM_001173990.2:c.218G>T	chr11:g.61161437G>T	27.1	0.823	3.12	0	p.Arg73Leu	NM_001173990.2:c.218G>T	chr11:g.61161437G>T	27.1	0.823	3.12	0
UW193-3	*TMEM216*	p.Arg73Leu	NM_001173990.2:c.218G>T	chr11:g.61161437G>T	27.1	0.823	3.12	0	p.Arg73Leu	NM_001173990.2:c.218G>T	chr11:g.61161437G>T	27.1	0.823	3.12	0
UW198-3	*TMEM216*	p.Arg73Leu	NM_001173990.2:c.218G>T	chr11:g.61161437G>T	27.1	0.823	3.12	0	p.Arg73Leu	NM_001173990.2:c.218G>T	chr11:g.61161437G>T	27.1	0.823	3.12	0
UW223-3	*TMEM216*	p.Arg73Leu	NM_001173990.2:c.218G>T	chr11:g.61161437G>T	27.1	0.823	3.12	0	p.Arg73Leu	NM_001173990.2:c.218G>T	chr11:g.61161437G>T	27.1	0.823	3.12	0
UW224-3	*TMEM216*	p.Arg73Leu	NM_001173990.2:c.218G>T	chr11:g.61161437G>T	27.1	0.823	3.12	0	p.Arg73Leu	NM_001173990.2:c.218G>T	chr11:g.61161437G>T	27.1	0.823	3.12	0
UW233-3	*TMEM216*	p.Arg73Leu	NM_001173990.2:c.218G>T	chr11:g.61161437G>T	27.1	0.823	3.12	0	p.Arg73Leu	NM_001173990.2:c.218G>T	chr11:g.61161437G>T	27.1	0.823	3.12	0
UW233-4	*TMEM216*	p.Arg73Leu	NM_001173990.2:c.218G>T	chr11:g.61161437G>T	27.1	0.823	3.12	0	p.Arg73Leu	NM_001173990.2:c.218G>T	chr11:g.61161437G>T	27.1	0.823	3.12	0
UW234-11	*TMEM216*	p.Arg73Leu	NM_001173990.2:c.218G>T	chr11:g.61161437G>T	27.1	0.823	3.12	0	p.Arg73Leu	NM_001173990.2:c.218G>T	chr11:g.61161437G>T	27.1	0.823	3.12	0
UW234-17	*TMEM216*	p.Arg73Leu	NM_001173990.2:c.218G>T	chr11:g.61161437G>T	27.1	0.823	3.12	0	p.Arg73Leu	NM_001173990.2:c.218G>T	chr11:g.61161437G>T	27.1	0.823	3.12	0
UW234-3	*TMEM216*	p.Arg73Leu	NM_001173990.2:c.218G>T	chr11:g.61161437G>T	27.1	0.823	3.12	0	p.Arg73Leu	NM_001173990.2:c.218G>T	chr11:g.61161437G>T	27.1	0.823	3.12	0
UW234-4	*TMEM216*	p.Arg73Leu	NM_001173990.2:c.218G>T	chr11:g.61161437G>T	27.1	0.823	3.12	0	p.Arg73Leu	NM_001173990.2:c.218G>T	chr11:g.61161437G>T	27.1	0.823	3.12	0
UW234-5	*TMEM216*	p.Arg73Leu	NM_001173990.2:c.218G>T	chr11:g.61161437G>T	27.1	0.823	3.12	0	p.Arg73Leu	NM_001173990.2:c.218G>T	chr11:g.61161437G>T	27.1	0.823	3.12	0
UW251-3	*TMEM216*	p.Arg85*	NM_001173990.2:c.253C>T	chr11:g.61165269C>T	12.99	NA	2.71	0.0243	p.Arg73Leu	NM_001173990.2:c.218G>T	chr11:g.61161437G>T	27.1	0.823	3.12	0
UW098-3	*TMEM237*	p.Gln26*	NM_001044385.2:c.76C>T	chr2:g.202504987G>A	18.43	NA	4	0	splice	NM_001044385.2:c.943+1G>T	chr2:g.202492798C>A	23	NA	4.53	0
UW005-3	*TMEM67*	splice	NM_153704.5:c.1674+3A>G	chr8:g.94805527A>G	12.86	NA	4.07	0	p.Gln376Glu	NM_153704.5:c.1126C>G	chr8:g.94794683C>G	24.4	0.23	5.01	0
UW030-3	*TMEM67*	p.Phe637Leu	NM_153704.5:c.1911C>A	chr8:g.94809412C>A	26.9	1	2.44	0	p.Pro358Leu	NM_153704.5:c.1073C>T	chr8:g.94794630C>T	31	0.993	5.17	0
UW051-3	*TMEM67*	p.Leu349Ser	NM_153704.5:c.1046T>C	chr8:g.94793953T>C	29.8	0.9	5.73	0	p.Ile833Thr	NM_153704.5:c.2498T>C	chr8:g.94821126T>C	28	0.871	5.71	0.0116
UW053-3	*TMEM67*	splice	NM_153704.5:c.1961-2A>C	chr8:g.94809557A>C	22.8	NA	4.41	0	p.Phe590Ser	NM_153704.5:c.1769T>C	chr8:g.94807731T>C	16.45	0.996	5.56	0
UW053-4	*TMEM67*	splice	NM_153704.5:c.1961-2A>C	chr8:g.94809557A>C	22.8	NA	4.41	0	p.Phe590Ser	NM_153704.5:c.1769T>C	chr8:g.94807731T>C	16.45	0.996	5.56	0
UW054-3	*TMEM67*	p.Pro130Arg	NM_153704.5:c.389C>G	chr8:g.94770787C>G	24.4	0.732	5.82	0	p.Trp225*	NM_153704.5:c.675G>A	chr8:g.94784840G>A	39	NA	5.67	0
UW055-3	*TMEM67*	p.Ile833Thr	NM_153704.5:c.2498T>C	chr8:g.94821126T>C	28	0.871	5.71	0.116	splice	NM_153704.5:c.2556+1G>T	chr8:g.94821185G>T	24.6	NA	5.71	0
UW055-4	*TMEM67*	p.Ile833Thr	NM_153704.5:c.2498T>C	chr8:g.94821126T>C	28	0.871	5.71	0.116	splice	NM_153704.5:c.2556+1G>T	chr8:g.94821185G>T	24.6	NA	5.71	0
UW056-3	*TMEM67*	p.Met257Val	NM_153704.5:c.769A>G	chr8:g.94792875A>G	23.3	0.093	5.86	0	p.Arg172Gln	NM_153704.5:c.515G>A	chr8:g.94777642G>A	23.2	0.997	4.02	0
UW057-3	*TMEM67*	splice	NM_153704.5:c.978+3A>G	chr8:g.94793213A>G	10.19	NA	5.84	0	p.Phe942Cys	NM_153704.5:c.2825T>G	chr8:g.94827593T>G	26.8	0.956	3.26	0
UW060-3	*TMEM67*	p.Cys615Arg	NM_153704.5:c.1843T>C	chr8:g.94808198T>C	32	0.782	5.28	0	p.Leu349Ser	NM_153704.5:c.1046T>C	chr8:g.94793953T>C	29.8	0.9	5.73	0
UW061-3	*TMEM67*	p.Arg208*	NM_153704.5:c.622A>T	chr8:g.94777845A>T	26.3	NA	-3.99	0.0077	p.Gln841Pro	NM_153704.5:c.2522A>C	chr8:g.94821150A>C	23.3	0.331	5.71	0
UW063-3	*TMEM67*	p.Ile833Thr	NM_153704.5:c.2498T>C	chr8:g.94821126T>C	28	0.871	5.71	0.0116	p.Arg451*	NM_153704.5:c.1351C>T	chr8:g.94798513C>T	38	NA	2.77	0
UW064-3	*TMEM67*	p.Cys100*	NM_153704.5:c.300C>A	chr8:g.94768082C>A	36	NA	3.13	0	p.Ile833Thr	NM_153704.5:c.2498T>C	chr8:g.94821126T>C	28	0.871	5.71	0.0116
UW065-3	*TMEM67*	p.Pro485Ser	NM_153704.5:c.1453C>T	chr8:g.94800112C>T	27.6	0.736	4.69	0	p.Arg441Cys	NM_153704.5:c.1321C>T	chr8:g.94798483C>T	36	1	5.7	0
UW072-3	*TMEM67*	p.Cys615Arg	NM_153704.5:c.1843T>C	chr8:g.94808198T>C	32	0.782	5.28	0	p.Met252Thr	NM_153704.5:c.755T>C	chr8:g.94792861T>C	23.6	0.384	5.86	0
UW073-3	*TMEM67*	p.Cys615Arg	NM_153704.5:c.1843T>C	chr8:g.94808198T>C	32	0.782	5.28	0	p.Tyr513Cys	NM_153704.5:c.1538A>G	chr8:g.94803510A>G	13.7	0.999	5.43	0
UW083-3	*TMEM67*	p.Tyr513Cys	NM_153704.5:c.1538A>G	chr8:g.94803510A>G	24.9	0.999	5.43	0	p.Ile833Thr	NM_153704.5:c.2498T>C	chr8:g.94821126T>C	28	0.871	5.71	0.0116
UW083-4	*TMEM67*	p.Tyr513Cys	NM_153704.5:c.1538A>G	chr8:g.94803510A>G	13.7	0.999	5.43	0	p.Ile833Thr	NM_153704.5:c.2498T>C	chr8:g.94821126T>C	28	0.871	5.71	0.0116
UW084-3	*TMEM67*	p.Asn242Ser	NM_153704.5:c.725A>G	chr8:g.94792831A>G	25.9	0.952	5.84	0	p.Asn242Ser	NM_153704.5:c.725A>G	chr8:g.94792831A>G	25.9	0.952	5.84	0
UW085-1	*TMEM67*	p.Pro82Arg	NM_153704.5:c.245C>G	chr8:g.94768027C>G	20.9	0.028	5.02	0	p.Met252Thr	NM_153704.5:c.755T>C	chr8:g.94792861T>C	23.6	0.384	5.86	0
UW085-2	*TMEM67*	p.Pro82Arg	NM_153704.5:c.245C>G	chr8:g.94768027C>G	18.42	0.028	5.02	0	p.Met252Thr	NM_153704.5:c.755T>C	chr8:g.94792861T>C	23.6	0.384	5.86	0
UW085-3	*TMEM67*	p.Pro82Arg	NM_153704.5:c.245C>G	chr8:g.94768027C>G	18.42	0.028	5.02	0	p.Met252Thr	NM_153704.5:c.755T>C	chr8:g.94792861T>C	19.81	0.384	5.86	0
UW086-3	*TMEM67*	p.Pro82Ser	NM_153704.5:c.244C>T	chr8:g.94768026C>T	22.1	0.034	5.91	0	p.Gly195Ilefs*13	NM_153704.5:c.579_580delAG	chr8:g.94777802_94777803delA	30	NA	5.53	0
UW285-3	*TMEM67*	p.Thr244Ala	NM_153704.5:c.730A>G	chr8:g.94792836A>G	27.1	0.955	5.84	0	p.Thr244Ala	NM_153704.5:c.730A>G	chr8:g.94792836A>G	27.1	0.955	5.84	0
UW298-3	*TMEM67*	p.Arg764*	NM_153704.5:c.2290C>T	chr8:g.94815880C>T	17.83	NA	4.99	0	p.Thr372Lys	NM_153704.5:c.1115C>A	chr8:g.94794672C>A	33	0.997	5.17	0
UW310-3	*TMEM67*	p.His790Asn	NM_153704.5:c.2368C>A	chr8:g.94817035C>A	28.4	0.997	5.86	0	p.Gly934Glu	NM_153704.5:c.2801G>A	chr8:g.94827569G>A	27	1	5.76	0
UW313-3	*TMEM67*	p.Arg208*	NM_153704.5:c.622A>T	chr8:g.94777845A>T		NA	-3.99	0.0077	p.Tyr513Cys	NM_153704.5:c.1538A>G	chr8:g.94803510A>G	13.7	0.999	5.43	0

"maximum MAF" is based on the Exome Variant Server data (http://evs.gs.washington.edu/EVS/) and indicates the highest minor allele frequency in European or African American samples

LIKELY CAUSAL RDVs requiring functional validation

UW ID	Gene	mutation1	cDNA1	genomic1	CADD	Polyphen2	GERP	maximum MAF	mutation2	cDNA2	genomic2	CADD	Polyphen2	GERP	maximum MAF
UW201-3	*AHI1*	splice	NM_001134831.1:c.1626+4_1626+5insTTAC	chr6:g.135769423_135769424insGTAA	19.22	NA	5.86	0	splice	NM_001134831.1:c.1626+4_1626+5ins	chr6:g.135769423_135769424in	19.22	NA	5.86	0
UW317-3	*C5orf42*	p.Arg2660*	NM_023073.3:c.7978C>T	chr5:g.37154075G>A	37	NA	5.21	0.0116	p.Leu1276Leu (coding-synonym	NM_023073.3:c.3828T>C	chr5:g.37187928A>G	12.48	NA	-3.72	0.1279
UW082-3	*CC2D2A*	p.Ser1615Leufs*16	NM_001080522.2:c.4843_4846delTCTC	chr4:g.15603028_15603031delTCTC	22.4	NA	5.69	0.0176	intron	NM_001080522.2:c.3976-3C>A	chr4:g.15587777C>A	16.6	NA	2.97	0
UW249-3	*CC2D2A*	intron	NM_001080522.2:c.3975+4_3975+7delAGTA	chr4:g.15581798_15581801delAGTA	26.5	NA	5.35	0	p.Asp1556Val	NM_001080522.2:c.4667A>T	chr4:g.15601322A>T	22.1	0.982	5.75	0.0266

UW320-3	*CC2D2A*	p.Arg520*	NM_001080522.2:c.1558C>T	chr4:g.15534907C>T	39	NA	4.53	0	intron	NM_001080522.2:c.3594+5G>A	chr4:g.15572124G>A	12.88	NA	5.39	0
UW136-3	*CEP290*	p.Tyr2024*	NM_025114.3:c.6072C>A	chr12:g.88462362G>T	39	NA	-0.582	0	p.Asn781Asn (coding-synonymo	NM_025114.3:c.2343T>C	chr12:g.88505003A>G	16.11	NA	5.86	0
UW136-4a	*CEP290*	p.Tyr2024*	NM_025114.3:c.6072C>A	chr12:g.88462362G>T	39	NA	-0.582	0	p.Asn781Asn (coding-synonymo	NM_025114.3:c.2343T>C	chr12:g.88505003A>G	16.11	NA	5.86	0
UW318-3	*MKS1*	p.Arg165Cys	NM_017777.3:c.493C>T	chr17:g.56292124G>A	23.1	0.975	5.74	0	p.Arg463Arg (coding-synonymou	NM_017777.3:c.1389G>T	chr17:g.56284464C>A	21.8	NA	2.89	0
UW058-3	*TMEM67*	intron	NM_153704.5:c.2322+2dup	chr8:g.94815914dupT	15.41	NA	5.91	0.0227	p.Lys99Asn	NM_153704.5:c.297G>T	chr8:g.94768079G>T	24.2	0.602	4.91	0
UW059-3	*TMEM67*	p.Glu361*	NM_153704.5:c.1081G>T	chr8:g.94794638G>T	37	NA	4.29	0	intron	NM_153704.5:c.2661+5G>A	chr8:g.94821394G>A	17.41	NA	5.71	0
UW062-3	*TMEM67*	intron	NM_153704.5:c.2322+2dup	chr8:g.94815914dupT	15.41	NA	5.91	0.0227	p.Thr372Lys	NM_153704.5:c.1115C>A	chr8:g.94794672C>A	33	0.997	5.17	0
UW069-3	*TMEM67*	p.Leu696Phe	NM_153704.5:c.2086C>T	chr8:g.94809684C>T	28.3	0.907	3.79	0	intron	NM_153704.5:c.2322+5delG	chr8:g.94815917delG	17.32	NA	5.91	0
UW319-3	*TMEM216*	p.Ile72Ile (coding-syn	NM_001173990.2:c.216T>C	chr11:g.61161435T>C	11.68	NA	-2.27	0	p.Ile72Ile (coding-synonymous)	NM_001173990.2:c.216T>C	chr11:g.61161435T>C	11.68	NA	-2.27	0

Control samples with two RDVs (or homozygous or hemizygous RDVs)

CONTROLS	Gene	mutation 1	cDNA 1	genomic 1	CADD	Polyphen 2	GERP	maximum MAF	mutation 2	cDNA 2	genomic	CADD	P2	GERP	maximum MAF
ND11622	*TMEM67*	p.Cys615Arg	NM_153704.5:c.1843T>C	chr8:g.94808198T>C	22.4	0.782	5.28	0	p.Gly791Ser	NM_153704.5:c.2371G>A	chr8:g.94817038G>A	35	0.998	5.86	0
ND13333	*TCTN1*	p.Phe266Cys	NM_001082538.2:c.797T>G	chr12:g.111072559T>G	15.21	0.82	0.416	0	Val347Ile	NM_001082538.2:c.1039G>A	chr12:g.111078889G>A	20.4	0.103	3.98	0
ND10891	*OFD1*	splice	NM_003611.2:c.936-2A>G	chrX:g.13769366A>G	22.2	NA	5.76	0.0149	splice	NM_003611.2:c.936-2A>G	chrX:g.13769366A>G	22.2	NA	5.76	0.0149
ND05706	*KIF7*	p.Arg859Trp	NM_198525.2:c.2575C>T	chr15:g.90176934G>A	17.55	0.994	2.98	0.0077	p.Arg859Trp	NM_198525.2:c.2575C>T	chr15:g.90176934G>A	17.55	0.994	2.98	0.0077
ND09659	*KIF7*	p.Gln994Arg	NM_198525.2:c.2981A>G	chr15:g.90174856T>C	17.06	0.497	5.18	0.1164	p.Leu956Pro	NM_198525.2:c.2867T>C	chr15:g.90176079A>G	17.44	0.994	5.22	0

Table S6. Individuals with two possible causes of JS. Variants in bold are more likely to be the cause.

UW ID	Gene	mutation1	cDNA1	genomic1	CADD	Polyphen2	GERP	maximum MAF	mutation2	cDNA2	genomic2	CADD	Polyphen2	GERP	maximum MAF
UW040-5	***TMEM216***	**p.Arg73Leu**	**NM_001173990.2:c.218G>T**	**chr11:g.61161437G>T**	**18.61**	**0.823**	**3.12**	**0**	**p.Arg73Leu**	**NM_001173990.2:c.218G>T**	**chr11:g.61161437G>T**	**18.61**	**0.823**	**3.12**	**0**
	CSPP1	p.Glu980Lys	NM_024790.6:c.2938G>A	chr8:g.68084775G>A	15.55	0.689	3.59	0	p.Pro1160Ser	NM_024790.6:c.3478C>T	chr8:g.68107640C>T	15.34	0.26	4.62	0.118
UW236-3	*C5ORF42*	p.Ala1200Val	NM_023073.3:c.3599C>T	chr5:g.37198877G>A	29.6	0.997	5.28	0.0116	p.Ala1200Val	NM_023073.3:c.3599C>T	chr5:g.37198877G>A	29.6	0.997	5.28	0.0116
	CC2D2A	p.Pro721Ser	NM_001080522.2:c.2161C>T	chr4:g.15542617C>T	29.7	1	4.94	0.0505	p.Pro721Ser	NM_001080522.2:c.2161C>T	chr4:g.15542617C>T	29.7	1	4.94	0.0505
UW278-3	***C5ORF42***	**p.Gly2663Alafs*40**	**NM_023073.3:c.7988_7989delGA**	**chr5:g.37154064_37154065delTC**	**24.1**	**NA**	**-0.221**	**0**	**p.Gly2663Alafs*40**	**NM_023073.3:c.7988_7989delGA**	**chr5:g.37154064_37154065delTC**	**24.1**	**NA**	**-0.221**	**0**
	CSPP1	p.Arg658Gly	NM_024790.6:c.1972A>G	chr8:g.68062029A>G	23.6	0.262	5.96	0.027	p.Arg658Gly	NM_024790.6:c.1972A>G	chr8:g.68062029A>G	23.6	0.262	5.96	0.027
	CSPP1	p.Ser1087Leu	NM_024790.6:c.3260C>T	chr8:g.68102939C>T	14.42	0.082	4.32	0	p.Ser1087Leu	NM_024790.6:c.3260C>T	chr8:g.68102939C>T	14.42	0.082	4.32	0
UW279-3	*C5ORF42*	p.Tyr607Thrfs*6	NM_023073.3:c.1819delT	chr5:g.37226878delA	25.8	NA	5.26	0	p.Glu142Lys	NM_023073.3:c.424G>A	chr5:g.37244623C>T	22.9	0.998	5.69	0
	OFD1	p.Lys432Glu	NM_003611.2:c.1294A>G	chrX:g.13774769A>G	18.94	0.052	3.74	0.0892	p.Lys432Glu	NM_003611.2:c.1294A>G	chrX:g.13774769A>G	18.94	0.052	3.74	0.0892
UW293-3	***C2CD3***	**p.Arg62***	**NM_001286577.1:c.184C>T**	**chr11:g.73879530G>A**	**22.1**	**NA**	**5.57**	**0**	**p.Arg62***	**NM_001286577.1:c.184C>T**	**chr11:g.73879530G>A**	**22.1**	**NA**	**5.57**	**0**
	CEP290	p.Ile364Met	NM_025114.3:c.1092T>G	chr12:g.88519120A>C	25.4	0.997	4.62	0.118	p.Asp321Glu	NM_025114.3:c.1092T>G	chr12:g.88519120A>C	26.9	0.999	5.26	0
	TTC21B	p.Asp806His	NM_024753.4:c.2416G>C	chr2:g.166767882C>G	17.99	0.894	5.69	0	p.Leu433Leu (coding-synonymous)	NM_024753.4:c.1299G>A	chr2:g.166785732C>T	18.48	NA	1.12	0

Supplementary Table S7: Detailed phenotypic description for individuals with *B9D2* mutations

ID	Mutations	MTS	retina	kidney	liver	Coloboma	Encephalocele	PD	Other
UW284-3	p.Gly155Ser (mat) p.Pro74Ser (pat)	+	NA	-	NA	-	+ (foramen magnum encephalocele)	+	**Oral features**: Cleft palate, tongue tumors, **Skeletal features**: tibial and fibular mesomelic dysplasia, **Neurological features**: shunted hydrocephalus, seizures, interpeduncular heterotopia **Dysmorphic features**: small palpebral fissures **Visual features**: poor pupillary response to light, optic disks normal **Other**: micropenis, hearing loss, patent ductus arteriosus
UW309-3	p.Leu36Pro hmz	+	NA	-	-	-	-	+	**Neurological features**: seizures and abnormal EEG **Dysmorphic features**: frontal bossing, epicanthus, dysplastic ears, down turned corners of mouth, retrognathia, ptosis, right eye exotropia **Other**: Hypospadias

MTS Molar Tooth Sign*, PD* polydactyly, *NA* not available, *EEG* Electro-encephalogram, *mat* maternal, *pat* paternal, *hmz* homozygous

Supplementary Table S8: Recurrent alleles

Gene	allele	n unrelated* families	Reported country of origin or ethnicity (*n families*)
AHI1	**Q423X**	**3**	Armenian (1), Australian (1), Native American/mixed European (EU) (1)
C5ORF42	**p.Gly2663Alafs*40**	**4**	**Saudi Arabian (4)**
C5ORF42	**L595X**	**3**	mixed EU (3)
C5ORF42	**p.Thr2755Asnfs*8**	**3**	mixed EU (2), mixed EU /Native American (1)
C5ORF42	**R2493X**	**3**	Native American/ mixed EU (1), French Canadian (1), Native American/ mixed EU (1)
C5ORF42	**R2904X**	**4**	mixed EU/Canadian (1), mixed EU (2), African American/Korean/mixed EU (1)
C5ORF42	**W2593X**	**3**	Saudi Arabian (2), India (1)
CC2D2A	**D1556V**	**7**	Mixed EU (5), Australian (1), Native American/ mixed EU /Filipino (1)
CC2D2A	**P1122S**	**3**	Saudi Arabian (3)
CC2D2A	**R1528C**	**4**	Turkish (1), mixed EU (2), Trinidadian/ mixed EU (1)
CC2D2A	**T1116M**	**3**	Brazilian (1), mixed EU (2)
CC2D2A	**Val1097Phefs*2**	**4**	mixed EU (4)
CEP290	**G1890X**	**10**	India (3), mixed EU (3), Saudi Arabian (1), Iraqi (1), Canadian/ mixed EU (1), mixed EU /Indian (1)
CEP290	**K1575X**	**3**	mixed EU /Thai (1), mixed EU (2)
CSPP1	**NM_024790.6:c.2953+1G>A**	**3**	Brazilian (3)
CSPP1	**p.Tyr1071***	**3**	Brazilian (3)
NPHP1	**deletion**	**5**	Turkish (1), Native American/ mixed EU /French Canadian (1), Peruvian/ mixed EU (1), mixed EU (2)
TMEM216	**R73L**	**10**	**Ashkenazi (10)**
TMEM67	**I833T**	**5**	mixed EU (4), Japanese/mixed EU (1)

* not reported to be related; alleles previously described in specific ethnic groups are highlighted. The number in parenthesis indicates the number of families for each country of origin or ethnicity.

Supplementary Table S9. Gene-Phenotype Correlations in a large JS cohort

	Retina	Kidney	Liver	Polydactyly	Coloboma	Encephalocele
AHI1	**2.3** (1.1-5.2) p=0.03	**0.9** (0.4-2.4) p=0.90	p=0.15	p=0.06	p=0.02	p=0.24
C5ORF42	**0.4** (0.1-1.1) p=0.08	**0.4** (0.12-1.1) p=0.06	**0.4** (0.1-1.7) p=0.28	**2.7** (1.2-5.9) p=0.01	**0.15** (0.02-1.1) p=0.04	**1.2** (0.3-4.2) p=0.73
CC2D2A	**0.5** (0.3-2.0) p=0.52	**0.4** (0.1-1.2) p=0.13	**0.4** (0.1-1.9) p=0.40	p=0.01	**0.2** (0.02-1.4) p=0.1	**0.9** (0.2-3.9) p=1.0
CEP290	**22.9** (6.7-78.4) p<0.0001	**3.3** (1.6-7.1) P=0.001	0.2 (0.03-1.9) p=0.23	0.3 (0.04-2.0) p=0.22	0.2 (0.02-1.5) p=0.1	**3.5** (1.2-10.2) p=0.01
CSPP1	**0.6** (0.1-2.7) p=0.73	p=0.03	**1.0** (0.2-4.8) p=1.0	p=0.23	p=0.22	**1.1** (0.1-9.0) p=1.0
INPP5E	**1.6** (0.4-5.7) p=0.50	**1.1** (0.3-4.3) p=1.0	**0.8** (0.1-6.3) p=1.0	p=0.6	p=0.61	p=1.0
MKS1	**3.6** (0.6-21.7) p=0.16	**0.5** (0.06-4.2) p=0.7	**2.6** (0.5-13.6) p=0.25	**1.5** (0.2-13.5) p=0.54	p=0.59	p=1.0
NPHP1	p=0.56	3.0 (0.4-21.) p=0.26	p=1.0	p=1.0	p=1.0	p=1.0
OFD1	p=1.0	**1.5** (0.1-16.7) p=1.0	**2.1** (0.2-20.6) p=0.45	**6.1** (0.8-44.2) p=0.10	p=1.0	**13.1** (1.8-97.0) p=0.03
RPGRIP1L	**0.7** (0.1-3.2) p=0.38	**4.7** (1.3-17.0) p=0.02	**1.3** (0.1-11.0) p=0.59	**4.2** (1.1-15.3) p=0.04	p=1.0	**1.4** (0.2-11.3) p=0.55
TCTN2	**1.2** (0.1-13.0) p=1.0	p=0.58	p=1.0	**18.7** (1.9-182.9) p=0.01	**10.1** (0.9-113.5) p=0.08	**13.6** (2.6-70.8) p=0.007
TMEM216	p=0.06	**2.2** (0.7-7.1) p=0.18	**0.6** (0.1-4.4) p=1.0	3.1 (0.9-10.7) p=0.08	p=1.0	p=0.61
TMEM67	**0.1** (0.01-0.8) p=0.006	**2.0** (0.9-4.5) p=0.07	**17.3** (7.2-42.0) p<0.0001	P=0.05	**22.9** (8.6-61.1) p<0.0001	**2.3** (0.6-8.4) p=0.18

Odds ratios are indicated in **bold** followed by the 95% Confidence Interval in brackets. Statistical significance (Fisher's exact test if <5 observations are present in one category or Chi-Square test in all other situations) is indicated below with the respective p-value. Cells with significant positive correlations are shaded in yellow, and those remaining significant after Bonferroni correction are shaded in green. Cells shaded in orange indicate negative correlations. In cells without odds ratios, no individuals with the relevant clinical feature were observed to have that genetic cause. In those cells, the p-value indicates the likelihood that there is a correlation even in the absence of an individual with the feature and the genetic cause.