Title: Joubert Syndrome *GeneReview* — Molecular Genetics – Less Common Genetic Causes
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Joubert Syndrome: Less Common Genetic Causes

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OFD1 (CXORF5)

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ARL13B

Gene structure. *ARL13B* is a ten-exon gene that encodes a 428-amino acid protein.

Pathogenic variants. Two families with a phenotype typical of classic Joubert syndrome had missense and/or nonsense variants in this gene; one of these individuals also had evidence of a retinopathy [Cantagrel et al 2008].

Normal gene product. *ARL13B* encodes ADP-ribosylation factor-like protein 13B, a member of the ADP-ribosylation factor-like family. Multiple transcript variants result from alternate splicing; two protein isoforms are known. The AR13B protein is a small GTPase in the Ras superfamily that contains both N-terminal and C-terminal guanine nucleotide-binding motifs. It is localized to the cilia and plays a role in cilia formation and maintenance as well as sonic hedgehog signaling.

Abnormal gene product. In *C elegans*, pathogenic variants in the homolog *arl13* exhibit defective cilium morphology, localization, and anterograde intraflagellar transport [Cevik et al 2010]. Mice with defects in the murine ortholog have neural tube defects and polydactyly, as well as an embryonic-lethal phenotype [Cantagrel et al 2008, Doherty 2009].

B9D1. See Tables A and B.

B9D2. See Tables A and B.

CEP41

Gene structure. The gene consists of 11 exons and spans approximately 50 kb. There are two different isoforms that are alternatively spliced.

Pathogenic variants. All individuals with JS and pathogenic variants in *CEP41* had homozygous splice-site variants. Heterozygous *CEP41* variants have been identified in five additional individuals with Joubert syndrome, three of whom had heterozygous potentially deleterious variants in other ciliopathy genes (*KIF7* and *CC2D2A*). Heterozygous changes in this gene have also been described in individuals with Bardet-Biedl syndrome and Meckel syndrome, supporting a role for *CEP41* in digenic inheritance and suggesting that CEP41 may act as a modifier for other ciliopathies. [Lee et al 2012a].

Normal gene product. *CEP41* encodes two proteins of 373 and 54 amino acids, respectively; the longer transcript encodes a 41-kd protein with two coiled-coil domains and a rhodanese-like domain. It localizes to the centrioles and cilia in several different cell lines and appears to regulate tubulin glutamylation by facilitating transport of a glutamylation enzyme [Lee et al 2012a].

Abnormal gene product. Zebrafish embryos injected with morphant *Cep41* demonstrate peripheral heart edema, tail defects, and other phenotypes associated with ciliary genes in the knockdown animals. However, the broad range of phenotypes in knockout mice included exencephaly, dilated pericardial sac, and lethality to normal. Further experiments demonstrated that CEP41 morphants had specific ultrastructural tubulin defects and were deficient in glutamylation of tubulin, the component of microtubules that forms the structural axoneme of the cilia [Lee et al 2012a].

IFT172. See Tables A and B.

KIF7

Gene structure. *KIF7* (the vertebrate homolog of the *Drosphila* costa [costal-2] gene) comprises 19 exons and encodes a 1343-amino acid protein.

Pathogenic variants. The pathogenic variants that cause hydrolethalus syndrome, acrocallosal syndrome, and JSRD are typically nonsense variantss or frameshift variants leading to nonsense-mediated decay or premature stop codons and are distributed across the gene [Dafinger et al 2011, Putoux et al 2011]. In addition,

heterozygous *KIF7* pathogenic variants were identified in nine persons with other ciliopathies, including Bardet-Biedl syndrome, Meckel syndrome, Pallister-Hall syndrome, OFD VI, and JSRD; four of these individuals had two pathogenic variants in other genes associated with BBS and one with JSRD had two *MKS3* pathogenic variants [Dafinger et al 2011, Putoux et al 2011]. Based on rescue studies in morphant zebrafish embryos, it is likely that the *KIF7* pathogenic variants exacerbate the phenotype of other ciliopathies, especially BBS [Putoux et al 2011].

Normal gene product. *KIF7* encodes a member of the kinesin family, a putative ciliary motor protein that regulates Hedgehog signaling. The KIF7 protein has a kinesin motor domain, a Gli-binding domain, and a coiled-coil domain. KIF7 has been noted to co-precipitate with Nephrocystin-1 [Dafinger et al 2011] and to form a complex with Gli proteins both at the cilium base and, when bound by ligand, at the cilium tip [Putoux et al 2011].

Abnormal gene product. Discruption of KIF7 expression in cell lines causes defects in cilia formation, abnormal centrosomal duplication, and Golgi fragmentation, suggesting that microtubule stability and growth are impaired [Dafinger et al 2011]. Loss of Kif7 in mice causes polydactyly, skeletal defects, exencephaly and early lethality in mice [Liem et al 2009]. Absent KIF7 expression also causes upregulation of GLI transcription factor targes, consistent with a role in Hedgehog signaling [Putoux et al 2011].

OFD1 (*CXORF5*)

Gene structure. This gene escapes X-chromosome inactivation, comprises 23 exons, and encodes a 1012-amino acid protein that interacts with lebercilin (encoded by *LCA5*). There are two alternative splice variants: CXORF5-2 differs from CXORF5-1 by an insertion of 663 bp resulting from the use of an alternative 3-prime splice site in intron 9. CXORF5-1 encodes a deduced 1,011-amino acid protein containing a large number of predicted coiled-coil alpha-helical domains. CXORF5-2 encodes a deduced protein of 367 amino acids; the first 353 residues of CXORF5-2 and CXORF5-1 are identical.

Pathogenic variants. Two families with X-linked recessive inheritance have frameshift variants in exon 21, c.2844_2850delAGACAAA and c.2767delG, which diminishes the amount of full-length mRNA produced, with resultant effects on protein function [Coene et al 2009]. A third family has an 18-bp deletion in exon 8, resulting in an in-frame deletion of six amino acids [Field et al 2012].

Table 9. *OFD1* Pathogenic Variants Discussed in This *GeneReview*

DNA Nucleotide Change	Predicted Protein Change	Reference Sequences
c.689_706del18	p.Ile230_Lys235del	NM_003611.2 NP_003602.1
c.2767delG	p.Glu923LysfsTer3	
c.2844_2850delAGACAAA	p.Lys948AsnfsTer8	

See Quick Reference for an explanation of nomenclature. GeneReviews follows the standard naming conventions of the Human Genome Variation Society (www.hgvs.org).

Normal gene product. The coiled-coil regions of oral-facial-digital syndrome 1 protein are predicted to interact with the first two coiled-coil domains of lebercilin. Both proteins localize to the pericentriolar region in human and rat retinal cell lines.

Pathogenic variants in *OFD1* cause X-linked dominant oral-facial-digital syndrome type I, but the few *OFD1* pathogenic variants in males with JS are predicted to have a less severe effect on the function of the protein than the pathogenic variants observed in OFD I [Coene et al 2009, Field et al 2012].

Abnormal gene product. Pathogenic variants in *CXORF5* have been found to weaken the interaction with lebercilin to varying degrees, with recessive pathogenic variants having some residual binding activity, versus dominant ones that abolish binding and cause X-linked oral-facial-digital syndrome type 1 (lethal in males). In addition, the pericentriolar localization of the protein is abolished in females with oral-facial-digital syndrome type 1.

PDE6D. See Tables A and B.

POC1B. See Tables A and B.

TCTN1

Gene structure. *TCTN1* (tectonic family member 1) is a member of the tectonic family of membrane and secreted proteins. It has at least five splice isoforms, comprises 13 exons, and encodes a 593-amino acid protein [Reiter & Skarnes 2006].

Pathogenic variants. A homozygous pathogenic variant in the obligatory splice acceptor consensus sequence of intron 1 (c.221-2A>G) of *TCTN1* was identified in two affected children in a family from Bangladesh but not in 48 other families with JSRD or in four families that mapped to the region [Garcia-Gonzalo et al 2011].

Table 10. *TCTN1* Pathogenic Variants Discussed in This *GeneReview*

DNA Nucleotide Change	Predicted Protein Change	Reference Sequences
c.221-2A>G	-	NM_001082538.2 NP_001076007.1

See Quick Reference for an explanation of nomenclature. GeneReviews follows the standard naming conventions of the Human Genome Variation Society (www.hgvs.org).

Normal gene product. Tectonic-1 is a signal-sequence-containing protein that localizes to the membrane-spanning transition zone complex, a region between the basal body and ciliary axoneme that regulates ciliogenesis. In mice, Tctn1 is required for ciliogenesis in a tissue-dependent manner and forms a complex with other JSRD- and Meckel-associated proteins, such as Mks1, Tmem216,Tmem67, Cep290 Tctn2, and Cc2d2a [Reiter & Skarnes 2006, Garcia-Gonzalo et al 2011].

Abnormal gene product. TCTN1 regulates Hedgehog signaling, required for both activation and inhibition of ventral patterning of the neural tube. *Tctn1* homozygous null

mice die during embryogenesis with holoprosencephaly and expansion of dorsal gene expression [Reiter & Skarnes 2006].

TCTN3

Gene structure. *TCTN3* (tectonic family member 3) has 14 coding exons, at least two alternatively spliced forms, and is a member of the tectonic gene family that includes *TCTN1* and *TCTN2* [Thomas et al 2012].

Pathogenic variants. Homozygous truncating variants in this gene have been identified with a severe OFD IV phenotype characterized by long bones bowing, tibial hypoplasia, polydactyly, cystic kidneys, oralfacial anomalies, and encephalocele. Less severe missense variants have been identified in a form of JSRD characterized by digital and axial skeletal anomalies including scoliosis [Thomas et al 2012].

Normal gene product. *TCTN3* encodes a 607-amino acid protein with a transmembrane domain. Although TCTN3 is not critical for cilia biogenesis in the kidney, it encodes a protein that is necessary for GLI3 processing and functioning in the sonic hedgehog pathway and is part of the B9 transition zone complex at the cilium/plasma membrane border [Thomas et al 2012].

Abnormal gene product. Fibroblasts from patients with pathogenic variants in *TCTN3* fail to respond to sonic sedgehog agonists, suggesting a defect in sonic hedgehog signaling [Thomas et al 2012].

TMEM138

Gene structure. The gene contains five exons, the first of which is non-coding. The 23-kb intergenic region between *TMEM138* and *TMEM216* appears to coordinate the expression of these two ciliary genes, both of which can cause JSRD [Lee et al 2012b].

Pathogenic variants. Pathogenic variants in *TMEM138* were identified when pathogenic variants in *TMEM216* were absent in about half of the families linked to 11q12.2; a search for other causative genes identified *TMEM138*, adjacent to *TMEM216* in a head-to-tail configuration. Four missense variants in conserved residues and one splice-site variant have been identified in affected individuals with JSRD [Lee et al 2012b].

Normal gene product. The normal gene product (NP_057548.1) comprises 162 amino acids and has an N-terminal signal sequence followed by 3 transmembrane domains. TMEM138 and TMEM216 are required for ciliogenesis, and each localizes to a distinct vesicle pool that carries proteins necessary for ciliary assembly from the Golgi to the primary cilia; one of the proteins that colocalizes with TMEM138 is CEP290 [Lee et al 2012b].

Abnormal gene product. Fibroblasts from individuals with the mutant protein display shortened cilia. Zebrafish with morpholino knockdown of TMEM138 have the ciliary phenotypes of pericardial effusion, kinked tail, and gastrulation defects [Lee et al 2012b].

TMEM231

Gene structure. There are multiple *TMEM231* transcript variants, with at least six exons each [Srour et al 2012].

Pathogenic variants. The two pathogenic variants identified thus far disrupt the translation start site of one isoform or predict a nonsense change or missense change predicted to be damaging. These pathogenic variants are very rare, even in the French-Canadian population [Srour et al 2012, Srour et al 2015]. A complex gene conversion event involving an adjacent pseudogene proved to be pathogenic in one reported family [Maglic et al 2016].

Normal gene product. There are at least three isoforms encoded by *TMEM231* with one or two transmembrane domains [Srour et al 2012]. TMEM231 is a transmembrane protein localized to the base of the ciliary axoneme where it is part of the B9 complex that forms a barrier between the cilium and plasma membrane; almost all of the proteins that form this complex cause JSRD and/or MKS when altered [Chih et al 2011].

Abnormal gene product. Knockdown of TMEM231 disrupts the ciliary barrier and the localization of B9 complex components to the transition zone, with reduction in formation of cilia. The *Tmem231* knockout mice die during embryonic development with many features characteristic of ciliopathies, including vascular defects, polydactyly, and eye abnormalities [Chih et al 2011].

TMEM237 (*ALS2CR4*)

Gene structure. *TMEM237* is a 14-exon gene encoding two alternatively spliced transcripts, the largest of which encodes a 408-amino acid protein [Huang et al 2011].

Pathogenic variants. Pathogenic variants in individuals with JS include nonsense, frameshift, large insertions, and splice-site variants. The Hutterite variant, p.Arg18Ter, is estimated to have a carrier frequency of 6% in this population [Huang et al 2011].

Table 11. *TMEM237* Pathogenic Variants Discussed in This *GeneReview*

DNA Nucleotide Change	Predicted Protein Change	Reference Sequences
c.52C>T	p.Arg18Ter	NM_001044385.2 NP_001037850.1

See Quick Reference for an explanation of nomenclature. GeneReviews follows the standard naming conventions of the Human Genome Variation Society (www.hgvs.org).

Normal gene product. Transmembrane protein 237 contains four transmembrane domains and has both N- and C-termini directed to the cytoplasm. In mouse kidney cells, it localizes to the transition zone at the proximal region of primary cilia, and in mouse photoreceptor cells, it localizes to the connecting cilium and outer segments [Huang et al 2011].

Abnormal gene product. Loss of TMEM237 in mammalian cells causes defects in ciliogenesis and Wnt signaling. In zebrafish, disruption of tmem237 expression results in defects in gastrulation. TMEM237 appears to functionally interact with NPHP4,

RPGRIP1L, TMEM216, and other proteins implicated in the ciliary transition zone [Huang et al 2011].

TTC21B

Gene structure. The gene has 29 coding exons, encodes a presumed 1,316-amino acid protein of approximately 150 kd, and is predicted to contain 11 tetratricopeptide repeat (TPR) domains [Davis et al 2011].

Pathogenic variants. Homozygous or compound heterozygous pathogenic variants in this gene have been identified in individuals with NPHP and JATD. Sequencing of a clinically diverse cohort of 753 individuals or families with ciliopathies (NPHP, BBS, MKS, JATD, JS) revealed pathogenic variants in *TTC21B* in 5%, representing a significant contribution; of these, one third had an additional mutant allele in one of 13 established ciliopathy genes in *trans*, suggesting the possibility of digenic inheritance. Within this cohort, three individuals with JS were heterozygous for a *TTC21B* mutant allele but had no other pathogenic variants identified. The p.Pro209Leu hypomorphic allele was identified in several probands with NPHP with or without extrarenal manifestations. The pathogenicity of these variants was confirmed by a variety of functional analyses [Davis et al 2011].

Table 12. *TTC21B* Pathogenic Variants Discussed in This *GeneReview*

DNA Nucleotide Change	Predicted Protein Change	Reference Sequences
c.626C>T	p.Pro209Leu	NM_024753.4 NP_079029.3

See Quick Reference for an explanation of nomenclature. GeneReviews follows the standard naming conventions of the Human Genome Variation Society (www.hgvs.org).

Normal gene product. The gene product is THM1, “tetratricopeptide repeat-contatining hedgehog modulator-1,” also known as IFT139, an axonemal protein required for retrograde intraflagellar transport [Davis et al 2011].

Abnormal gene product. Knockout of the orthologous murine gene *Ttc21b* is responsible for the 'alien' (aln) locus in mouse which shows ciliary defects and impaired retrograde intraflagellar transport [Tran et al 2008]. Functional deficits in zebrafish morphants were consistent with ciliary defects [Davis et al 2011].

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