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NLM Citation: Parisi M, Glass I. Joubert Syndrome. 2003 Jul 9 [Updated 2017 Jun 29]. In: Adam MP, Feldman J, Mirzaa GM, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2025.
Bookshelf URL: https://www.ncbi.nlm.nih.gov/books/

Joubert Syndrome

Synonyms: JBTS, Joubert Syndrome and Related Disorders (JSRD), JS

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Created: July 9, 2003; Updated: June 29, 2017.

Summary

Clinical characteristics

Classic Joubert syndrome (JS) is characterized by three primary findings:

- A distinctive cerebellar and brain stem malformation called the molar tooth sign (MTS)
- Hypotonia
- Developmental delays

Often these findings are accompanied by episodic tachypnea or apnea and/or atypical eye movements. In general, the breathing abnormalities improve with age, truncal ataxia develops over time, and acquisition of gross motor milestones is delayed. Cognitive abilities are variable, ranging from severe intellectual disability to normal. Additional findings can include retinal dystrophy, renal disease, ocular colobomas, occipital encephalocele, hepatic fibrosis, polydactyly, oral hamartomas, and endocrine abnormalities. Both intra- and interfamilial variation are seen.

Diagnosis/testing

The clinical diagnosis of JS is based on the presence of characteristic clinical features and MRI findings. To date pathogenic variants in 34 genes are known to cause JS; 33 of these are autosomal recessive and one is X-linked. A molecular diagnosis of JS can be established in about 62%-94% of individuals with a clinical diagnosis of JS by identification of biallelic pathogenic variants in one of the 33 autosomal recessive JS-related genes or a heterozygous pathogenic variant in the one X-linked JS-related gene.

Management

Treatment of manifestations: Infants and children with abnormal breathing may require stimulatory medications (e.g., caffeine); supplemental oxygen; mechanical support; or tracheostomy in rare cases. Other interventions may include speech therapy for oromotor dysfunction; occupational and physical therapy; educational support,

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including special programs for the visually impaired; and feedings by gastrostomy tube. Surgery may be required for polydactyly and symptomatic ptosis and/or strabismus. Nephronophthisis, end-stage kidney disease, liver failure and/or fibrosis are treated with standard approaches.

Surveillance: Annual evaluations of growth, vision, and liver and kidney function; periodic neuropsychologic and developmental testing.

Agents/circumstances to avoid: Nephrotoxic medications such as nonsteroidal anti-inflammatory drugs in those with renal impairment; hepatotoxic drugs in those with liver impairment.

Genetic counseling

JS is predominantly inherited in an autosomal recessive manner. JS caused by pathogenic variants in *OFD1* is inherited in an X-linked manner. Digenic inheritance has been reported.

For autosomal recessive inheritance: at conception, each sib of an affected individual has a 25% chance of being affected, a 50% chance of being an asymptomatic carrier, and a 25% chance of being unaffected and not a carrier. Once the pathogenic variants have been identified in an affected family member, carrier testing for at-risk family members, prenatal testing for pregnancies at increased risk, and preimplantation genetic testing are possible. For pregnancies known to be at increased risk for JS, prenatal diagnosis by ultrasound examination with or without fetal MRI has been successful.

Diagnosis

Diagnostic criteria for Joubert syndrome (JS) continue to evolve but most authors concur that the neuroradiologic finding of the molar tooth sign is obligatory [Valente et al 2008, Parisi 2009, Brancati et al 2010].

The diagnosis of Joubert syndrome is based on the presence of the following three primary criteria:

- **The molar tooth sign.** The MRI appearance of hypoplasia of the cerebellar vermis and accompanying brain stem abnormalities in an axial plane through the junction of the midbrain and pons (isthmus region) [Maria et al 1997, Maria et al 1999b, Quisling et al 1999]. The molar tooth sign comprises an abnormally deep interpeduncular fossa; prominent, straight, and thickened superior cerebellar peduncles; and hypoplasia of the vermis, the midline portion of the cerebellum (Figures 1A, 1B) [Maria et al 1999b]. A high-quality MRI with thin (3-mm thickness) axial cuts through the posterior fossa from the midbrain to the pons as well as standard axial, coronal, and sagittal cuts is recommended.
- **Hypotonia in infancy with later development of ataxia**
- **Developmental delays / intellectual disability**

Additional features often identified in individuals with JS:

- Abnormal breathing pattern (alternating tachypnea and/or apnea)
- Abnormal eye movements, typically oculomotor apraxia or difficulty in smooth visual pursuit and jerkiness in gaze and tracking [Saraiva & Baraitser 1992, Steinlin et al 1997, Maria et al 1999b, Tusa & Hove 1999]

Other findings that may occur in fewer than half of individuals with JS include retinal dystrophy, renal disease, ocular colobomas, occipital encephalocele, hepatic fibrosis, polydactyly, oral hamartomas, and other abnormalities. The term "classic" or "pure" JS has been used to refer to JS without any of these other findings. In reality, however, a significant proportion of individuals diagnosed with classic JS in infancy or early childhood may manifest one or more of these findings over time.

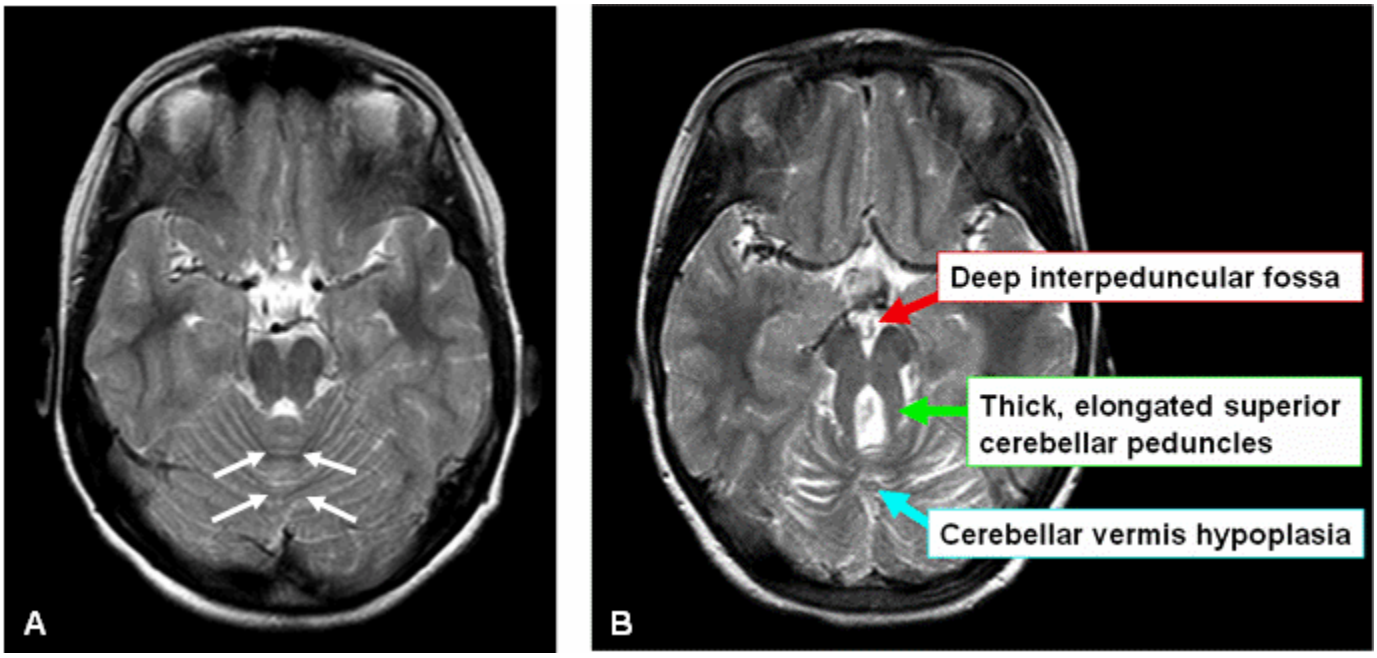

Figure 1. Molar tooth sign in Joubert syndrome

A. Axial MRI image through the cerebellum and brain stem of a normal individual showing intact cerebellar vermis (outlined by white arrows)

B. Axial MRI image through the cerebellum and brain stem of a child with Joubert syndrome. Arrows indicate the three key components of the molar tooth sign.

Establishing the Diagnosis

The clinical diagnosis of JS is based on the presence of characteristic clinical features and MRI findings. To date pathogenic variants in 34 genes are known to cause JS; 33 of these are autosomal and one is X-linked. A molecular diagnosis of JS can be established in about 62%-94% of individuals with a clinical diagnosis of JS by identification of biallelic pathogenic (or likely pathogenic) variants in one of the 33 autosomal recessive JS-related genes or a heterozygous pathogenic (or likely pathogenic) variant in the one X-linked JS-related gene [Bachmann-Gagescu et al 2015a] (see Tables 1a and 1b).

Note: (1) Per ACMG/AMP variant interpretation guidelines, the terms "pathogenic variant" and "likely pathogenic variant" are synonymous in a clinical setting, meaning that both are considered diagnostic and can be used for clinical decision making [Richards et al 2015]. Reference to "pathogenic variants" in this *GeneReview* is understood to include likely pathogenic variants. (2) The identification of variant(s) of uncertain significance cannot be used to confirm or rule out the diagnosis.

Molecular genetic testing approaches can include a combination of gene-targeted testing (**a multigene panel**) and genomic testing (**comprehensive genomic sequencing**). Gene-targeted testing requires that the clinician determine which gene(s) are likely involved, whereas genomic testing does not. Because of the extensive clinical and genetic heterogeneity in JS, Vilboux et al [2017] have suggested starting with a multigene panel, followed by exome sequencing if a molecular diagnosis has not been established.

- **A multigene panel** that includes some or all of the 34 JS-genes and other genes of interest (see Genetically Related Disorders). Note: (1) The genes included in the panel and the diagnostic sensitivity of the testing used for each gene vary by laboratory and are likely to change over time. (2) Some multigene panels may include genes not associated with the condition discussed in this *GeneReview*; thus, clinicians need to

determine which multigene panel is most likely to identify the genetic cause of the condition while limiting identification of variants of uncertain significance and pathogenic variants in genes that do not explain the underlying phenotype. (3) In some laboratories, panel options may include a custom laboratory-designed panel and/or custom phenotype-focused exome analysis that includes genes specified by the clinician. (4) Methods used in a panel may include sequence analysis, deletion/duplication analysis, and/or other non-sequencing-based tests. For this disorder testing that includes deletion/duplication analysis is recommended (see Table 1).

For an introduction to multigene panels click here. More detailed information for clinicians ordering genetic tests can be found here.

- **Comprehensive genomic testing** (when clinically available) includes exome sequencing and genome sequencing. For an introduction to comprehensive genomic testing click here. More detailed information for clinicians ordering genomic testing can be found here.

Note: While single-gene testing or serial single-gene testing is rarely useful and typically NOT recommended because of the vast clinical and genetic heterogeneity of JS, **targeted analysis** for pathogenic variants in a specific gene can be performed first in individuals of the following ethnicity/ancestry if appropriate:

- Ashkenazi Jewish: p.Arg73Leu in *TMEM216* [Edvardson et al 2010]
- Dutch: p.Arg2904Ter in *CPLANE1* [Kroes et al 2016]
- French Canadian: several variants in *CPLANE1*, *CC2D2A*, *NPHP1*, and *TMEM231* [Srour et al 2015]
- Hutterite: p.Arg18Ter in *TMEM237* [Huang et al 2011], c.363_364delTA in *CSPP1* [Shaheen et al 2014]
- Japanese: c.6012-12T>A in *CEP290* [Suzuki et al 2016]

See Table 1a for the most common genetic causes of JS (i.e., pathogenic variants of any one of the genes included in this table account for >1% of JS) and Table 1b for less common genetic causes of JS (pathogenic variants of any one of the genes included in this table are reported in only a few families).

Table 1a. Molecular Genetics of Joubert Syndrome: Most Common Genetic Causes

Gene [1, 2]	% of JS Attributed to Pathogenic Variants in Gene	Proportion of Pathogenic Variants [3] Detected by Method	
		Sequence analysis [4]	Gene-targeted deletion/ duplication analysis [5]
AHI1	~7%-10% [6, 7, 8]	>95%	See footnote 9.
CPLANE1	8%-14% [7, 8, 10]	100%	None reported
CC2D2A	~8%-11% [7, 8, 11]	Close to 100%	See footnote 12.
CEP290	7%-10% [7, 8, 13, 14]	~99%	See footnote 15.
CSPP1	2%-4% [7, 8, 16]	100%	None reported
INPP5E	2%-4% [7, 8]	100%	None reported
KIAA0586	~2%-7% [8, 17]		Two reported, one recurrent multiexon deletion [18]
MKS1	~2%-6% [7, 8, 19]	~95%	See footnote 20.
NPHP1	~1%-2% [7, 8, 21, 22]	See footnote 22.	20%-25% [22]
RPGRIP1L	1%-4% [7, 8, 23]	100%	None reported
TCTN2	~1% [7]	13/13 [24]	None reported
TMEM67	~6%-20% [7, 8, 9, 12, 25]	~99%	See footnote 26.

Table 1a. continued from previous page.

Gene [1, 2]	% of JS Attributed to Pathogenic Variants in Gene	Proportion of Pathogenic Variants [3] Detected by Method	
		Sequence analysis [4]	Gene-targeted deletion/ duplication analysis [5]
TMEM216	~2%-3% [7, 8, 27]	8/8 [26]	None reported

Pathogenic variants of any one of the genes included in this table account for >1% of JS.
1. Genes are listed alphabetically.
2. See Table A. Genes and Databases for chromosome locus and protein.
3. See Molecular Genetics for information on pathogenic variants detected.
4. Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or pathogenic. Variants may include small intragenic deletions/insertions and missense, nonsense, and splice site variants; typically, exon or whole-gene deletions/duplications are not detected. For issues to consider in interpretation of sequence analysis results, click here.
5. Gene-targeted deletion/duplication analysis detects intragenic deletions or duplications. Methods used may include a range of techniques such as quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification (MLPA), and a gene-targeted microarray designed to detect single-exon deletions or duplications.
6. Parisi et al [2006], Valente et al [2006a]
7. Bachmann-Gagescu et al [2015a] tested 440 individuals from 375 families for pathogenic variants in 27 JS-related genes.
8. Vilboux et al [2017] identified pathogenic variants in 81 (94%) of 86 families tested (100 individuals total) using a combination of 27-gene multigene panel and exome sequencing.
9. Three reported [Utsch et al 2006, Bachmann-Gagescu et al 2015a, Watson et al 2016]
10. Kroes et al [2016] evaluated 22 JS-related genes and 599 additional ciliary genes in a cohort of 51 northern Europeans with JS. Unlike other cohorts, this group identified *CPLANE1* pathogenic variants in 12% of their cohort.
11. Gorden et al [2008], Doherty et al [2010]. The prevalence of *CC2D2A* pathogenic variants in one large cohort was 16/209 (7.7%) [Bachmann-Gagescu et al 2012].
12. Two reported [Mougou-Zerelli et al 2009, Su et al 2015]
13. Data from Sayer et al [2006], Valente et al [2006b], Valente et al [2008], Travaglini et al [2009] and Bachmann-Gagescu et al [2015a] support 7%-10%. In contrast, only one of 51 cases (2%) in a northern European cohort was positive [Kroes et al 2016].
14. Suzuki et al [2016] reported 83% yield of variant analysis in a cohort of 30 families (all but 3 were Japanese), with pathogenic variants identified in *TMEM67* (26% of cohort), *CEP290* (22% of cohort) and *OFD1*, *INPP5E*, *AHI1*, and *CPLANE1* (each in 7.4% of the cohort).
15. One reported [Travaglini et al 2009]
16. Tuz et al [2014], Akizu et al [2014]
17. Pathogenic variants in *KIAA0586* accounted for nine (2.5%) of 366 families with JS in one cohort [Bachmann-Gagescu et al 2015b] but may be more prevalent than previously realized due to the high frequency of a single-base deletion (c.428delG) in the general population [Roosing et al 2015] and a broad range of clinical phenotypes [Alby et al 2015, Malicdan et al 2015].
18. In three of six individuals with compound heterozygous pathogenic variants in *KIAA0586*, one pathogenic variant was an 800-bp deletion of exons 8-10 [Malicdan et al 2015].
19. MKS1 pathogenic changes were identified in two separate series: in 2/260 individuals with JS [Romani et al 2014] and in 9/371 families with JS [Slaats et al 2016].
20. Four reported [Kyttälä et al 2006, Frank et al 2007, Abu-Safieh et al 2012, Szymanska et al 2012]
21. May be higher in individuals with nephronophthisis
22. Homozygous deletions have been associated with rare cases of JS. Deletion/duplication analysis alone will detect a heterozygous deletion but not a single-nucleotide variant in *NPHP1*; this genotype is expected to be rare. The common ~290 kb deletion is the most frequently detected.
23. Arts et al [2007], Delous et al [2007], Parisi [2009]
24. Juric-Sekhar et al [2012], Bachmann-Gagescu et al [2015a]
25. Baala et al [2007], Brancati et al [2009], Doherty et al [2010]
26. One reported [Khaddour et al 2007]
27. Fourteen (~3%) of 462 families with JS had pathogenic variants in *TMEM216* [Valente et al 2010].
28. Valente et al [2010], Lee et al [2012b]

Table 1b. Molecular Genetics of Joubert Syndrome: Less Common Genetic Causes

Gene [1, 2, 3]	Comment
ARL13B	2 families; phenotype ranged from classic JS to JS w/occipital encephalocele & pigmentary retinopathy [Cantagrel et al 2008]; no deletions/duplications reported.

Table 1b. continued from previous page.

Gene [1, 2, 3]	Comment
B9D1	2 families, both w/"pure" form of JS; pathogenic variants in this gene also cause MKS. No deletions/duplications reported [Romani et al 2014].
B9D2	2 families, both w/polydactyly & 1 w/encephalocele, cleft palate, & tongue hamartomas; pathogenic variants in this gene also cause MKS. No deletions/duplications reported [Bachmann-Gagescu et al 2015a].
C2CD3	2 families identified in 1 series, both w/cleft palate and/or oral frenulae suggestive of features of OFD. No deletions/duplications reported [Bachmann-Gagescu et al 2015a].
CEP41	3 families w/8 individuals w/JS described w/pathogenic variants in *CEP41*, based on screening at least 725 individuals w/JS, many of whom had been excluded for pathogenic variants in known JS-related genes. Slightly more than 50% of affected persons have demonstrated unilateral or bilateral postaxial polydactyly. Only 2 individuals have evidence of retinal disease, 1 of whom had unilateral coloboma, unilateral kidney disease, & ambiguous genitalia & died at age 7 days. Within 1 family, all 5 affected males had micropenis & 2 had growth hormone deficiency. Only splice site variants have been identified; no deletions/duplications reported [Lee et al 2012a].
CEP104	3 families, all w/"pure" form of JS; no deletions/duplications reported [Srour et al 2015].
CEP120	4/491 individuals w/JS had missense, frameshift, nonsense, or splice variants in this gene; phenotypes ranged from "pure" JS to MKS, OFD, and JS-JATD; no large deletions/duplications reported [Shaheen et al 2015b, Roosing et al 2016a].
IFT172	1/440 individuals with JS had missense pathogenic variants in this gene [Bachmann-Gagescu et al 2015a]. 2/12 families w/missense and/or truncating pathogenic variants had overlapping features of JS & JS-JATD (one w/ Mainzer-Saldino syndrome features as well) including retinal dystrophy, hepatic fibrosis, NPHP, & cerebellar vermis hypoplasia. No deletions/duplications reported [Halbritter et al 2013].
KATNIP (*KIAA0556*)	Homozygous truncating pathogenic variants in this gene identified in 3 sibs of a consanguineous family; 2/3 had panhypopituitarism (the male had micropenis & the female had a hypoplastic pituitary on MRI) [Sanders et al 2015]. In another consanguineous family, 2 sibs w/classic JS features had homozygous truncating pathogenic variants; no deletions/duplications reported [Roosing et al 2016b].
KIF7	3/440 families had pathogenic variants in this gene [Bachmann-Gagescu et al 2015a]. Individuals often have OFD features, w/or w/o other CNS findings such as agenesis/hypoplasia of the corpus callosum, hydrocephalus, & macrocephaly [Dafinger et al 2011, Putoux et al 2011]. The combination of polydactyly & these CNS findings suggests acrocallosal and/or hydrolethalus syndromes [Putoux et al 2011]. Nonsense & frameshift pathogenic variants predominate; no deletions/duplications reported.
OFD1	X-linked; no deletions/duplications reported. Pathogenic variants in this gene identified in 4/440 families [Bachmann-Gagescu et al 2015a] & in 2/250 families (2/84 w/only males affected) [Coene et al 2009]. Features include encephalocele, hydrocephalus, macrocephaly, polymicrogyria, polydactyly, & retinal disease. 1 family also had renal cystic disease, hydrocephalus, macrocephaly, & polymicrogyria [Field et al 2012].
PDE6D	In 1 consanguineous family w/3 sibs (w/a homozygous splice site variant), phenotype included renal hypoplasia, retinal dystrophy, microphthalmia, ocular coloboma, & postaxial polydactyly [Thomas et al 2014].
POC1B	A homozygous pathogenic missense variant in this gene was identified in an extended Iraqi family with LCA, enlarged, polycystic kidneys (resembling ADPKD rather than NPHP), & classic features of JS w/o liver fibrosis. Of note, the same homozygous pathogenic variant was identified in a family w/severe & slowly progressive cone-rod dystrophy w/o features of JS [Beck et al 2014]. No deletions/duplications reported.
TCTN1	1/440 families had pathogenic variants in this gene [Bachmann-Gagescu et al 2015a]. Two sibs w/homozygous splice site variants had fronto-temporal pachygyria but no retinal or renal findings [Garcia-Gonzalo et al 2011]. No deletions/duplications reported.

Table 1b. continued from previous page.

Gene [1, 2, 3]	Comment
TCTN3	1/440 families had pathogenic variants in this gene [Bachmann-Gagescu et al 2015a]. 1/58 families (for whom known JS-genes were excluded) had biallelic pathogenic variants [Thomas et al 2012]. Homozygous truncating variants were identified in 5 pedigrees w/a severe prenatal lethal form of OFD type IV (Mohr-Majewski syndrome); however, since the phenotype also included postaxial polydactyly, cystic renal disease, bile duct proliferation, & occipital encephalocele, it is debatable whether this represents a type of OFD or MKS. 2 probands from a Turkish family w/JS, who had a homozygous missense variant, had scoliosis w/variable polydactyly, oral findings, horseshoe kidney, & ventricular septal defect [Thomas et al 2012]. No deletions/duplications reported.
TMEM107	Of 238 individuals w/JS or "OFD VI," 1 set of consanguineous twins who were homozygous for a missense variant in this gene had retinopathy & features of OFD including postaxial polydactyly; another male w/classic JS & retinopathy had compound heterozygous pathogenic variants [Lambacher et al 2016]. No deletions/duplications reported.
TMEM138	1/440 families had pathogenic variants in this gene [Bachmann-Gagescu et al 2015a]. 11 individuals from 8 consanguineous Arab families had coloboma (6), retinal dystrophy (3), cystic kidney, or NPHP (3). Polydactyly has been observed; 1 fetus w/MKS had an encephalocele [Lee et al 2012b]. No deletions/duplications reported
TMEM231	Pathogenic variants in this gene account for some individuals w/JS of French Canadian descent. 3 persons in 2 families had a severe phenotype (lack of ambulation, aggressive behaviors, lack of independent living skills). 2 have macroscopic renal cysts & retinal disease; 1 has postaxial polysyndactyly [Srour et al 2012a]. A pathogenic gene conversion event between this gene & its pseudogene has been described [Maglic et al 2016].
TMEM237	1/440 families had pathogenic variants in this gene [Bachmann-Gagescu et al 2015a]. Only 2/201 individuals w/JS & 90 individuals w/MKS/JS had pathogenic variants in this gene [Huang et al 2011]. This form of JS was originally described as MKS in the Hutterite population [Boycott et al 2007], in which the carrier rate is estimated at 6% [Huang et al 2011]. Encephalocele, hydrocephalus, & cystic kidney disease are common. The "morning glory disc anomaly" has also been described in an extended family from Austria w/biallelic pathogenic variants [Janecke et al 2004, Huang et al 2011]. A 24-kb deletion including *TMEM237* exon 1 & 1a extending into the adjacent gene has been identified [Watson et al 2016].
TTC21B	To date, no individuals w/JS & biallelic pathogenic variants in this gene have been reported. The functional significance of a single (heterozygous) pathogenic variant is unknown. No clinical information was provided on 3 persons with a heterozygous change. See *TTC21B*, **Pathogenic variants** (pdf). In a clinically diverse cohort of 753 individuals w/a ciliopathy, 5% had pathogenic variants in this gene; however, only 33% had a 2nd pathogenic variant in a different ciliopathy gene [Davis et al 2011].
ZNF423	1 consanguineous family w/infantile-onset NPHP, cerebellar vermis hypoplasia, & situs inversus had homozygous pathogenic missense variants in this gene; 2/96 other individuals w/JS had heterozygous changes in the gene in specific interaction domains, leading to proposed (but not proven) loss of function via a dominant-negative mechanism [Chaki et al 2012]. No deletions/duplications reported.

Pathogenic variants of any one of the genes listed in this table are reported in only a few families (i.e., account for <1% of JS).
ADPKD = autosomal dominant polycystic kidney disease; JS-JATD = Jeune asphyxiating thoracic dystrophy; LCA = Leber congenital amaurosis; MKS = Meckel syndrome; NPHP = nephronophthisis; OFD = oral-facial-digital syndrome

1. Genes are listed alphabetically.
2. See Table A. Genes and Databases for chromosome locus and protein.
3. Genes are not described in detail in Molecular Genetics, but may be included here (pdf).

Clinical Characteristics

Clinical Description

Classic Joubert syndrome (JS) is characterized by the three primary findings of: a distinctive cerebellar and brain stem malformation called the molar tooth sign (MTS), hypotonia, and developmental delays. Often these findings are accompanied by episodic tachypnea or apnea and/or atypical eye movements. In general, the breathing abnormalities improve with age, truncal ataxia develops over time, and acquisition of gross motor

milestones is delayed. Cognitive abilities are variable, ranging from severe intellectual disability to normal. Additional findings can include retinal dystrophy, renal disease, ocular colobomas, occipital encephalocele, hepatic fibrosis, polydactyly, oral hamartomas, and endocrine abnormalities. Table 2 associates phenotypic features with genes; Table 3 associates genes with phenotypic features. Both intra- and interfamilial phenotypic variation are seen in JS.

Many of the clinical features of JS are evident in infancy [Joubert et al 1969, Boltshauser & Isler 1977]. The findings of nystagmus, oculomotor apraxia, and abnormal breathing patterns can be observed in all clinical subtypes. Most children with JS develop truncal ataxia and, in combination with hypotonia, exhibit delayed acquisition of gross motor milestones.

Nystagmus. Many children with Joubert syndrome demonstrate horizontal nystagmus at birth that improves with age. Torsional and pendular rotatory nystagmus have also been observed.

Oculomotor apraxia is often identified in childhood rather than in infancy, perhaps because of under-recognition of the finding [Steinlin et al 1997]. Many children with oculomotor apraxia demonstrate head thrusting as a compensatory mechanism for their inability to initiate saccades [Hodgkins et al 2004, Khan et al 2008, Weiss et al 2009]. Horizontal head titubation (i.e., a "no-no" head tremor) has been described in infants and young children younger than age two years [Poretti et al 2014]. Visual acuity and functional vision may improve with age as a result of visual maturation, in spite of significantly aberrant eye movements at birth [M Parisi and A Weiss, personal observation].

Respiratory findings. Many children with JS exhibit apnea, tachypnea, or both, sometimes alternating, particularly in the neonatal period [Saraiva & Baraitser 1992, Steinlin et al 1997, Maria et al 1999a, Valente et al 2008]. Although some infants have died of apnea, episodic apnea generally improves with age and may completely disappear [Maria et al 1999b]. Children with JS are at increased risk for sleep apnea, including central (particularly in infancy and childhood) and obstructive (particularly in later childhood/adolescence related to tongue hypertrophy, hypotonia, and obesity) [Parisi 2009]. A survey of self-reported sleep behaviors in individuals with JS using a validated sleep questionnaire suggested sleep-related breathing disorders in six of the 14 individuals surveyed [Kamdar et al 2011]. Some individuals with Leber congenital amaurosis resulting from biallelic pathogenic variants in *CEP290* have also been found to have abnormalities in motile respiratory cilia that may predispose to respiratory symptoms including chronic rhinitis, recurrent sinusitis, and bronchitis [Papon et al 2010].

Central nervous system findings

- **Cognitive abilities** are variable, ranging from severe intellectual disability to normal cognitive function [Poretti et al 2009]; a few individuals have attended college. When present, intellectual disability is typically in the moderate range [Steinlin et al 1997, Hodgkins et al 2004, Bulgheroni et al 2016, Summers et al 2017]. A correlation between severity of cerebellar vermis hypoplasia and cognitive impairment was identified in a study of 110 persons with JS [Poretti et al 2017].
- **Speech apraxia,** a common finding, may account for the observed discrepancy between speech comprehension and verbal abilities [Hodgkins et al 2004, Braddock et al 2006].
- **Abnormal EEG and/or seizures** are present in some affected individuals; the exact incidence is unknown [Saraiva & Baraitser 1992]. One study identified greater cognitive impairment in individuals with JS and an abnormal EEG [Summers et al 2017].
- **Autism** has been reported in some children with JS [Holroyd et al 1991, Ozonoff et al 1999]; however, more recent surveys suggest that many of these behavioral disturbances do not represent classic autism spectrum disorder [Takahashi et al 2005].
- **Behavioral findings** including inattention, hyperactivity, and atypical behaviors such as temper tantrums are present in some children and adolescents [Deonna & Ziegler 1993, Hodgkins et al 2004, Farmer et al

2006]. Emotional and behavior issues were reported in almost 40% in one survey of 54 individuals with JS [Bulgheroni et al 2016]. In another survey of 76 individuals, behavior issues were more likely to manifest as internalizing (anxiety, depression) than externalizing (aggression, oppositional defiance) [Summers et al 2017].

JS Clinical Subtypes

See Table 2 and Table 3.

Table 2. Joubert Syndrome: Clinical Subtypes

Name of Clinical Subtype	Mandatory Features in Addition to Primary Criteria [1]	Strongly Associated Features [2]	Other Names	Genes (bold = major gene)
Classic or pure Joubert syndrome			JS; JS type A	Many genes
Joubert syndrome w/ retinal disease (JS-Ret)	Retinal dystrophy (including LCA)		JS type B	***AHI1*** ***CEP290*** *CEP41* *INPP5E* *MKS1* *TMEM107* *TMEM138* *TMEM216*
Joubert syndrome w/ renal disease (JS-Ren)	NPHP (includes cystic kidney disease)			*AHI1* *CC2D2A* *CEP290* *NPHP1* *OFD1* *RPGRIP1L* *TMEM138* *TMEM216* *TMEM237* *ZNF423*
Joubert syndrome w/ oculorenal disease (JS-OR)	Retinal dystrophy (incl LCA); NPHP	CHF (occasional)	JS type B; CORS; Senior-Løken syndrome; Dekaban-Arima syndrome	*AHI1* *CC2D2A* ***CEP290*** *NPHP1* *POC1B* *RPGRIP1L* *TMEM216* *TMEM231* *TMEM237*
Joubert syndrome w/ hepatic disease (JS-H)	CHF	Colobomas; NPHP	COACH syndrome; Gentile syndrome	*CC2D2A* *CEP290* *INPP5E* *RPGRIP1L* ***TMEM67***

Table 2. continued from previous page.

Name of Clinical Subtype	Mandatory Features in Addition to Primary Criteria [1]	Strongly Associated Features [2]	Other Names	Genes (bold = major gene)
Joubert syndrome w/oral-facial-digital features (JS-OFD)	Tongue hamartomas; oral frenulae; polydactyly [3]	Cleft lip/palate	Varadi-Papp syndrome; OFD VI; OFD IV; Mohr-Majewski syndrome	*B9D2* *C2CD3* *CPLANE1* *CEP120* *KIF7* *OFD1* *TCTN2* *TCTN3* *TMEM107* *TMEM216*
Joubert syndrome w/ acro-callosal features (JS-AC)	Agenesis of corpus callosum; polydacyly [3]	Hydrocephalus	Acrocallosal syndrome	*KIF7*
Joubert syndrome w/ Jeune asphyxiating thoracic dystrophy features (JS-JATD)	Skeletal dysplasia (short ribs, small thorax, short limbs, renal cystic disease)	Polydactyly [3]; cone-shaped epiphyses; CHF	Jeune asphyxiating thoracic dystrophy; Mainzer-Saldino syndrome	*CEP120* *CSPP1* *IFT172* *KIAA0586*

Adapted from Brancati et al [2010]. This classification scheme should not be interpreted as definitive, given the extreme clinical heterogeneity of the manifestations and the variable age of onset of many of these features.
AC = acro-callosal; CHF = congenital hepatic fibrosis ; COACH = cerebellar vermis hypoplasia, oligophrenia, ataxia, coloboma, and hepatic fibrosis; CORS = cerebello-oculo-renal syndromes; H = hepatic; JATD = Jeune asphyxiating thoracic dystrophy; LCA = Leber congenital amaurosis; NPHP = nephronophthisis; OFD = oral-facial-digital syndrome; OR = oculorenal; Ren = renal; Ret = retinal
1. Primary criteria = molar tooth sign (MTS), hypotonia, developmental delay (DD)
2. Other features including encephalocele, postaxial polydactyly, other structural brain malformations (including polymicrogyria), congenital heart defects, Hirschsprung disease, and situs defects can be seen in these subtypes but are not major features.
3. Polydactyly is often postaxial, especially of hands, and preaxial, especially of feet. Distinctive for OFD VI syndrome: mesaxial or central polydactyly with a Y-shaped metacarpal.

Joubert syndrome with retinal disease (JS-Ret) is characterized by a pigmentary retinopathy that may be indistinguishable from classic retinitis pigmentosa; it can occasionally be severe with neonatal onset of congenital blindness and an attenuated or extinguished electroretinogram that resembles Leber congenital amaurosis (LCA) [Tusa & Hove 1999]. However, the retinal disease may not be progressive and is not always present in infancy or early childhood [Steinlin et al 1997]. One survey of 235 families with JSRD identified retinal dystrophy in 30% [Doherty 2009].

- **Ocular colobomas** are most often described as chorioretinal [Saraiva & Baraitser 1992, Parisi 2009] and may be associated with hepatic fibrosis, as in the COACH syndrome variant [Doherty et al 2010]. One survey described colobomas in 19% of families with JSRD [Doherty 2009]. A retinal change described as the "morning glory disc anomaly" has been described in an extended Austrian family from the Tyrolean region with biallelic *TMEM237* pathogenic variants [Janecke et al 2004, Huang et al 2011].
- **Other.** Variably present:
  - Ptosis, strabismus, and/or amblyopia
  - Third nerve palsy [Hodgkins et al 2004]

Joubert syndrome with renal disease (JS-Ren) has been described traditionally in two forms (nephronophthisis and cystic dysplasia); however, these now appear to be part of a continuum with the specific renal manifestation varying by stage of renal disease. Juvenile nephronophthisis, a form of chronic tubulointerstitial nephropathy, often presents in the first or second decade of life with polydipsia, polyuria, urine-concentrating defects, growth

restriction, and/or anemia. Progression to end-stage kidney disease occurs on average by age 13 years [Hildebrandt et al 1998]. Renal changes visible on ultrasound examination occur late in the course and consist of small, scarred kidneys with increased echogenicity and occasional cysts at the corticomedullary junction, findings consistent with cystic dysplasia (i.e., multiple variably sized cysts in immature kidneys with fetal lobulations) [Saraiva & Baraitser 1992, Steinlin et al 1997, Satran et al 1999].

In addition to the nephronophthisis and cystic dysplasia spectrum, a second type of renal disease that resembles autosomal recessive polycystic kidney disease (ARPKD) has been reported.

- Three individuals with JS caused by biallelic *TMEM67* pathogenic variants were reported to have renal disease more typical of ARPKD, with enlarged, diffusely microcystic kidneys and early-onset severe hypertension as well as congenital hepatic fibrosis; in addition, they exhibited chronic anemia characteristic of nephronophthisis [Gunay-Aygun et al 2009].
- In the Hutterite population, approximately 70% of probands with JS caused by biallelic *TMEM237* pathogenic variants have cystic renal disease and abnormal renal function, with hypertension reported in some [Boycott et al 2007, Huang et al 2011].

Renal disease has been reported in 23% [Doherty 2009] and 30% [Saraiva & Baraitser 1992] of persons with JS. These prevalence values may increase as a cohort ages, as renal disease can develop during childhood and adolescence [Steinlin et al 1997].

Joubert syndrome with oculorenal disease (JS-OR). Retinal disease and renal impairment often occur together in the same individual, and many of JS-related genes are associated with both renal cystic disease and retinal dystrophy, a combination sometimes known as Senior-Løken syndrome [Parisi 2009, Brancati et al 2010] (Table 2). In the past JS-OR was also known as Dekaban Arima syndrome (retinopathy, cystic dysplastic kidneys), which can be evident prenatally or at birth.

Joubert syndrome with hepatic disease (JS-H). Hepatic fibrosis is usually progressive but rarely symptomatic at birth. Congenital hepatic fibrosis is a developmental disorder of the portobiliary system characterized histologically by defective remodeling of the ductal plate (ductal plate malformation), abnormal branching of the intrahepatic portal veins, and progressive fibrosis of the portal tracts. Clinical findings include enlarged, abnormally shaped liver, relatively well-preserved hepatocellular function, and portal hypertension resulting in splenomegaly, hypersplenism, and gastroesophageal varices.

Hepatic fibrosis was observed in 18% of individuals with JS in one cohort [Doherty 2009].

When present in JS, hepatic fibrosis is often associated with chorioretinal colobomas and sometimes with renal disease. The combination of *c*olobomas, cognitive impairment ("*o*ligophrenia"), *a*taxia, *c*erebellar vermis hypoplasia, and *h*epatic fibrosis has been termed COACH syndrome [Satran et al 1999, Gleeson et al 2004, Doherty et al 2010].

Joubert syndrome with oral-facial-digital features (JS-OFD). Oral findings can include midline upper-lip cleft, midline groove of tongue, hamatomas of the alveolar ridge (Figure 2B), cleft palate, oral frenulae, and tongue lobulations or hamartomas. Craniofacial features often include wide-spaced eyes or telecanthus, hypoplastic alae nasi, and micrognathia.

Polydactyly is described in 8%-19% of probands [Doherty 2009, Brancati et al 2010]. Polydactyly can be unilateral or bilateral and is often postaxial (Figure 2C), although preaxial polydactyly of the toes is also frequently reported (Figure 2D) [Saraiva & Baraitser 1992].

Mesaxial polydactyly, in which the extra digit occurs between the central digits and is often accompanied by a Y-shaped metacarpal, has been described in some individuals with JS, many of whom have other features of oral-facial-digital syndrome type VI/Varadi-Papp syndrome [Gleeson et al 2004]. OFD VI has now been defined as a

form of JS, requiring the MTS as well as one or more of the following features: tongue hamartoma/oral frenula/upper-lip notch, mesaxial polydactyly, and hypothalamic hamartoma [Poretti et al 2012].

Joubert syndrome with acrocallosal features (JS-AC). Agenesis of the corpus callosum is common in JS [Valente et al 2005]. In one survey of 20 individuals with JS, 80% had some degree of callosal dysgenesis [Senocak et al 2010]. Callosal abnormalities are relatively frequent in those with biallelic *KIF7* pathogenic variants [Bachmann-Gagescu et al 2015a], suggesting overlap with acrocallosal syndrome (see Genetically Related Disorders) in which polydactyly and hydrocephalus are also seen [Putoux et al 2011].

Joubert syndrome with Jeune asphyxiating thoracic dystrophy (JS-JATD). Features of JATD (see Genetically Related Disorders) and the related short-rib thoracic dysplasia condition, Mainzer-Saldino syndrome, have been reported in several children with a JS, reflecting the shared ciliary origin of these conditions [Lehman et al 2010, Halbritter et al 2013, Shaheen et al 2015b].

Other Findings in JS Not Specific to a Given Subtype

Scoliosis has been described, most likely related to early hypotonia.

Endocrine abnormalities have been described; they include pituitary hormone dysfunction ranging from isolated growth hormone deficiency or thyroid hormone deficiency to more extensive panhypopituitarism or micropenis in males [Delous et al 2007, Wolf et al 2007, Parisi 2009, Sanders et al 2015].

Obesity may be increased in JS, suggesting an association with the ciliary disorder Bardet-Biedl syndrome; the identification of biallelic pathogenic variants in *INPP5E* in both JS and MORM syndrome (*m*ental retardation, *o*besity, *r*etinal dystrophy, and *m*icropenis) reinforces this association [Bielas et al 2009, Jacoby et al 2009].

Typical facial features including long face with bitemporal narrowing, high-arched eyebrows, ptosis, prominent nasal bridge with anteverted nostrils, triangular-shaped mouth, prognathism, and low-set ears are sometimes described [Maria et al 1999a] (Figure 2A); however, these features can be difficult to discern in infancy and are thus far nonspecific. Nonetheless, many observers report a "Joubert syndrome facies" [Braddock et al 2007]. The craniofacial features in those with biallelic *KIF7* pathogenic variants often include macrocephaly, frontal bossing, hypertelorism, high palate, and micrognathia [Dafinger et al 2011, Putoux et al 2011].

Heart defects have been described in a number of individuals with JS, in some cases assocated with features of oral-facial-digital syndrome, and have included septal defects, aortic valve anomalies, and coarctation of the aorta [Bachmann-Gagescu et al 2015a].

Laterality defects including situs inversus are seen in some individuals [Parisi 2009].

Hirschsprung disease has been described in a few individuals [Brancati et al 2010].

Conductive hearing loss may result from middle ear infections [Kroes et al 2010]. Sensorineural hearing loss has been described.

Tongue hypertrophy. Many have rhythmic tongue movements that may lead to tongue hypertrophy.

Other CNS malformations

- Cerebellar hemisphere enlargement [Poretti et al 2017], cerebellar heterotopias [Saraiva & Baraitser 1992] and cerebellar folial disorganization [Senocak et al 2010, Poretti et al 2011]
- Abnormal collections of cerebrospinal fluid in the fourth ventricle or the posterior fossa that resemble Dandy-Walker malformation; in approximately 10% of individuals in one survey [Maria et al 2001] and in ~42% in another [Poretti et al 2017]
- Occipital encephalocele (Figure 2E) or meningocele [Genel et al 2004]

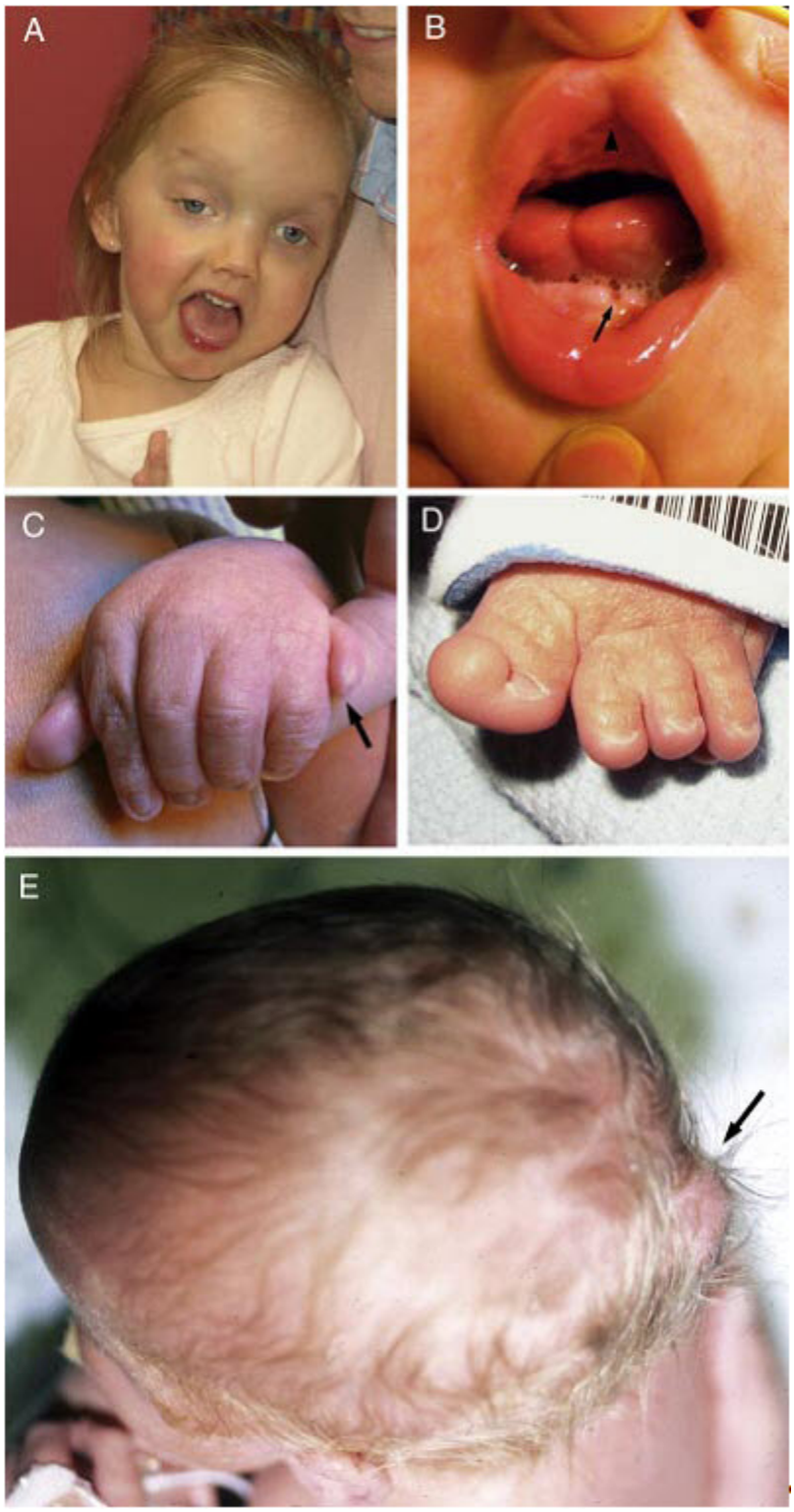

Figure 2. Clinical features in JSRD

A. Facial features in a girl with JS/COACH syndrome at age 27 months showing broad forehead, arched eyebrows, strabismus, eyelid ptosis (on right eye), and open mouth configuration indicating reduced facial tone

B. Oral findings in a child with oral-facial-digital syndrome-like features of JS showing midline upper lip cleft (arrowhead), midline groove of tongue, and bumps of the lower alveolar ridge (arrow)

C. Left hand of an infant with JS and postaxial polydactyly (arrow)

D. Left foot of an infant with JS and preaxial polydactyly of the hallux

E. View from above of an infant with a small occipital encephalocele with protrusion of the occiput of the skull (arrow)

Used by permission: Parisi [2009]. Facial photograph used with permission of the family.

- Abnormal brain stem and hypothalamic hamartomas, particularly in those with oral-facial-digital syndrome type VI-related findings [Poretti et al 2011]
- Ventriculomegaly [Quisling et al 1999, Senocak et al 2010, Putoux et al 2011] or hydrocephalus requiring shunting without classic signs of Dandy-Walker malformation [Genel et al 2004]
- Hippocampal malformation/malrotation, described in 80% in individuals in one limited survey [Senocak et al 2010] and in 15%-18% in two larger surveys [Poretti et al 2011, Poretti et al 2017]
- Cortical anomalies including heterotopias, dysplasia, pachygyria, polymicrogyria [Gleeson et al 2004, Dixon-Salazar et al 2004], and neuroepithelial cysts [Marsh et al 2004, Senocak et al 2010]
- Abnormal nuclei and tracts of the pons, cerebellum, and medulla based on neuropathologic evaluation [Doherty 2009]; absence of decussation of the corticospinal and superior cerebellar tracts based on diffusion tensor imaging [Poretti et al 2007]; and abnormal activation patterns during motor tasks based on functional MRI studies [Parisi et al 2004b]

Phenotype Correlations by Gene

Table 3 includes preliminary information on genotype-phenotype correlations.

Table 3. Genes Associated with JS by Phenotypic Features

Gene	Phenotypic Feature (in addition to the molar tooth sign)								Allelic/ Related Disorder [3]
	Retinal dystrophy	Coloboma [1]	Renal	Oculorenal [2]	Hepatic [1]	Oral	Polydactyly	Other	
AHI1	++ [4]	(+)	+ [5]	+	(+)			Polymicrogyria [6]	
CPLANE1					(+)	+ [7]	+ [7]	Founder effects in French Canadian [8] & Dutch populations [9]	OFD VI
CC2D2A	+	+	+	+	+ [10]			Encephalocele, ventriculomegaly, seizures [11]; milder phenotype in French Canadian population [12]	Meckel syndrome [13]
CEP290	++	+	++	++ [14]	+			Encephalocele; cardiac; situs inversus; other [15]	LCA, Meckel syndrome, BBS
CSPP1	(+)		(+)	(+)	(+)			SNHL; corpus callosum hypoplasia; encephalocele; founder variant in Hutterite population [16]	Meckel syndrome, JATD [17]
INPP5E	+		+	+	(+)		+		MORM syndrome [18]

Table 3. continued from previous page.

Gene	Phenotypic Feature (in addition to the molar tooth sign)								Allelic/ Related Disorder [3]
	Retinal dystrophy	Coloboma [1]	Renal	Oculorenal [2]	Hepatic [1]	Oral	Polydactyly	Other	
KIAA0586	(+)	+				(+)	(+)	Broad range of phenotypes: severe HLS (& cleft palate) to JATD w/short ribs & narrow thorax to pure JS [19]	HLS, JATD
MKS1	(+)							Kidney/liver findings & PD described in 1 individual [20]	Meckel syndrome
NPHP1	+		++	+				"Mild molar tooth" sometimes described [21]	Juvenile NPHP type 1, Cogan syndrome
RPGRIP1L	(+)	(+)	++	+	(+)		(+)	Encephalocele	Meckel syndrome, retinal disease [22]
TCTN2 [21]								Clubfoot [23]	Meckel syndrome [24]
TMEM67		+ [25]	+		++ [26, 27]		(+)	Encephalocele	Meckel syndrome [28]

Table 3. continued from previous page.

Gene	Phenotypic Feature (in addition to the molar tooth sign)								Allelic/ Related Disorder [3]
	Retinal dystrophy	Coloboma [1]	Renal	Oculorenal [2]	Hepatic [1]	Oral	Polydactyly	Other	
TMEM216 [29]	(+)	(+)	++	+	(+)	+	+	Cardiac findings; encephalocele	Meckel syndrome

(+) = feature is uncommon but has been described; + = feature is present in some cases; ++ = Major feature; HLS = hydrolethalus syndrome; NPHP = nephronophthisis; LCA = Leber congenital amaurosis; BBS = Bardet-Biedl syndrome; MORM = mental retardation, truncal obesity, retinal dystrophy, micropenis [Jacoby et al 2009]; OFD = oral-facial-digital syndrome; PD = polydactyly; JATD = jeune asphyxiating thoracic dystrophy; SNHL = sensorineural hearing loss

1. May include COACH syndrome: cerebellar vermis hypoplasia, oligophrenia, ataxia, coloboma, and hepatic fibrosis

2. This refers to retinal disease plus kidney disease; terms used in the past include: Senior-Løken syndrome (retinopathy and juvenile-onset nephronophthisis); Dekaban-Arima syndrome (retinopathy, cystic dysplastic kidneys).

3. See Genetically Related Disorders for details.

4. The most common clinical association in those with biallelic *AHI1* pathogenic variants is retinal dystrophy, present in approximately 80% [Valente et al 2008]. Early-onset congenital blindness [Valente et al 2006a] and liver involvement [Vilboux et al 2017] have been described.

5. Renal disease consistent with nephronophthisis has also been described [Parisi et al 2006, Utsch et al 2006].

6. Dixon-Salazar et al [2004], Gleeson et al [2004]

7. The phenotype most closely resembles pure or classic Joubert syndrome, with several individuals exhibiting preaxial, postaxial, and/or mesaxial polydactyly and a few with retinal involvement [Srour et al 2015] or liver involvement [Vilboux et al 2017]. None of the affected individuals (ranging in age from 1.5 to 52 years) has evidence of renal impairment or liver disease [Srour et al 2012a, Srour et al 2012b, Srour et al 2015]. Pathogenic variants in this gene also cause OFD VI, with features of preaxial and/or mesaxial polydactyly and hypothalamic hamartoma typical [Lopez et al 2014, Romani et al 2015].

8. Pathogenic variants in this gene are the cause of JS in the original family described by Joubert et al [1969]. Several pathogenic variants recur in the French Canadian population found in the lower St. Lawrence region of Quebec province [Srour et al 2012b, Srour et al 2015].

9. Kroes et al [2016]

10. Hepatic involvement has been described [Gorden et al 2008, Noor et al 2008].

11. Those with pathogenic variants in *CC2D2A* have an increased likelihood of ventriculomegaly and seizures [Bachmann-Gagescu et al 2012].

12. Srour et al [2012a]

13. Null alleles are associated with the Meckel syndrome phenotype and missense and/or hypomorphic variants with JS [Tallila et al 2008, Mougou-Zerelli et al 2009].

14. Up to 50% of individuals with both retinal and renal involvement harbor biallelic pathogenic variants in *CEP290* [Valente et al 2008].

15. The phenotypic spectrum is very broad, including congenital blindness, ocular colobomas, renal disease, encephaloceles, septal heart disease, and situs abnormalities.

16. Shaheen et al [2014], Vilboux et al [2017]

17. Pathogenic variants in this gene have been described in phenotypes ranging from classic JS with occasional retinopathy and sensorineural hearing loss [Akizu et al 2014] to the JS-JATD phenotype with features of Jeune skeletal dysplasia [Tuz et al 2014] to a lethal MKS-like phenotype [Shaheen et al 2014]. Thin corpus callosum, occipital encephalocele, and heterotopias have also been described [Akizu et al 2014, Tuz et al 2014].

18. Jacoby et al [2009]

19. Pathogenic variants in this gene cause a wide spectrum of ciliopathy phenotypes, from "pure" JS with relatively mild manifestations and impairment [Bachmann-Gagescu et al 2015b, Roosing et al 2015] to features of Jeune asphyxiating thoracic dystrophy (small chest, short ribs, short stature) [Alby et al 2015, Malicdan et al 2015] to severe features of hydrolethalus syndrome with hydrocephalus and fetal or perimatal demise [Alby et al 2015]. This broad range of phenotypes is not explained by the nature of the pathogenic variants, as many afftected individuals have homozygous or compound heterozygous truncating variants due to frameshifts, aberrant splice, or nonsense variants.

20. Individuals with JS caused by *MKS1* pathogenic variants have at least one variant with partial function (e.g., a missense variant that retains some function), in contrast to more severe variants described in those with MKS [Romani et al 2014, Slaats et al 2016]. Most of the affected individuals have a relatively mild phenotype, characterized by classic JS with or without retinal dystrophy. Only one reported individual (out of a group of 9 with pathogenic variants in this gene) had additional features of renal echogenicity, liver fibrosis, and postaxial polydactyly [Slaats et al 2016].

21. Some individuals with biallelic pathogenic variants in *NPHP1* and JS have a distinctive appearance of the molar tooth sign: elongated but thin superior cerebellar peduncles and milder vermis hypoplasia [Parisi et al 2004a].

22. RPGRIP1L pathogenic variants also cause Meckel syndrome. Of note, more severe loss-of-function pathogenic variants predict a more severe (and in many cases, lethal) Meckel phenotype [Delous et al 2007, Wolf et al 2007].

Nomenclature

The term "Joubert syndrome and related disorders" (JSRD) has been used in the past to describe conditions that share the molar tooth sign and the clinical features of classic Joubert syndrome and also have other organ system involvement. In an evolving nomenclature designed to reduce reliance on confusing and inconsistently used eponyms, at least eight clinical subtypes of JS that share the three primary findings have been proposed (Table 2) [Brancati et al 2010]. More recently, "Joubert syndrome" has become the accepted term to describe all forms of JS.

In the past, some of the following disorders were described as distinct syndromes, but more recent studies indicate that many individuals with these disorders demonstrate the molar tooth sign [Satran et al 1999, Gleeson et al 2004]. Examples of such autosomal recessive disorders include the following:

- **Dekaban-Arima syndrome** (retinopathy, cystic dysplastic kidneys) [Dekaban 1969]
- **Senior-Løken syndrome** (SLS; retinopathy and juvenile-onset nephronophthisis) [Løken et al 1961, Senior et al 1961]
- **COACH syndrome** (*c*erebellar vermis hypoplasia, *o*ligophrenia, *a*taxia, *c*oloboma, and *h*epatic fibrosis) [Verloes & Lambotte 1989, Gentile et al 1996]
- **Varadi-Papp syndrome** (oral-facial-digital syndrome VI [OFD VI]) includes cerebellar vermis hypoplasia, oral frenulae, tongue hamartomas, and midline cleft lip as well as the distinctive feature of central polydactyly with a Y-shaped metacarpal [Münke et al 1990]. Renal and cardiac involvement have been described.

Prevalence

The prevalence of Joubert syndrome (JS) has not been determined. Many authors use a range between 1:80,000 and 1:100,000, but this may represent an underestimate [Kroes et al 2007, Parisi et al 2007, Brancati et al 2010].

There is a relatively high prevalence of JS in the French Canadian population, with several founder variants noted. The family first described by Joubert et al [1969] has been traced to a founder who immigrated to Quebec from France in the 1600s [Badhwar et al 2000]. However, in this family and others, it appears that there are multiple *CPLANE1* pathogenic variant-containing haplotypes in the French Canadian population. In fact, in 35 French Canadian families, pathogenic variants were identified in 33 (94%) in the following genes (number of affected families given in parentheses): *CPLANE1* (14), *CC2D2A* (9), *NPHP1* (3), *TMEM231* (2); and *CEP290*, *TMEM67*, *TCTN1*, *OFD1*, *B9D1*, *C2CD3*, and *CEP104* (1 family each). Many French Canadian individuals are compound heterozygous for different pathogenic variants in either *CPLANE1*, *CC2D2A*, *TMEM231*, or *NPHP1* [Srour et al 2012a, Srour et al 2012b, Srour et al 2015].

A different founder variant in *CPLANE1*, p.Arg2904Ter, occurs in the Dutch population [Kroes et al 2016].

A *TMEM216* founder variant, p.Arg73Leu, has a carrier rate of 1:92-1:100 in the Ashkenazi Jewish population [Edvardson et al 2010, Valente et al 2010].

In a Canadian Hutterite population, ten related individuals with a MKS-like phenotype including encephaloceles and cystic kidneys were homozygous for a nonsense pathogenic variant (c.52C>T; p.Arg18Ter) in *TMEM237*, reflecting a carrier frequency of 6% in this population [Huang et al 2011]. Two different Schmiedeleut Hutterite families had the same homozygous pathogenic frameshift variant, c.363_364delTA, in *CSPP1* [Shaheen et al 2014], representing a separate founder variant.

In a survey of Japanese families with JS, 6/27 had pathogenic variants in *CEP290*, with c.6012-12T>A found on nine out of 12 disease alleles; 7/27 families had pathogenic variants in *TMEM67* but no founder alleles were identified [Suzuki et al 2016].

Genetically Related Disorders

Pathogenic variants in genes that cause Joubert syndrome (JS) have also been identified in disorders with clinical findings that overlap with JS; thus, in many instances it has become difficult to determine if a previously recognized disorder is truly distinct from JS (i.e., is an allelic disorder) or is part of the spectrum of JS (see Table 3). Brief descriptions of some of those disorders follow.

Acrocallosal syndrome (ACLS) (OMIM 200990), an autosomal recessive disorder, is characterized by macrocephaly, intellectual disability, agenesis of the corpus callosum and occasional posterior fossa abnormalities, ocular hypertelorism, polyaxial polydactyly of the hands, and preaxial polydactyly of the feet. It has been postulated that ACLS is allelic to **hydrolethalus syndrome**. Identification of several families with both disorders and *KIF7* pathogenic variants confirms the proposed association; of note, several of the probands had evidence of the molar tooth sign (MTS) on cranial imaging, suggesting that ACLS and JS may represent overlapping ciliopathies [Putoux et al 2011].

Bardet-Biedl syndrome (BBS), usually inherited in an autosomal recessive manner, is characterized by cone-rod retinal dystrophy, truncal obesity, postaxial polydactyly, cognitive impairment, hypogonadotropic hypogonadism in males, genital malformations in females, and renal disease that may include structural malformations, renal hypoplasia, hydronephrosis, cystic kidneys, and glomerulonephritis. Progressive retinal impairment often causes blindness; renal failure may cause significant morbidity. Some affected individuals have hepatic fibrosis. Although many individuals are ataxic with poor coordination, cerebellar involvement or structural malformations are not typical [Baskin et al 2002]. Pathogenic variants in at least 19 genes, all of which play a role in the primary cilium, have been described. Pathogenic variants in *CEP290, MKS1,* and *NPHP1* have been shown to cause both BBS and JS [Leitch et al 2008, Zaghloul & Katsanis 2009, Knopp et al 2015].

Cogan syndrome (OMIM 257550), an autosomal recessive familial form of congenital oculomotor apraxia, is characterized by defective horizontal voluntary eye movements with jerkiness. Oculomotor apraxia is also a common manifestation of JS. Detailed neuroimaging via fiber tracking suggests that there may be subtle differences in some of the pathways in Cogan syndrome versus JS [Merlini et al 2010].

Some individuals with Cogan syndrome also have cerebellar vermis hypoplasia with evidence of the molar tooth sign [Whitsel et al 1995, Sargent et al 1997], and occasionally develop nephronophthisis. The approximately 290-kb *NPHP1* homozygous deletion or compound heterozygosity for the approximately 290-kb deletion and an *NPHP1* sequence variant have been identified in some individuals with Cogan syndrome [Saunier et al 1997, Betz et al 2000].

Hydrolethalus syndrome (HLS) (OMIM PS236680), a lethal autosomal recessive disorder, is associated with midline brain anomalies (usually hydrocephaly or anencephaly with a keyhole foramen magnum), migrognathia, postaxial polydactyly of the hands, and preaxial polydactyly of the feet. In the Finnish population, pathogenic variants in *HYLS1* have been identified [Mee et al 2005]. Pathogenic variants in *KIF7* were identified in a consanguineous Algerian pedigree in which four affected fetuses had features consistent with HLS, but also a midbrain-hindbrain malformation similar to the MTS [Putoux et al 2011]. Pathogenic variants in *KIAA0586* have also been described in fetuses with HLS as well as in individuals with JS and a variety of ciliopathy phenotypes [Alby et al 2015].

Jeune asphyxiating thoracic dystrophy (JATD) is an autosomal recessive skeletal dysplasia characterized by a long, narrow thorax, short stature, short limbs, polydactyly, and renal cystic disease, with skeletal findings that may include cone-shaped epiphyses in hands and feet, irregular metaphyses, shortened ilium, and trident-shaped acetabulum. It is often lethal in infancy secondary to respiratory insufficiency. More than 12 ciliary genes and/or loci have been identified (including several intraflagellar transport proteins). Heterozygous pathogenic variants in *TTC21B* have been identified in three families with JATD with one proband demonstrating

compound heterozygosity for a null allele and a hypomorphic allele [Davis et al 2011]. Pathogenic variants in *CSPP1* [Tuz et al 2014] and *KIAA0586* [Malicdan et al 2015] have been identified in individuals with JS and manifestations of JATD.

Leber congenital amaurosis (LCA), a severe dystrophy of the retina, typically becomes evident in the first year of life. Visual function is usually poor and often accompanied by nystagmus, sluggish or near-absent pupillary responses, photophobia, high hyperopia, and keratoconus. Visual acuity is rarely better than 20/400. A characteristic finding is Franceschetti's oculodigital sign, comprising eye poking, pressing, and rubbing. The appearance of the fundus is extremely variable. While the retina may initially appear normal, a pigmentary retinopathy reminiscent of retinitis pigmentosa is frequently observed later in childhood. The electroretinogram is characteristically "nondetectable" or severely subnormal. Pathogenic variants in at least 17 genes cause LCA, and pathogenic variants in *CEP290* account for about 20% of LCA, with one homozygous intronic pathogenic variant accounting for at least 20% of isolated congenital blindness in European cohorts [den Hollander et al 2006].

Mainzer-Saldino syndrome (MZSDS) is an autosomal recessive disorder described by the three diagnostic criteria of retinal dystrophy, renal disease (typically nephronophthisis), and phalangeal cone-shaped epiphyses. Variable findings include cerebellar hypoplasia, a narrow thorax, hepatic fibrosis, and dolichocephaly, with significant overlap with features of JATD and pathogenic variants in *IFT140* described in both conditions [Mainzer et al 1970, Perrault et al 2012]. Pathogenic variants in *IFT172*, another component of the intraflagellar transport apparatus, have been described in those with JATD, MZSDS, and JS [Halbritter et al 2013].

A term that has been used to encompasse Ellis-van Creveld syndrome (EVC), short-rib polydactyly syndrome (SRPS), JATD, and MZSDS is **short-rib thoracic dysplasia (SRTD)** (OMIM PS208500) with or without polydactyly; these conditions are autosomal recessive skeletal ciliopathies that are characterized by a constricted thoracic cage, short ribs, shortened tubular bones, and a "trident" appearance of the acetabular roof. There is clearly a great deal of overlap between these skeletal dysplasias and some forms of JS.

Meckel syndrome (OMIM PS249000), an autosomal recessive disorder, is characterized by the triad of cystic renal disease, posterior fossa abnormalities (usually occipital encephalocele), and the hepatic ductal plate malformation leading to hepatic fibrosis and bile duct proliferation. Polydactyly is relatively common. Cerebellar vermis hypoplasia has been described in some individuals. Meckel syndrome is usually lethal in the prenatal or perinatal period [Kyttälä et al 2006, Smith et al 2006]. Pathogenic variants in at least 21 genes have been identified in Meckel syndrome [Knopp et al 2015]. Pathogenic variants in at least 18 of these genes, *CEP290, TMEM67, RPGRIP1L, CC2D2A, CEP41, MKS1, B9D1, B9D2, TMEM138, TMEM231, TCTN2, TCTN3, TMEM237, CPLANE1, CSPP1, CEP120, TMEM107,* and *TMEM216,* have also been identified in individuals with JS [Parisi 2009, Valente et al 2010, Thomas et al 2012, Romani et al 2014, Bachmann-Gagescu et al 2015a, Knopp et al 2015, Shaheen et al 2015a, Roosing et al 2016a, Slaats et al 2016]. In many cases, pathogenic variants that predict a more severe effect on protein function such as transcription termination or null variants are associated with the lethal Meckel syndrome phenotype, while milder pathogenic variants such as missense variants are associated with JS [Romani et al 2014, Slaats et al 2016]. In some families the identical pathogenic variants can be found in a fetus with Meckel syndrome and a child with a JS, highlighting that these disorders can represent a spectrum [Valente et al 2010].

MORM (*m*ental retardation, truncal obesity, retinal dystrophy, micropenis) syndrome (OMIM 610156), an autosomal recessive disorder, appears to be related to Bardet-Biedl syndrome and is caused by pathogenic variants in *INPP5E* [Bielas et al 2009, Jacoby et al 2009]. Individuals with this condition have normal growth parameters and life span with a congenital non-progressive retinal dystrophy and static mild-to-moderate cognitive impairment; in contrast to Bardet-Biedl syndrome, there is no polydactyly, apparent hypogonadism, or obvious renal disease [Hampshire et al 2006].

Nephronophthisis, an autosomal recessive kidney disease characterized by renal tubular atrophy and progressive interstitial fibrosis with later development of medullary cysts, is caused by pathogenic variants in at least 19 genes [Hildebrandt et al 2009, Hurd & Hildebrandt 2011, Wolf 2015]. The age of onset of end-stage kidney disease can be variable, thereby defining subtypes such as infantile, juvenile, and adolescent. A homozygous, approximately 290-kb deletion of *NPHP1* is identified in approximately 25% of individuals with juvenile nephronophthisis [Hoefele et al 2005, Saunier et al 2005, Hildebrandt et al 2009] and is causative in a small subset of individuals with JS. Note: The most common form, juvenile nephronophthisis, can also be a renal manifestation in JS. Conversely, it is estimated that 10% of individuals with nephronophthisis have extrarenal findings, which can include the molar tooth sign in some cases [Saunier et al 2005].

Oral-facial-digital syndrome describes a heterogeneous group of disorders characterized by facial features, oral abnormalities (often lobulated tongue and oral frenula), and digital anomalies such as polydactyly. Based on other associated clinical features, at least 13 clinical subtypes have been described. These features also overlap considerably with Meckel syndrome, short-rib polydactyly syndrome, and JS. Of the genes identified thus far for OFD, all have all had ciliary roles, and several overlap with JS.

Oral-facial-digital syndrome type I (OFD1) is associated with dysfunction of primary cilia and is characterized by the following abnormalities:

- Oral (lobed tongue, hamartomas or lipomas of the tongue, cleft of the hard or soft palate, accessory gingival frenulae, hypodontia and other dental abnormalities)
- Facial (ocular hypertelorism or telecanthus, hypoplasia of the alae nasi, median cleft or pseudocleft of the upper lip, micrognathia)
- Digital (brachydactyly, syndactyly of varying degrees, and clinodactyly of the fifth finger; duplicated hallux [great toe]; preaxial or postaxial polydactyly of the hands)
- Brain (intracerebral cysts, corpus callosum agenesis, cerebellar agenesis with or without Dandy-Walker malformation)
- Kidney (polycystic kidney disease)

Up to 50% of individuals with OFD1 have some degree of intellectual disability that is usually mild. Almost all affected individuals are female. However, males with OFD1 have been described, mostly as malformed fetuses delivered by women with OFD1.

Of note, the phenotypic spectrum was broadened with recognition that the clinical features described in four individuals (hydrops fetalis, jaundice, brisk deep tendon reflexes, seizures, and trilobate left lung) [Terespolsky et al 1995, Brzustowicz et al 1999] were associated with pathogenic variants in *OFD1* [Budny et al 2006]. Pathogenic variants in *OFD1* have also been described in rare males with JS and features of OFD [Coene et al 2009, Field et al 2012].

Oral-facial-digital syndrome type IV (OFD IV, Mohr-Majewski syndrome) (OMIM 258860) is characterized by hallucal and postaxial polysyndactyly, tibial dysplasia, and variable short ribs, cystic kidneys, and brain anomalies. Pathogenic truncating variants in *TCTN3* were identified in several pedigrees with a severe lethal OFD IV phenotype and bowing of long bones, cystic kidneys, occipital encephalocele, and bile duct proliferation of the liver but without short ribs; several of these fetuses also displayed vermis agenesis suggestive of the molar tooth sign [Thomas et al 2012]. Of note, this phenotype overlaps with Meckel syndrome and with JS.

Oral-facial-digital syndrome type VI (OFD VI, Varadi-Papp syndrome) (OMIM 277170). Individuals with OFD VI often have mesaxial polydactyly, in which the extra digit occurs between the central digits and is often accompanied by a Y-shaped metacarpal, as well as cerebellar vermis hypoplasia, oral frenulae, tongue lobulations or hamartomas (Figure 2B), and craniofacial features that include wide-spaced eyes and midline lip groove. Renal and cardiac involvement have been described [Münke et al 1990]. Problems with mastication, swallowing, and respiration may result. OFD VI has been defined as a form of JS, requiring the MTS as well as one or more

of the following features: tongue hamartoma/oral frenula/upper lip notch, mesaxial polydactyly, and hypothalamic hamartoma [Poretti et al 2012]. One group identified pathogenic variants in *CPLANE1* in 9/11 families with OFD VI [Lopez et al 2014]. Features of preaxial and/or mesaxial polydactyly and hypothalamic hamartoma were more likely related to *CPLANE1* pathogenic variants, whereas tongue hamartomas and lingual frenula were not associated with pathogenic variants in this gene [Lopez et al 2014, Romani et al 2015]. Another group identified *CPLANE1* pathogenic variants in only two of 17 individuals with OFD VI; pathogenic variants in *TMEM216, TMEM107,* and *OFD1* have also been reported in OFD VI [Romani et al 2015, Lambacher et al 2016].

Differential Diagnosis

Disorders in the differential diagnosis include the disorders discussed in Genetically Related Disorders.

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease in an individual diagnosed with Joubert syndrome (JS), the following baseline evaluations to identify the extent of disease in affected infants/children are recommended [Parisi et al 2007] (full text). Recommendations were developed by a consensus panel and are outlined on the Joubert Syndrome and Related Disorders Foundation website.

- Examination of high-quality MRI scan to assess for cerebral malformations, neuronal migration disorders, or cephaloceles that could portend a poorer prognosis or seizures, if not done at the time of diagnosis
- A baseline neurologic evaluation with particular attention to tone, respiratory pattern (tachypnea and apnea), eye movements, development, and cerebellar function
- Sleep history with polysomnogram as baseline evaluation and particularly if symptomatic apnea is present
- Assessment of oromotor function by a speech therapist and/or by fluoroscopic swallowing studies
- Developmental assessment with age-appropriate tools
- Evaluation by a pediatric ophthalmologist via dilated eye examination for colobomas and retinal changes, as well as strabismus and ptosis, with consideration of specialized testing such as visual-evoked potentials, electroretinogram, and ocular motility testing
- Abdominal ultrasound examination to evaluate for hepatic fibrosis or renal cysts and/or findings consistent with nephronophthisis (e.g., loss of corticomedullary differentiation)
- Tests of renal function, including blood pressure, blood urea nitrogen (BUN), serum creatinine concentration, complete blood count (CBC), and urinalysis from first-morning void for specific gravity to test concentrating ability (if feasible)
- Liver function tests including serum concentrations of transaminases, albumin, bilirubin, and prothrombin time
- For males with micropenis or any child with signs of growth hormone deficiency, endocrine evaluation for other pituitary abnormalities
- Skeletal survey and/or limb radiographs if there is suspicion of a skeletal dysplasia such as short-rib polydactyly or JATD
- Consultation with a clinical geneticist to document family history, to evaluate growth and head size, and to evaluate for other anomalies including polydactyly, dysmorphic facial features, tongue tumors/lobulations, and micropenis

Treatment of Manifestations

Respiratory

- Infants and children with abnormal breathing patterns should be considered for apnea monitoring if the abnormality is severe. Supportive therapy may include stimulatory medications such as caffeine or supplementary oxygen, particularly in the newborn period.
- Anesthetic management during surgical procedures for infants with significant respiratory disturbance may be accomplished in some cases by the use of:
  - Regional anesthesia without opioids to avoid exacerbation of apneic episodes [Vodopich & Gordon 2004];
  - Alpha-2 agonists such as clonidine or dexmedetomidine to avoid respiratory depression and other complications of opioids while achieving motion-free images [Sriganesh et al 2014].
- In rare cases, mechanical support and/or tracheostomy may be considered in a child with severe respiratory dysfunction.
- Aggressive treatment of middle ear infections is indicated to avoid conductive hearing loss.

Hypotonia and therapeutic interventions

- Appropriate management and therapy of oromotor dysfunction by a speech therapist
- Nasogastric feeding tubes or gastrostomy tube placement for feeding in children with severe dysphagia
- Occupational, physical, and speech therapy through early intervention programs
- Individualized educational assessment and support for school-aged children to maximize school performance
- Periodic neuropsychologic and developmental testing at appropriate ages

Other CNS malformations

- Neurosurgical consultation is indicated for those with evidence of hydrocephalus (rapidly increasing head circumference and/or bulging fontanelle). Note: When hydrocephalus occurs in JS, it rarely requires shunting.
- Posterior fossa cysts and fluid collections rarely require intervention.
- Encephalocele may require primary surgical closure.
- Seizures should be evaluated and treated by a neurologist using standard anti-seizure medication.
- A variety of psychotropic medications have been used to treat the behavioral complications in Joubert syndrome; no single medication has been uniformly effective for all children.

Ophthalmologic

- Surgery as needed for symptomatic ptosis, strabismus, or amblyopia
- Corrective lenses for refractive errors
- Possible vision therapies for oculomotor apraxia, although specific studies are lacking in this disorder
- Interventions for the visually impaired when congenital blindness or progressive retinal dystrophy are present

Renal disease

- Consultation with a nephrologist is indicated.
- End-stage kidney disease (ESKD) resulting from nephronophthisis frequently requires dialysis and/or kidney transplantation during the teenage years or later.
- Hypertension, anemia, and other complications of ESKD require specific treatment.

Hepatic fibrosis

- Consultation with a gastroenterologist is indicated.
- Liver failure and/or fibrosis should be managed by a gastroenterologist with arrangements for surgical intervention such as portal shunting for esophageal varices and portal hypertension, as appropriate.

- Some individuals have needed orthotopic liver transplantation.

Skeletal

- Surgical treatment for polydactyly
- Appropriate medical management by an orthopedic specialist for scoliosis

Other

- Orofacial clefting is treated by standard surgical interventions.
- Tongue tumors that impair normal swallowing or cause respiratory obstruction may require surgical resection.
- Symptoms of obstructive sleep apnea and/or tongue hypertrophy in older individuals may require evaluation with a polysomnogram and/or by an otolaryngologist for consideration of adenoidectomy, tonsillectomy, or surgical tongue reduction. Some children have used BiPAP or C-PAP at night.
- Consultation with an endocrinologist for menstrual irregularities and for pituitary hormone deficiency (with hormone replacement as indicated) is appropriate.
- Obesity should be managed with appropriate measures, including diet, exercise, and behavioral therapies
- Congenital heart defects and situs abnormalities should be treated by conventional therapies.
- Surgical correction of Hirschsprung disease (if present) is indicated.

Prevention of Secondary Complications

Antibiotic prophylaxis for surgical and dental procedures is indicated for individuals with structural cardiac anomalies.

Surveillance

Because no uniformly reliable distinguishing characteristics allow prediction of the complications that may develop in an infant or young child with Joubert syndrome, a number of annual evaluations are recommended (see also Joubert Syndrome and Related Disorders Foundation website):

- Pediatric and neurologic evaluation and monitoring of growth, sexual maturation, breathing (including apnea symptoms), and motor function
- Neuropsychological and developmental evaluation and testing, as appropriate
- Ophthalmologic evaluation for visual acuity, tracking ability, and development of retinal dystrophy
- Abdominal ultrasound examination for evaluation of possible liver and kidney abnormalities
- Liver function tests
- Evaluation of renal function: measurement of blood pressure, serum concentrations of BUN and creatinine, CBC, and assessment of first-morning void urinalysis

Agents/Circumstances to Avoid

Individuals with renal impairment should avoid nephrotoxic medications such as nonsteroidal anti-inflammatory drugs.

Individuals with liver impairment should avoid hepatotoxic medications.

Evaluation of Relatives at Risk

Sibs or relatives who have clinical features similar to those of an individual with JS warrant genetic consultation. If the pathogenic variant(s) have been identified in a proband, testing symptomatic relatives for these pathogenic variants is appropriate.

See Genetic Counseling for issues related to testing of at-risk relatives for genetic counseling purposes.

Therapies Under Investigation

Search ClinicalTrials.gov in the US and EU Clinical Trials Register in Europe for information on clinical studies for a wide range of diseases and conditions. Note: There may not be clinical trials for this disorder.

Genetic Counseling

Genetic counseling is the process of providing individuals and families with information on the nature, mode(s) of inheritance, and implications of genetic disorders to help them make informed medical and personal decisions. The following section deals with genetic risk assessment and the use of family history and genetic testing to clarify genetic status for family members; it is not meant to address all personal, cultural, or ethical issues that may arise or to substitute for consultation with a genetics professional. —ED.

Mode of Inheritance

Joubert syndrome (JS) is inherited predominantly in an autosomal recessive manner.

OFD1-related JS is inherited in an X-linked manner (click here (pdf) for discussion of X-linked inheritance).

Risk to Family Members (Autosomal Recessive Inheritance)

Parents of a proband

- The parents of an affected child are obligate heterozygotes (i.e., carriers of one pathogenic variant in a JS-related gene).
- Heterozygotes are asymptomatic and are not at risk of developing the disorder.

Sibs of a proband

- At conception, each sib of an affected individual has a 25% chance of being affected, a 50% chance of being an asymptomatic carrier, and a 25% chance of being unaffected and not a carrier.
- Heterozygotes (carriers) are asymptomatic and are not at risk of developing the disorder.

Offspring of a proband

- The offspring of a proband are obligate heterozygotes (carriers) for a pathogenic variant in a JS-related gene.
- Although no individuals with JS are reported to have reproduced, the broad spectrum of cognitive impairment now known in this condition may increase the likelihood that reports of individuals who have had offspring will be forthcoming.

Other family members. Each sib of the proband's parents is at a 50% risk of being a carrier of a pathogenic variant in a JS-related gene.

For information about risk to family members – X-linked inheritance (*OFD1*-related) click here (pdf).

Carrier Detection

Carrier testing for at-risk relatives requires prior identification of the JS-related pathogenic variant(s) in the family.

Related Genetic Counseling Issues

See Management, Evaluation of Relatives at Risk for information on evaluating at-risk relatives for the purpose of early diagnosis and treatment.

Family planning

- The optimal time for determination of genetic risk, clarification of carrier status, and discussion of the availability of prenatal/preimplantation genetic testing is before pregnancy.
- It is appropriate to offer genetic counseling (including discussion of potential risks to offspring and reproductive options) to young adults who are affected, are carriers, or are at risk of being carriers.

DNA banking. Because it is likely that testing methodology and our understanding of genes, pathogenic mechanisms, and diseases will improve in the future, consideration should be given to banking DNA from probands in whom a molecular diagnosis has not been confirned (i.e., the causative pathogenic mechanism is unknown). For more information, see Huang et al [2022].

Prenatal Testing and Preimplantation Genetic Testing

Molecular genetic testing. Once the JS-related pathogenic variant(s) have been identified in an affected family member, prenatal and preimplantation genetic testing for JS are possible.

Differences in perspective may exist among medical professionals and within families regarding the use of prenatal testing. While most centers would consider use of prenatal testing to be a personal decision, discussion of these issues may be helpful.

Prenatal imaging. First-trimester diagnosis of JS for pregnancies at 25% risk has been reported using ultrasound examination to identify structural brain abnormalities such as encephalocele [van Zalen-Sprock et al 1996, Wang et al 1999]. More typically, prenatal diagnosis in at-risk fetuses has been accomplished by prenatal ultrasound examination of the posterior fossa and/or kidneys (for cysts and enlarged and/or hyperechoic kidneys) and digits (for polydactyly) as early as the second trimester [Ní Scanaill et al 1999, Aslan et al 2002, Doherty et al 2005]. In reality, prenatal sonographic findings in fetuses with JS are relatively nonspecific and include increased nuchal translucency, enlarged cisterna magna, cerebellar vermis aplasia/hypoplasia, occipital encephalocele, and ventriculomegaly, making definitive diagnosis of JS difficult in the absence of a family history. Moreover, the cerebellar vermis is a relatively late-developing structure, and may not cover the fourth ventricle until 18 weeks' gestation, making visualization of the molar tooth sign (MTS) difficult earlier in gestation [Bromley et al 1994]. The use of 2D ultrasound and 3D sonographic reconstruction with surface rendering has allowed visualization of the MTS as early as 22 weeks in several fetuses without a prior family history of JS [Quarello et al 2014].

Accurate prenatal diagnosis of JS in an at-risk fetus has been achieved by serial prenatal ultrasound imaging starting at 11 to 12 weeks' gestation, with detailed evaluation of cerebellar and other fetal anatomy through 20 weeks' gestation, followed by fetal MRI imaging at 20 to 22 weeks' gestation [Doherty et al 2005]. In a series of 12 pregnancies at 25% risk of having a fetus with JS, one center was able to correctly diagnose JS in the three affected fetuses based on fetal MRI findings at the pontomesencephalic junction (including the MTS) as early as 22 weeks' gestation [Saleem & Zaki 2010]. In the earliest reported diagnoses to date, MTS was identified in two separate at-risk pregnancies at 17 to 18 weeks' gestation via fetal MRI [Saleem et al 2011]. Although prenatal imaging, including fetal MRI, is useful in the diagnosis of posterior fossa anomalies, its sensitivity and specificity for the diagnosis of JS is unknown, and its use has not been systematically evaluated.

For a couple who has already had a child with JS, the presence of findings that suggest a prenatal diagnosis of Joubert syndrome and related disorders (e.g., encephalocele, renal cystic changes, polydactyly, or posterior fossa anomalies on fetal imaging) is highly significant; however, the absence of these signs does not preclude a

diagnosis of Joubert syndrome and related disorders because of the unknown sensitivity of imaging and because of intrafamilial variability.

Resources

GeneReviews staff has selected the following disease-specific and/or umbrella support organizations and/or registries for the benefit of individuals with this disorder and their families. GeneReviews is not responsible for the information provided by other organizations. For information on selection criteria, click here.

- **Joubert Syndrome and Related Disorders Foundation**
  Phone: 952-240-4853
  jsrdf.org
- **MedlinePlus**
  Joubert Syndrome
- **National Institute of Neurological Disorders and Stroke (NINDS)**
  Joubert Syndrome
- **Apraxia Kids**
  Phone: 412-785-7072
  Email: info@apraxia-kids.org
  apraxia-kids.org
- **Ciliopathy Alliance**
  United Kingdom
  ciliopathyalliance.org

Molecular Genetics

Information in the Molecular Genetics and OMIM tables may differ from that elsewhere in the GeneReview: tables may contain more recent information. —ED.

Table A. Joubert Syndrome: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
AHI1	6q23.3	Jouberin	AHI1 @ LOVD	AHI1	AHI1
ARL13B	3q11.1-q11.2	ADP-ribosylation factor-like protein 13B	ARL13B database	ARL13B	ARL13B
B9D1	17p11.2	B9 domain-containing protein 1	B9D1 @ LOVD	B9D1	B9D1
B9D2	19q13.2	B9 domain-containing protein 2		B9D2	B9D2
C2CD3	11q13.4	C2 domain-containing protein 3		C2CD3	C2CD3
CC2D2A	4p15.32	Coiled-coil and C2 domain-containing protein 2A		CC2D2A	CC2D2A
CEP41	7q32.2	Centrosomal protein of 41 kDa		CEP41	CEP41
CEP104	1p36.32	Centrosomal protein of 104 kDa		CEP104	CEP104
CEP120	5q23.2	Centrosomal protein of 120 kDa		CEP120	CEP120
CEP290	12q21.32	Centrosomal protein of 290 kDa		CEP290	CEP290

Table A. continued from previous page.

CPLANE1	5p13.2	Ciliogenesis and planar polarity effector 1	C5orf42 @ LOVD	CPLANE1	CPLANE1
CSPP1	8q13.1-q13.2	Centrosome and spindle pole-associated protein 1		CSPP1	CSPP1
IFT172	2p23.3	Intraflagellar transport protein 172 homolog		IFT172	IFT172
INPP5E	9q34.3	Phosphatidylinositol polyphosphate 5-phosphatase type IV	INPP5E @ LOVD	INPP5E	INPP5E
KATNIP	16p12.1	Katanin-interacting protein		KATNIP	KATNIP
KIAA0586	14q23.1	Protein TALPID3		KIAA0586	KIAA0586
KIF7	15q26.1	Kinesin-like protein KIF7	KIF7 @ LOVD	KIF7	KIF7
MKS1	17q22	Tectonic-like complex member MKS1	MKS1 @ LOVD	MKS1	MKS1
NPHP1	2q13	Nephrocystin-1	NPHP1 @ LOVD	NPHP1	NPHP1
OFD1	Xp22.2	Centriole and centriolar satellite protein OFD1	OFD1 @ LOVD	OFD1	OFD1
PDE6D	2q37.1	Retinal rod rhodopsin-sensitive cGMP 3',5'-cyclic phosphodiesterase subunit delta		PDE6D	PDE6D
POC1B	12q21.33	POC1 centriolar protein homolog B		POC1B	POC1B
RPGRIP1L	16q12.2	Protein fantom		RPGRIP1L	RPGRIP1L
TCTN1	12q24.11	Tectonic-1	TCTN1 @ LOVD	TCTN1	TCTN1
TCTN2	12q24.31	Tectonic-2		TCTN2	TCTN2
TCTN3	10q24.1	Tectonic-3		TCTN3	TCTN3
TMEM67	8q22.1	Meckelin	TMEM67 @ LOVD	TMEM67	TMEM67
TMEM107	17p13.1	Transmembrane protein 107		TMEM107	TMEM107
TMEM138	11q12.2	Transmembrane protein 138		TMEM138	TMEM138
TMEM216	11q12.2	Transmembrane protein 216	TMEM216 database	TMEM216	TMEM216
TMEM231	16q23.1	Transmembrane protein 231		TMEM231	TMEM231
TMEM237	2q33.1	Transmembrane protein 237	TMEM237 @ LOVD	TMEM237	TMEM237
TTC21B	2q24.3	Tetratricopeptide repeat protein 21B		TTC21B	TTC21B
ZNF423	16q12.1	Zinc finger protein 423		ZNF423	ZNF423

Data are compiled from the following standard references: gene from HGNC; chromosome locus from OMIM; protein from UniProt. For a description of databases (Locus Specific, HGMD, ClinVar) to which links are provided, click here.

Table B. OMIM Entries for Joubert Syndrome (View All in OMIM)

213300	JOUBERT SYNDROME 1; JBTS1
243910	ARIMA SYNDROME
300170	OFD1 CENTRIOLE AND CENTRIOLAR SATELLITE PROTEIN; OFD1
300804	JOUBERT SYNDROME 10; JBTS10
602676	PHOSPHODIESTERASE 6D; PDE6D
604557	ZINC FINGER PROTEIN 423; ZNF423
607100	NEPHROCYSTIN 1; NPHP1
607386	INTRAFLAGELLAR TRANSPORT 172; IFT172
608091	JOUBERT SYNDROME 2; JBTS2
608629	JOUBERT SYNDROME 3; JBTS3
608894	ABELSON HELPER INTEGRATION SITE 1; AHI1
608922	ADP-RIBOSYLATION FACTOR-LIKE GTPase 13B; ARL13B
609583	JOUBERT SYNDROME 4; JBTS4
609863	TECTONIC FAMILY, MEMBER 1; TCTN1
609883	MKS TRANSITION ZONE COMPLEX SUBUNIT 1; MKS1
609884	TRANSMEMBRANE PROTEIN 67; TMEM67
610142	CENTROSOMAL PROTEIN, 290-KD; CEP290
610178	KIAA0586 GENE; KIAA0586
610188	JOUBERT SYNDROME 5; JBTS5
610523	CENTROSOMAL PROTEIN, 41-KD; CEP41
610688	JOUBERT SYNDROME 6; JBTS6
610937	RPGRIP1-LIKE; RPGRIP1L
611254	KINESIN FAMILY MEMBER 7; KIF7
611560	JOUBERT SYNDROME 7; JBTS7
611654	CENTROSOME SPINDLE POLE-ASSOCIATED PROTEIN 1; CSPP1
611951	B9 DOMAIN-CONTAINING PROTEIN 2; B9D2
612013	COILED-COIL AND C2 DOMAINS-CONTAINING PROTEIN 2A; CC2D2A
612014	TETRATRICOPEPTIDE REPEAT DOMAIN-CONTAINING PROTEIN 21B; TTC21B
612285	JOUBERT SYNDROME 9; JBTS9
612291	JOUBERT SYNDROME 8; JBTS8
613037	INOSITOL POLYPHOSPHATE-5-PHOSPHATASE, 72-KD; INPP5E
613277	TRANSMEMBRANE PROTEIN 216; TMEM216
613446	CENTROSOMAL PROTEIN, 120-KD; CEP120
613820	NEPHRONOPHTHISIS 12; NPHP12
613846	TECTONIC FAMILY, MEMBER 2; TCTN2
613847	TECTONIC FAMILY, MEMBER 3; TCTN3
614144	B9 DOMAIN-CONTAINING PROTEIN 1; B9D1
614173	JOUBERT SYNDROME 13; JBTS13

Table B. continued from previous page.

614423	TRANSMEMBRANE PROTEIN 237; TMEM237
614424	JOUBERT SYNDROME 14; JBTS14
614459	TRANSMEMBRANE PROTEIN 138; TMEM138
614464	JOUBERT SYNDROME 15; JBTS15
614465	JOUBERT SYNDROME 16; JBTS16
614571	CILIOGENESIS AND PLANAR POLARITY EFFECTOR COMPLEX, SUBUNIT 1; CPLANE1
614615	JOUBERT SYNDROME 17; JBTS17
614784	POC1 CENTRIOLAR PROTEIN B; POC1B
614815	JOUBERT SYNDROME 18; JBTS18
614844	NEPHRONOPHTHISIS 14; NPHP14
614949	TRANSMEMBRANE PROTEIN 231; TMEM231
614970	JOUBERT SYNDROME 20; JBTS20
615636	JOUBERT SYNDROME 21; JBTS21
615665	JOUBERT SYNDROME 22; JBTS22
615944	C2 CALCIUM-DEPENDENT DOMAIN-CONTAINING PROTEIN 3; C2CD3
616183	TRANSMEMBRANE PROTEIN 107; TMEM107
616490	JOUBERT SYNDROME 23; JBTS23
616650	KATANIN-INTERACTING PROTEIN; KATNIP
616654	JOUBERT SYNDROME 24; JBTS24
616690	CENTROSOMAL PROTEIN, 104-KD; CEP104
616781	JOUBERT SYNDROME 25; JBTS25
616784	JOUBERT SYNDROME 26; JBTS26
617120	JOUBERT SYNDROME 27; JBTS27
617121	JOUBERT SYNDROME 28; JBTS28
617761	JOUBERT SYNDROME 31; JBTS31

Molecular Pathogenesis

All of the genes in which pathogenic variants are known to cause Joubert syndrome (JS) localize to the primary cilium and/or basal body and centrosome where they may play a role in the formation, morphology, and/or function of these organelles. The cilia are membrane-found, hair-like projections that are anchored by the basal body.

Motile cilia have a 9+2 microtubule axonemal structure that allows for movement and flow of fluids; they are found on specialized cell types such as respiratory epithelia and spermatozoa. Primary cilia have a 9+0 microtubule structure and are usually non-motile. Primary cilia are found on most cell types and appear to play a role in cellular chemo- and mechanosensation and cell signaling, including the WNT, sonic hedgehog (SHH), and PDGF signaling pathways involved in differentiation, cell division, and planar cell polarity.

Ciliopathies, conditions caused by defects in one or more of the many proteins important in ciliary function, share many features including renal disease, retinal dystrophy, and polydactyly [reviewed in Badano et al 2006]. The association of ciliary defects with specific phenotypes has not been completely elucidated, but in the case of

the hindbrain malformation seen in Joubert syndrome, it is known that SHH signaling is critical for both dorsal-ventral patterning of the neural tube and cerebellar granule cell proliferation [Doherty 2009].

Note: Detailed information about JS-related genes in which pathogenic variants account for more than 1% of JS (see Table 1a) appears in this section. Detailed information about JS-related genes in which pathogenic variants account for less than 1% of JS (see Table 1b) appears here (pdf).

AHI1

Gene structure. *AHI1* comprises 28 exons and several alternative splice variant forms. The most common full-length transcript is 5,528 bp.

Pathogenic variants. Homozygous nonsense, missense, and splicing variants, deletions, and insertions have been reported [Dixon-Salazar et al 2004, Ferland et al 2004, Parisi et al 2006, Romano et al 2006, Utsch et al 2006]. (For more information, see Table A, **Locus Specific**.)

Normal gene product. 1196-amino acid protein, AHI1 (also termed jouberin). The protein includes a coiled-coil domain, an SH3 domain, and six WD40 repeats hypothesized to mediate a variety of functions including signal transduction, RNA processing, and vesicular trafficking.

Abnormal gene product. Loss of AHI1 function causes Joubert syndrome. In Ahi1-null mouse strains that survive, the phenotype ranges from a perinatal lethal phenotype to early retinal degeneration with a failure of proper development of the photoreceptor sensory cilia and outer segments [Westfall et al 2010].

CPLANE1

Gene structure. This reference sequence (NM_023073.3) comprises 53 exons. *CPLANE1* encodes a predicted 3,197-amino acid protein (NP_075561.3) [Srour et al 2012b, Srour et al 2015].

Pathogenic variants. Eight different pathogenic variants have been found in 14 affected individuals from a number of unrelated families of French Canadian descent, several are linked to a distinct haplotype that represents a different founder effect in the French Canadian population [Srour et al 2012b, Srour et al 2015]. Many affected individuals are compound heterozygotes for two different pathogenic variants. Another founder variant has been described in the Dutch population (p.Arg2904Ter) [Kroes et al 2016], and pathogenic variants have also been described in those with an OFD VI phenotype [Lopez et al 2014, Romani et al 2015].

Table 4. *CPLANE1* Pathogenic Variants Discussed in This *GeneReview*

DNA Nucleotide Change	Predicted Protein Change	Reference Sequences
c.4006C>T	p.Arg1336Trp	NM_023073.3 NP_075561.3
c.4804C>T	p.Arg1602Ter	
c.6354dupT	p.Ile2119TyrfsTer2	
c.6407delC	p.Pro2136HisfsTer31	
c.7400+1G>A	--	NM_023073.3
c.7477C>T	p.Arg2493Ter	NM_023073.3 NP_075561.3
c.8710C>T	p.Arg2904Ter	
c.4690G>A	p.Ala1564Thr	See footnote 1.

Variants listed in the table have been provided by the authors. *GeneReviews* staff have not independently verified the classification of variants.
GeneReviews follows the standard naming conventions of the Human Genome Variation Society (varnomen.hgvs.org). See Quick Reference for an explanation of nomenclature.
1. The c.4690G>A (p.Ala1564Thr) variant occurs in an alternate exon (exon 40a) suggested by Srour et al [2015].

Normal gene product. The encoded protein has features of a transmembrane protein and a putative coiled-coil domain. Proteomic studies have suggested protein interactions with proteins important in neurodevelopment. It appears to be widely expressed in a variety of tissues, including the central nervous system, but little else is known about the gene.

Abnormal gene product. The disease-associated variants are predicted to result in loss of function, aberrant splicing, exon skipping (c.7400+1G>A), or missense variants predicted by protein prediction algorithms to be damaging [Srour et al 2012b, Srour et al 2015].

CC2D2A

Gene structure. This 38-exon gene encodes a 1620-amino acid protein that shares domains in common with the *RPGRIP1L*-encoded protein.

Pathogenic variants. Variants in this gene cause Meckel syndrome and JSRD, including the COACH syndrome variant; null variants are associated with the more severe (and often lethal) Meckel syndrome phenotype [Mougou-Zerelli et al 2009]. Several pathogenic variants and likely founder effects have been identified in *CC2D2A* in French Canadians [Srour et al 2012b, Srour et al 2015].

Normal gene product. The protein has coiled-coil and a C2 calcium-binding domain and appears to play a critical role in cilia formation. Multiple transcript variants arise from alternative splicing. CC2D2A localizes to the basal body and physically interacts with CEP290 [Gorden et al 2008].

Abnormal gene product. Loss of CC2D2A protein results in human disease.

Loss of function in the zebrafish homolog results in pronephric cysts (the equivalent of kidney cysts) and other changes consistent with ciliary dysfunction [Gorden et al 2008].

CEP290

Gene structure. The gene comprises 54 exons and spans 93.2 kb of genomic DNA, with a full-length transcript size of 7972 bp. Alternative splicing results in several different isoforms.

Pathogenic variants. More than 100 distinct pathogenic variants have been identified in *CEP290*, with the vast majority of them predicted to be truncating (40 nonsense and 48 frameshift out of 112 total). One large heterozygous partial deletion associated with JS has also been identified, but most truncating variants are caused by small insertions or deletions. Only three variants are missense; 20 affect splicing [Coppieters et al 2010].

The spectrum of phenotypes associated with pathogenic variants in *CEP290* is broad, including LCA, nephronophthisis, Senior-Løken syndrome, JS, Meckel syndrome, and Bardet-Biedl syndrome (see Table 3). Although clear genotype-phenotype correlations are difficult to establish, some limited associations have been described and are summarized in the locus-specific database CEP290base [Coppieters et al 2010].

Normal gene product. *CEP290* encodes centrosomal protein of 290 kd (also termed nephrocystin-6), which comprises 2479 amino acid residues. Nephrocystin-6 is a centrosomal protein known to modulate the activity of ATF4, a transcription factor implicated in renal cyst formation. The protein contains 13 putative coiled-coil domains, a region with homology to SMC (structural maintenance of chromosomes) ATPases, six KID motifs, three tropomyosin homology domains, and an ATP/GTP binding site motif A. The protein localizes to the centrosome and cilia and has sites for N-glycosylation, tyrosine sulfation, phosphorylation, N-myristoylation, and amidation. Nephrocystin-6 has also been shown to interact with other JSRD-associated proteins, including CC2D2A and meckelin [Gorden et al 2008, Leitch et al 2008, Tallila et al 2008].

Abnormal gene product. Loss of CEP290 function causes disease. Knockdown experiments in zebrafish result in abnormal cerebellar, renal, and retinal development [Sayer et al 2006]. Evidence suggests that this protein is

expressed in the cerebellum during murine embryogenesis [Valente et al 2006b]. Two naturally occurring animal models with pathogenic variants in *cep290* have been identified, in the *rd16* mouse and in Abyssinian cats; both exhibit progressive retinal degeneration but no renal or cerebellar defects [Coppieters et al 2010].

CSPP1

Gene structure. *CSPP1* encodes a short, 876-amino acid isoform and a long, 1221-amino acid isoform [Patzke et al 2006, Tuz et al 2014].

Pathogenic variants. Nonsense truncating, frameshift truncating, and splice site variants make up the majority of reported pathogenic variants and fall throughout the protein [Akizu et al 2014, Tuz et al 2014]. One missense variant resulting in abnormal splicing and introduction of a downstream frameshift has been described [Tuz et al 2014]. There do not appear to be any clear genotype-phenotype correlations to explain the broad range of phenotypes of individuals with pathogenic variants in this gene.

Table 5. *CSPP1* Pathogenic Variants Discussed in This *GeneReview*

DNA Nucleotide Change	Predicted Protein Change	Reference Sequences
c.363_364delTA	p.His121GlnfsTer22	NM_024790.6 NP_079066.5

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Normal gene product. Centrosome spindle pole-associated protein 1 (CSPP1) encoded by this gene is 101.5 kd (142 kd for the long isoform) and contains five coiled-coil domains.It interacts with centrosomes and plays a role in cell-cycle progression and spindle organization during mitosis [Patzke et al 2006].

Abnormal gene product. Fibroblasts from affected individuals with *CSPP1*-related JS showed defects in ciliogenesis, with fewer and/or short cilia [Tuz et al 2014]. Impaired sonic hedgehog signaling has also been noted [Shaheen et al 2014].

INPP5E

Gene structure. *INPP5E* comprises nine exons and 3440 bp of mRNA and encodes a 644-amino acid protein.

Pathogenic variants. Missense variants within the catalytically active phosphatase domain in this gene cause some forms of JSRD [Bielas et al 2009]. In one family with the Bardet-Biedl syndrome-like MORM syndrome, the identified pathogenic variant results in premature truncation of the protein and deletion of the terminal 18 amino acids [Jacoby et al 2009].

Normal gene product. The protein encoded by this gene is 72-kd inositol polyphosphate 5-phosphatase (also known as inositol 1,4,5-trisphosphate [InsP3] 5-phosphatase), an enzyme that is involved in phosphatidylinositol signaling by mobilizing intracellular calcium and acting as a second messenger mediating cell responses to various stimuli. This enzyme localizes to the central core of the primary cilium and appears to affect its metabolism of phosphotidylinositol and stability [Jacoby et al 2009].

Abnormal gene product. The JS-associated pathogenic variants impair the 5-phosphatase activity of the enzyme and alter the ciliary phosphotidylinositol ratio, destabilizing the cilia. Mice with homozygous deletions of the orthologous gene die soon after birth and exhibit anophthalmos, polydactyly, cystic kidneys, skeletal abnormalities, cleft palate, and cerebral anomalies such as exencephaly [Jacoby et al 2009]. Deletion of the terminal 18 amino acids appears to affect localization of the protein within the cilium [Jacoby et al 2009].

KIAA0586

Gene structure. *KIAA0586* (*TALPID3*) comprises 34 exons and encodes a 1644-amino acid protein in its longest isoform, with at least six isoforms described [Roosing et al 2015].

Pathogenic variants. The pathogenic variants that cause the broad spectrum of findings are typically truncating variants or occasionally missense variants [Alby et al 2015, Bachmann-Gagescu et al 2015b, Malicdan et al 2015, Roosing et al 2015].

One relatively common pathogenic variant (c.428delG) is predicted to occur in the general population at a frequency of 1/300 [Roosing et al 2015], and in several cohorts, a second likely pathogenic variant has not yet been identified [Bachmann-Gagescu et al 2015b, Roosing et al 2015].

Of note, a recurrent multiexon deletion in *KIAA0586* that results in early termination of the protein was identified by Malicdan et al [2015]; it is not clear if such a large-scale intragenic deletion was evaluated in the cohorts reported by other groups.

Table 6. *KIAA0586* Pathogenic Variants Discussed in This *GeneReview*

DNA Nucleotide Change	Predicted Protein Change	Reference Sequences
c.428delG	p.Arg143LysfsTer4	NM_001244189.1 NP_001231118.1
del exon 8-exon 10	--	NM_001244189.1

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Normal gene product. *KIAA0586* encodes a centrosomal protein that is predicted to have four coiled-coil domains and a C-terminal proline-rich domain. It is required for ciliogenesis and for hedgehog signaling. The orthologous protein in chicken is TALPID3, which is essential for sonic hedgehog transduction in the limbs, neural tube, and somites of the developing chick [Malicdan et al 2015].

Abnormal gene product. KIAA0586 assists in the assembly of the ring-like structure at the distal end of centrioles to mediate protein trafficking to the cilia; loss of KIAA0586 leads to formation of ciliary vesicles and failure of centrosome migration. Disruption of *KIAA0586* expression in chick embryos, mutated mouse, and zebrafish embryos results in cells that lack primary cilia and causes facial, limb, and neural tube defects [Malicdan et al 2015]. In one series, *KIAA0586* pathogenic variants all occurred before the highly conserved domain necessary for centrosome localization [Malicdan et al 2015]. Moreover, fibroblasts derived from patients with *KIAA0586* pathogenic variants demonstrate reduced ciliation, shorter cilia when present, and altered sonic hedgehog signaling [Alby et al 2015, Malicdan et al 2015].

MKS1

Gene structure. *MKS1* is 21,170 bp in length, comprises 18 exons, and encodes a 559-amino acid protein. Multiple transcript variants encode different isoforms of this gene.

Pathogenic variants. A variety of missense, nonsense, and other truncating variants have been described in this gene, including a recurrent variant (p.Ser372del) in four out of 11 individuals with JS caused by pathogenic variants in this gene [Romani et al 2014, Slaats et al 2016]. For individuals with more severe Meckel syndrome phenotypes, the *MKS1* variants are predicted to be more damaging than those with JS, who generally carry at least one nontruncating variant in this gene.

Table 7. *MKS1* Pathogenic Variants Discussed in This *GeneReview*

DNA Nucleotide Change	Predicted Protein Change	Reference Sequences
c.1115_1117delCCT	p.Ser372del	NM_017777.3 NP_060247.2

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Normal gene product. The protein encoded by this gene localizes to the transition zone of the basal body and is required for formation of the primary cilium in ciliated cells. More severe variants in this gene result in Meckel syndrome type 1 and in Bardet-Biedl syndrome type 13.

Abnormal gene product. By testing fibroblasts from individuals with JS and pathogenic variants in this gene, Slaats et al [2016] observed that the cells had a normal or reduced number of cilia that were more variable in length than those from control individuals. In addition, there was altered distribution of the key ciliary proteins ARL13B and INPP5E; INPP5E is typically distributed along the cilium in an ARL13B-dependent manner that requires a functional transition zone, which appears to be defective in these individuals [Slaats et al 2016].

NPHP1

Gene structure. *NPHP1* comprises 20 exons; its cDNA is 3,713 bp. The gene resides in a region flanked by two large inverted repeat elements and encodes nephrocystin-1.

Pathogenic variants. In addition to a homozygous, approximately 290-kb deletion encompassing *NPHP1* and portions of another gene, *BENE* [Saunier et al 2000, Parisi et al 2004a], occasional single-nucleotide variants in *NPHP1* have also been identified [Hoefele et al 2005]. (For more information, see Table A.) Some individuals with more severe phenotypes than familial juvenile nephronophthisis type 1 or Senior-Løken syndrome (see Table 3) have the homozygous *NPHP1* deletion as well as a heterozygous change in *AHI1* or *CEP290*, suggesting the contribution of modifier genes [Tory et al 2007].

Normal gene product. Nephrocystin-1, a protein of 733 amino acids, has an src homology domain 3 (SH3) domain that may mediate interactions with other proteins. Nephrocystin appears to localize to the primary cilium of the cell, to cell-cell adherens junctions, and to the basal body, where it may function in the control of cell division and in cell-cell and cell-matrix adhesion signaling [Hildebrandt et al 2009]. Nephrocystin interacts with the AHI1 protein as well as with the proteins INVS, NPHP3, and NPHP4, which are encoded by genes mutated in other forms of nephronophthisis.

Abnormal gene product. The association of nephrocystin-1 with many other ciliary proteins and its known localization to the cilium/basal body in renal epithelium suggests a critical role in renal tubular development.

RPGRIP1L

Gene structure. The gene comprises 26 exons and 3948 bp and encodes a 1315-amino acid protein.

Pathogenic variants. A wide variety of missense, nonsense, and splice variants have been identified. In general, more severe truncating variants are associated with the lethal Meckel syndrome phenotype, while less severe variants cause JSRD, including the COACH variant [Delous et al 2007, Wolf et al 2007]. In addition, the p.Ala229Thr variant is associated with the development of retinal degeneration in individuals with ciliopathies caused by pathogenic variants in other genes [Khanna et al 2009].

Table 8. *RPGRIP1L* Pathogenic Variants Discussed in This *GeneReview*

DNA Nucleotide Change	Predicted Protein Change	Reference Sequences
c.685G>A	p.Ala229Thr	NM_015272.2 NP_056087.2

Variants listed in the table have been provided by the authors. *GeneReviews* staff have not independently verified the classification of variants.
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Normal gene product. The protein encoded by this gene (protein fantom) has coiled-coil domains, a C2 calcium-binding domain, a RPGR (retinitis pigmentosa GTPase regulator) interacting domain, and a centrosomal protein-related domain. It can localize to the basal body-centrosome complex or to primary cilia and centrosomes in ciliated cells. The protein interacts with nephrocystin-4, the protein defective in some forms of nephronophthisis and Senior-Løken syndrome [Arts et al 2007]. Two transcript variants encoding different protein isoforms have been identified for *RPGRIP1L*.

Abnormal gene product. Loss of RPGRIP1L function is associated with disease. In addition, the p.Ala229Thr change appears to alter the interaction of the *RPGRIP1L*-encoded protein with RPGR protein, resulting in loss of photoreceptor cells [Khanna et al 2009].

TCTN2

Gene structure. *TCTN2* (tectonic family member 2) comprises 18 exons and encodes several transcripts, the longest of which is 697 amino acids. The gene encodes an N-terminal signal peptide and a C-terminal transmembrane domain that is conserved in the *Drosophila* ortholog [Reiter & Skarnes 2006].

Pathogenic variants. Nonsense, frameshift, and splice site variants in this gene have been implicated in JSRD and MKS [Sang et al 2011, Shaheen et al 2011].

Normal gene product. Tectonic-2. In mice, the Tctn2 protein is known to regulate hedgehog signaling and ciliogenesis. It interacts with Mks1 and Cc2d2a.

Abnormal gene product. Loss of TCNTN2 function is associated with disease. The concept of a ciliary "interactome" involving NPHP, JS, and MKS proteins has been proposed to explain the modular nature of the ciliary structure and the different functions of interacting clusters of proteins involved in a variety of cellular processes [Sang et al 2011].

TMEM67 (*MKS3*)

Gene structure. The gene comprises 28 exons and spans 62.0 kb of genomic DNA with a full-length transcript size of 3,467 bp [Smith et al 2006]. There is at least one splice variant form of 29 exons and length of 3,280 bp encoding a protein with 995 residues [Ensembl Database].

Pathogenic variants. Pathogenic variants identified in individuals with Joubert syndrome and related disorders include splice site variants resulting in abnormal transcripts and missense variants, both presumably representing hypomorphic alleles with milder phenotypes than the more severe lethal variants causing Meckel syndrome [Smith et al 2006, Baala et al 2007]. Pathogenic variants in this gene are particularly prevalent in individuals with JS and liver involvement (the COACH variant) [Iannicelli et al 2010].

Normal gene product. Meckelin, a 995-amino acid protein with a calculated molecular weight of 108 kd, is predicted to contain a signal peptide, at least two cysteine-rich repeats, and a 490-amino acid extracellular region, followed by seven transmembrane domains and a small 30-residue cytoplasmic tail [Smith et al 2006]. The protein has been localized to the primary cilium and plasma membrane of renal and biliary epithelial cells

and other ciliated cells and has been shown to interact with the MKS1 protein involved in Meckel syndrome. Meckelin is involved in centrosome migration to the apical cell surface during early ciliogenesis, and is essential for ciliary development and function [Dawe et al 2007].

Abnormal gene product. Loss of TMEM67 function is associated with disease. The spontaneous rat mutant *wpk/wpk*, with a single-nucleotide variant in *TMEM67*, exhibits polycystic kidneys and hydrocephalus with agenesis of the corpus callosum [Smith et al 2006]. A comparable phenotype is observed in the spontaneous murine deletion mutants, which typically die by age three weeks of polycystic nephropathy; some also develop hydrocephalus [Cook et al 2009].

TMEM216

Gene structure. *TMEM216* comprises six exons. The longest splice isoform (NM_001173990) encodes a 148-amino acid protein. There are multiple splice variants. The 23-kb intergenic region between *TMEM216* and *TMEM138* appears to coordinate the expression of these two ciliary genes, both of which can cause JS [Lee et al 2012b].

Pathogenic variants. Pathogenic variants include missense, nonsense, and splice variants. One common variant (c.218G>T), resulting in the protein change p.Arg73Leu, appears to be a founder variant in the Ashkenazi Jewish population with carrier frequency of 1:92 to 1:100 [Edvardson et al 2010, Valente et al 2010]. Pathogenic variants, many of which are predicted to produce a truncated protein, also cause the lethal Meckel syndrome phenotype [Valente et al 2010].

Table 9. *TMEM216* Pathogenic Variants Discussed in This *GeneReview*

DNA Nucleotide Change	Predicted Protein Change	Reference Sequences
c.218G>T	p.Arg73Leu	NM_001173990.2 NP_001167461.1

Variants listed in the table have been provided by the authors. *GeneReviews* staff have not independently verified the classification of variants.
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Normal gene product. The longest isoform is transmembrane protein 216, a tetraspan transmembrane protein containing four hydrophobic transmembrane domains. These proteins appear to regulate signaling and trafficking properties of other partner proteins, including Wnt receptors. TMEM216 localizes to the base of primary cilia and forms a complex with meckelin, another transmembrane protein defective in JSRD encoded by *TMEM67* [Valente et al 2010]. In addition, TMEM216 and TMEM138 are required for ciliogenesis, as each localizes to a distinct vesicle pool that carries proteins necessary for ciliary assembly from the Golgi to the primary cilia [Lee et al 2012b].

Abnormal gene product. Disruption of *tmem216* in zebrafish causes defects in gastrulation as well as other changes typical of altered ciliary function [Valente et al 2010].

For information about genes in Table 1b, click here (pdf).

Chapter Notes

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Revision History

- 29 June 2017 (bp) Comprehensive update posted live
- 11 April 2013 (cd/mp) Revision: mutations in *TMEM231* and *TCTN3* identified to cause JSRD; clarification of the uncertainty of a role for mutation in *TTC21B*; sequence analysis and deletion/duplication analysis available clinically for mutations in *C5orf42* and *CEP41*; edits to Figure 2
- 13 September 2012 (cd) Revision: sequence analysis available clinically for *TCTN1*, *TCTN2*, *TTC21B*, and *TMEM13*; deletion/duplication analysis available for *TMEM138*
- 14 June 2012 (cd/mp) Revision: targeted mutation analysis for the *TMEM216* founder mutation c.218G>T available clinically
- 24 May 2012 (cd/mp) Revision: Joubert syndrome 11, 15, 16, and 17 result from mutations in *TTC21B*, *CEP41*, *TMEM138*, and *C5orf52* respectively
- 29 March 2012 (me) Comprehensive update posted live
- 8 March 2007 (cd) Revision: mutations in *TMEM67 (MKS3)* identified in 3/22 individuals with JS who did not have *NPHP1* deletions; *MKS3* is sixth JS locus.
- 4 August 2006 (cd) Revision: clinical testing and prenatal diagnosis available for *CEP290* mutations
- 25 July 2006 (cd) Revision: *AHI1* sequence analysis clinically available; prenatal diagnosis for *AHI1* and *NPHP1* clinically available
- 30 June 2006 (ca) Revision: mutations in *CEP290 (NPHP6)* identified in individuals with JTS
- 24 February 2006 (me) Comprehensive update posted live
- 9 July 2003 (me) Review posted live
- 27 January 2003 (mp) Original submission

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