GENEReviews

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Joubert Syndrome

[*Includes: AHI1-Related Joubert Syndrome, CORS2-Related Joubert Syndrome, JBTS1-Related Joubert Syndrome, TMEM67-Related Joubert Syndrome, NPHP1-Related Joubert Syndrome, CEP290-Related Joubert Syndrome*]

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Summary

Disease characteristics. Joubert syndrome is characterized by a distinctive cerebellar and brainstem malformation, hypotonia, developmental delays, and either episodic hyperpnea or apnea or atypical eye movements or both. Most children with Joubert syndrome develop truncal ataxia. Delayed acquisition of gross motor milestones is common. Cognitive abilities are variable, ranging from severe mental retardation to normal. In general, the breathing abnormalities improve with age. The delineation of the phenotypic spectrum of Joubert syndrome remains unresolved, and both intra- and interfamilial variation are seen. Other features sometimes identified in Joubert syndrome include retinal dystrophy, renal disease, ocular colobomas, occipital encephalocele, hepatic fibrosis, polydactyly, oral hamartomas, and endocrine abnormalities. Approximately 10% of individuals with Joubert syndrome have abnormal collections of cerebrospinal fluid in the posterior fossa that may resemble Dandy-Walker malformation.

Diagnosis/testing. The diagnosis of Joubert syndrome is based on the presence of characteristic clinical features and the "molar tooth sign" on cranial magnetic resonance imaging (MRI), resulting from hypoplasia of the cerebellar vermis and accompanying brainstem abnormalities on axial imaging through the junction of the midbrain and pons (isthmus region). The resulting images resemble the section of a tooth. Four causative genes in which mutations appear to account for no more than 10% of cases of Joubert syndrome each are *NPHP1*, *CEP290*, *AHI1*, and *TMEM67(MKS3)*; the other causative genes are unknown. Molecular genetic testing is clinically available for all four genes.

Management. Therapy for infants and children affected with Joubert syndrome with abnormal breathing includes stimulatory medications such as caffeine or supplemental oxygen; mechanical support; or tracheostomy in rare cases. Interventions for hypotonia and cognitive impairment include treatment of oromotor dysfunction by a speech therapist; early intervention programs for occupational, physical, and educational support; and periodic neuropsychologic and developmental testing. Gastrostomy tube placement may be considered for children with

severe dysphagia. Neurosurgical consultation is required for individuals with evidence of hydrocephalus; encephalocele may require primary surgical closure. Management of ophthalmologic problems includes surgery as needed for symptomatic ptosis, strabismus, or amblyopia; corrective lenses for refractive errors; and possible therapies for oculomotor apraxia. Therapies for the visually impaired are recommended for those with congenital blindness or progressive retinal dystrophy. Complications of end-stage renal disease resulting from cystic kidney disease or nephronophthisis often require specific treatments such as dialysis and/or kidney transplantation. Individuals with liver failure and/or fibrosis may require surgical intervention such as portal shunting or orthotopic liver transplantation. Polydactyly may require surgery. Annual evaluations of growth, vision, and liver and kidney function are recommended.

Genetic counseling. Joubert syndrome is inherited in an autosomal recessive manner. 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 an at-risk sib is known to be unaffected, the chance of his/her being a carrier is 2/3. Carrier testing for at-risk family members is available if the mutations have been identified in the proband. Prenatal diagnosis for mutations in *AHI1*, *CEP290*, *TMEM67*, and *NPHP1* mutations is available if the mutations have been identified in the proband or carrier parents. Prenatal diagnosis using ultrasound examination with or without fetal MRI has been successful.

Diagnosis

Clinical Diagnosis

Diagnostic criteria for Joubert syndrome have not been formally established. For clinical purposes, the following features support a diagnosis of Joubert syndrome. The diagnosis of "classic" Joubert syndrome is based on the presence of:

- **The "molar tooth sign,"** the MRI appearance of hypoplasia of the cerebellar vermis and accompanying brainstem abnormalities in an axial plane through the junction of the midbrain and pons (isthmus region) [Maria et al 1997; Maria, Quisling et al 1999; 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 and 1B) [Maria, Quisling et al 1999]. The molar tooth sign is an obligatory finding in Joubert syndrome.
- The clinical features of:
  - **Hypotonia in infancy** with later development of ataxia
  - **Developmental delays/mental retardation**
  - **Abnormal breathing pattern** (alternating tachypnea and/or apnea)

    AND/OR
  - **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, Quisling et al 1999; Tusa & Hove 1999; Bennett et al 2003]

Molecular Genetic Testing

GeneReviews designates a molecular genetic test as clinically available only if the test is listed in the GeneTests Laboratory Directory *by either a US CLIA-licensed laboratory or a non-US clinical laboratory. GeneTests does not verify laboratory-submitted information or warrant*

any aspect of a laboratory's licensure or performance. Clinicians must communicate directly with the laboratories to verify information.—ED.

Genes. Four genes causing Joubert syndrome have been identified:

- *NPHP1* [Parisi et al 2004, Castori et al 2005]
- *AHI1* [Dixon-Salazar et al 2004, Ferland et al 2004, Parisi et al 2006, Utsch et al 2006]
- *CEP290(NPHP6*) [Sayer et al 2006; Valente, Silhavey et al 2006]
- *TMEM67(MKS3)* [Baala et al 2007]

Other loci. The genes at two additional loci have not yet been identified:

- **JBTS1** (locus name). Two consanguineous Arab families from Oman showed linkage to 9q34 [Saar et al 1999]. Although some studies failed to show linkage to this locus [Blair et al 2002, Bennett et al 2003], several additional families have been mapped to this region [Valente et al 2005].
- **CORS2 (JBTS2)** (locus name). An extended Italian family with consanguinity [Valente et al 2003], several Arab families [Keeler et al 2003], and two additional families (Portuguese and Turkish) [Valente et al 2005] show linkage to the pericentromeric region of chromosome 11.

Clinical uses

- Confirmatory diagnostic testing
- Carrier testing
- Prenatal diagnosis

Clinical testing

- ***NPHP1.*** A homozygous deletion of *NPHP1* has been identified in a few individuals with Joubert syndrome. The detection rate for this mutation in individuals with Joubert syndrome is not known but is estimated to be 1-2% [Parisi et al 2004, Castori et al 2005, Parisi et al 2006]. However, in subsets of individuals with Joubert syndrome and juvenile nephronophthisis and/or renal insufficiency, the mutation detection rate may be higher.

  Note: (1) Because the typical symptoms of renal disease do not occur until the second decade of life, it may not be possible to determine the presence or absence of renal disease at the time of diagnosis of Joubert syndrome in a young person. (2) The same deletion is a common mutation identified in juvenile nephronophthisis (and in some individuals with Cogan oculomotor apraxia) (see Allelic Disorders).

- ***AHI1.*** The mutation rate is not yet known; in one study, however, 13 of 117 (11%) individuals with Joubert syndrome had *AHI1* mutations [Parisi et al 2006].
- ***CEP290.*** In one study, seven of 96 individuals with Joubert syndrome (7%) had identifiable *CEP290* mutations [Sayer et al 2006]. In a second series of consanguineous families in which the four other Joubert syndrome loci had been previously excluded, 5/18 had causative *CEP290* mutations [Valente, Silhavey et al 2006]. However, it is unclear at this time as to the exact prevalence of *CEP290* mutations in Joubert syndrome, as a large Joubert cohort-based study has not been undertaken.

- ***TMEM67(MKS3).*** Baala et al (2007) identified disease-causing mutations in *TMEM67* (also known as *MKS3*) in three of 22 individuals with JS who did not have *NPHP1* deletions. *TMEM67* is the sixth locus for JS, and as such can be referred to as JBTS6.

Table 1 summarizes molecular genetic testing for this disorder.

Table 1. Molecular Genetic Testing Used in Joubert Syndrome

Test Methods	Mutations Detected	Mutation Detection Frequency [1]	Test Availability
FISH or deletion analysis	*NPHP1* deletion	~1-2% [2]	Clinical Testing
Sequence analysis	*AHI1* sequence variations	~11% [3]	Clinical Testing
Sequence analysis	*CEP290* sequence variations	~10% [4]	Clinical Testing
Sequence analysis	*TMEM67*	~10% [5]	Clinical Testing

1. Proportion of affected individuals with a mutation(s) as classified by gene/locus, phenotype, population group, and/or test method
2. May be higher in individuals with renal disease
3. Parisi et al 2006
4. Sayer et al 2006; Valente, Silhavey et al 2006
5. Mutations in *TMEM67(MKS3)* identified in 3/22 individuals with JS who did not have NPHP1 deletions [Baala et al 2007]

Interpretation of test results. For issues to consider in interpretation of sequence analysis results, click here.

Genetically Related (Allelic) Disorders

NPHP1

- **Juvenile nephronophthisis (nephronophthisis type 1).** A homozygous ~290-kb deletion of *NPHP1* is the causative molecular defect in approximately 30% of individuals with juvenile nephronophthisis [Hoefele et al 2005, Saunier et al 2005]. Juvenile nephronophthisis is characterized by renal tubular atrophy and progressive interstitial fibrosis with later development of medullary cysts (see Differential Diagnosis). Some individuals with juvenile nephronophthisis and *NPHP1* deletions have the molar tooth sign on cranial imaging. The number of individuals with this feature in the absence of other findings of Joubert syndrome (e.g., hypotonia, developmental delay, and eye movement abnormalities), though it has not been determined, is likely to be low.

  Some individuals with *NPHP1* molecular defects have retinal dystrophy in combination with juvenile nephronophthisis, termed Senior-Løken syndrome.

- **Cogan syndrome.** This autosomal recessive familial form of congenital oculomotor apraxia is characterized by defective horizontal voluntary eye movements with jerkiness. Some individuals 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 *NPHP1* homozygous deletion has been identified in some individuals [Saunier et al 1997, Betz et al 2000], although the relationship between this condition, Joubert syndrome, and juvenile nephronophthisis is unclear.

AHI1. The majority of individuals with *AHI1* molecular defects have retinal dystrophy, and a few have also demonstrated renal insufficiency consistent with juvenile nephronophthisis, which is suggestive of Senior-Løken syndrome [Parisi et al 2006].

CEP290. Senior-Løken syndrome is the only other phenotype associated with mutations in CEP290 (see Differential Diagnosis) [Sayer et al 2006].

TMEM67Mutations in *TMEM67* have been identified in individuals with Meckel-Gruber syndrome whose families are from Pakistan and Oman [Smith et al 2006].

Clinical Description

Natural History

Joubert syndrome is characterized by hypotonia, developmental delays, and either breathing abnormalities or atypical eye movements, or both [Saraiva & Baraitser 1992; Steinlin et al 1997; Maria, Bolthauser et al 1999; Bennett et al 2003]. However, the delineation of the phenotypic spectrum of Joubert syndrome remains unresolved, in part because of variability in clinical features in affected individuals, many of whom were reported before the molar tooth sign was described.

Both intra- and interfamilial phenotypic variation is seen in Joubert syndrome. In the family of four affected sibs originally reported by Joubert et al (1969), significant variability of the cerebellar findings was evident: two had agenesis of the posterior inferior cerebellar vermis, a third had complete agenesis of the cerebellar vermis, and a fourth had complete agenesis of the cerebellar vermis and an occipital meningoencephalocele. Discordant phenotypes were observed in a set of monozygotic twins with Joubert syndrome; both had the molar tooth sign on MRI, but anatomic, neurologic, and developmental findings differed greatly [Raynes et al 1999].

A reported male:female ratio of approximately 2:1 [Saraiva & Baraitser 1992] was not confirmed in other surveys [Steinlin et al 1997].

Many of the clinical features of Joubert syndrome are evident in infancy [Joubert et al 1969, Boltshauser & Isler 1977]. Most children with Joubert syndrome develop truncal ataxia and, in combination with hypotonia, exhibit delayed acquisition of gross motor milestones. Many have rhythmic tongue movements that may lead to tongue hypertrophy. Although some infants have died of apnea, episodic apnea generally improves with age and may completely disappear [Maria, Quisling et al 1999].

Individuals with Joubert syndrome exhibit clinical heterogeneity. Some of the following organ system involvement may define different forms of Joubert syndrome, sometimes termed "Joubert syndrome and related disorders" (summarized in Differential Diagnosis). Whether these related disorders represent subtypes of Joubert syndrome or distinct syndromes is debated; resolution may need to await identification of the causative genes.

Central nervous system findings

- **Cognitive abilities** are variable, ranging from severe mental retardation to normal; a few individuals have attended college. When present, mental retardation is commonly in the moderate range [M Parisi, I Glass, personal observations].
- **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; however, the exact incidence is unknown [Saraiva & Baraitser 1992].

- **Autism** has been reported in a number of children with Joubert syndrome [Holroyd et al 1991, Ozonoff et al 1999]; however, more recent surveys suggest that many of these behavioral disturbances do not represent classic autism [Takahashi et al 2005].
- **Behavioral problems,** including impulsivity and temper tantrums, are present in some children and adolescents [Deonna & Ziegler 1993, Hodgkins et al 2004, Farmer et al 2006].

Other CNS malformations. In addition to the molar tooth sign, these may include:

- Abnormal collections of cerebrospinal fluid in the fourth ventricle or the posterior fossa that resemble Dandy-Walker malformation (~10% of individuals) [Maria et al 2001]
- Occipital encephalocele or meningocele [Genel et al 2004]
- Hydrocephalus requiring shunting without classic signs of Dandy-Walker syndrome [Genel et al 2004]
- Agenesis of the corpus callosum [Valente et al 2005]
- Neuroepithelial cysts [Marsh et al 2004]
- Polymicrogyria, a rare finding that may represent a unique subtype of Joubert syndrome [Gleeson et al 2004] in individuals with *AHI1* mutations [Dixon-Salazar et al 2004]
- Heterotopias [Saraiva & Baraitser 1992].

Other features sometimes identified in individuals with Joubert syndrome include the following:

Ophthalmologic findings. Retinal disease consists of 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 (ERG) that resembles Leber congenital amaurosis. However, the retinal disease may not be progressive and is not always present in infancy or early childhood [Steinlin et al 1997].

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

Oculomotor apraxia is often identified in childhood rather than infancy, perhaps because of under-recognition of this 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]. Visual acuity 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].

Ptosis, strabismus, and/or amblyopia may be present.

Third nerve palsy may be present [Hodgkins et al 2004].

Ocular colobomas are most often described as chorioretinal [Saraiva & Baraitser 1992].

Renal disease is rarely present at birth but can develop during childhood and adolescence [Steinlin et al 1997]. Renal manifestations can include:

- **Cystic dysplasia,** visualized on renal ultrasound examination as multiple variably-sized cysts in immature kidneys with fetal lobulations [Saraiva & Baraitser 1992,

Steinlin et al 1997, Satran et al 1999]. This finding, which may be present prenatally or at birth, has been considered a feature of Dekaban-Arima syndrome (see Differential Diagnosis).

- **Juvenile nephronophthisis,** a form of chronic tubulointerstitial nephropathy [Saunier et al 2005]. Juvenile nephronophthisis often presents in the first or second decade of life with polydipsia, polyuria, urine concentrating defects, growth retardation, and/or anemia. Progression to end-stage renal disease (ESRD) occurs by an average age of 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.

Although these two renal lesions were considered distinct in the past, one recent report re-interpreted the histologic changes that had been identified as cystic dysplastic kidneys in individuals with Dekaban-Arima syndrome as nephronophthisis [Kumada et al 2004]. This suggests that they may represent part of a continuum of nephronophthisis with the specific renal manifestation dependent on factors such as the age of the affected individual and the stage of disease.

It has been proposed that Joubert syndrome be classified into two groups, those with retinal dystrophy and those without retinal dystrophy. In this classification, renal disease is present in only the group with retinal involvement ("type B") [King et al 1984, Saraiva & Baraitser 1992]. Subsequent observations have not always been consistent with this scheme [Steinlin et al 1997, Chance et al 1999]. Nonetheless, the evidence thus far suggests that retinal disease and renal impairment often occur together, as the three known causative genes for Joubert syndrome are associated with both renal cystic disease and retinal dystrophy [Parisi et al 2006, Sayer et al 2006].

Hepatic fibrosis occurs in some individuals with Joubert syndrome and is usually progressive but rarely symptomatic at birth. Hepatic fibrosis is often associated with chorioretinal colobomas and sometimes with renal disease. The combination of colobomas, mental retardation ("oligophrenia"), ataxia, cerebellar vermis hypoplasia, and hepatic fibrosis has been termed COACH syndrome [Satran et al 1999, Gleeson et al 2004]. In the authors' experience, many children with COACH syndrome also have classic features of Joubert syndrome and the molar tooth sign [M Parisi and W Dobyns, personal observations] (see Differential Diagnosis).

Polydactyly can be unilateral or bilateral and is often postaxial, although preaxial polydactyly of the toes is also frequently reported [Saraiva & Baraitser 1992]. Mesaxial polydactyly has been described in some individuals with Joubert syndrome, many of whom have other features of oral-facial-digital syndrome type VI [Gleeson et al 2004] (see Differential Diagnosis).

Other. Some males with Joubert syndrome have had micropenis; other children have had growth hormone deficiency or panhypopituitarism [M Parisi, personal observations]. The significance of these observations remains to be clarified.

Tongue lobulations and oral frenulae may be present, particularly in those with features of oral-facial-digital VI/Varadi-Papp syndrome. Problems with mastication, swallowing, and respiration may result.

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, Bolthauser et al 1999]; however, these features can be difficult to discern in infancy and are thus far nonspecific. Nonetheless, many observers report a "Joubert facies" [Braddock et al 2003].

Genotype-Phenotype Correlations

Preliminary genotype-phenotype correlations are possible.

NPHP1. Thus far, all individuals with an *NPHP1* deletion have demonstrated renal impairment compatible with juvenile nephronophthisis [Parisi et al 2004, Castori et al 2005]; in one person, retinal dystrophy was also described [Castori et al 2005]. The molar tooth sign may have a distinctive appearance in these individuals, with elongated but thin superior cerebellar peduncles and milder vermis hypoplasia.

AHI1. In one study, 11 of 12 families with disease-causing *AHI1* mutations had evidence of retinal dystrophy [Parisi et al 2006]. Only three families with *AHI1* mutations have had documented renal disease consistent with nephronophthisis [Parisi et al 2006, Utsch et al 2006]; in one survey, the onset was in the third decade of life [Parisi et al 2006]. Another group did not identify renal disease in their cohort of 10 families with *AHI1* mutations, although early-onset congenital blindness was described in several subjects [Valente, Brancati et al 2006].

Limited data prevent drawing conclusions about whether the polymicrogyria observed with Joubert syndrome in individuals with disease-causing *AHI1* mutations represents a unique subtype of Joubert syndrome [Dixon-Salazar et al 2004, Gleeson et al 2004] as it has not been found in the majority of those with identified *AHI1* mutations thus far [Parisi et al 2006].

CEP290. All families with *CEP290* mutations who have had head imaging performed demonstrate cerebellar vermis hypoplasia and/or the MTS. In the majority of families with causative *CEP290* mutations, affected individuals have demonstrated retinal dystrophy, and several have had congenital blindness [Sayer et al 2006; Valente, Silhavey et al 2006]. Renal disease consistent with nephronophthisis has also been identified in many families with *CEP290* mutations [Sayer et al 2006], which, and in combination with retinal dystrophy, represents Senior-Løken syndrome. Other phenotypes have included nonspecific renal cortical cysts, ocular colobomas, and encephaloceles [Sayer et al 2006; Valente, Silhavey et al 2006].

TMEM67. While all three of the affected individuals with *TMEM67* mutations and a clinical diagnosis of Joubert syndrome manifest cerebellar vermis hypoplasia and/or the MTS, two of them lack the classic features of Meckel syndrome (encephalocele, renal cysts, polydactyly, and hepatic fibrosis). The other subject did have cystic kidneys and liver disease [Baala et al 2007]. Further correlations await identification of additional individuals with Joubert syndrome and mutations in this gene.

Nomenclature

The term "Joubert syndrome" is reserved for those individuals fulfilling the diagnostic criteria that require the presence of the molar tooth sign on MRI (see Clinical Diagnosis). This may also be termed "classic Joubert syndrome."

The term "Joubert syndrome and related disorders" (JSRD) describes conditions that share the molar tooth sign and the clinical features of Joubert syndrome, but that also have other manifestations that may represent a distinct syndrome. At least eight conditions in which a subset of affected individuals demonstrates the molar tooth sign have been identified [Satran et al 1999, Gleeson et al 2004; see Disorders with the molar tooth sign and Table 2, Differential Diagnosis]. There is debate whether these represent subtypes of Joubert syndrome or distinct syndromes.

Clarification of the appropriate use of the term "Joubert syndrome and related disorders" or "cerebello-oculo-renal syndromes" (CORS) awaits identification of the causative genes for these disorders.

Prevalence

The prevalence of Joubert syndrome has been estimated from a small sample set of affected families to be 1:258,000 [Flannery & Hudson 1994]. However, this figure likely represents an underestimate of the true prevalence of the condition, as it was calculated prior to the recognition of the role of the molar tooth sign in diagnosis. A prevalence of 1:100,000 is a reasonable estimate for purposes of genetic counseling [D Flannery and M Parisi, personal discussions].

A founder effect has been noted in the French-Canadian population. 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]. Other founder effects are likely.

Differential Diagnosis

For current information on availability of genetic testing for disorders included in this section, see GeneTests Laboratory Directory. —ED.

Disorders with the molar tooth sign: Joubert syndrome and related disorders (JSRD). Although the following autosomal recessive disorders were reported prior to the description of the molar tooth sign, more recent studies indicate that many individuals with these disorders demonstrate the molar tooth sign [Pellegrino et al 1997, Chance et al 1999, Satran et al 1999, Gleeson et al 2004]. The nosology of syndromes with the molar tooth sign summarized in Table 2 is complex and still evolving.

- **Dekaban-Arima syndrome** (retinopathy, cystic dysplastic kidneys) [Dekaban 1969]
- **Severe retinal dysplasia** with congenital blindness that resembles Leber congenital amaurosis
- **COACH syndrome** (**c**erebellar vermis hypoplasia, **o**ligophrenia, **a**taxia, **c**oloboma, and **h**epatic fibrosis) [Verloes & Lambotte 1989, Gentile et al 1996]
- **Senior-Løken syndrome** (SLS; retinopathy and juvenile-onset nephronophthisis) [Løken et al 1961, Senior et al 1961]
- **Varadi-Papp syndrome** (OFD VI) includes cerebellar vermis hypoplasia, oral frenula, tongue hamartomas, and midline cleft lip, as well as the distinctive feature of central polydactyly with a Y-shaped metacarpal [Munke et al 1990]. Renal and cardiac involvement has been described. The molar tooth sign has been observed in at least one person [Gleeson et al 2004].
- **Nephronophthisis** is caused by mutations in at least six genes, including *NPHP1* (see Allelic Disorders). The infantile-onset form of nephronophthisis (NPHP2) is associated with mutations in *INVS*, the gene encoding inversin. The phenotype in NPHP2 may include situs inversus and is typically more severe than Joubert syndrome [Otto et al 2003]. Mutations in *NPHP3* and *NPHP4* appear to be rare causes of juvenile nephronophthisis [Hoefele et al 2005]. Mutations in *NPHP5(IQCB1*) are associated almost exclusively with Senior-Løken syndrome with early development of retinal dystrophy [Otto et al 2005].
- **Cogan oculomotor apraxia syndrome** is congenital oculomotor apraxia, associated in some individuals with a molar tooth sign and/or nephronophthisis. Mutations in *NPHP1* have been identified in a few cases [Saunier et al 1997, Betz et al 2000].

Table 2. Clinical Features of Joubert Syndrome and Related Cerebello-Oculo-Renal Disorders

Feature	Classic Joubert	Dekaban-Arima	Joubert-LCA-Like	COACH	Senior-Løken	OFD VI Varadi	Juvenile Nephron-ophthisis	Cogan OMA
Neurologic								
Cerebellar vermis hypoplasia and ataxia	+	+	+	+	(+)	+	(+)	(+)
Molar tooth sign on MRI	+	(+)	+	(+)	(+)	(+)	(+)	(+)
Developmental delay/mental retardation	+	+	+	+	(+)	+	(+)	(+)
Episodic tachypnea ± apnea	+	+	+	(+)	(+)	(+)	?	?
Dandy-Walker-like malformation	(+)	?	?	?	?	?	(+)	?
Occipital cephalocele	(+)	(+)	(+)	(+)	(+)	(+)	–	–
Eyes								
Retinal dystrophy	(+)	+	+	+	+	–	(+)	?
Severe visual impairment/LCA	–	+	+	(+)	(+)	–	?	?
Oculomotor apraxia	+	(+)	(+)	(+)	(+)	(+)	(+)	+
Coloboma	–	?	?	+	?	?	–	–
Kidneys								
Cystic dysplasia	–	+	–	–	–	(+)	–	–
Nephronophthisis	(+)	–	–	(+)	+	–	+	(+)
Other								
Facial dysmorphism	(+)	?	(+)	?	(+)	(+)	?	?
Hepatic fibrosis-cirrhosis	–	(+)	–	+	?	–	–	–
Polydactyly	(+)	?	(+)	?	?	+ [1]	–	–
Tongue hamartomas/oral frenulae	–	–	–	–	–	+	–	–
Early death	(+)	+	(+)	(+)	(+)	(+)	?	?
Genes	*NPHP1*, *AHI 1*, *CEP290*, *T MEM67*, others	?	*AHI1*, *CEP2 90*, others	*TMEM67*	*NPHP1, 3, 4, 5*, *CEP290*, others	?	*NPHP1, 3, 4*, *CEP290*, others	*NPHP1*, others

Adapted from Chance et al 1999, Satran et al 1999, Bennett et al 2003, Gleeson et al 2004, Parisi et al 2004

+ = Present

(+) = Sometimes present

– = Absent

? = Unknown

LCA-like = Leber congenital amaurosis-like

OMA = Oculomotor apraxia

1. Often central, with Y-shaped metacarpal

Bardet-Biedl syndrome (BBS). Bardet-Biedl syndrome (BBS) is characterized by cone-rod retinal dystrophy, truncal obesity, postaxial polydactyly, cognitive impairment,

hypogonadotrophic hypogonadism in males, genital malformations in females, and renal disease, which can include structural malformations, renal hypoplasia, hydronephrosis, cystic kidneys, and glomerulonephritis. Progressive retinal impairment often causes blindness and 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]. At least eleven genes have been described, many of which have functions in the primary cilium analogous to *NPHP1*. Inheritance is autosomal recessive.

Other syndromes with cerebellar vermis hypoplasia. Other conditions to consider in the differential diagnosis of Joubert syndrome are those with cerebellar vermis hypoplasia or dysgenesis without the molar tooth sign on MRI [Bordarier & Aicardi 1990, Ramaekers et al 1997]. These include:

- **Dandy-Walker malformation.** This hindbrain malformation is characterized by cerebellar hypoplasia of the vermis and/or hemispheres with an enlarged retrocerebellar cerebrospinal fluid collection continuous with the fourth ventricle (often misnamed a posterior fossa "cyst"). Associated findings in some individuals include agenesis or hypoplasia of the corpus callosum and hydrocephalus [Patel & Barkovich 2002]. MRI findings distinguish Dandy-Walker malformation from the molar tooth sign [Maria et al 2001].
- **X-linked cerebellar hypoplasia.** Males with this disorder exhibit hypotonia at birth and moderate mental retardation; they may develop ataxia, macrocephaly, and seizures [Philip et al 2003]. Strabismus and genital hypoplasia are common [Bergmann et al 2003]. Carrier females may have milder impairment. Mutations in the X-linked gene *OPHN1* that encodes oligophrenin 1 are associated with at least one form of this disorder.
- **Ataxia and oculomotor apraxia type 1 (AOA1) and ataxia and oculomotor apraxia type 2 (AOA2).** These two autosomal recessive disorders are caused by mutations in the genes encoding aprataxin *(APTX*) and senataxin *(SETX*), respectively. Findings include childhood-onset progressive cerebellar ataxia with associated cerebellar atrophy on MRI imaging and oculomotor apraxia. Peripheral neuropathy develops over time, and mental retardation may be present. In AOA1, the onset is age six to eight years; affected individuals also have hypoalbuminemia. In AOA2 the age of onset is later (age 15-17 years); affected individuals have elevated serum alpha-fetoprotein concentration [Le Ber et al 2005].
- **Congenital disorders of glycosylation (CDG).** [See Congenital Disorders of Glycosylation Overview, Congenital Disorder of Glycosylation Type Ia (CDG-Ia)]. Features shared with Joubert syndrome include delays in development, hypotonia, ataxia, and strabismus. Additional features of CDG-Ia are abnormal subcutaneous fat distribution in infancy, inverted nipples, and oftentimes, a progressive degenerative course [Jaeken & Hagberg 1991]. Affected individuals are not reported to have breathing abnormalities, polydactyly, renal problems, or the molar tooth sign, although they may have cerebellar hypoplasia with or without pontine involvement. CDG is characterized by abnormalities of glycoprotein glycosylation. Serum transferrin isoelectric focusing is abnormal in most forms of CDG and hence, useful in diagnosis of CDG; serum transferrin isoelectric focusing is normal in Joubert syndrome [Morava et al 2004].
- **3-C syndrome (cranio-cerebello-cardiac syndrome, Ritscher-Schinzel syndrome).** Characterized by partial or complete cerebellar vermis hypoplasia, 3-C syndrome is often associated with a cyst of the fourth ventricle similar to that observed

in Dandy-Walker malformation. Other findings include congenital heart defects such as atrioventricular septal defect and a specific craniofacial configuration that may include cleft palate and ocular colobomas [Kosaki et al 1997]. Mental retardation is common but variable. Diagnostic criteria have been proposed [Leonardi et al 2001]. Autosomal recessive inheritance is implied by reports of multiple sets of affected sibs and consanguineous parents. Subtelomeric deletions of chromosome 6p have also been described [Descipio et al 2005].

- **The pontocerebellar hypoplasias/atrophies.** This heterogeneous group of disorders may exhibit autosomal recessive inheritance or represent a prenatal or perinatal insult. Many affected individuals exhibit cerebellar vermis hypoplasia, but in contrast to Joubert syndrome, they also display hypoplasia of the pons and no molar tooth sign on cranial MRI [Barth 1993]. Some individuals have progressive motor degeneration similar to that in spinal muscular atrophy and others have dyskinesia; most have severe impairment and poor prognosis.
- **Oral-facial-digital (OFD) syndromes II and III.** It is unknown if the molar tooth sign is present in these forms of OFD.
  - OFD II (Mohr syndrome) is characterized by tongue tumors with abnormal frenulae, midline facial clefts, and polydactyly in addition to cerebellar vermis agenesis [Reardon et al 1989].
  - OFD III is characterized by mental retardation and postaxial polydactyly [Sugarman et al 1971].
- **Meckel-Gruber syndrome.** This disorder is characterized by occipital encephalocele, polydactyly, and polycystic kidneys. Liver developmental defects, including hepatic fibrosis, bile duct proliferation, and ductal plate malformation are relatively common. Cerebellar vermis hypoplasia has been described in some individuals. At least three loci have been mapped [Morgan et al 2002] and two of the genes identified [Kyttala et al 2006, Smith et al 2006]. Mutations in one of these genes, *TMEM67*, have been identified in individuals with Joubert syndrome (see Molecular Genetic Testing and Allelic Disorders). Inheritance is autosomal recessive.

Management

Evaluations Following Initial Diagnosis

Baseline evaluations identify the extent of disease in affected infants/children. Recommendations are also outlined on the Joubert Syndrome Foundation and Related Cerebellar Disorders Web site.

- 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 to evaluate for the presence of the molar tooth sign and other cerebral malformations or cephaloceles
- A baseline neurologic evaluation with particular attention to respiratory pattern (tachypnea and apnea) and eye movement abnormalities
- Sleep history with polysomnogram to evaluate for symptomatic apnea
- Genetic evaluation to document family history, to evaluate growth and head size, and to evaluate for less common findings such as polydactyly, dysmorphic facial features, tongue tumors/lobulations, and micropenis
- For males with micropenis or signs of growth hormone deficiency, endocrinologic evaluation for other pituitary abnormalities

- 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 for colobomas and retinal changes, with consideration of specialized testing such as visual-evoked potentials (VEP), electroretinogram (ERG), and ocular motility testing
- Abdominal ultrasound examination to evaluate for renal cysts and/or renal fibrosis and hepatic fibrosis
- 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
- Liver function tests including transaminases, albumin, and bilirubin

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 regional anesthesia without the use of opioids to avoid exacerbation of apneic episodes [Vodopich & Gordon 2004].
- In rare cases, mechanical support and/or tracheostomy may be considered in a child with severe respiratory dysfunction.

Hypotonia and therapeutic interventions

- Appropriate management and therapy of oromotor dysfunction by a speech therapist
- Gastrostomy tube placement for feeding for children with severe dysphagia
- Occupational and physical 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 fontanel).
- Hydrocephalus rarely requires shunting.
- Posterior fossa cysts and fluid collections rarely require intervention.
- Encephalocele may require primary surgical closure.
- Seizures should be evaluated by EEG and treated with standard antiepileptic drugs (AEDs) under the management of a neurologist.

- A variety of psychotropic medications have been used to treat the behavioral complications in Joubert syndrome, and 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
- Therapies for the visually impaired when congenital blindness or progressive retinal dystrophy is present

Renal disease

- Consultation with a nephrologist is indicated.
- Nephronophthisis frequently requires dialysis and/or kidney transplantation during the teenage years or later.
- Hypertension, anemia, and other complications of end-stage renal disease (ESRD) may also 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 as appropriate.
- Some individuals have needed orthotopic liver transplantation.

Polydactyly

- Surgical treatment

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.
- Endocrinologic consultation for menstrual irregularities indicated.

Surveillance

Since no distinguishing characteristics have been found to 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 Foundation and Related Cerebellar Disorders Web site):

- Pediatric evaluation and monitoring of growth and sexual maturation
- Ophthalmologic evaluation for visual acuity, tracking ability, and development of retinal dystrophy. (All individuals with *AHI1* or *CEP290* mutations are at high risk for retinal dystrophy.)

- Abdominal ultrasound examination for evaluation of possible liver and kidney abnormalities
- Liver function tests
- Evaluation of renal function: measurement of blood pressure, BUN, creatinine, CBC, and assessment of first-morning void urinalysis (All individuals with Joubert syndrome who are homozygous for the *NPHP1* deletion, those with *CEP290* mutations, and possibly those with *AHI1* mutations are at high risk for nephronophthisis and require monitoring of renal function by a nephrologist.)

Agents/Circumstances to Avoid

Individuals with renal impairment should avoid nephrotoxic medications such as NSAIDS (non-steroidal anti-inflammatory drugs).

Individuals with liver impairment should avoid hepatotoxic medications.

Therapies Under Investigation

Search ClinicalTrials.gov for access to information on clinical studies for a wide range of diseases and conditions. Note: There may not be clinical trials for this disorder.

Other

Genetics clinics are a source of information for individuals and families regarding the natural history, treatment, mode of inheritance, and genetic risks to other family members as well as information about available consumer-oriented resources. See the GeneTests Clinic Directory.

Support groups have been established for individuals and families to provide information, support, and contact with other affected individuals. The Resources section (below) may include disease-specific and/or umbrella support organizations.

Genetic Counseling

Genetic counseling is the process of providing individuals and families with information on the nature, 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. This section is not meant to address all personal, cultural, or ethical issues that individuals may face or to substitute for consultation with a genetics professional. To find a genetics or prenatal diagnosis clinic, see the GeneTests Clinic Directory.

Mode of Inheritance

Joubert syndrome is inherited in an autosomal recessive manner.

Risk to Family Members

Parents of a proband

- The parents of a proband are obligate heterozygotes and therefore carry one mutant allele.
- Heterozygotes are asymptomatic.

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.
- Once an at-risk sib is known to be unaffected, the chance of his/her being a carrier is 2/3.
- Heterozygotes (carriers) are asymptomatic.

Offspring of a proband. The offspring of a proband are obligate carriers. Although no individuals with Joubert syndrome have been 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 of a proband. Each sib of the proband's parents is at a 50% risk of being a carrier.

Carrier Detection

Carrier testing for at-risk family members is available on a clinical basis once the disease-causing mutations have been identified in the proband.

Related Genetic Counseling Issues

Family planning. The optimal time for determination of genetic risk, clarification of carrier status, and discussion of the availability of prenatal testing is before pregnancy.

DNA banking. DNA banking is the storage of DNA (typically extracted from white blood cells) for possible future use. Because it is likely that testing methods and our understanding of genes, mutations, and diseases will improve in the future, consideration should be given to banking DNA of affected individuals. DNA banking is particularly relevant in situations in which the sensitivity of currently available testing is less than 100%. See DNA Banking for a list of laboratories offering this service.

Prenatal Testing

Molecular genetic testing. Prenatal diagnosis for pregnancies at increased risk for *AHI1*-, *CEP290*-, *TMEM67*-, or *NPHP1*-related Joubert syndrome is possible by analysis of DNA extracted from fetal cells obtained by amniocentesis usually performed at about 15-18 weeks' gestation or chorionic villus sampling (CVS) at about ten to 12 weeks' gestation. Both disease-causing alleles of an affected family member must be identified before prenatal testing can be performed.

Note: Gestational age is expressed as menstrual weeks calculated either from the first day of the last normal menstrual period or by ultrasound measurements.

Prenatal imaging. First-trimester diagnosis of Joubert syndrome 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 and digits as early as the second trimester [Ni Scanaill et al 1999, Aslan et al 2002, Doherty et al 2005].

Accurate prenatal diagnosis of Joubert syndrome in an at-risk fetus has been achieved by serial prenatal ultrasound imaging starting at 11-12 weeks' gestation, with detailed evaluation of cerebellar and other fetal anatomy through 20 weeks' gestation, followed by fetal MRI imaging at 20-22 weeks' gestation [Doherty et al 2005]. Although fetal MRI is useful in diagnosis of

posterior fossa anomalies [Levine et al 2003, Adamsbaum et al 2005], its sensitivity in Joubert syndrome has not been systematically evaluated.

For a couple who has already had a child with Joubert syndrome, the presence of findings that suggest a prenatal diagnosis of Joubert syndrome (such as 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 because of the unknown sensitivity of imaging and because of intrafamilial variability.

Preimplantation genetic diagnosis (PGD) may be available for families in which the disease-causing mutations have been identified in an affected family member. For laboratories offering PGD, see Testing.

Molecular Genetics

Information in the Molecular Genetics tables is current as of initial posting or most recent update. —ED.

Table A. Molecular Genetics of Joubert Syndrome

Locus Name	Gene Symbol	Chromosomal Locus	Protein Name
CORS2 (JBTS2)	Unknown	11p12-q13.3	Unknown
JBTS1	Unknown	9q34.3	Unknown
JBTS3	*AHI1*	6q23.3	Jouberin
JBTS4	*NPHP1*	2q13	Nephrocystin-1
JBTS5	*CEP290*	12q21.32	Centrosomal protein Cep290
JBTS6	*TMEM67*	8q21.1-q22.1	Meckelin

Data are compiled from the following standard references: Gene symbol from HUGO; chromosomal locus, locus name, critical region, complementation group from OMIM; protein name from Swiss-Prot.

Table B. OMIM Entries for Joubert Syndrome

213300	JOUBERT SYNDROME 1; JBTS1
243910	ARIMA SYNDROME
607100	NEPHROCYSTIN; NPHP1
608091	JOUBERT SYNDROME 2; JBTS2
608629	JOUBERT SYNDROME 3; JBTS3
608894	ABELSON HELPER INTEGRATION SITE 1; AHI1
609583	JOUBERT SYNDROME 4; JBTS4
609884	TRANSMEMBRANE PROTEIN 67; TMEM67
610142	CENTROSOMAL PROTEIN, 290-KD; CEP290
610188	JOUBERT SYNDROME 5; JBTS5
610688	JOUBERT SYNDROME 6; JBTS6

Table C. Genomic Databases for Joubert Syndrome

Locus Name	Gene Symbol	Entrez Gene	HGMD
CORS2 (JBTS2)	Unknown	373067 (MIM No. 608091)	
JBTS1	Unknown	50955 (MIM No. 213300)	
JBTS3	*AHI1*	54806 (MIM No. 608894)	AHI1
JBTS4	*NPHP1*	4867 (MIM No. 607100)	NPHP1
JBTS5	*CEP290*	80184 (MIM No. 610142)	
JBTS6	*TMEM67*	91147 (MIM No. 609884)	

For a description of the genomic databases listed, click here.

NPHP1

Normal allelic variants: *NPHP1* contains 20 exons and its cDNA is 3,713 bp. The gene resides in a region flanked by two large inverted repeat elements.

Pathologic allelic variants: A homozygous ~290-kb deletion encompassing the *NPHP1* gene and portions of another gene, *BENE* [Saunier et al 2000, Parisi et al 2004]; occasional point mutations in the *NPHP1* gene have also been identified [Hoefele et al 2005]. (For more information, see Genomic Databases table above.)

Normal gene product: Nephrocystin-1, a protein of 733 amino acids. Nephrocystin has an SH3 domain that may mediate interactions with other proteins. Nephrocystin appears to localize to the primary cilium of the cell as well as to cell-cell adherens junctions, and interacts with proteins whose genes are mutated in other forms of nephronophthisis, including *INVS*, *NPHP3*, and *NPHP4*.

Abnormal gene product: Absence of nephrocystin-1 protein

AHI1

Normal allelic variants: *AHI1* has 28 exons and several alternative splice variant forms. The most common full-length transcript is 5,528 nt.

Pathologic allelic variants: Homozygous nonsense, missense, deletion, insertion, splicing mutations [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 Genomic Databases table above.)

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, such as signal transduction, RNA processing, and vesicular trafficking.

Abnormal gene product: Presumed lack of functional protein or protein with altered function

CEP290

Normal allelic variants: The gene contains 55 exons and spans 93.2 kb of genomic DNA, with a full-length transcript size of 7,951 nt [Sayer et al 2006].

Pathologic allelic variants: A variety of nonsense and frameshift mutations have been identified, with one nucleotide change (p.G5668T) resulting in a nonsense mutation (p.G1890X) identified in four of 12 families [Sayer et al 2006; Valente, Silhavey et al 2006].

One homozygous missense mutation has been identified (p.W7C) in one family [Valente, Silhavey et al 2006].

Normal gene product: Nephrocystin-6, a 290-kd protein comprising 2479 amino acid residues. Nephrocystin-6 contains 13 putative coiled-coil domains, as well as a nuclear localization signal, a region with homology to SMC ATPases (structural maintenance of chromosomes), six RepA/Rep+ protein KID motifs, three tropomyosin homology domains, and an ATP/GTP binding site motif. Nephrocystin-6 is a centrosomal protein known to modulate the activity of ATF4, a transcription factor implicated in renal cyst formation. Knockdown experiments in zebrafish result in abnormal cerebellar, renal, and retinal development [Sayer et al 2006], and there is evidence that this protein is expressed in the cerebellum during murine embryogenesis [Valente, Silhavey et al 2006].

Abnormal gene product: A lack of functional protein or production of a protein with altered function is presumed.

***TMEM67(MKS3*)**

Normal allelic variants: The gene has 28 exons and spans 62.0 kb of genomic DNA with a full-length transcript size of 3,467 nt [Smith et al 2006]. There is at least one splice variant form of 29 exons and length of 3,280 nt encoding a protein with 985 residues [Ensembl Database].

Pathologic allelic variants: Mutations identified in individuals with Joubert syndrome include splice-site mutations resulting in abnormal transcripts and missense mutations, both presumably representing hypomorphic alleles with milder phenotypes than the more severe lethal mutations causing Meckel syndrome [Smith et al 2006, Baala et al 2007].

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, potentally serving as a membrane receptor involved in signaling during ciliary development [Dawe et al 2007].

Abnormal gene product: Production of a protein with altered function is presumed on the basis of the mutations identified in individuals with Joubert syndrome [Baala et al 2007].

Resources

GeneReviews provides information about selected national organizations and resources for the benefit of the reader. GeneReviews is not responsible for information provided by other organizations. Information that appears in the Resources section of a GeneReview is current as of initial posting or most recent update of the GeneReview. Search GeneTests*for this disorder and select* 

for the most up-to-date Resources information.—ED.

Joubert Syndrome Foundation & Related Cerebellar Disorders
6931 South Carlinda Avenue
Columbia MD 21046
Email: jjgund@aol.com
www.joubertsyndrome.org

National Institute of Neurological Disorders and Stroke
Joubert Syndrome Information Page

Genetic Alliance BioBank
A centralized biological and data [consent/clinical/environmental] repository to enable translational genomic research on rare genetic diseases.
Phone: 202-966-5557
Email: sterry@geneticalliance.org
www.biobank.org

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Medical Genetic Searches: A specialized PubMed search designed for clinicians that is located on the PubMed Clinical Queries page. PubMed

Published Statements and Policies Regarding Genetic Testing

No specific guidelines regarding genetic testing for this disorder have been developed.

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Chapter Notes

Author Notes

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Revision History

- 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 to live Web site
- 9 July 2003 (me) Review posted to live Web site
- 27 January 2003 (mp) Original submission

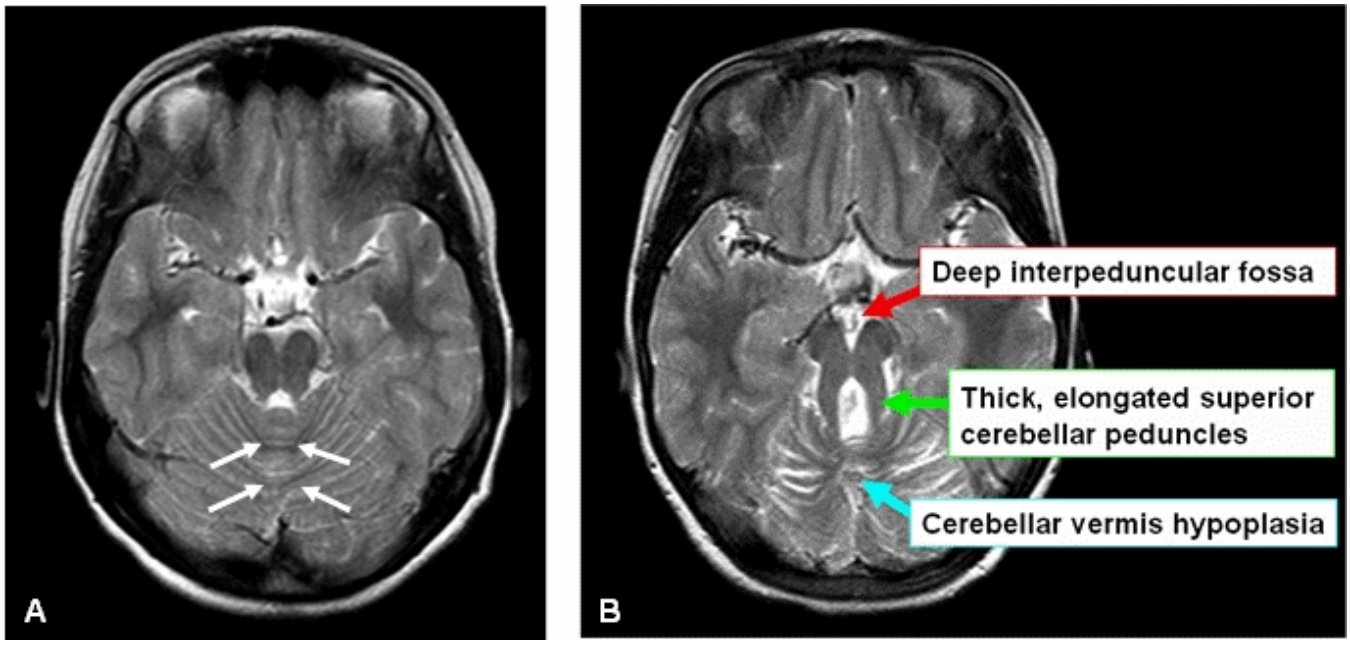

Figure 1.
A. Axial MRI image through the cerebellum and brainstem of a normal individual showing intact cerebellar vermis (outlined by white arrows)
B. Axial MRI image through the cerebellum and brainstem of a child with Joubert syndrome. Arrows indicate the three key components of the molar tooth sign.