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Clinical and molecular features of Joubert syndrome and related disorders

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Abstract

Joubert syndrome (JBTS; OMIM 213300) is a rare, autosomal recessive disorder characterized by a specific congenital malformation of the hindbrain and a broad spectrum of other phenotypic findings that is now known to be caused by defects in the structure and/or function of the primary cilium. The complex hindbrain malformation that is characteristic of JBTS can be identified on axial magnetic resonance imaging and is known as the molar tooth sign (MTS); other diagnostic criteria include intellectual disability, hypotonia, and often, abnormal respiratory pattern and/or abnormal eye movements. In addition, a broad spectrum of other anomalies characterize Joubert syndrome and related disorders (JSRD), and may include retinal dystrophy, ocular coloboma, oral frenulae and tongue tumors, polydactyly, cystic renal disease (including cystic dysplasia or juvenile nephronophthisis), and congenital hepatic fibrosis. The clinical course can be variable, but most children with this condition survive infancy to reach adulthood. At least 8 genes cause JSRD, with some genotype-phenotype correlations emerging, including the association between mutations in the *MKS3* gene and hepatic fibrosis characteristic of the JSRD subtype known as COACH syndrome. Several of the causative genes for JSRD are implicated in other ciliary disorders, such as juvenile nephronophthisis and Meckel syndrome, illustrating the close association between these conditions and their overlapping clinical features that reflect a shared etiology involving the primary cilium.

Keywords

Joubert syndrome; COACH syndrome; molar tooth sign; ciliary disorder; ciliopathy; cerebellar vermis hypoplasia

INTRODUCTION

Historical

In 1969, Dr. Marie Joubert and colleagues first described four siblings with cognitive impairment, ataxia, episodic tachypnea, eye movement abnormalities, and cerebellar vermis agenesis in a large French-Canadian family with consanguinity traced 11 generations to a common ancestor [Joubert et al., 1969]. Based on this and many subsequent reports, autosomal recessive inheritance has been inferred for Joubert syndrome (JBTS). In 1997, Maria et al. [1997] described the midbrain-hindbrain malformation seen on cranial magnetic resonance imaging (MRI), which consists of hypoplasia of the midline cerebellar vermis that resembles the cross-section through a molar tooth (the “molar tooth sign” or MTS) [Maria et al., 1999b] and is now considered pathognomonic for the disorder [Parisi et al., 2007; Valente et al., 2008] (Fig. 1A–D). The term “Joubert syndrome and related disorders” (JSRD) has been

applied to those conditions that have in common the MTS but may also have other distinctive features and will be described subsequently [Gleeson et al., 2004]. The first gene identified for this condition was identified in 2004 [Parisi et al., 2004a], and a total of 8 genes have been determined to be causative thus far.

Prevalence

The prevalence of JSRD has been estimated as approximately 1:100,000 in the United States [Parisi and Glass, 2007], but this is likely an underestimate given the broad spectrum of features, particularly in those with milder manifestations.

CLINICAL DIAGNOSIS

Classic Joubert syndrome

The features necessary for a diagnosis of classic JBTS include the following [Joubert et al., 1969; Maria et al., 1999a; Parisi and Glass, 2007; Saraiva and Baraitser, 1992; Steinlin et al., 1997]: (1) The molar tooth sign on axial views from cranial MRI studies comprised of these 3 findings: cerebellar vermis hypoplasia (CVH), deepened interpeduncular fossa, and thick, elongated superior cerebellar peduncles (Fig. 1A–D) [Maria et al., 1997; Maria et al., 1999b]; (2) intellectual impairment/developmental delay, of variable degree; (3) hypotonia in infancy; (4) one or both of the following (not required but supportive of the diagnosis): irregular breathing pattern in infancy (episodic apnea and/or tachypnea, sometimes alternating) and abnormal eye movements (nystagmus and/or oculomotor apraxia (OMA)).

Many children with Joubert syndrome exhibit dysmorphic facial features that include broad forehead, arched eyebrows, eyelid ptosis, wide-spaced eyes, open mouth configuration, and facial hypotonia (Fig. 2A) [Braddock et al., 2007; Maria et al., 1999a]. Some individuals with JBTS also have polydactyly of the hands and/or feet, which can take many forms [Saraiva and Baraitser, 1992] (Fig. 2B).

Joubert syndrome and related disorders (JSRD)

JSRD encompasses classic JBTS as described above as well as conditions with other features such as central nervous system anomalies (including occipital encephalocele, corpus callosal agenesis), ocular coloboma, retinal dystrophy, renal disease (including cystic dysplasia or nephronophthisis, NPHP), and hepatic fibrosis. When the ocular and renal systems are involved, the syndromes are sometimes described as cerebello-oculo-renal syndromes (CORS) [Valente et al., 2008; Valente et al., 2003]. An association between kidney disease and retinal involvement has been observed, with the specific findings of NPHP plus retinal dystrophy known as Senior-Løken syndrome [Gleeson et al., 2004; King et al., 1984; Saraiva and Baraitser, 1992; Satran et al., 1999]. One JSRD is the condition known by the acronym COACH syndrome (Coloboma, Oligophrenia/developmental delay, Ataxia, Cerebellar vermis hypoplasia, Hepatic fibrosis) [Satran et al., 1999; Verloes and Lambotte, 1989], which has more recently been described as requiring the MTS with evidence of liver disease, specifically congenital hepatic fibrosis [Doherty et al., 2009]. Liver involvement, when coupled with renal cystic disease, has prompted inclusion of JSRD as a congenital hepatorenal fibrocystic disease [Adams et al., 2008; Johnson et al., 2003].

Central Nervous System

Neuropathological studies of brains from individuals with JBTS have shown that the radiologic finding of the MTS correlates with hypoplasia and midline cleaving of the cerebellar vermis, often with inferior aplasia and superior dysplasia of the vermis, and abnormalities of the nuclei of the pons, cerebellum, and medulla (including the inferior olivary, solitary, and trigeminal nerve nuclei) [Friede and Boltshauser, 1978; Yachnis and Rorke, 1999]. Absence of

decussation of the corticospinal and superior cerebellar tracts has been demonstrated by diffusion tensor imaging [Poretti et al., 2007], and abnormal activation patterns during motor tasks was shown by functional MRI [Parisi et al., 2004b; Poretti et al., 2007], suggesting that the anatomical malformation has complex functional consequences. Approximately 10% of individuals with JSRD demonstrate fluid collections in the posterior fossa resembling the Dandy-Walker malformation [Maria et al., 2001]. Although hydrocephalus is uncommon in JSRD, rare patients have required a shunt for symptomatic elevations of intracranial pressure [Genel et al., 2004]. In addition, occipital encephaloceles or meningoceles have been observed [Arts et al., 2007; Gleeson et al., 2004; Joubert et al., 1969; Saraiva and Baraitser, 1992] (Fig. 2C), suggesting overlap with Meckel syndrome (MKS), a typically prenatal or perinatal lethal ciliopathy characterized by brain anomalies (especially encephalocele), cystic renal dysplasia, and the hepatic ductal plate malformation. Other brain anomalies in JSRD have included polymicrogyria [Dixon-Salazar et al., 2004; Giordano et al., 2009; Gleeson et al., 2004], agenesis of the corpus callosum [Gorden et al., 2008; Valente et al., 2005], and cerebellar heterotopias [Saraiva and Baraitser, 1992].

Cognitive impairment in JSRD is highly variable, with many children exhibiting moderately severe disability [Steinlin et al., 1997]. In one series, the average age of independent sitting was 19 months and the average age of walking was 4 years for those who developed these skills [Maria et al., 1999a]. The clinical features related to the complex hindbrain malformation include ataxia, which typically becomes apparent as children develop ambulation, and ocular, oral-motor and speech dyspraxia. Some children require assistive devices or use sign language to communicate given expressive language impairment [Fennell et al., 1999]. Seizures have been reported in some children with JSRD, although there are no consistent predictive radiologic features. Some children with JSRD and autistic features have been described [Holroyd et al., 1991; Ozonoff et al., 1999], although other authors have proposed that classic autism is not a typical feature [Takahashi et al., 2005]. Behavioral problems, typically impulsivity, perseveration, and temper tantrums, appear to be relatively common [Hodgkins et al., 2004], particularly with increasing age.

Ophthalmologic

There is a broad spectrum of ocular findings in JSRD. Abnormalities of ocular motility are very common, particularly nystagmus, which can be horizontal, vertical and/or torsional, and typically has a pendular, or sometimes see-saw pattern; and OMA, which is characterized by difficulty in smooth visual tracking, dysconjugate eye movements, and head thrusting to compensate for poor saccade initiation [Hodgkins et al., 2004; Khan et al., 2008; Tusa and Hove, 1999; Weiss et al., 2009]. Nystagmus and OMA are often present at birth and may improve with age. Other common ocular anomalies that may require medical or surgical treatment include strabismus, amblyopia, and ptosis. Third nerve palsy, Duane anomaly [Hodgkins et al., 2004], and optic disc drusen [Sturm et al., 2009] have also been observed. There are two basic forms of retinal disease, identified in about a third of subjects: severe congenital blindness with a flat electroretinogram (ERG) recording known as Leber congenital amaurosis [Ivarsson et al., 1993; Tusa and Hove, 1999]; and a later-onset pigmentary retinopathy that often manifests with night blindness in childhood and has a variable course [Saraiva and Baraitser, 1992; Steinlin et al., 1997]. Coloboma, a congenital ocular developmental defect, is present in a subset of individuals with JSRD and typically involves the choroid and retina [Saraiva and Baraitser, 1992] but rarely the iris. Many children with unilateral or bilateral colobomas also develop liver disease, as in COACH syndrome [Gleeson et al., 2004; Verloes and Lambotte, 1989], but colobomas are not a necessary feature of this disorder [Gentile et al., 1996], as only 71% of individuals with COACH syndrome in a large cohort had this finding [Doherty et al., 2009]. However, retinal dystrophy is not typical in COACH syndrome, in contrast to other JSRDs [Doherty et al., 2009].

Renal

Kidney disease is relatively common in JSRD, with a prevalence of up to 30% of subjects in early surveys [Saraiva and Baraitser, 1992]; this estimate may be even higher with long-term followup given its age-dependent penetrance. Two different forms of kidney disease have traditionally been described: cystic dysplasia and juvenile nephronophthisis (NPHP) [Saunier et al., 2005]. Cystic dysplasia may be identified prenatally or congenitally by ultrasound findings multiple cysts of many different sizes in immature kidneys with fetal lobulations [Dekaban, 1969; Saraiva and Baraitser, 1992; Satran et al., 1999; Steinlin et al., 1997]. This finding is characteristic of Dekaban-Arima syndrome, a JSRD that includes congenital blindness and occasional encephalocele [Dekaban, 1969; Gleeson et al., 2004; King et al., 1984; Matsuzaka et al., 1986; Satran et al., 1999].

The other, more common renal disorder in JSRD is juvenile NPHP, characterized by tubulointerstitial nephritis and cysts concentrated at the cortico-medullary junction [Hildebrandt and Zhou, 2007]. Most children present with urine concentrating defects in the first or second decade of life as manifested by polydipsia, polyuria, anemia, and growth failure, with a rise in serum creatinine around 9 years and progression to end-stage renal disease by approximately 13 years of age [Hildebrandt et al., 1998; Hildebrandt and Zhou, 2007; Saunier et al., 2005]. The less common infantile and adolescent forms of NPHP have progression to ESRD by 1 and 19 years, respectively. Ultrasound changes early during the disease include increased renal echogenicity, with small, scarred kidneys only observed after progression of the disease. Mutations in at least 9 ciliary genes have been identified in individuals with NPHP, about 20% of whom have extrarenal manifestations [Saunier et al., 2005], including cerebellar malformations, oculomotor apraxia (OMA), and retinal dystrophy (Senior-Løken syndrome) [Gleeson et al., 2004; Helou et al., 2007; Hildebrandt and Zhou, 2007; Otto et al., 2005; Satran et al., 1999]. Although cystic dysplasia and NPHP have been considered distinct entities, in at least one report, the cystic kidneys from deceased individuals with Dekaban-Arima syndrome demonstrated pathologic changes typical of NPHP [Kumada et al., 2004]. Thus, it is probable that the renal disease in JSRD is part of a continuum of findings with the common etiology involving abnormal ciliary proteins leading to tubular dysfunction.

In rare cases, the congenital renal disease in JSRD consists of enlarged kidneys, microscopic cysts distributed throughout the cortex and medulla, and infantile hypertension, similar to the renal disease of autosomal recessive polycystic kidney disease (ARPKD). Several of these patients have *MKS3* mutations like those with COACH syndrome [Gunay-Aygun et al., 2009].

In two separate series of subjects with COACH syndrome, 42% and 46%, respectively, had kidney disease [Brancati et al., 2009; Doherty et al., 2009]. However, a literature review showed that 77% of COACH subjects had renal disease [Doherty et al., 2009], likely reflecting the older average age of subjects reported in the literature, and possible ascertainment bias. The spectrum of renal disease in COACH is similar to other JSRD.

Hepatic

Hepatic involvement in JSRD is likely underreported, as manifestations of liver disease are usually not apparent at birth. However, because current management guidelines recommend routine screening for liver dysfunction in all children with a JSRD, hepatic involvement is being identified presymptomatically, and ~9% of families in a large cohort were recently reported as having clinically apparent liver disease [Doherty et al., 2009]. COACH syndrome [MIM 216360] was first proposed in 1989 by Verloes and Lambotte in 3 individuals (including two siblings) with Cerebellar vermis hypoplasia, Oligophrenia, Ataxia, Colobomas, and Hepatic fibrosis [Verloes and Lambotte, 1989]. In 1999, Satran et al. [1999] suggested that

COACH syndrome represented a subtype of JSRD with the distinctive finding of liver involvement, and in 2004, Gleeson et al. demonstrated that the CVH in COACH syndrome represented the MTS [Gleeson et al., 2004], thereby affirming its status as a JSRD. A recent review of 26 previously unreported subjects with COACH syndrome demonstrated the similarities between these patients and 43 individuals previously reported in the medical literature with a constellation of findings consistent with COACH syndrome [Doherty et al., 2009]. Thus, many authors consider COACH syndrome the equivalent of JBTS with congenital hepatic fibrosis [Brancati et al., 2009; Doherty et al., 2009]. It is likely that the liver disease in COACH syndrome is related to the ductal plate malformation described in Meckel syndrome (MKS), with an excess of bile duct-like profiles and portal fibrosis [Doherty et al., 2009].

The liver disease in COACH syndrome has demonstrated variable progression. Some JSRD/COACH patients present with evidence of portal hypertension, including hematemesis, esophageal varices or portosystemic shunting, and occasionally life-threatening bleeding events [Brancati et al., 2009; Doherty et al., 2009]. Others present with elevated or fluctuating levels of serum transaminases (ALT or AST) or gamma-glutamyl transferase (GGT). Physical examination findings may include hepatomegaly with or without splenomegaly. Radiologically, increased echogenicity and cysts may be visible on liver ultrasound, and dilated intrahepatic bile ducts on liver MRI or magnetic resonance cholangiopancreatography [Brancatelli et al., 2005]. Treatment for liver disease includes medical management such as oral ursodiol and surgical intervention including sclerotherapy for varices, splenectomy, and portal shunt placement. In some cases, hepatic fibrosis has progressed to end-stage liver failure and required liver with or without renal transplantation, typically in the second decade of life or beyond [Brancati et al., 2009; Doherty et al., 2009; Gentile et al., 1996; Herzog et al., 2002; Uemura et al., 2005].

Skeletal/limbs

The skeletal findings in JSRD include cone-shaped epiphyses and polydactyly. Cone-shaped epiphyses have been most often observed in children with Mainzer-Saldino syndrome (cerebellar ataxia with NPHP and retinal dystrophy) [Mainzer et al., 1970]. Polydactyly, observed in 16% of subjects in one survey [Saraiva and Baraitser, 1992], is often postaxial (Fig. 2B), although preaxial polydactyly of the hands or great toes has been observed (Fig. 2C). Mesaxial polydactyly (an extra digit between the middle digits often associated with a Y-shaped metacarpal) has been described in individuals with the oral-facial-digital type VI syndrome (OFD VI, also known as Varadi-Papp syndrome), a JSRD with oral frenulae, lingual tumors or hamartomas, and craniofacial findings that include wide-spaced eyes and a midline lip groove [Gleeson et al., 2004; Munke et al., 1990]. A few children with the MTS and a probable JSRD exhibit small thoracic cavities with rib abnormalities in the spectrum of Jeune asphyxiating thoracic dystrophy (personal observations), suggesting overlap between these ciliary conditions. With age, some children with JSRD develop scoliosis related to abnormal tone.

Other

Endocrine abnormalities are not uncommon in JSRD, and some children exhibit pituitary hormone dysfunction such as isolated growth hormone or thyroid hormone deficiency, or even more extensive panhypopituitarism, with some males demonstrating micropenis [Delous et al., 2007; Parisi et al., 2007; Wolf et al., 2007]. Normal progression through puberty has been described in both sexes. Anecdotal evidence exists for a significant risk to develop obesity, particularly with the onset of puberty (personal observation). This observation is not surprising given the obvious similarities between JSRD and other ciliary disorders such as Bardet-Biedl syndrome (BBS) in which obesity is a well-known feature, and the recent identification of mutations in the *INPP5E* gene as causative of both JSRD and MORM (Mental retardation,

Obesity, Retinal dystrophy, and Micropenis) [Bielas et al., 2009; Hampshire et al., 2006; Jacoby et al., 2009]. Situs defects have also been described in JSRD [Brancati et al., 2007], similar to other ciliopathies.

Prenatal diagnosis

For couples who have had a prior affected child, there are several options for prenatal diagnosis in subsequent pregnancies. If the disease-causing mutations have been identified, prenatal diagnosis by DNA testing is feasible. For other at-risk pregnancies, prenatal imaging via ultrasound and/or fetal MRI is the best and most practical diagnostic option. Extracranial anomalies such as polydactyly or renal cysts and major structural brain malformations such as encephalocele may facilitate prenatal diagnosis of JSRD as early as the first trimester when a prior history is present [Wang et al., 1999] or may suggest the diagnosis in absence of a prior history. Early diagnosis is more difficult when extracranial findings are not present, because CVH cannot be reliably diagnosed until 18–20 weeks gestation [Bromley et al., 1994], and the MTS has not been reported prior to 27 weeks gestation [Fluss et al., 2006]. In the absence of a family history, prenatal diagnosis is possible but challenging given the spectrum of outcomes for isolated prenatal CVH [Phillips et al., 2006]. An imaging protocol for prenatal diagnosis has been proposed, although its sensitivity and specificity for JSRD have not been systematically evaluated [Doherty et al., 2005].

MOLECULAR GENETICS OF JSRD

Eight causative genes and one additional locus

Mutations in the eight ciliary/basal body genes *INPP5E*, *AHI1*, *NPHP1*, *CEP290*, *TMEM67*, *MKS3*, *RPGRIP1L*, *ARL13B*, and *CC2D2A* have been identified in subjects with JSRD (Table I). The additional locus, JBTS2 (also known as CORS2), has been mapped by linkage analysis to chromosome 11 [Keeler et al., 2003; Valente et al., 2003], but the causative gene is unknown. This locus was simultaneously identified in consanguineous families of different ethnicities and variable phenotypes, with some developing renal disease, others retinal dystrophy, and encephaloceles, colobomas, and polydactyly also described [Valente et al., 2005]. It is possible that the JBTS2 locus is the same as a locus identified for MKS, which has been mapped to a nearby region on 11q13 [Valente et al., 2008].

INPP5E—The first locus for JSRD was mapped to 9q34 in two consanguineous Arab families in which several affected individuals developed retinal dystrophy, but renal disease was not described in those original reports [Saar et al., 1999; Sztriha et al., 1999; Valente et al., 2005]. The *INPP5E* gene was recently identified as causative, and the retinal phenotype is predominant, but in 1/7 families, cystic echogenic kidneys are apparent in the affected individuals and in 2/7 affected families, hepatic fibrosis has developed [Bielas et al., 2009]; thus, it is possible that *INPP5E* represents another COACH gene. Interestingly, the mutations in individuals with JSRD are all missense changes within the phosphatase domain, whereas the mutations identified with the family with the BBS-related obesity syndrome, MORM, is a nonsense mutation in the terminal exon [Jacoby et al., 2009]. This gene encodes an inositol polyphosphate-5-phosphatase E necessary for cilia stability, and indicates a link between phosphatidylinositol signaling and ciliary function [Bielas et al., 2009].

AHI1—Mutations in the 20-exon gene, *AHI1* (Abelson Helper Integration site 1), have been identified in JSRD [Dixon-Salazar et al., 2004; Ferland et al., 2004; Parisi et al., 2006; Romano et al., 2006; Utsch et al., 2006; Valente et al., 2006a]. In one survey of 117 subjects, 11% had causative *AHI1* mutations [Parisi et al., 2006], whereas another survey of 137 subjects identified 7.3% with mutations in this gene [Valente et al., 2006a]. The most common clinical association in *AHI1*-related JSRD is retinal dystrophy, occurring in ~80% of those with

mutations [Valente et al., 2008]. Renal disease consistent with NPHP has been observed in some subjects [Parisi et al., 2006; Utsch et al., 2006]. However, no subjects with *AHI1* mutations have had features of encephalocele, polydactyly, or liver fibrosis. Other CNS anomalies including polymicrogyria, corpus callosum anomalies, and frontal lobe atrophy have been described in some individuals with *AHI1* mutations [Dixon-Salazar et al., 2004]. The mouse orthologous protein, Ahi1, localizes to the basal body and is necessary for formation of the primary cilium and intracellular vesicle transport [Hsiao et al., 2009].

NPHP1—The first gene associated with JSRD, the 30-exon *NPHP1* (Nephronophthisis 1) gene, was previously identified as causing juvenile NPHP [Hildebrandt et al., 1997; Saunier et al., 2000; Saunier et al., 2005]. *NPHP1* resides within a ~290 kb region of genomic DNA flanked by large inverted repeat elements on chromosome 2q13 that is homozygously deleted in JSRD or NPHP [Parisi et al., 2004a]; a few individuals are compound heterozygotes for a deletion and a point mutation in *NPHP1* [Tory et al., 2007]. The *NPHP1* mutation detection rate for the purely renal disorder (juvenile nephronophthisis) is approximately 20–30% [Hildebrandt and Zhou, 2007; Saunier et al., 2005], whereas the mutation rate is only about 1–3% in individuals with JSRD [Castori et al., 2005; Parisi et al., 2004a; Valente et al., 2008]. Some individuals with the common deletion have congenital OMA known as Cogan syndrome [Betz et al., 2000], and others have Senior-Løken syndrome with retinal impairment [Caridi et al., 2006; Castori et al., 2005], but in general, the neurologic symptoms tend to be milder than in many children with JSRD. The *NPHP1* deletion appears to be identical in the different disorders, but the seeming paradox of how such diverse phenotypes can result from the same molecular defect has some tentative answers; several individuals with NPHP who also had neurological impairment or the MTS harbored homozygous deletions of *NPHP1* in combination with a heterozygous change in *AHI1* or *CEP290*, suggesting that the addition of multiple genetic defects may cause more severe phenotypes [Tory et al., 2007]. Thus far, the appearance of the MTS in individuals with *NPHP1* deletions appears to be milder than the “typical” MTS, with elongation and thinning of the superior cerebellar peduncles rather than thickening, and less severe vermis hypoplasia [Castori et al., 2005; Parisi et al., 2004a] (Fig. 1E,F).

CEP290—The large, 54-exon *CEP290* gene has been associated with multiple clinical disorders ranging from isolated Leber congenital amaurosis to JSRD, MKS, and BBS [Baala et al., 2007a; Frank et al., 2008; Zaghoul and Katsanis, 2009]. Most subjects with JSRD due to *CEP290* mutations have retinal dystrophy or congenital blindness, and many also develop renal disease consistent with NPHP or renal cortical cysts [Sayer et al., 2006; Valente et al., 2006b]. *CEP290* was identified as causative in 7 of 96 individuals with JSRD (7%) in one series [Sayer et al., 2006] and in about half of cases of JSRD with both retinal and renal involvement [Brancati et al., 2007; Helou et al., 2007; Perrault et al., 2007; Sayer et al., 2006; Tory et al., 2007; Valente et al., 2008; Valente et al., 2006b]. Findings in some affected individuals have included ocular colobomas, encephaloceles, septal heart defects, hepatic disease, and situs anomalies. Mutations in *CEP290* have also been reported in individuals with Senior-Løken syndrome without neurologic impairment [Helou et al., 2007; Sayer et al., 2006; Tory et al., 2007]. Mutations in this gene have been identified in at least 21% of patients with isolated Leber congenital amaurosis in two European series [den Hollander et al., 2006; Perrault et al., 2007]; most of these individuals are homozygous for a common intronic point mutation that allows production of some residual wild-type protein, hypothesized to account for a milder phenotype than the complete loss-of-function mutations found in JSRD and other more severe phenotypes.

TMEM67/MKS3—The 28-exon *TMEM67/MKS3* (Transmembrane protein 67/ Meckel syndrome, type 3) gene encodes a 995-amino acid protein plays a role in primary cilium

formation and interacts with other known ciliary proteins [Dawe et al., 2007]. Originally identified as causative for MKS [Smith et al., 2006], mutations in this gene have been reported in JSRD [Baala et al., 2007b; Brancati et al., 2009; Gunay-Aygun et al., 2009], and in a large cohort of 232 unselected families with JSRD, 19 had mutations identified in the *MKS3* gene (8%), with the majority of these manifesting hepatic disease [Doherty et al., 2009]. In fact, for those with a clinical diagnosis of COACH syndrome, the prevalence of *MKS3* mutations was 83% (19/23) of subjects in this series [Doherty et al., 2009] and 57% (8/14) in another [Brancati et al., 2009]. The *MKS3* mutations identified in MKS are typically compound heterozygous missense and truncating mutations or homozygous splice-site mutations [Baala et al., 2007b; Consugar et al., 2007; Khaddour et al., 2007; Smith et al., 2006], whereas the disease-associated mutations in JSRD/COACH tend to be missense mutations or the combination of a missense mutation and a splice-site or nonsense mutation, with very few mutations overlapping with those seen in MKS [Brancati et al., 2009; Doherty et al., 2009]. Hypomorphic missense mutations in *MKS3* have also been identified in patients with NPHP and liver fibrosis in the absence of the MTS or neurologic symptoms [Otto et al., 2009]. This pattern suggests that more severe loss-of-function mutations are more likely to cause the lethal MKS syndrome, with milder mutations associated with less severe neurologic phenotypes. In addition, for individuals with JSRD and ocular colobomas, regardless of liver status, 53% had mutations in *MKS3* [Doherty et al., 2009].

RPGRIP1L—Mutations in the *RPGRIP1L* gene were first identified in patients with the renal form of JSRD [Arts et al., 2007; Delous et al., 2007]. The phenotypic spectrum includes predominantly renal disease (typically, NPHP), with some affected individuals manifesting occipital encephaloceles and polydactyly, and rarely, retinal disease or colobomas; a few have had scoliosis, clubfoot, or pituitary hormone deficiency [Arts et al., 2007; Brancati et al., 2008; Delous et al., 2007; Wolf et al., 2007]. Hepatic fibrosis and COACH syndrome have been described in individuals with JSRD due to *RPGRIP1L* [Arts et al., 2007; Doherty et al., 2009; Wolf et al., 2007]. The *RPGRIP1L* gene also causes MKS, with a tendency toward more severe mutations predicted to have a more severe effect on protein function [Delous et al., 2007; Wolf et al., 2007]. Overall, estimates of the prevalence of *RPGRIP1L* mutations in the cerebello-renal form of JSRD range from ~9% [Wolf et al., 2007] to 12% [Brancati et al., 2008], with lower estimates (~1–4%) in unselected cohorts [Arts et al., 2007; Brancati et al., 2008; Doherty et al., 2009; Valente et al., 2008].

ARL13B—This 10-exon gene encodes a protein that is a member of the Ras GTPase family, and localizes to the primary cilia of cerebellar neurons, kidney, and retina. Two families with a phenotype typical of classic JBTS have been identified with mutations in this gene, with two affected individuals also exhibiting occipital encephalocele and one exhibiting pigmentary retinopathy [Cantagrel et al., 2008].

CC2D2A—The 38-exon *CC2D2A* gene was first identified in an extended consanguineous Pakistani family with autosomal recessive cognitive impairment with retinitis pigmentosa [Noor et al., 2008]; later review of cranial MRI scans from two of the affected individuals revealed the MTS, thereby establishing the condition as a JSRD [Gorden et al., 2008]. The phenotype has ranged from classic JBTS to JBTS with encephalocele to the COACH phenotype with coloboma, liver and kidney involvement [Gorden et al., 2008]. *CC2D2A* has been shown to interact with CEP290 and to localize to the basal body [Gorden et al., 2008]. This gene has also been identified in cases of MKS [Tallila et al., 2008]. Overall, it is estimated to cause almost 10% of JSRD [Doherty et al., 2009; Gorden et al., 2008].

Genetic heterogeneity of JSRD

These eight genes account for an estimated 50% of causative mutations in JSRD [Doherty et al., 2009; Valente et al., 2008] (Table I). It has become clear that the same JSRD gene can cause multiple different phenotypes (allelic heterogeneity), and several different genes can be associated with the same clinical features (locus heterogeneity). For example, three genes (*MKS3*, *RPGRIP1L*, and *CC2D2A*) account for over 95% of mutations in the COACH population [Doherty et al., 2009]. In addition, clinical features can vary between affected siblings within the same family, apparent even in the original family described [Joubert et al., 1969]; this intrafamilial variability supports the existence of genetic modifiers and epistatic effects. For many individuals or families with JSRD, the identification of only a single mutation in one of the causative genes suggests the possibility that mutations in other JSRD- or MKS-associated genes may be contributing to the disorder, a phenomenon known as oligogenic inheritance which is known to occur in JSRD and related ciliary disorders. A prime example is the identification of heterozygous changes in *AH11* or *CEP290* in individuals with homozygous *NPHP1* deletions, with the presumption that the three genetic changes in concert leading to the more severe neurologic phenotype [Tory et al., 2007]. In addition, several loss-of-function *RPGRIP1L* alleles, including one relatively common variant (A229T), appear to correlate with retinal dystrophy in patients with ciliopathies due to other genes [Khanna et al., 2009].

The emerging genotype-phenotype correlations that have been described may simplify the quest for a causative gene in an affected individual, and an algorithm for testing the known genes in a subject with JSRD based on clinical findings is proposed in Fig. 3. For example, given the strong correlation between *MKS3* mutations and liver disease and coloboma in JSRD, initial testing of the *MKS3* gene is recommended for a patient with either or both of these findings. Commercial clinical testing is available for many of the JSRD genes, with research laboratories also providing some testing options. It is important to remember that testing guidelines will continue to evolve as knowledge increases and that many manifestations are age-dependent and may not be present in infants or young children. In addition, the etiology will remain elusive in up to half of all patients, as additional JSRD genes remain to be identified, as supported by the observation of consanguineous families that do not map to any of the known loci [Boycott et al., 2007; Janecke et al., 2004; Valente et al., 2005].

OUTCOME AND MANAGEMENT OF JSRD

When a diagnosis of JSRD is suspected, a detailed cranial MRI to evaluate for the MTS is essential, as well as other evaluations that have been outlined previously [Parisi and Glass, 2007]. Given the marked heterogeneity in this group of disorders and the relatively high frequency of associated medical conditions, it is difficult to make generalizations about outcomes. At birth, some infants have severe manifestations of altered respiratory control requiring mechanical ventilation and/or tracheostomy in rare cases. For children with significant feeding difficulties related to hypotonia or dyscoordinated oromotor function, nasogastric feeding tubes or gastrostomy placement have been necessary to prevent aspiration and provide adequate caloric intake. Rarely, seizures that have proved difficult to control have compromised long-term survival; these are more likely in individuals with structural brain malformations in addition to the MTS. However, the vast majority of infants and children diagnosed with JSRD survive the neonatal period and many demonstrate improvement with time in their tone, respiratory function, and feeding behaviors [Parisi et al., 2007]. Initiation of periodic, comprehensive developmental assessments and a program of interventions including special education, physical, occupational, and speech therapy, with adaptive equipment as needed, have shown significant benefits in attainment of developmental milestones for many children with JSRD.

Because of the risk of later development of retinal, renal, and hepatic complications, ongoing monitoring is essential. Recommendations for surveillance and management in JSRD have been developed [Parisi and Glass, 2007] and are available online (<http://www.joubertsyndrome.com/>), with the recognition that an evaluation and management plan must be individualized for each child's unique medical needs. In addition to annual pediatric, neurologic, and developmental assessments, annual ophthalmologic evaluation is recommended to monitor eye movement abnormalities, strabismus, and ptosis, with surgical correction if appropriate. An annual retinal exam (with electroretinogram if indicated) is recommended to identify the onset of pigmentary retinopathy. In order to detect renal disease in its early stages, annual evaluation for reduced urine concentrating ability or anemia can be accomplished by a first-morning void urinalysis for specific gravity and complete blood count; annual BUN, creatinine, abdominal ultrasound scan, and blood pressure measurement are other useful studies to identify and monitor renal disease, which may require dialysis and renal transplantation if progressive. Annual liver evaluation by measurement of hepatic serum markers (transaminases, albumin, bilirubin, prothrombin time) and ultrasound as appropriate can detect liver abnormalities, with further evaluation and monitoring as needed. Surgical interventions for esophageal varices or portal hypertension and liver transplantation may be necessary for those with COACH syndrome. Individuals with JSRD are at risk for sleep apnea, both central (especially in infancy) and obstructive (related to tongue enlargement, hypotonia, and obesity) and may require medical or surgical interventions if apnea is detected by polysomnography. Endocrine disorders may require hormone replacement.

CONCLUSION: JSRD IS A CILIOPATHY

The gene products associated with JSRD are known to localize to the primary cilium and/or basal body and centrosome apparatus that has been identified in almost all cell types [Adams et al., 2008; Badano et al., 2006], and many of these proteins are important for the structure, function, and/or stability of the this organelle and its related structures. Primary cilia are multiprotein complexes containing microtubules, adherens proteins, and other cytoskeletal components and play a role in intraflagellar transport, cell division, tissue differentiation, establishment of body axis, growth, and mechanosensation involved in cellular signaling processes [Badano et al., 2006]. These unique organelles, once believed to be vestigial structures, are essential for signal transduction processes that underlie many aspects of vertebrate development and morphogenesis, including the sonic hedgehog, Wnt/beta-catenin, and PDGF receptor alpha signaling pathways, and more recently, Ras-GTP and Phosphatidylinositol signaling [Bielas et al., 2009; Cantagrel et al., 2008; Christensen et al., 2007]. It appears that the cilium may serve a unique structural role by sequestering growth factors and/or receptors within a subcellular compartment that enables efficient processing of developmental signals to allow specific programs to proceed [Zaghloul and Katsanis, 2009]. In addition, the proper cell polarity and orientation of tubular structures in tissues such as the renal epithelium via planar cell polarity signaling requires normal ciliary function, and disruption of this process leads to cystic kidney disease [Zaghloul and Katsanis, 2009]. The expanding group of human disorders known as ciliopathies share overlapping clinical manifestations that reflect the critical role that cilia play in the growth and differentiation of the involved tissues, ranging from the neural tube to renal, biliary and retinal epithelium, to the developing limb bud [Badano et al., 2006].

JSRD, like many of the disorders considered ciliopathies, shows considerable heterogeneity in clinical features and molecular basis. The clinical features of JSRD are shared by many ciliary disorders, and typically involve the renal epithelium, retinal photoreceptor cells, central nervous system, body axis, sensory organs, and others. In fact, these recurring manifestations have inspired some investigators to develop an algorithm to predict which conditions are likely to be ciliopathies by virtue of their known clinical features alone [Badano et al., 2006]. Perhaps

it is not surprising that the overlap in clinical features between JSRD and other ciliopathies such as MKS and BBS, is also reflected by the overlap of their genetic basis. Evidence suggests that the heterogeneity in clinical presentation is likely the result of modifying genetic factors or oligogenic effects [Leitch et al., 2008; Tory et al., 2007; Zaghloul and Katsanis, 2009].

The major challenges in ciliopathy research remain identification of the remaining causative genes, elucidation of the complex genetic interactions that underlie phenotypic diversity, and translation of research findings into practical clinical guidelines and treatments for affected individuals. Great strides have been made in the field of JSRD research over the past 10 years since the first gene was mapped and in the five years since the first causative gene was reported. However, the genetic etiology for almost half of all individuals with JSRD remains unknown, providing a significant burden for families who wish to have maximum reproductive options. Nonetheless, genotype-phenotype correlations are emerging, and as more genes are identified, this information will allow refinement of management recommendations and targeted therapeutics for the medical complications that can arise in those with JSRD. Discovery of new genes for JSRD and related ciliopathies may provide further information about the function of the primary cilium, basal body, and centrosome, and may also lead to valuable insights into mechanisms of cerebellar, renal, retinal, and hepatobiliary development.

Biography

Melissa Parisi is a clinical geneticist, previously at Seattle Children's Hospital and the University of Washington, Seattle, now based at the National Institutes of Health (NIH) where she is Chief of the Intellectual and Developmental Disabilities Branch of the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development. She has served as the chair of the Scientific Advisory Board of the Joubert Syndrome Foundation and Related Cerebellar Disorders Parent Group.

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Figure 1.

The Molar Tooth Sign (MTS). The typical appearance of the cerebellar vermis on (A) axial and (B) mid-sagittal imaging in a normal individual. C: In a patient with JSRD, the molar tooth sign (MTS) is apparent (between arrows) reflecting a deepened interpeduncular fossa, thickened, elongated superior cerebellar peduncles, and vermis hypoplasia. D: The sagittal image from the same individual with JSRD demonstrates an abnormally positioned and elevated fourth ventricle (arrowhead) with hypoplastic cerebellar vermis (surrounded by five small arrows). E: The “mild” MTS on sagittal imaging of an individual with JSRD due to homozygous *NPHP1* mutations shows thin, elongated superior cerebellar peduncles (arrows); in (F), the axial image shows a less severe elevation of the fourth ventricle (arrowhead) with

less vermis hypoplasia (outlined by small arrows). Derived from [Parisi et al., 2007; Parisi et al., in press].

Figure 2.

Clinical features in JSRD. A: Facial features in a girl with JSRD/COACH syndrome at 27 months of age showing broad forehead, arched eyebrows, strabismus, eyelid ptosis (on subject's right in particular), and open mouth configuration indicating reduced facial tone. B: Oral findings in a subject with oral-facial-digital syndrome-like features of JSRD 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 JSRD and postaxial polydactyly (arrow). D: Right foot of an infant with JSRD and preaxial polydactyly of the hallux. E: View from above of an infant with a small occipital encephalocele showing the protrusion of the occiput of the skull (arrow). (Facial photograph used with permission of the family.)

Figure 3.

Proposed algorithm for genetic testing in JSRD based on clinical features.

* See figure 1E, F for example of the “mild” MTS.

§ Testing for *INPP5E* mutations in individuals with liver disease may be warranted, but insufficient data are available to make a determination for this gene.

BUN, blood urea nitrogen; Cr, creatinine; AST, aspartate aminotransferase; ALT, alanine aminotransferase. Derived from [Doherty, 2009].

Table 1

Molecular genetics of Joubert syndrome and related disorders (JSRD)

Locus name	Gene symbol	Chromosome locus	Protein name	Types of mutations	MTS	Liver	Col	RD	Renal	PD	OE	Key Clinical features	Proportion of JSRD/ reference(s)
JBTS1	<i>INPP5E</i>	9q34.3	Inositol polyphosphate-5-phosphatase E	Missense (phosphatase domain)	++	-	-	+	-	-	-	Retinal	? [Bielas et al., 2009; Saar et al., 1999]
JBTS2	<i>CORS2</i>	11p12-q13.3	unknown	NA	++	-	+	+	+	+	+	Variable	? [Keeler et al., 2003; Valente et al., 2003]
JBTS3	<i>AH11</i>	6q23.3	Joubertin	Nonsense, FS, splice (missense)	++	-	+/-	++	+	-	-	Retinal	7-11% [Parisi et al., 2006; Valente et al., 2006a]
JBTS4	<i>NPHP1</i>	2q13	Nephrocystin-1	Large homozygous deletion, (missense)	+/-	-	-	+	++	-	-	Renal (retinal)	1-3% [Castori et al., 2005; Parisi et al., 2004; Valente et al., 2008]
JBTS5	<i>CEP290</i>	12q21.3	Centrosomal protein of 290 kDa	Nonsense, FS, splice, (missense)	++	+	+	++	++	-	+	Retinal, renal	~10% [Sayer et al., 2006; Valente et al., 2008; Valente et al., 2006b]
JBTS6	<i>TMEM67/MKS3</i>	8q21.1-q22.1	Meckelin	Missense, splice	++	++	+	-	+	+/-	+	Liver involvement	8-10% [Baala et al., 2007; Doherty et al., 2009]
JBTS7	<i>RPGRIP1L</i>	16q12.2	RPGR-interacting protein 1-like protein	Missense, FS, splice, nonsense	++	+	+/-	+/-	++	+	+	Renal	2-4% [Arts et al., 2007; Brancati et al., 2008; Delouis et al., 2007; Valente et al., 2008]
JBTS8	<i>ARL13B</i>	3q11.2	ADP-Ribosylation factor-like 13B	Missense, (nonsense)	++	-	-	+	-	-	+	Very rare	<1% [Cantagrel et al., 2008]
JBTS9	<i>CC2D2A</i>	4p15.3	Coiled-coil and C2 Domains-containing protein 2A	Missense, nonsense, splice, FS	++	+	+	+	+	-	+	Variable	8-9% [Doherty et al., 2009; Gordon et al., 2008]

- = not described; +/- = rare; + = present in some cases; ++ = common; ? = unknown. Col = coloboma; FS = frameshift mutation; MTS = molar tooth sign; NA = not applicable; OE = occipital encephalocele; PD = polydactyly; RD = retinal dystrophy. Derived from [Parisi et al., in press].