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Joubert syndrome: insights into brain development, cilium biology and complex disease

Dan Doherty, MD, PhD

University of Washington and Seattle Children's Hospital, Seattle, WA

Dan Doherty: ddoher@u.washington.edu

Introduction

In 1969, Marie Joubert could hardly have predicted the importance of the obscure autosomal recessive disorder now named Joubert syndrome (JS).^{1,2} Almost 30 years after the first description of hypotonia, ataxia, abnormal eye movements and alternating hyperpnea/apnea in four French Canadian siblings, the “molar tooth sign,” was identified as the key feature on magnetic resonance imaging (MRI).³ Seven years later, the first causal genes were identified (*NPHP1* and *AHI1*),^{4–6} followed quickly by *CEP290*, *RPGRIP1L*, *TMEM67/MKS3*, *ARL13B* and *CC2D2A*.^{7–11} All of these genes and their gene products have been associated with the primary cilium and basal body (PC/BB), subcellular organelles whose central roles in diverse cellular processes have only recently been appreciated (for reviews see Yoder, 2008),¹² making JS one of the rapidly expanding group of disorders termed ciliopathies.¹³ In addition to its importance for understanding the genetic networks underlying normal and abnormal brain development, JS represents a relatively simple model for more common, genetically complex disorders, in which multiple genetic and environmental factors contribute to the phenotype seen in a given patient.

Clinical features

Many features of JS (mid-hindbrain malformation, retinal dystrophy, cystic renal disease, congenital hepatic fibrosis and polydactyly) overlap with ciliopathies in general and Meckel syndrome (MKS) in particular (Table 1). Recent evidence indicates that these overlapping phenotypic features reflect a shared molecular pathophysiology involving the PC/BB organelle (see “Clinical and genetic overlap with other disorders” below).

Brain Imaging

The term molar tooth sign was coined by Maria et al. (1997) to refer to the appearance of long, thick superior cerebellar peduncles, a deep interpeduncular fossa and vermis hypoplasia/aplasia in the same axial slice on brain MRI (Fig 1A, D).³ When these features are not captured in the same slice, the following imaging can be features useful in confirming a JS diagnosis. Vermis hypoplasia is best assessed on sagittal views (Fig 1B, E, H); however, this can be difficult when the hemispheres impinge on the midline. The acquisition of thinner slices has made this less of a problem for more recent clinical imaging studies. Vermis size must also be assessed on axial and coronal views, paying particular attention to whether cerebrospinal fluid is present

in the midline between the hemispheres (Fig 1A, C, D, F, G). The vermis hypoplasia in JS is unlikely to be due to atrophy, since the vermis has been noted to be small on the earliest possible prenatal imaging at 14–16 weeks gestation (D. Doherty, personal observations). Evaluation of the 4th ventricle on sagittal views is also informative. In patients with JS, the roof of the 4th ventricle is oriented more horizontally than usual, even when the vermis as a whole is not rotated superiorly (Fig 1B, H). Finally, although not entirely specific for JS, the 4th ventricle opens widely immediately inferior to the tectum, rather than remaining quite narrow for several millimeters (Fig 1B). When the vermis is completely absent and a large posterior fossa cyst is present, the radiologic diagnosis of JS can be difficult. A variety of additional imaging features have been observed, including agenesis of the corpus callosum (Fig 1K),^{14,15} encephalocele (Fig 1I),^{1,16,17} hydrocephalus,^{14,18} posterior fossa cysts (often labeled Dandy-Walker malformation or Dandy-Walker variant),¹⁹ cerebellar¹⁷ and cortical heterotopias (Fig 1J), and polymicrogyria.^{5,16}

Brain pathology

Neuropathology findings have been reported in at least 15 individuals with JS, ranging from 18 weeks gestation to 31 years of age (Table 2).^{1,3,8,20–30} Lack of standardization limits the conclusions that can be drawn from these reports; nonetheless, a number of the findings have been reported in more than one case. In addition to vermis hypoplasia, the most frequent structures noted to be abnormal are: the deep cerebellar nuclei, the inferior olivary nuclei, multiple cranial nerve nuclei and the decussations of the superior cerebellar peduncles and pyramidal tracts. It is not clear from the pathology which abnormalities are primary and which are secondary. Diffusion tensor imaging and tractography are consistent with defects in the decussation of the superior cerebellar peduncles.^{31–33}

Eye findings

Abnormal eye movements are uniformly present in JS though variable in severity.^{1–3,34–38} The presence of nystagmus, saccades instead of smooth pursuit and tracking/acquiring targets with head movements rather than eye movements are the predominant clinical signs. Quantitative eye movement recordings demonstrate that the gains (target velocity/eye velocity) for smooth pursuit, saccades, optokinetic nystagmus and vestibuloocular reflex are variably reduced.^{35,39,40} Each of these oculomotor deficits reflect abnormalities of specific neural ensembles in the cerebellar vermis (oculomotor, nodulus, uvula), flocculus/paraflocculus, deep cerebellar nuclei, vestibular nuclei, pontine nuclei and/or inferior olives. Retinal dystrophy (Fig 2A) with visual loss occurs in a subset of patients with JS. Early onset of the retinal dystrophy shares overlapping clinical features with Leber congenital amaurosis, and preservation of vision despite markedly abnormal electroretinogram (ERG) findings supports more severe involvement of rod versus cone photoreceptors in some cases.^{34,41} Chorioretinal coloboma (Fig 2B), identified in 19% of our cohort, is associated with significant visual impairment if the macula or optic nerve are involved. Strabismus and ptosis are additional ocular findings that may be corrected with surgical intervention.

Cognition and behavior

While most reports indicate that patients with JS have substantial cognitive impairment, the range of ability is quite broad.^{25,42,43} A convenience sample of 32 patients aged 1–17 years (mean 6 years) evaluated with the Child Development Inventory displayed a mean developmental age equivalent of 19 months.⁴⁴ Developmental and intelligence quotients between 30 and 80 have been reported in patients with JS;^{38,42} however, the substantial motor and speech impairments make it difficult to accurately measure underlying cognitive ability. Similarly, autism has been reported in children with JS,^{45–47} but the severe oral-motor dyspraxia and oculomotor issues in JS cause speech delay and abnormal eye contact,

complicating the assessment of two core features of the diagnosis (communication and social interaction). Takahashi et al. (2006) reported that none of 31 patients with JS exceeded the Autism Behavior Checklist cutoff for autism, and they did not find increased load of neuropsychiatric issues seen in families of individuals with autism.⁴⁸ In our experience, many patients with JS are very interested in social interaction, engage in pretend play and exhibit theory of mind, features inconsistent with autism.

Kidney findings

Similar to the retinal disease seen in JS, the renal disease ranges in severity, from cystic renal dysplasia overlapping with MKS (Fig 2D) to classic nephronophthisis (Fig 2E) with onset in late childhood or later.⁴⁹⁻⁵⁰ The first sign of later onset renal disease is often failure to concentrate urine (salt-losing renal insufficiency) followed by echogenic kidneys on ultrasound and eventual renal failure. In patients with *AH1* mutations, onset of renal disease has been reported in young adults.⁵¹⁻⁵² Saraiva and Baraitser (1992) reported renal disease in 30% of cases in the literature,¹⁷ similar to the 23% in our cohort.

Liver disease

COACH syndrome (Cerebellar vermis hypoplasia, **O**ligophrenia - developmental delay/mental retardation, **A**taxia, **C**olobomas, and **H**epatic fibrosis) is considered a sub-type of JS.^{16,53,54} Clinically, the liver disease can be asymptomatic or present with mildly elevated serum transaminases, but more often, it is identified by liver imaging or signs of portal hypertension (varices, hepatosplenomegaly, ascites and rarely, upper GI bleeding). Biopsy findings are in the spectrum of the ductal plate malformation (Fig 2H) and congenital liver fibrosis (Fig 2I), and the fibrosis is progressive at least in some cases.⁵⁵ Severe disease requires porto-systemic shunting or liver transplantation and can result in death. Liver disease occurs in 18% of our cohort; however, this may be an over-estimate of the true prevalence since we have focused on recruiting patients with liver disease.

Skeletal

Polydactyly is seen in 19% of our cohort and is a feature of many ciliopathies. Most frequently, it is post-axial (Fig 2F), although it can be pre-axial or very rarely, mesaxial. In general, polydactyly is not functionally significant, and surgical correction is at the discretion of the patient/family. As in many children with hypotonia, scoliosis is a common complication and requires close monitoring, especially during puberty.

Other

While many patients with JS display dysmorphic facial features, no easily recognizable facial appearance has been described,^{56,57} in contrast to well-known disorders like Down and Williams syndromes. Oral frenulae, tongue hamartomas, micropenis and pituitary dysfunction have also been reported in small numbers of patients.^{16,17} Despite the presence of obvious breathing abnormalities in most infants with JS, the prevalence of central and obstructive sleep apnea in older children is likely under appreciated.

Medical Management

Guidelines for the evaluation and management of patients with JS were developed by a consensus panel convened by the Joubert syndrome Foundation and Related Cerebellar Disorders, and have been published elsewhere.⁵⁸ These recommendations include yearly ophthalmologic evaluation, urinalysis, renal and liver ultrasounds, as well as serum transaminases, BUN, and creatinine to monitor for and allow early treatment of the medical complications described above. Lifelong monitoring for obstructive and central sleep apnea is

also warranted. Specific developmental and behavioral supports for JS do not exist, and interventions are tailored to the needs of each individual.

Prevalence

Although the prevalence of JS has been estimated by Flannery and Hudson (1994)⁵⁹ and Parisi and Glass (2007)⁵⁸ to be 1/100,000–1/250,000, no population-based prevalence data exist. Based on the 30 patients we follow in our center that draws patients from a region of ~10 million people, a very conservative estimate of the minimum prevalence is ~1/300,000.

Genetics of JS and diagnostic testing strategy

Mutations in seven genes (*NPHP1*, *AH11*, *CEP290*, *RPGRIP1L*, *MKS3/TMEM67*, *CC2D2A* and *ARL13B*) and 2 additional loci (9q34, 11p12-11q13.3) have been associated with JS.^{4–11,60–65} In our cohort, *NPHP1*, *AH11*, *RPGRIP1L*, *ARL13B*, *CC2D2A* and *MKS3/TMEM67* account for <50% of subjects. Due to its large size (54 exons), we have not sequenced *CEP290* in most of our cohort, but it is reported to be responsible for JS in at least 7% of cases.^{11,66}

With the advent of improved sequencing technologies, it will likely become possible to sequence all of the JS-related genes simultaneously; however, clinical testing currently involves sequencing each gene individually, so strategies to prioritize testing are important to save time and money. The strongest genotype-phenotype correlation to date is between *MKS3* mutations and clinically apparent liver disease (elevated transaminases, portal hypertension and/or liver fibrosis on biopsy). Thus, all patients with JS and liver disease should be tested first for *MKS3* mutations. Genotype-phenotype correlations involving the other genes are not as strong (Table 3). For instance, patients with *NPHP1* deletions invariably have renal disease and less severe brain malformation. Most subjects with *AH11* mutations have retinal dystrophy, but very few have renal disease. In contrast, *CEP290* mutations cause a spectrum of phenotypes, from isolated JS, to JS with retinal and renal disease, to severe MKS. *RPGRIP1L* mutations also cause a broad spectrum of disease with renal and liver involvement, but only rarely retinal dystrophy. Based on these observations, gene sequencing can be prioritized based on the clinical scenario (Fig 3).

Clinical and genetic overlap with other disorders: the ciliopathies

Although similarities between MKS and JS had been noted as early as 1987,⁶⁷ it was not until *CEP290* mutations were found in subjects with JS¹¹ and MKS⁶⁸ that the allelic nature of these syndromes was revealed. Since that time, mutations in *RPGRIP1L*, *CC2D2A* and *MKS3/TMEM67* have been shown to cause both MKS and JS.^{7,8,10,14,69,70} Similarly, *NPHP1* mutations can cause isolated nephronophthisis⁷¹ or mild forms of JS.^{4,72} The most striking example is *CEP290*, where mutations can cause JS,¹¹ MKS^{68,73} and BBS⁷⁴, as well as isolated LCA^{75,76} and nephronophthisis.⁷⁷ This is in keeping with work in humans and model systems showing that loss of function in genes with related functions cause similar phenotypes (reviewed in Brunner et al. 2004).⁷⁸

As with many disorders, the spectrum of phenotypes associated with JS has expanded due to increased diagnosis in patients with related phenotypes, as well as advances in molecular testing. With the expanded phenotypes has come increasing overlap with other ciliopathies, particularly MKS and BBS, making the clinical classification of individual patients challenging. Not surprisingly in retrospect, these disorders now share molecular causes at least at the level of the genes (if not the specific mutations) involved.

Further complicating matters is emerging evidence for oligogenic inheritance, whereby full penetrance of a phenotype requires mutations in more than one gene. Thus, genetic modifiers may account for the often remarkable variability that is observed in ciliopathies.^{74,79–82} This has been most clearly demonstrated in BBS;⁸¹ however, a higher than expected prevalence of heterozygous *CEP290* and *AH11* sequence variants was detected in patients with JS caused by mutations in both copies of *NPHP1*.⁸³ In summary, clinical categorizations and causal mutations provide complementary information. Clinical categories remain important for directing diagnostic testing and providing prognostic information, while identifying the mutations involved allows for diagnostic, carrier and prenatal testing, as well as precise recurrence risk counseling.

Primary cilium/basal body and molecular mechanisms

Cilia are specialized, membrane-bound, hair-like structures that project from the cell surface (Fig 4). Each cilium is composed of a microtubule cytoskeleton (the axoneme) surrounded by a specialized membrane and anchored in the cell by the basal body. *Motile cilia* have doublet microtubules arranged in a 9+2 concentric pattern and are present on a variety of cell types including respiratory epithelia, brain ependymal lining cells and sperm. *Primary cilia* lack the central two microtubules (9+0 axoneme) and are usually non-motile, with the important exception of the cilia of the primitive node that rotate clockwise to generate the leftward nodal fluid flow required for establishing left-right asymmetry in vertebrates (reviewed in Shiratori and Hamada 2006 as well as Hirokawa et al., 2006).^{84–90}

Primary cilia or modifications thereof are present in most cell types, including renal tubule epithelial cells, retinal photoreceptors, chondrocytes, fibroblasts and neurons. In general, the microtubules that form the axoneme are nucleated by the basal body that forms from the mother centriole when it docks at the plasma membrane after cell division (reviewed in Marshall, 2008).⁹¹ Intraflagellar transport (IFT) proteins including dynein and kinesin motors are required for the assembly and function of cilia (reviewed in Pedersen and Rosenbaum).⁹²

Ciliary membranes contain receptors and ion channel proteins mediating mechano/chemo-sensation and other types of cell signaling. Mounting evidence supports a role for the PC/BB in the sonic hedgehog (SHH), WNT and PDGF α signaling pathways that control diverse processes such as cell division, differentiation, migration and planar cell polarity. SHH binding to its transmembrane receptor, patched (PTCH), results in increased localization of smoothened (SMO) to the primary cilium. This binding abolishes the inhibitory effect of PTCH on SMO and transduces signals to the nucleus via the GLI transcription factors, resulting in de-repression and activation of SHH target genes (reviewed in Satir and Christensen 2007).⁹³ SHH signaling is required for at least two major processes in hindbrain development: early for dorsal-ventral patterning of the neural tube, and later for proliferation of the cerebellar granule cells.^{94–95}

In light of the phenotypic overlap between JS and other ciliopathies, it is not surprising that the proteins encoded by all of the JS genes have been shown to localize to the PC/BB or directly interact with components of the PC/BB (Table 4).^{7,10,11,14,61,65,69,96–98} In addition, mutations in the mouse orthologs of two JS genes (*rpgril1* and *arl13b*) disrupt cilium number/morphology and cause aberrant dorsal-ventral patterning of the early neural tube,^{96,99} but later defects in brain development have not been explored. It is unclear whether the human *RPGRIP1L* and *ARL13B* phenotypes are milder because the mutations identified in humans have less severe effects on overall PC/BB function, effects on a subset of PC/BB functions or effects outside the PC/BB. Disruption of cilium function by loss of *ift88* function after E13 in the mouse cerebellum results in markedly decreased granule cell proliferation without disruption in overall patterning of the cerebellum or brainstem.^{100,101} Purkinje cells are also

abnormal, potentially secondary to the granule cell defect. Conditional loss of *kif3a* function generates a similar phenotype, supporting a specific role for the cilium. Given the requirement for IFT proteins in granule cell proliferation, it would not be surprising if RPGRIP1L and ARL13B were also required for granule cell proliferation, likely via effects on SHH signaling.

The JS genes are highly conserved across all vertebrates, with orthologs in additional species as distantly related as sea urchin, nematodes and insects. *NPHP1* encodes nephrocystin-1 which interacts with AHI1, other NPHP proteins and components of cell-cell and cell-matrix signaling pathways. Nephrocystin-1 is localized to the transition zone of the PC/BB in renal epithelia and also to the adherens junctions and focal adhesions in a cell cycle dependent manner (reviewed in Hildebrandt and Zhou, 2007).¹⁰²

RPGRIP1L encodes the RPGRIP1L protein which, like its retinally-expressed homolog RPGRIP, interacts with the *NPHP4* gene product, nephrocystin-4, a ciliary protein defective in some cases of isolated nephronophthisis and Senior-Løken syndrome (nephronophthisis plus retinal dystrophy/LCA).⁷ Mutations in both *RPGRIP1L* and *NPHP4* disrupt this interaction. RPGRIP1L localizes to the basal body and also colocalizes with CEP290 in brain and kidney. Knockout of the murine ortholog of *RPGRIP1L*, results in ciliary assembly/functional defects, abnormal left-right asymmetry and preaxial polydactyly, all likely resulting from disturbed *Shh* signaling.⁹⁹

The protein encoded by *CEP290* localizes to centrosomes and the mitotic spindle in a cell cycle dependent manner and has been shown to directly activate the ATF4 transcription factor in cultured cells.^{11,103} A homozygous in-frame deletion found in a murine retinal dysplasia model (rd16) abolished interaction with RPGR, a microtubule transport protein, suggesting a specific role for CEP290 in microtubule-based ciliary transport.¹⁰⁴ More recently, CEP290 has been implicated in vesicle transport and cilium formation/maintenance through its interactions with PCM1105 and CP110106 as well as its role in transport of G-proteins into olfactory cilia.¹⁰⁷

TMEM67/MKS3 encodes the meckelin protein which localizes to the primary cilium and to the plasma membrane. MKS3 interacts with MKS1 and knockdown of either MKS1 or MKS3 by siRNA in ciliated renal epithelia blocked migration of the basal body to the plasma membrane and primary cilium formation.⁶¹ In contrast to these results, cilia are present, albeit elongated and dysmorphic, in a recently published *mks3* knockout mouse.¹⁰⁸

AHI1 encodes a protein with WD40 and SH3 domains and is highly expressed in human fetal brain and kidney. In postnatal mouse brain, expression is detected at higher levels in the cerebellar dentate nuclei and the deep cortical neurons that form the corticospinal tract, potentially correlating with the failure of decussation observed in functional and neuropathological studies of JS.^{5,6} *AHI1* localizes to the cell junctions and centrosomes in cultured cells and interacts with NPHP1 and HAP1.^{65,109}

ARL13B is an ADP ribosylation factor (Arf) related gene in the Ras superfamily of small GTPases, some of which have been implicated in cytoskeletal dynamics, lipid metabolism and vesicle trafficking. ARL13B localizes to cilia in the mouse node, neural tube and fibroblasts, and an *arl13b* null mutation in mice causes neural tube defects, polydactyly and aberrant *Shh* signaling in the neural tube.^{96,110} Loss of function in the zebrafish *scorpion* mutant results in abnormal body shape and pronephric (kidney) cysts.¹¹¹

CC2D2A encodes a protein with similar overall structure to RPGRIP1L including coiled-coil domains, a C2 domain and an overlapping centrosomal protein related domain. CC2D2A physically interacts with CEP290 and loss of *Cc2d2a* function in the zebrafish *sentinel* mutant

results in abnormal body shape and pronephric (kidney) cysts that is strongly exacerbated by knockdown of *Cep290* function.¹⁴

Recently, the BBS proteins have been shown to form a complex (the BBSome) that associates with PCM1 and rab8, and is required for sorting proteins to the cilium.¹¹² CEP290 has been shown to be part of the complex and is required for transporting olfactory receptors to the olfactory cilium.¹⁰⁵⁻¹⁰⁷ Other BBS proteins share homology with chaperonins and are likely required to help build the BBSome complex (reviewed in Tobin and Beales, 2007).¹¹³ The JS gene products share protein domains with BBS gene products including coiled coils (RPGRIPL, CC2D2A, CEP290, ARL13B, and BBS2, 4, 7, 9), WD40 repeats (AHI1 and BBS1, 2, 7) and Rab GTPase motifs (ARL13B and ARL6), so it is tempting to hypothesize that the JS proteins also function as a multi-protein complex with members that play similar roles to the BBS proteins.

Despite remarkable advances in the genetics of JS, little is known about how specific gene defects result in abnormal brain development. A few hypotheses can be generated based on the limited data available. As described above, the brain malformation in JS comprises at least several components: 1) decreased vermis size (likely due to decreased cell numbers); 2) aberrant axonal pathfinding (disrupted decussation of the superior cerebellar peduncles and pyramids); and 3) possible abnormal neuronal migration (fragmented dentate nuclei, cerebellar and cortical heterotopias, “pachygyric” inferior olives).

One theory proposes that the vermis hypoplasia in JS is due to decreased granule cell proliferation caused by aberrant SHH signaling via defective cilia; however, conditional knockout of *kif3a* and *ift88* in the developing mouse cerebellum results in markedly decreased size of the cerebellar hemispheres and vermis,^{100,101} so somehow, mutations that cause JS would have to affect the vermis preferentially. Alternatively, defective dorsal-ventral patterning could result in alterations to the cells fated to become the cerebellar vermis and deep cerebellar nuclei. To date, defective SHH signaling in the developing cerebellum has not been reported in the existing mouse models for JS. An alternative theory is that subtle alterations in specification of the mid-hindbrain boundary and resulting rhombomere identities could underlie JS. SHH signaling^{115,116} and cilium function¹¹⁷ are required for normal specification of the mid-hindbrain boundary and altered segment identity could affect the birth, cell fate, persistence or migration of cerebellar cell types. Consistent with this theory is the observation that the vermis develops from the most rostral portion of rhombomere 1 after morphogenetic movements transform the rostral-caudal axis into a medial-lateral orientation.¹¹⁸ Tissue-specific elimination of JS gene function at various stages of mid-hindbrain development may clarify the mechanisms, but given the complexity of PC/BB function, it is likely that none of the theories above will fully explain the mid-hindbrain phenotype in JS.

Future Directions

Despite great progress in the understanding of JS, many questions remain unanswered. Clinically, prenatal diagnosis remains an issue for >50% of families in which the genetic cause has not been identified. Prognostic information in the literature is limited by small numbers of patients, diverse ascertainment strategies, short duration of follow-up and lack of standardized assessments. We do not yet have accurate information on the easiest outcomes to measure: lifespan and cause of death. The neuropathological findings in humans and model organisms are incompletely characterized, and while the known genes are implicated in the PC/BB, the precise molecular function of these genes remains elusive and many of the players have yet to be identified. Furthermore, the details of how PC/BB dysfunction results in brain malformation and organ dysfunction in JS remain to be explored.

Technological breakthroughs may help with some of these issues (e.g. re-sequencing many genes to identify genetic modifiers that more fully explain JS phenotypes), while other issues will require time-consuming, detail-oriented patient phenotyping. Autopsies (pre- and post-natal) have the potential to reveal the most information about the human brain malformation in JS and should be performed by experienced neuropathologists whenever possible. Finally, high-throughput technologies to evaluate protein-protein interaction networks combined with genetic approaches in model systems to validate the protein-protein interactions will yield a more accurate view of the genetic/protein networks underlying JS as well as normal brain development.

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Figure 1. MRI findings in JS

(A–C) Classic Molar tooth sign (A) Axial T2-weighted image of vermis hypoplasia, long, thick superior cerebellar peduncles and deep interpeduncular fossa; (B) Sagittal T1-weighted image of vermis hypoplasia and elevation of the roof of the 4th ventricle; (C) Coronal T2-weighted image of vermis hypoplasia and thick superior cerebellar peduncles; (D–F) “Mild” molar tooth sign (D) Axial T2-weighted image of mild vermis hypoplasia and long, mildly thick superior cerebellar peduncles; (E) Sagittal T1-weighted image of mild vermis hypoplasia and elevation of the roof of the 4th ventricle; (F) Coronal T2-weighted image of vermis hypoplasia and thick superior cerebellar peduncles (G–I) Fetal MRI at 22 weeks gestation (G) Axial SSFSE image of vermis hypoplasia and large posterior fossa fluid collection; (H) Sagittal SSFSE image of

vermis hypoplasia and abnormal configuration of the roof of the 4th ventricle; (I) Axial SSFSE image of a small encephalocele (arrowhead); (J) Axial T2-weighted image of periventricular nodular heterotopias (black arrows), vermis hypoplasia and deep sulcus in the left temporal lobe; (K) Sagittal T1-weighted image of agenesis of the corpus callosum (asterisk) and elevation of the roof of the 4th ventricle. Note that the vermis hypoplasia in B, D and K is somewhat obscured by the hemispheres impinging on the midline. SSFSE=Single Shot Fast Spin Echo

Figure 2. Clinical features in JS

(A) Pigmentary retinal dystrophy; (B) Chorioretinal coloboma (pale area); (C) Occipital encephalocele in a 19 week gestation fetus; (D) Nephronophthisis in a mature kidney: interstitial scarring with mild inflammation and tubular atrophy. Basement membranes (dark purple) around several tubules and Bowman's capsule show marked redundancy with wrinkling and lamellation. Periodic Acid Schiff (PAS), 100X. (E) Cystic-dysplastic kidney in a 19 week gestation fetus: round, partially collapsed cysts are seen in all parts of the nephron as well as decreased numbers of glomeruli, excessive stroma and interruption of the nephrogenic zone (upper right, subcapsular). H&E, 40X; (F) Postaxial polydactyly in a 19 week gestation fetus; (G) Normal mature liver: the portal triad contains a branch of the portal vein (left), hepatic artery (middle) and similarly sized bile duct (right) embedded in a small amount of supportive collagen. Trichrome, 200X; (H) Ductal plate malformation in a 22 week gestation fetus: multiple large ducts that parallel the limiting plate and encircle hepatic artery branches are evidence of biliary dysgenesis. Trichrome, 200X; (I) Congenital hepatic fibrosis in a 9 year old: the portal triad has moderate fibrosis and an excess of bile ducts and hepatic artery branches with only minimal inflammation. Images courtesy of Meral Gunay-Aygun, Ekaterini Tsilou (A), Avery Weiss (B), Joseph Siebert (C, F), Laura Finn (D, E, G-I).

Figure 3. Prioritized genetic testing for JS based on current genotype-phenotype information

While each of the JS genes can cause a spectrum of phenotypes, patients with a mild MTS, particularly if they have nephronphthisis, should be tested for *NPHP1* deletions and if negative, point mutations. Those with liver disease should be tested for *MKS3/TMEM67* mutations, followed by *CC2D2A* and *RPGRIP1L*. Retinal plus renal disease should prompt testing for *CEP290* mutations. Isolated retinal disease should prompt *AHI1* testing followed by *CEP290*, while isolated renal disease should prompt *RPGRIP1L* testing. Patients without organ complications should be tested for *AHI1*, *CC2D2A* and *CEP290* (particularly the G1890X mutation). If mutations are not found using this strategy, sequencing the remaining genes should be considered. The yield for the currently available DNA testing is 40–50%.

Figure 4. Primary cilium/basal body, JS gene products and the SHH, WNT and PDGF α signaling pathways

The known JS-associated proteins are depicted in red and have been shown to localize to the basal body and/or primary cilium in at least some contexts. ARL13B, RPGRIP1L and possibly MKS3, CEP290 and CC2D2A are required for primary cilium/basal body formation or maintenance^{61,69,96,99,119}. Direct contact between proteins indicates *in vivo* or *in vitro* evidence for physical interactions that are likely cell type and cell cycle dependent. Activation of the SHH signaling pathway (orange) relieves the suppression of SMO activity by PTCH, allowing SMO to enter the cilium and alter the balance of GLI activator and repressor transcription factors to control cell fates in a wide variety of tissues (reviewed in Eggenschwiler and Anderson 2007; Wong and Reiter 2008).^{120,121} *arl13b* and *rpgr1l* mutations in mice disrupt SHH signaling and cause randomization of left-right asymmetry, neural tube defects and polydactyly.⁹⁶⁻⁹⁹ The primary cilium/basal body is required for PDGF α signaling pathway (blue) that is involved in regulation of the cell cycle, cytoskeletal organization and cell migration (reviewed in Andrae et al. 2008; Christensen et al. 2008).¹²²⁻¹²³ Although the mechanism is unknown, the PC/BB also plays a role in regulating the balance between

canonical (green) and non-canonical (black) WNT pathways (reviewed in Clevers 2006; Gerdes and Katsanis 2008).124,125

Table 1

Prevalence of clinical features in a cohort of 235 families with JS. Core features seen in 100% of subjects: hypotonia, ataxia, intellectual disability, MTS/CVH

Feature	% in our cohort
Encephalocele	6
Chorioretinal coloboma	19
Retinal dystrophy	30
Cystic kidney disease	23
Liver disease ¹	18
Polydactyly	19

Table 2Pathological brain abnormalities reported in patients with JS^{1,3,8,20–30}

Structure	Pathologic finding	N ¹
Cerebellar vermis	Hypoplastic	17/17
Cerebellar flocculus	Absent	2/17
Cerebellar hemispheres	Dysplastic	4/17
Dentate nucleus	Fragmented	10/15
Other deep cerebellar nuclei	Not found	7/15
Superior and inferior colliculi	Fused	2/15
Pyramidal decussation (corticospinal tracts)	Hypoplastic/absent	5/15
Inferior olives	Hypoplastic/dysplastic ²	7/15
Superior cerebellar peduncle decussation	Hypoplastic/absent	4/15
Dorsal column nuclei	Hypoplastic/dysplastic	3/15
Cranial nerve nuclei	Hypoplastic/dysplastic	5/15

¹ Denominators differ because two reports did not include histopathology² King et al. (1984) reported hyperplasia of the inferior olives

Table 3

Phenotypic features and other disorders associated with JS genes/loci

Gene/locus	%*	MTS	Retina	PD	Kidney	Liver	OE	coloboma	Other disorders
<i>RPGRIP1L</i>	3	+	+/-	+	++	+	+	+/-	MKS
<i>NPHP1</i>	1	+/-	+/-	-	++	-	-	-	NPH, Cogan OMA
<i>CEP290</i>	~10	+	++	+/-	++	+	+	+/-	MKS, LCA, BBS
<i>MKS3</i>	9	+	-	+	+	++	+	++	MKS
<i>AH11</i>	8	++	++	-	+/-	-	-	-	-
<i>ARL13B</i>	<1	+	+/-	-	-	-	+/-	-	-
<i>CC2D2A</i>	9	+	+/-	+/-	+	+/-	+/-	+/-	MKS
9q34	?	+	+/-	-	+	-	+/-	-	?
Chr11	?	+	-	-	+	-	-	+/-	?
Total	<50								

MTS=Molar Tooth Sign; OE=Occipital Encephalocoele; OMA=OculoMotor Apraxia; PD=Polydactyly; ++ = commonly reported; + = reported in some cases; +/- = infrequently reported; - = not reported.

* all percentages based on our cohort except for *CEP290* (based on the literature)

Table 4

JS gene function

Gene	Size (aa)	PC/BB function	Domains	Animal mutant
<i>NPHP1</i>	732	BB localization; Interaction w/NPHP2-4, AHI1	SH3	M ¹¹⁴
<i>RPGRIP1L</i>	1315	PC defects; BB and PC localization; Interaction w/NPHP4	C2, CC, RID	M ⁹⁹
<i>CEP290</i>	2481	BB localization	CC, SMC, more	no
<i>TMEM67/MKS3</i>	995	PC defects; BB and PC localization; Interaction w/MKS1	7TM, cysteine rich	M ¹⁰⁸ R ⁷⁰
<i>AHI1</i>	1196	BB localization; Interaction w/NPHP1	CC, WD40, SH3	no
<i>ARL13B</i>	428	PC defects; PC localization	CC, GTP, proline rich	M ⁹⁶ Z ⁹
<i>CC2D2A</i>	1620	BB localization; Interaction w/CEP290, IFT88	CC	Z ¹⁴

aa=amino acid; BB=basal body; C2=Protein kinase C Ca²⁺ binding domain; CC=coiled-coil; GTP=GTP-binding domain; M = Mouse; PC=primary cilium; R = Rat; RID= RPGR interacting domain; SH3=src homology domain; SMC=Structural Maintenance of Chromosomes chromosome segregation ATPase; TM=Transmembrane domain; Z=Zebrafish;