



## Next Generation Sequencing Panel for Joubert and Meckel Gruber Syndrome

### Joubert syndrome

Joubert syndrome (JBTS) is characterized by hypotonia, oculomotor apraxia, nystagmus, and intellectual disability. In these patients, brain MRI reveals the pathognomonic “molar tooth sign” (MTS) with absent or hypoplastic cerebellar vermis, deepened interpenduncular fossa, and elongated superior cerebellar peduncles. The term Joubert syndrome and related disorders (JSRD) is used to describe individuals who, in addition to having the core neurological features, also have additional findings including retinal dystrophy, ocular colobomas, kidney disease, liver fibrosis, occipital encephalocele, oral hamartomas, endocrine abnormalities and polydactyly (1).

### Meckel Gruber syndrome

Meckel Gruber syndrome (MKS) is the most common syndromic form of neural tube defect and the classic triad of clinical features is characterized by occipital encephalocele, cystic kidneys and fibrotic changes to the liver. The clinical phenotype has since been broadened to include features such as postaxial polydactyly, skeletal dysplasia, microphthalmia, genital anomalies, cleft lip and palate, and heart defects (2).

The genes implicated in JSRD and MKS all play roles in the formation or function of sensory cilia. Primary cilia are essential for vertebrate development, and mutations affecting this organelle underlie a large group of human malformation syndromes, the ciliopathies. To date, mutations in the Joubert/Meckel-Gruber Syndrome Panel account for approximately 50% of Joubert syndrome cases (1). Mutations in the Meckel Gruber Syndrome Panel account for approximately 75% of cases of Meckel Gruber syndrome (2).

*Our Joubert/Meckel-Gruber Syndrome Panel includes analysis all 33 genes listed below.*

*Our Meckel-Gruber Syndrome Panel includes analysis of the 15 genes listed below.*

Joubert/Meckel-Gruber Syndrome				Meckel-Gruber Syndrome	
AHI1	CEP290	MKS1	TMEM107	B9D1	TCTN2
ARL13B	CSPP1	NPHP1	TMEM138	B9D2	TCTN3
B9D1	IFT172	NPHP3	TMEM216	CC2D2A	TMEM67
B9D2	INPP5E	PDE6D	MEM231	CEP290	TMEM107
C5orf42	KIAA0556	RPGRIP1L	TMEM237	CSPP1	TMEM216
CC2D2A	KIAA0586	TCTN1	TTC21B	KIF14	TMEM231
CEP104	KIF7	TCTN2		MKS1	
CEP120	KIF14	TCTN3		NPHP3	
CEP41	OFD1	TMEM67		RPGRIP1L	

Genes	Associated Disorder(s)	Clinical Features / Molecular Pathology
<i>AHI1</i>	JBTS3	Parisi <i>et al</i> , 2006 identified mutations in <i>AHI1</i> in 13/117 patients with JSRD (3). Valenti <i>et al</i> , 2006, identified <i>AHI1</i> mutations in 7.3% of their patient cohort (4). Nonsense, frameshift, missense and splice site pathogenic sequences have all been described. Retinal dystrophy is a common occurrence in individuals with <i>AHI1</i> mutations (5). <i>AHI1</i> codes for a component of a protein complex in the basal body, a ring-like structure that functions in the transition zone at the base of cilia. This complex acts as a barrier to restrict protein diffusion between plasma and ciliary membranes.
<i>ARL13B</i>	JBTS8	Mutations in <i>ARL13B</i> account for less than 1% of patients with JSRD and the majority of mutations identified in <i>ARL13B</i> to date are missense (6). The <i>ARL13B</i> gene, encoding ADP-ribosylation factor-like protein 13B, is a small GTPase belonging to the class of Arf/Ar1 family within the Ras superfamily of small GTPases involved in diverse cellular functions.

<i>B9D1</i>	MKS9	In a fetus with MKS, Hopp <i>et al</i> (2011) identified a patient who was compound heterozygous for a splice-donor site change in <i>B9D1</i> and a 1.7 Mb <i>de novo</i> deletion encompassing the other allele (7). The fetus inherited an additional likely pathogenic missense change in <i>CEP290</i> from its mother, suggesting possible oligogenic inheritance in this disorder.
<i>B9D2</i>	MKS10	In two fetuses with MKS from a consanguineous family, Dowdle <i>et al</i> (2011) identified a homozygous missense mutation in <i>B9D2</i> (8). Mouse mutations in <i>B9d2</i> compromise ciliogenesis and result in phenotypes consistent with MKS.
<i>C5orf42</i>	JBTS17	Strour <i>et al</i> , 2012 identified mutations in <i>C5orf42</i> in 7 French Canadian families with JSRD (9). Nonsense, splice site and missense mutations have been identified in <i>C5orf42</i> . The <i>C5orf42</i> protein features a transmembrane protein and is expressed widely in the brain.
<i>CC2D2A</i>	JBTS9, MKS6	Mutations in <i>CC2D2A</i> represent a cause of both JSRD and MKS and are responsible for approximately 10% of each disorder (10). Like <i>AHI1</i> , <i>CC2DA</i> codes for a component of a protein complex in the basal body, a ring-like structure that functions in the transition zone at the base of cilia. This complex acts as a barrier to restrict protein diffusion between plasma and ciliary membranes.
<i>CEP104</i>	JBTS	Biallelic mutations in <i>CEP104</i> have been identified in three unrelated patients with a neurologic form of Joubert Syndrome. Their clinical features include molar tooth sign on MRI, oculomotor apraxia and developmental delay with absence of polydactyly, retinopathy and nephropathy (11). The <i>CEP104</i> protein localizes on the distal end of the primary cilium during ciliogenesis, and may be required for ciliogenesis and maintaining structural integrity at the ciliary tip (OMIM# 616690).
<i>CEP120</i>	JBTS	Roosing <i>et al.</i> (2016) identified nine distinct biallelic mutations in the <i>CEP120</i> gene in four patients with Joubert Syndrome, and two fetuses with overlapping ciliopathy phenotypes. All patients with Joubert Syndrome presented with a neurological phenotype consisting of hypotonia, developmental delay and cognitive impairment with no retinal, kidney, liver or skeletal involvement (12). Homozygous mutations in <i>CEP120</i> have also been reported in short-rib thoracic dysplasia with or without polydactyly (OMIM# 613446)
<i>CEP41</i>	JBTS15	Lee <i>et al</i> , 2012 identified three different homozygous splicing mutations in the <i>CEP41</i> gene in affected members of three consanguineous (Egyptian and Portuguese) families with JSRD (13). Heterozygous missense changes in <i>CEP41</i> have also been reported in several ciliopathies including MKS and Bardet Biedl syndrome.
<i>CEP290</i>	JBTS5, MKS4	Mutations in <i>CEP290</i> account for approximately 20% of patients with JSRD and in a handful of families with MKS and Meckel-like syndrome (14). The vast majority of mutations in <i>CEP290</i> are truncating. Mutations in <i>CEP290</i> have also been identified in individuals with Leber Congenital Amaurosis, Bardet-Biedl syndrome and Senior-Loken syndrome. The <i>CEP290</i> gene encodes a centrosomal protein involved in ciliary assembly and ciliary trafficking.
<i>CSPP1</i>	JBTS21, MKS	In 19 patients from 15 families with JSRD, Tuz <i>et al.</i> (2014) identified biallelic truncating mutations in <i>CSPP1</i> (15). Among these patients, there was a broad spectrum of phenotypic severity, including four of these individuals who also had features of Jeune asphyxiating thoracic dystrophy. Shaheen, <i>et al.</i> (2014) further expanded the phenotypic spectrum with a report of a consanguineous family in which two affected siblings had features of Meckel-Gruber syndrome due to a homozygous truncating mutation in <i>CSPP1</i> (16). Zebrafish knockouts of <i>cspp1</i> were consistent with the phenotype observed in other JSRD and resulted in reduced ciliary localization, further supporting the loss of <i>CSPP1</i> as a cause of ciliopathies (15).
<i>IFT172</i>	JBTS	Halbritter, <i>et al.</i> (2013) identified homozygous or compound heterozygous mutations in 12 families affected by the skeletal ciliopathies asphyxiating thoracic dystrophy (ATD), Sensenbrenner syndrome, and Mainzer-Saldino syndrome (MZSDS). Affected individuals exhibited abnormalities of the thorax and/or long bones and additionally had renal, hepatic, or retinal involvement. In two of the families studies, individuals additionally had cerebellar hypoplasia or aplasia, consistent with co-occurrence of Joubert syndrome with the skeletal ciliopathy (17).
<i>INPP5E</i>	JBTS	Bielas <i>et al.</i> (2009) identified 5 different homozygous missense mutations in <i>INPP5E</i> in 7 consanguineous families from the United Arab Emirates, Turkey, Egypt and Italy (18). Mutations in <i>INPP5E</i> that cause JSRD are typically missense changes. The <i>INPP5E</i> protein cleaves the 5-position phosphate from soluble inositol phosphates or inositol phospholipids and is localized predominantly to the primary cilium.
<i>KIAA0556</i>	JBTS	Sanders <i>et al</i> (2015) identified a novel homozygous truncating variant in <i>KIAA0556</i> in three siblings in a consanguineous Saudi Arabian family. The three children suffered from developmental delay (two with pituitary abnormalities) and were suspected to have a diagnosis of Joubert syndrome based on neuroimaging studies. Mouse studies by the same group showed that <i>KIAA0556</i> deficiency results in hydrocephalus, and is consistent with the relatively mild phenotype observed in the affected siblings. In addition, studies in <i>C. elegans</i> support a ciliary function for <i>KIAA0556</i> (19). Subsequent studies by Roosing <i>et al</i> (2016) identified another consanguineous family in which two siblings with a clinical diagnosis of Joubert syndrome were found to have homozygous mutations in <i>KIAA0556</i> (20).

<i>KIAA0586</i>	JBTS23	Roosing <i>et al.</i> (2015) identified homozygous or compound heterozygous mutations in <i>KIAA0586</i> in 6/145 patients with unexplained Joubert syndrome (21). The majority of reported mutations were protein-truncating. Bachmann-Gagescu <i>et al.</i> (2015) found biallelic mutations in <i>KIAA0586</i> in approximately 2.5% of patients from a large cohort of individuals affected with Joubert syndrome. All individuals with <i>KIAA0586</i> mutations were reportedly at the mild end of the Joubert syndrome spectrum (22).
<i>KIF7</i>	JBTS12	Truncating mutations in <i>KIF7</i> have been identified in a handful of patients with JBTS (23). The relative contribution of mutations in this gene to JSRD remains unknown, as a limited number of individuals with mutations have been described. The <i>KIF7</i> gene encodes a cilia-associated protein belonging to the kinesin family that plays a role in the hedgehog signaling pathway.
<i>KIF14</i>	MKS12	Filges <i>et al.</i> (2014) identified compound heterozygous truncating mutations in <i>KIF14</i> in two sibling fetuses with a lethal fetal congenital anomaly syndrome consistent with Meckel Gruber syndrome. Findings included oligohydramnios, intrauterine growth retardation, severe microcephaly, renal agenesis/hypoplasia, complex brain malformations, and genitourinary malformations (24).
<i>OFD1</i>	JBTS10, OFD1	To date, three families with X-linked Joubert syndrome have been identified with truncating mutations in <i>OFD1</i> (25). Mutations in <i>OFD1</i> are also implicated in Oral-facial-digital syndrome type 1, a disorder whose features include midline oral clefts (lip, palate and tongue), nodules (hamartomas) on the tongue, and digital abnormalities, including brachydactyly, syndactyly and polydactyly.
<i>MKS1</i>	MKS1	Mutations in <i>MKS1</i> account for approximately 10% of patients with MKS (2). Truncating, frameshift and splice site mutations have been reported. Missense mutations in <i>MKS1</i> do not appear to be causative for MKS (2). <i>MKS1</i> is widely expressed in the brain, liver, kidney and developing digits.
<i>NPHP1</i>	JBTS4	Parisi <i>et al.</i> identified homozygous and compound heterozygous deletions of the <i>NPHP1</i> gene in individuals with mild JBTS (3, 26). The most consistent clinical findings are development of nephronophthisis with or without retinal dystrophy, milder developmental delay, and a distinctive molar tooth sign on radiologic imaging. Deletions of <i>NPHP1</i> are also responsible for 20-30% of the purely renal forms of juvenile nephronophthisis and only about 1-3% of individuals with JSRD (5).
<i>NPHP3</i>	MKS7	In four families in which a total of seven individuals had features consistent with MKS, Bergmann <i>et al.</i> (2008) identified homozygous or compound heterozygous mutations in <i>NPHP3</i> (27). Splice-site, nonsense, and missense mutations were observed. Mutations in <i>NPHP3</i> are also responsible for approximately 1% of juvenile nephronophthisis (28).
<i>PDE6D</i>	JBTS22	In a consanguineous family in which three of five siblings were affected with JBTS, Thomas <i>et al.</i> (2014) identified a homozygous splice-site mutation leading to an in-frame deletion of <i>PDE6D</i> exon 3 (29). Mutations were not identified in an additional 940 patients with clinically diagnosed ciliopathy conditions, indicating that this is a rare cause of JBTS. <i>Pde6d</i> knockdown in zebrafish was shown to alter both eye and kidney development (29).
<i>RPGRIP1L</i>	JBTS7, MKS5	Mutations in <i>RPGRIP1L</i> account for approximately 2-4% of patients with JSRD and the phenotypic spectrum includes predominantly renal disease (5). Delous <i>et al.</i> , 2007 identified homozygous and compound heterozygous truncating mutations in 3 fetuses with MKS (30). Mutations in <i>RPGRIP1L</i> that cause MKS tend to be protein-truncating and have a more severe effect on protein function.
<i>TCTN1</i>	JBTS13	Garcia-Gonzalo <i>et al.</i> 2011 identified a homozygous splice site mutation in <i>TCTN1</i> in a consanguineous family from Bangladesh (31). The relative contribution of mutations in this gene to JSRD remains unknown, as a limited number of individuals with mutations have been described.
<i>TCTN2</i>	MKS8	A homozygous splice site mutation in <i>TCTN2</i> was identified by Shaheen <i>et al.</i> (2011) in a consanguineous Saudi family with 5 pregnancies affected with MKS (32). <i>Tctn2</i> -null mice lack nodal cilia and have a minimal amount of cilia in the neural tube (31).
<i>TCTN3</i>	JBTS18, OFD4, MKS	Thomas <i>et al.</i> (2012) identified a homozygous mutation in <i>TCTN3</i> in a consanguineous Turkish family with two siblings with Joubert syndrome (33). Homozygous or compound heterozygous mutations in <i>TCTN3</i> have also been associated with orofacioidigital syndrome type 4 (OFD4), which has a high degree of clinical overlap with Meckel Gruber syndrome (33). Functional studies of <i>TCTN3</i> have found that it is necessary for transduction of the SHH signaling pathway.
<i>TMEM67</i>	JBTS6, MKS3	Doherty <i>et al.</i> , 2009, identified mutations in <i>TMEM67</i> in 19/232 (8%) of individuals with JSRD (34). Mutations in <i>TMEM67</i> also account for approximately 12% of patients with MKS (2). Mutations identified in MKS rarely overlap with the mutations seen in JSRD and it has been hypothesized that more severe loss of function mutations are more likely to cause MKS, while milder mutations are more associated with JSRD (5).

<i>TMEM107</i>	JBTS, MKS13	Shaheen <i>et al.</i> (2015) identified a homozygous truncating mutation in <i>TMEM107</i> in two consanguineous families with a history of a pregnancy with a clinical diagnosis of Meckel Gruber syndrome (35). Additionally, Lambacher <i>et al.</i> (2016) identified a compound heterozygous mutation in <i>TMEM107</i> in a patient with features of Joubert syndrome (36). Fibroblasts from this patient exhibited reduced ciliation and the cilia that formed were abnormally long (36).
<i>TMEM138</i>	JBTS16	Lee <i>et al.</i> , 2012 identified missense and splicing mutations in <i>TMEM138</i> in 6 consanguineous Arab families with JSRD (37). The phenotype included the molar tooth sign on brain imaging, oculomotor apraxia, variable coloboma, and rare kidney involvement and was indistinguishable from that caused by mutation in <i>TMEM216</i> gene.
<i>TMEM216</i>	JBTS2, MKS2	Valente <i>et al.</i> 2010 identified mutations in <i>TMEM216</i> in 14/462 (14%) of patients with JSRD (38). A common founder mutation (p.R12L) has been identified in the Ashkenazi Jewish population with a carrier rate of 1 in 92 (39). Mutations in <i>TMEM216</i> also account for less than 5% of patients with MKS (2).
<i>TMEM231</i>	JBTS20, MKS11	Srouf <i>et al.</i> (2012) identified compound heterozygous mutations in <i>TMEM231</i> in 3 individuals with Joubert syndrome from two unrelated French Canadian families (40). Knockout <i>Tmem231</i> mice show embryonic lethality with microphthalmia, polydactyly and patterning defects of the ventral spinal cord, consistent with a ciliopathy (41). Shaheen <i>et al.</i> (2013) identified homozygous mutations in <i>TMEM231</i> in two consanguineous families with classic Meckel-Gruber syndrome (42).
<i>TMEM237</i>	JBST14	Huang <i>et al.</i> , 2011 identified homozygous truncating mutations in the <i>TMEM237</i> in 10 related Canadian Hutterite families with JSRD (43). Screening of an additional 201 individuals with JSRD and 90 individuals with MKS identified two additional patients with mutations in <i>TMEM237</i> .
<i>TTC21B</i>	JATD, NPHP JSRD	Davis <i>et al.</i> 2011 sequenced <i>TTC21B</i> in 753 patients with some form of ciliopathy and identified homozygous or compound heterozygous mutations in one Jeune asphyxiating thoracic dystrophy (JATD) pedigree and five nephronophthisis (NPHP) pedigrees (44). In addition, heterozygous likely pathogenic mutations were identified in an additional 38 unrelated cases (5%), and one third of these had a second pathogenic mutation identified in a different ciliopathy gene. Individuals with Joubert syndrome related disorders (JSRD) and a single heterozygous mutation have been reported, although the functional significance of a single mutation is not clear.

### Test methods:

Comprehensive sequence coverage of the coding regions and splice junctions of all genes in this panel is performed. Targets of interest are enriched and prepared for sequencing using the Agilent SureSelect system. Sequencing is performed using Illumina technology and reads are aligned to the reference sequence. Variants are identified and evaluated using a custom collection of bioinformatic tools and comprehensively interpreted by our team of directors and genetic counselors. All novel and/or potentially pathogenic variants are confirmed by Sanger sequencing. The technical sensitivity of this test is estimated to be >99% for single nucleotide changes and insertions and deletions of less than 20 bp.

Our CNV detection algorithm was developed and its performance determined for the sole purpose of identifying deletions and duplications within the coding region of the gene(s) tested. Partial exonic copy number changes and rearrangements of less than 400 bp may not be detected by this methodology. Regions of high homology and repetitive regions may not be analyzed. This methodology will not detect low level mosaicism, balanced translocations, inversions, or point mutations that may be responsible for the clinical phenotype. The sensitivity of our deletion/duplication assay may be reduced when DNA extracted by an outside laboratory is provided.

### Joubert/Meckel-Gruber Syndrome Panel (33 genes)

Sample specifications: 3 to 10 cc of blood in a purple top (EDTA) tube  
 Cost: \$3000  
 CPT codes: 81406  
 81407  
 Turn-around time: 8 weeks

**Note: We cannot bill insurance for the above test.**

**Note: The sensitivity of our assay may be reduced when DNA is extracted by an outside laboratory.**

## Meckel-Gruber Syndrome Panel (15 genes)

Sample specifications:	3 to 10 cc of blood in a purple top (EDTA) tube
Cost:	\$2500
CPT codes:	81406 81407
Turn-around time:	8 weeks

**Note: We cannot bill insurance for the above test.**

**Note: The sensitivity of our assay may be reduced when DNA is extracted by an outside laboratory.**

### **Results:**

Results, along with an interpretive report, will be faxed to the referring physician. Additional reports will be provided as requested. All abnormal results will be reported by telephone.

***For more information about our testing options, please visit our website at [dnatesting.uchicago.edu](http://dnatesting.uchicago.edu) or contact us at 773-834-0555.***

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