Prenatal Joubert Syndrome and Related Disorders (JSRD) Panel Sequence Analysis and Exon-Level Deletion/Duplication Testing*

of 25 Genes

Panel Gene List: AHI1, ARL13B, B9D1, C5orf42, CC2D2A, CEP41, CEP290, CSPP1, IFT172, INPP5E, KIF7, MKS1, NPHP1*, NPHP3, OFD1, RPGRIP1L, TCTN1, TCTN2, TCTN3, TMEM67, TMEM138, TMEM216, TMEM231, TMEM237, TTC21B

*For NPHP1 gene, deletion/duplication testing only

Clinical Features:
Joubert syndrome is a brain malformation disorder characterized by the presence of a midbrain-hindbrain abnormality called the molar tooth sign, which results from cerebellar hypoplasia, thickened superior cerebellar peduncles, and a deepened interpeduncular fossa.1-3 Affected individuals demonstrate hypotonia, developmental delay, and variable cognitive impairment. Breathing abnormalities and oculomotor apraxia may also be observed. Retinal dystrophy, renal disease, occipital encephalocele, polydactyly, hepatic fibrosis, and other abnormalities are seen in variant forms of this disorder. Renal disease can range from nephronophthisis to cystic renal dysplasia.4 Joubert syndrome shares phenotypic overlap with other ciliopathies, including Bardet-Biedl, COACH, and Meckel-Gruber syndromes, and all of these disorders show significant clinical variability.1,5-8 Meckel-Gruber syndrome, in particular, shows close overlap with Joubert syndrome and is characterized by occipital encephalocele, cystic kidneys, hepatic defects, and other anomalies.9 A diagnostic algorithm has been proposed to address the clinical and genetic heterogeneity and aid in the molecular diagnosis of Joubert syndrome.1,2

Joubert syndrome and related disorders (JSRD) are identified in the prenatal period by the presence of the molar tooth sign on ultrasound.1 Additional features including other structural brain malformations, encephalocele, renal disease, polydactyly, and cleft lip/palate may also be seen.1 Other imaging methods such as 3D ultrasound or fetal MRI can be used to evaluate and diagnose JSRD in utero.1 Due to genetic heterogeneity and overlapping phenotypes, the specific diagnosis cannot be determined accurately with imaging alone. When available, genetic testing can aid in determining the precise diagnosis after the differential has been established by imaging.
Inheritance Pattern/Genetics:
The prevalence of Joubert syndrome and its variant forms is estimated to be approximately 1:100,000.\(^1\) Many genes have been associated with Joubert syndrome, although some are very rarely involved.\(^10\) These genes have important functions in the development of cilia in various organs.\(^3\) Cilia play a role in intraflagellar transport, cell division, tissue differentiation, establishment of body axis, growth, and mechanosensation involved in cellular signaling processes.\(^11,12\) The differential diagnosis for Joubert syndrome includes other ciliopathies, such as Bardet-Biedl, COACH, and Meckel-Gruber syndromes.\(^1,5-8\) Meckel-Gruber syndrome is caused by variants in several of the Joubert syndrome-related genes.\(^13\) Renal disease is also a common feature between Joubert syndrome and nephronophthisis; most variants in the NPHP1 gene are associated with isolated nephronophthisis, but approximately 9% of individuals with NPHP1 deletions have features of Joubert syndrome.\(^14\) The central nervous system, renal epithelium, and photoreceptor cells are commonly affected in this group of disorders.

The GeneDx Joubert Syndrome Panel includes 25 genes that are involved in Joubert syndrome and related disorders (JSRD). Variants in these genes typically have a loss-of-function effect and include missense, nonsense, splicing, and insertion-deletion changes, as well as exonic deletions.

Test Methods:
Using genomic DNA, coding exons and flanking splice junctions of the genes on this panel are enriched using a proprietary targeted capture method developed by GeneDx. The sequencing component of the test includes all genes in the table above except for NPHP1, as only a large homozygous deletion has been reported in association with Joubert syndrome. The products are sequenced on an Illumina instrument using paired end reads. The sequence data is aligned to reference sequences based on human genome build GRCh37/UCSC hg19. Sanger sequencing is used to compensate for low coverage and refractory amplifications. Concurrently, targeted array CGH analysis with exon-level resolution is performed to evaluate for a deletion or duplication of one or more exons for the genes included on the panel. The presence of any potentially disease-associated sequence variant(s) or copy number alteration(s) is confirmed by dideoxy DNA sequence analysis or quantitative PCR, respectively, or by other appropriate methods.

Additionally, genotype analysis of maternal and fetal DNA for several polymorphic markers to test for maternal cell contamination will be performed. Therefore, in all prenatal cases, a maternal sample should accompany the fetal sample.
Test Sensitivity:
The spectrum of variants in Joubert syndrome genes includes nonsense, missense, insertions, and multie exon deletions, causing predominantly loss-of-function effects. Specific founder variant alleles have been identified in some of the Joubert syndrome-related genes.¹ The sensitivity of sequencing and deletion/duplication analysis of the genes included in this panel in prenatal cases ascertained based on fetal ultrasound abnormalities is currently unknown, and the clinical sensitivity of this panel depends in part on the clinical phenotype of the fetus. Specific information about the diagnostic yield for each gene in selected populations is included in the following table.

The technical sensitivity of the sequencing test is estimated to be 98%. Deletions involving more than 20 bp and insertions involving more than 10 bp are not reliably detected by the sequencing methodology, and deletions or duplications of less than 500 bp are not reliably detected by array CGH. Note that small sections of a few individual genes have inherent sequence properties that yield suboptimal data and variants in those regions may not be identified.

<table>
<thead>
<tr>
<th>Gene</th>
<th>Protein</th>
<th>Inheritance</th>
<th>Disease Associations</th>
</tr>
</thead>
<tbody>
<tr>
<td>AHI1</td>
<td>Abelson helper integration site 1 (Jouberin)</td>
<td>AR</td>
<td>6-16% of JSRD¹⁵-¹⁹</td>
</tr>
<tr>
<td>ARL13B</td>
<td>ADP-ribosylation factor-like 13B</td>
<td>AR</td>
<td>Rare in JSRD ²⁰,²¹</td>
</tr>
<tr>
<td>B9D1</td>
<td>B9 domain-containing protein 1</td>
<td>AR</td>
<td>Rare in JSRD ¹⁷,²²,²³</td>
</tr>
<tr>
<td>C5orf42</td>
<td>Chromosome 5 open reading frame 42</td>
<td>AR</td>
<td>7-25% of JSRD¹⁵-¹⁷,²⁴; 45% of JSRD in French-Canadian²⁵; 82% of Oral-facial-digital syndrome type 6 (OFDVI)²⁶</td>
</tr>
<tr>
<td>CC2D2A</td>
<td>Coiled-coil and C2 domains-containing protein 2A</td>
<td>AR</td>
<td>2-10% of JSRD¹⁵,¹⁷,²⁷-³³</td>
</tr>
<tr>
<td>CEP41</td>
<td>Centrosomal protein, 41kDa</td>
<td>AR</td>
<td>Rare in JSRD ³⁴</td>
</tr>
<tr>
<td>CEP290</td>
<td>Centrosomal protein, 290kDa</td>
<td>AR</td>
<td>2-25% of JSRD¹⁵-¹⁷,³²,³³,³⁵-⁴⁰; 50% in JSRD with cerebello-oculo-renal phenotype (CORS)⁴¹</td>
</tr>
<tr>
<td>CSPP1</td>
<td>Centrosome and spindle pole associated protein 1</td>
<td>AR</td>
<td>2-5% of JSRD¹⁵,²⁶,⁴²-⁴⁴</td>
</tr>
<tr>
<td>IFT172</td>
<td>Intraflagellar transport 172</td>
<td>AR</td>
<td>Rare in JSRD²⁸,⁴⁵,⁴⁶</td>
</tr>
<tr>
<td>INPP5E</td>
<td>Inositol polyphosphate-5-phosphatase, 72kDa</td>
<td>AR</td>
<td>2-4% of JSRD¹⁵,¹⁷,²⁸,⁴⁷,⁴⁸</td>
</tr>
<tr>
<td>KIF7</td>
<td>Kinesin family member 7</td>
<td>AR</td>
<td>Rare in JSRD, fetal hydrolethalus and acrocallosal syndromes¹⁵,²⁸,⁴⁹-⁵²</td>
</tr>
<tr>
<td>MKS1</td>
<td>MKS1 B9-domain containing protein (Meckel syndrome type 1 protein)</td>
<td>AR</td>
<td>1-2% of JSRD¹⁵,²³,²⁸-⁴⁰; 7-30% of Meckel Gruber syndrome ⁹,¹³,³³,⁵³</td>
</tr>
<tr>
<td>NPHP1</td>
<td>Nephrocystin</td>
<td>AR</td>
<td>2-7% of JSRD (homozygous gene deletion)¹⁴,⁵⁴-⁵⁶</td>
</tr>
<tr>
<td>NPHP3</td>
<td>Nephrocystin 3</td>
<td>AR</td>
<td>3% of JSRD³⁶,⁵⁷-⁶⁰</td>
</tr>
</tbody>
</table>
**Test Information Sheet**

<table>
<thead>
<tr>
<th>OFD1 (CXorf5)</th>
<th>Oral-facial-digital syndrome 1 protein</th>
<th>Rare in JSRD&lt;sup&gt;15,17,28,61-64&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>RPGRIPL1 (NPHP8)</td>
<td>RPGRIPL1-like protein</td>
<td>AR</td>
</tr>
<tr>
<td>TCTN1</td>
<td>Tectonic family member 1</td>
<td>AR</td>
</tr>
<tr>
<td>TCTN2</td>
<td>Tectonic family member 2</td>
<td>AR</td>
</tr>
<tr>
<td>TCTN3</td>
<td>Tectonic family member 3</td>
<td>AR</td>
</tr>
<tr>
<td>TMEM67 (MKS3)</td>
<td>Transmembrane protein 67 (Meckelin)</td>
<td>AR</td>
</tr>
<tr>
<td>TMEM138</td>
<td>Transmembrane protein 138</td>
<td>AR</td>
</tr>
<tr>
<td>TMEM216</td>
<td>Transmembrane protein 216</td>
<td>AR</td>
</tr>
<tr>
<td>TMEM231</td>
<td>Transmembrane protein 231</td>
<td>AR</td>
</tr>
<tr>
<td>TMEM237 (ALS2CR4)</td>
<td>Transmembrane protein 237</td>
<td>AR</td>
</tr>
<tr>
<td>TTC21B</td>
<td>Tetrameric peptide repeat domain-containing protein 21B</td>
<td>AR</td>
</tr>
</tbody>
</table>

**References:**

10. Online Mendelian Inheritance in Man; [http://omim.org](http://omim.org)
23. Romani et al. (2014) Orphanet Journal Of Rare Diseases 9 :72 (PMID: 24886560)

207 Perry Parkway, Gaithersburg, MD 20877 | P: 301-519-2100 | F: 201-421-2010 | E: genedx@genedx.com
84. Davis et al. (2011) Nature Genetics 43 (3):189-96 (PMID: 21258341)