Prenatal Joubert Syndrome and Related Disorders (JSRD) Panel Sequence Analysis and Exon-Level Deletion/Duplication Testing of 29 Genes

Panel Gene List: AHI1, ARL13B, B9D1, B9D2, C5orf42, CC2D2A, CEP41, CEP104, CEP120, CEP290, CSPP1, IFT172, INPP5E, KIAA0586, KIF7*, MKS1, NPHP1, NPHP3, OFD1, RPGRIP1L, TCTN1, TCTN2, TCTN3, TMEM67, TMEM138, TMEM216, TMEM231, TMEM237, TTC21B. *Only whole gene deletions/duplications may be detected for the KIF7 gene

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 29 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 from the submitted specimen, the complete coding regions and splice site junctions of the genes on this panel are enriched using a proprietary targeted capture system developed by GeneDx for next-generation sequencing with CNV calling (NGS-CNV). The enriched targets are simultaneously sequenced with paired-end reads on an Illumina platform. Bi-directional sequence reads are assembled and aligned to reference sequences based on NCBI RefSeq transcripts and human genome build GRCh37/UCSC hg19. After gene specific filtering, data are analyzed to identify sequence variants and most deletions and duplications involving coding exons. Alternative sequencing or copy number detection methods are used to analyze regions with inadequate sequence or copy number data by NGS. Reported clinically significant variants are confirmed by an appropriate orthogonal method. Reportable variants include pathogenic variants, likely pathogenic variants, and variants of uncertain significance. Likely benign and benign variants, if present, are not routinely reported but are available upon request.

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 clinical 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 summarized in the following table(s).

The technical sensitivity of sequencing is estimated to be >99% at detecting single nucleotide events. It will not reliably detect deletions greater than 20 base pairs, insertions or rearrangements greater than 10 base pairs, or low-level mosaicism. The copy number assessment methods used with this test cannot reliably detect copy number variants of less than 500 base pairs or mosaicism and cannot identify balanced chromosome aberrations. Assessment of exon-level copy number events is dependent on the inherent sequence properties of the targeted regions, including shared homology and exon size. Gene specific exclusions for exon-level deletion/duplication testing for this panel are: KIF7 gene, only whole gene deletions or duplications may be detected.

Gene	Protein	Inheritance	Disease Associations
AHI1	Abelson helper integration site 1 (Jouberin)	AR	6-16% of JSRD[15-19]
ARL13B	ADP-ribosylation factor-like 13B	AR	Rare in JSRD [20,21]
B9D1	B9 domain-containing protein 1	AR	Rare in JSRD[17,22,23]
B9D2	B9 domain-containing protein 2	AR	Rare in JSRD[28,87]
C5orf42	Chromosome 5 open reading frame 42	AR	7-25% of JSRD[15-17,24]; 45% of JSRD in French-Canadian[25]; 82% of Oral-facial-digital syndrome type 6 (OFDVI)[26]
CC2D2A (MKS6)	Coiled-coil and C2 domains-containing protein 2A	AR	2-10% of JSRD[15,17,27-33]
CEP41	Centrosomal protein, 41kDa	AR	Rare in JSRD[34]
CEP104	Centrosomal protein, 104kDa	AR	Rare in JSRD[88]
CEP120	Centrosomal protein, 120kDa	AR	Rare in JSRD[89,90]
CEP290 (NPHP6)	Centrosomal protein, 290kDa	AR	2-25% of JSRD[15-17,32,33,35-40]; 50% in JSRD with cerebello-oculo-renal phenotype (CORS)[41]
CSPP1	Centrosome and spindle pole associated protein 1	AR	2-5% of JSRD[15,28,42-44]
IFT172	Intraflagellar transport 172	AR	Rare in JSRD[28,45,46]
INPP5E	Inositol polyphosphate-5-phosphatase, 72kDa	AR	2-4% of JSRD[15,17,28,47,48]
KIAA0586	TALPID3 protein	AR	2-7% of JSRD[91-95]
*KIF7**	Kinesin family member 7	AR	Rare in JSRD, fetal hydrolethalus and acrocallosal syndromes[15,28,49-52]
MKS1	MKS1 B9-domain containing protein (Meckel syndrome type 1 protein)	AR	1-2% of JSRD[15,23,28]; 7-30% of Meckel Gruber syndrome [9,13,33,53]
NPHP1	Nephrocystin 1	AR	2-7% of JSRD (homozygous gene deletion)[14,54-56]
NPHP3	Nephrocystin 3	AR	3% of JSRD[36,57-60]
OFD1 (CXorf5)	Oral-facial-digital syndrome 1 protein	XL	Rare in JSRD[15,17,28,61-64]
RPGRIP1L (NPHP8)	RPGRIP1-like protein	AR	2-5% in Joubert syndrome (mostly cerebro-renal type)[15,17,28,29,33,65-68]
TCTN1	Tectonic family member 1	AR	Rare in JSRD[15,16,69,70]
TCTN2	Tectonic family member 2	AR	Rare in JSRD[15,28,64,71-73]
TCTN3	Tectonic family member 3	AR	Rare in JSRD[15,71,74]
TMEM67 (MKS3)	Transmembrane protein 67 (Meckelin)	AR	1-10% of JSRD[6,15,17,28,32,36,75,76]; 15-28% of Meckel Gruber syndrome[9,33]; 75-83% of JSRD with liver involvement (including COACH syndrome)[29]

TMEM138	Transmembrane protein 138	AR	Rare in JSRD[15,33,77]
TMEM216	Transmembrane protein 216	AR	3% of JSRD[28,77,78]; Up to 100% of JSRD in Ashkenazi Jewish[78,79]; Rare in Oral-facial-digital syndrome type 6 (OFDVI)[26]
TMEM231	Transmembrane protein 231	AR	Rare in Joubert and Meckel Gruber syndromes[17,80-82]
TMEM237 (ALS2CR4)	Transmembrane protein 237	AR	Rare in Joubert and Meckel Gruber syndromes[15,16,33,53,83]
TTC21B	Tetratricopeptide repeat domain-containing protein 21B	AR	Unknown in JSRD[32,84-86]

* Only whole gene deletions/duplications may be detected for the KIF7 gene

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