Joubert Syndrome Panel

Test code: KI1001

The Blueprint Genetics Joubert Syndrome Panel is a 29 gene test for genetic diagnostics of patients with clinical suspicion of Joubert syndrome.

The panel covers genes associated with autosomal recessive forms of the disease and related disorders. This panel is estimated to provide molecular diagnosis for approximately 50% of patients with Joubert syndrome and related disorders. This Panel is part of the comprehensive Ciliopathy Panel and Retinal Dystrophy Panel.

About Joubert Syndrome

Classic Joubert syndrome (JS) is characterized by three primary findings, a distinctive cerebellar and brain stem malformation called the molar tooth sign (MTS), hypotonia and developmental delays. MTS, seen on magnetic resonance imaging (MRI), results from hypoplasia of the cerebellar vermis and midbrain-hindbrain malformations. Additional features associated with Joubert syndrome include retinal anomalies, nystagmus, ataxia, polydactyly, hepatic fibrosis, and renal disease. Prevalence estimates range between 1:80,000 and 1:100,000 but this may represent an underestimate. Overall, about 50% of individuals with Joubert syndrome and related disorders have pathogenic variants identified in one of the identified genes. Defective ciliary biology underlies JS and it shares substantial allelism with other ciliopathies.

Availability

Results in 3-4 weeks. We do not offer a maternal cell contamination (MCC) test at the moment. We offer prenatal testing only for cases where the maternal cell contamination studies (MCC) are done by a local genetic laboratory. Read more: http://blueprintgenetics.com/faqs/#prenatal

Gene set description

Genes in the Joubert Syndrome Panel and their clinical significance

<table>
<thead>
<tr>
<th>Gene</th>
<th>Associated phenotypes</th>
<th>Inheritance</th>
<th>ClinVar</th>
<th>HGMD</th>
</tr>
</thead>
<tbody>
<tr>
<td>AHI1</td>
<td>Joubert syndrome</td>
<td>AR</td>
<td>47</td>
<td>70</td>
</tr>
<tr>
<td>ARL13B</td>
<td>Joubert syndrome</td>
<td>AR</td>
<td>9</td>
<td>7</td>
</tr>
<tr>
<td>B9D1</td>
<td>Meckel syndrome</td>
<td>AR</td>
<td>8</td>
<td>8</td>
</tr>
<tr>
<td>B9D2</td>
<td>Meckel syndrome</td>
<td>AR</td>
<td>5</td>
<td>4</td>
</tr>
<tr>
<td>C5orf42</td>
<td>Orofaciodigital syndrome, Joubert syndrome</td>
<td>AR</td>
<td>63</td>
<td></td>
</tr>
<tr>
<td>CC2D2A</td>
<td>COACH syndrome, Joubert syndrome, Meckel syndrome</td>
<td>AR</td>
<td>64</td>
<td>80</td>
</tr>
<tr>
<td>CEP41</td>
<td>Joubert syndrome</td>
<td>AR/Digenic</td>
<td>7</td>
<td>10</td>
</tr>
<tr>
<td>CEP164</td>
<td>Nephronophthisis</td>
<td>AR</td>
<td>7</td>
<td>8</td>
</tr>
<tr>
<td>CEP290*</td>
<td>Bardet-Biedl syndrome, Leber congenital amaurosis, Joubert syndrome, Senior-Loken syndrome, Meckel syndrome</td>
<td>AR</td>
<td>79</td>
<td>252</td>
</tr>
<tr>
<td>CSPP1</td>
<td>Jeune asphyxiating thoracic dystrophy, Joubert syndrome</td>
<td>AR</td>
<td>22</td>
<td>23</td>
</tr>
<tr>
<td>INPP5E</td>
<td>Joubert syndrome, Mental retardation, truncal obesity, retinal dystrophy, and micropenis (MORM syndrome)</td>
<td>AR</td>
<td>19</td>
<td>41</td>
</tr>
<tr>
<td>KIAA0586</td>
<td>Short rib thoracic dysplasia with polydactyly, Joubert syndrome</td>
<td>AR</td>
<td>14</td>
<td>26</td>
</tr>
</tbody>
</table>
KIF7  Acrocallosal syndrome, Hydrolethalus syndrome, Al-Gazali-Bakalinova syndrome, Joubert syndrome  AR/Digenic  13  39

MKS1   Bardet-Biedl syndrome, Meckel syndrome  AR  39  47

NPHP1  Nephronophthisis, Joubert syndrome, Senior-Loken syndrome  AR  12  64

NPHP3  Nephronophthisis, Renal-hepatic-pancreatic dysplasia, Meckel syndrome  AR  20  71

OFD1   Simpson-Golabi-Behmel syndrome, Retinitis pigmentosa, Orofaciodigital syndrome, Joubert syndrome  XL  129  148

RPGRIPL  COACH syndrome, Joubert syndrome, Meckel syndrome, Retinal degeneration in ciliopathy, modifier  AD/AR  28  41

TCTN1  Joubert syndrome  AR  6  6

TCTN2  Joubert syndrome, Meckel syndrome  AR  15  13

TCTN3  Orofaciodigital syndrome (Mohr-Majewski syndrome), Joubert syndrome  AR  8  10

TMEM67  Nephronophthisis, COACH syndrome, Joubert syndrome, Meckel syndrome  AR  78  138

TMEM107  Joubert syndrome  AD/AR  7  2

TMEM138  Joubert syndrome  AR  6  6

TMEM216  Joubert syndrome, Meckel syndrome  AR  8  8

TMEM231  Joubert syndrome, Meckel syndrome  AR  7  16

TMEM237  Joubert syndrome  AR  6  10

TTC21B  Short-rib thoracic dysplasia, Nephronophthisis, Asphyxiating thoracic dysplasia (ATD; Jeune)  AR  6  47

ZNF423  Nephronophthisis, Joubert syndrome  AD/AR  7  6

*Some regions of the gene are duplicated in the genome leading to limited sensitivity within the regions. Thus, low-quality variants are filtered out from the duplicated regions and only high-quality variants confirmed by other methods are reported out. Read more.

Gene, refers to HGNC approved gene symbol; Inheritance to inheritance patterns such as autosomal dominant (AD), autosomal recessive (AR) and X-linked (XL); ClinVar, refers to a number of variants in the gene classified as pathogenic or likely pathogenic in ClinVar (http://www.ncbi.nlm.nih.gov/clinvar/); HGMD, refers to a number of variants with possible disease association in the gene listed in Human Gene Mutation Database (HGMD, http://www.hgmd.cf.ac.uk/ac/). The list of associated (gene specific) phenotypes are generated from CDG (http://research.nhgri.nih.gov/CGD/) or Orphanet (http://www.orpha.net/) databases.

Non-coding disease causing variants covered by the panel

<table>
<thead>
<tr>
<th>Gene</th>
<th>Genomic location HG19</th>
<th>HGVS</th>
<th>RefSeq</th>
<th>RS-number</th>
<th>Comment</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>CEP290</td>
<td>Chr12:88494960</td>
<td>c.2991+1655A&gt;G</td>
<td>NM_025114.3</td>
<td>rs281865192</td>
<td></td>
<td></td>
</tr>
<tr>
<td>OFD1</td>
<td>ChrX:13773245</td>
<td>c.1130-22_1130-19delAATT</td>
<td>NM_003611.2</td>
<td>rs312262865</td>
<td></td>
<td></td>
</tr>
<tr>
<td>OFD1</td>
<td>ChrX:13768358</td>
<td>c.935+706A&gt;G</td>
<td>NM_003611.2</td>
<td>rs730880283</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Test performance

Blueprint Genetics offers a comprehensive Joubert Syndrome Panel that covers classical genes associated with Joubert syndrome.
syndrome. The genes are carefully selected based on the existing scientific evidence, our experience and most current mutation databases. Candidate genes are excluded from this first-line diagnostic test. The test does not recognize balanced translocations or complex inversions, and it may not detect low-level mosaicism. The test should not be used for analysis of sequence repeats or for diagnosis of disorders caused by mutations in the mitochondrial DNA.

Analytical validation is a continuous process at Blueprint Genetics. Our mission is to improve the quality of the sequencing process and each modification is followed by our standardized validation process. Average sensitivity and specificity in Blueprint NGS Panels is 99.3% and 99.9% for detecting SNPs. Sensitivity to for indels vary depending on the size of the alteration: 1-10bps (96.0%), 11-20 bps (88.4%) and 21-30 bps (66.7%). The longest detected indel was 46 bps by sequence analysis. Detection limit for Del/Dup (CNV) analysis varies through the genome depending on exon size, sequencing coverage and sequence content. The sensitivity is 71.5% for single exon deletions and duplications and 99% for three exons’ deletions and duplications. We have validated the assays for different starting materials including EDTA-blood, isolated DNA (no FFPE) and saliva that all provide high-quality results. The diagnostic yield varies substantially depending on the used assay, referring healthcare professional, hospital and country. Blueprint Genetics’ Plus Analysis (Seq+Del/Dup) maximizes the chance to find molecular genetic diagnosis for your patient although Sequence Analysis or Del/Dup Analysis may be cost-effective first line test if your patient’s phenotype is suggestive for a specific mutation profile.

Bioinformatics

The sequencing data generated in our laboratory is analyzed with our proprietary data analysis and annotation pipeline, integrating state-of-the-art algorithms and industry-standard software solutions. Incorporation of rigorous quality control steps throughout the workflow of the pipeline ensures the consistency, validity and accuracy of results. The highest relevance in the reported variants is achieved through elimination of false positive findings based on variability data for thousands of publicly available human reference sequences and validation against our in-house curated mutation database as well as the most current and relevant human mutation databases. Reference databases currently used are the 1000 Genomes Project (http://www.1000genomes.org), the NHLBI GO Exome Sequencing Project (ESP; http://evs.gs.washington.edu/EVS), the Exome Aggregation Consortium (ExAC; http://exac.broadinstitute.org), ClinVar database of genotype-phenotype associations (http://www.ncbi.nlm.nih.gov/clinvar) and the Human Gene Mutation Database (http://www.hgmd.cf.ac.uk). The consequence of variants in coding and splice regions are estimated using the following in silico variant prediction tools: SIFT (http://sift.jcvi.org), Polyphen (http://genetics.bwh.harvard.edu/pph2/), and Mutation Taster (http://www.mutationtaster.org).

Through our online ordering and statement reporting system, Nucleus, the customer can access specific details of the analysis of the patient. This includes coverage and quality specifications and other relevant information on the analysis. This represents our mission to build fully transparent diagnostics where the customer gains easy access to crucial details of the analysis process.

Clinical interpretation

In addition to our cutting-edge patented sequencing technology and proprietary bioinformatics pipeline, we also provide the customers with the best-informed clinical report on the market. Clinical interpretation requires fundamental clinical and genetic understanding. At Blueprint Genetics our geneticists and clinicians, who together evaluate the results from the sequence analysis pipeline in the context of phenotype information provided in the requisition form, prepare the clinical statement. Our goal is to provide clinically meaningful statements that are understandable for all medical professionals, even without training in genetics.

Variants reported in the statement are always classified using the Blueprint Genetics Variant Classification Scheme modified from the ACMG guidelines (Richards et al. 2015), which has been developed by evaluating existing literature, databases and with thousands of clinical cases analyzed in our laboratory. Variant classification forms the cornerstone of clinical interpretation and following patient management decisions. Our statement also includes allele frequencies in reference populations and in silico predictions. We also provide PubMed IDs to the articles or submission numbers to public databases that have been used in the interpretation of the detected variants. In our conclusion, we summarize all the existing information and provide our rationale for the classification of the variant.

A final component of the analysis is the Sanger confirmation of the variants classified as likely pathogenic or pathogenic. This does not only bring confidence to the results obtained by our NGS solution but establishes the mutation specific test for family members. Sanger sequencing is also used occasionally with other variants reported in the statement. In the case of
variant of uncertain significance (VUS) we do not recommend risk stratification based on the genetic finding. Furthermore, in the case VUS we do not recommend use of genetic information in patient management or genetic counseling. For some cases Blueprint Genetics offers a special free of charge service to investigate the role of identified VUS.

We constantly follow genetic literature adapting new relevant information and findings to our diagnostics. Relevant novel discoveries can be rapidly translated and adopted into our diagnostics without delay. These processes ensure that our diagnostic panels and clinical statements remain the most up-to-date on the market.

**CPT codes**

SEQ 81479
DEL/DUP 81479

**ICD codes**

Commonly used ICD-10 codes when ordering the Joubert Syndrome Panel

<table>
<thead>
<tr>
<th>ICD-10</th>
<th>Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Q04.3</td>
<td>Joubert syndrome</td>
</tr>
</tbody>
</table>

**Accepted sample types**

- EDTA blood, min. 1 ml
- Purified DNA, min. 5μg
- Saliva (Oragene DNA OG-500 kit)

Label the sample tube with your patient’s name, date of birth and the date of sample collection.

Note that we do not accept DNA samples isolated from formalin-fixed paraffin-embedded (FFPE) tissue.

**Resources**

- Joubert Syndrome and Related Disorders Foundation
- Joubert Syndrome UK
- National Organization for Rare Disorders
- Gene Reviews