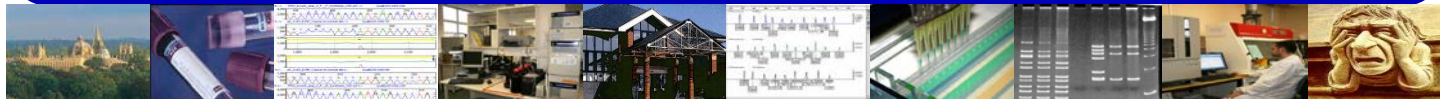


# Oxford Molecular Genetics Laboratory

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## Joubert syndrome and related disorders – 29 gene panel OMIM 213300, 243910, 216360, 277170, 266900

### INTRODUCTION

Classic Joubert syndrome (JS) is an autosomal recessive ciliopathy disorder characterised by a specific mid-hindbrain malformation ('molar tooth sign' on MRI), hypotonia, developmental delay plus or minus oculomotor apraxia and breathing abnormalities. The term 'Joubert syndrome and related disorders' (JSRD) is used to describe individuals with JS who have additional findings including retinal dystrophy, renal disease, ocular colobomas, occipital encephalocele, hepatic fibrosis, polydactyly, oral hamartomas and endocrine abnormalities. A number of previously recognised allelic disorders are now considered part of the JSRD spectrum, including Senior-Loken, Dekaban-Arima, COACH and Veradi-Papp syndromes.

JSRDs are genetically heterogeneous with at least 29 associated genes<sup>[1]</sup>. Mutations in these genes (see table below) together account for ~50% of JSRD cases<sup>[2]</sup>.

Gene	Gene Name	Frequency in patients with JSRD
<i>AHI1</i>	Abelson helper integration site 1	~7-10%
<i>ARL13B</i>	ADP-ribosylation factor-like 13B	<1%
<i>B9D1</i>	B9 protein domain 1	<1%
<i>B9D2</i>	B9 protein domain 2	Unknown
<i>C2CD3</i>	C2 calcium-dependent domain containing 3	Unknown
<i>C5orf42</i>	Chromosome 5 open reading frame 42	Unknown
<i>CC2D2A</i>	Coiled-coil and C2 domain containing C2	~10%
<i>CEP41</i>	Centrosomal protein 41kDa	<1%
<i>CEP290</i>	Centrosomal protein 290kDa	~10%
<i>CSPP1</i>	Centrosome and spindle pole associated protein 1	~2-5%
<i>INPP5E</i>	Inositol polyphosphate-5-phosphatase, 72kDa	Unknown
<i>KIF7</i>	Kinesin family member 7	Unknown
<i>MKS1</i>	Meckel syndrome, type 1	<1%
<i>NPHP1</i>	Nephronophthisis 1	<1-2%
<i>OFD1</i>	Oral facial digital syndrome 1	Rare
<i>PDE6D</i>	Phosphodiesterase 6D, cGMP-specific, rod, delta	Unknown
<i>POC1B</i>	POC1 centriolar protein B	Unknown
<i>RPGRIP1L</i>	RPGRIP-like	<2-4%
<i>TCTN1</i>	Tectonic family 1	Unknown
<i>TALPID3</i>	KIAA0586	~4%
<i>TCTN2</i>	Tectonic family 2	Unknown
<i>TCTN3</i>	Tectonic family 3	Unknown
<i>TMEM67</i>	Transmembrane protein 67	~10%
<i>TMEM138</i>	Transmembrane protein 138	Unknown
<i>TMEM216</i>	Transmembrane protein 216	~3%
<i>TMEM231</i>	Transmembrane protein 231	Unknown
<i>TMEM237</i>	Transmembrane protein 237	<1%
<i>TTC21B</i>	Tetratricopeptide repeat domain 21B	Unknown
<i>ZNF423</i>	Zinc finger protein 423	Unknown

### REFERRAL PROCEDURE

- Diagnostic referrals are accepted in probands with molar tooth sign on MRI and at least one of the following: eye movement disorder, hypotonia evolving into ataxia, developmental delay or abnormal breathing pattern. Referrals are accepted from Clinical Genetics, Paediatric Neurology or Consultants from relevant specialities.
- Carrier tests are only accepted from Clinical Genetics. Please contact the laboratory to discuss options for carrier screens (for screening of the appropriate gene in partners of known mutation carriers).
- Prenatal referrals are only accepted from Clinical Genetics or Prenatal Diagnosis. Prenatal testing must be discussed with the laboratory and arranged in advance.
- Clinical advice is available from Prof Andrea Nemeth, Consultant Clinical Geneticist (andrea.nemeth@ndcn.ox.ac.uk).

### STRATEGY AND TECHNICAL INFORMATION

- Diagnostic screens - Samples are prepared using Agilent's Haloplex Targeted Enrichment system. Next generation sequencing is performed on Illumina's MiSeq platform. Regions of interest are covered at a minimum of 30 reads. Average coverage is 97% at 30X for the gene panel. Multiplex amplification probe ligation analysis (MLPA) is undertaken for the *NPHP1* gene alone.
- Carrier screen – Sanger sequencing or NGS analysis of the appropriate gene (pathogenic gene variant found in partner).
- Carrier family tests and prenatal tests – Sanger sequencing (or MLPA if appropriate) for the familial pathogenic variants only.

### TARGET REPORTING TIMES

Diagnostic and carrier screen:	80 days
Carrier family tests:	10 days
Prenatal testing:	3 days

Libraries are sequenced on an Illumina MiSeq Desktop Sequencer. This will involve sequencing data generation in-house or by the High-Throughput Genomics Group at the Wellcome Trust Centre for Human Genetics, Oxford.

**N.B. Details are correct for the date of printing only – last updated 27/10/2015**