



## Joubert Syndrome 16

### Alternative Names

JBTS16

### Record Category

Disease phenotype

### WHO-ICD

Congenital malformations, deformations and chromosomal abnormalities > Congenital malformations of the nervous system

### Incidence per 100,000 Live Births

0-1

### OMIM Number

614465

### Mode of Inheritance

Autosomal recessive

### Gene Map Locus

11q12.2

### Description

Joubert syndrome (JS) is an inherited multi-visceral disorder caused by aberrant primary cilia formation and function. JS is characterized by the Molar Tooth Sign (MTS), a mid-hindbrain malformation easily identifiable through an axial brain MRI scan. Neurological features include hypotonia, ataxia, and cognitive impairment. The clinical phenotype additionally includes retinal, renal, hepatic -and more rarely- orofacial, skeletal, cardiac, genital, and endocrinal defects. JS is thought to affect 1 in 100,000 births; however the incidence in consanguineous populations is thought to be much higher (e.g. ~1 in 5000 for UAE).

JS16 (JBTS16) is a subtype of JS very similar to JBTS2, involving characteristic neurological features with mainly ocular involvement; renal, skeletal (polydactyly), and genital (cryptorchidism) defects are additional albeit relatively rarely reported features. The ocular phenotype involves retinal dystrophy, oculomotor apraxia, reduced

visual acuity, as well as chorioretinal and optic nerve coloboma. Renal involvement include cystic kidneys, nephronophthisis and nephrocalcinosis.

### Molecular Genetics

JBTS16 is an autosomal recessive disorder caused by homozygous mutations in *TMEM138*, a ciliary gene involved in trafficking intracellular vesicles containing essential proteins to the cilium. The first screening for pathogenic *TMEM138* variants reported 5 unique mutations (all in Arab and Pakistani families) including splice site and missense transition mutations.

### Epidemiology in the Arab World

#### Egypt

See United Arab Emirates > [Lee et al., 2012]

#### Oman

See United Arab Emirates > [Lee et al., 2012]

#### United Arab Emirates

Lee et al., (2012) identified *TMEM138* as a ciliary gene associated with JS (JBTS16), and performed the first mutation screening in a large group of JS cases. Three Emirati families, one Omani family, and two Egyptian families were reported, with affected members exhibiting the characteristic molar tooth sign. Among the Emirati families, 2 children from one family presented with ocular features including oculomotor apraxia (OMA) and coloboma. In the second family, 3 children presented with similar ocular features in addition to cystic kidneys and polydactyly each reported in 1 sibling; one sibling is deceased. In the third family, 3 adult siblings presented with retinal dystrophy. In the Omani family, 1 infant presented with OMA and coloboma, as well as cystic kidneys and hypertension; the family has 6 deceased siblings. Lastly, in the 2 Egyptian families only characteristic ocular features presented including OMA and coloboma presenting in 1 individual from 1 family, and OMA presenting in 1 individual in the other family.



Ben-Salem et al., (2014) reviewed the mutation spectrum for Joubert Syndrome in the Arab world. Among the cases, 3 individuals from 2 Emirati families were diagnosed with JBTS16 with unspecified clinical information. The Individuals harbored the same missense transversion mutation (p.Tyr130Cys) described by Lee et al. (2012).

Bizzari S et al., (2017) reported on two Emirati siblings with Joubert Syndrome 16 (JBTS16). The proband was born to consanguineous parents (1<sup>st</sup> cousins once removed); he was diagnosed at 17 months of age through identification of the molar tooth sign in brain imaging. He presented with hypotonia and global developmental delay. Additional symptoms involving ocular, renal, and genital defects included microphthalmia, nystagmus, minor coloboma, and esotropia, small renal subcortical cysts, as well as cryptorchidism. He exhibited a prominent forehead, an open normotensive anterior fontanelle, and pectus excavatum. His sister presented with similar symptoms. Whole Exome Sequencing identified a previously reported splice site mutation in *TMEM138*.

## References

Lee JH, Silhavy JL, Lee JE, Al-Gazali L, Thomas S, Davis EE, Bielas SL, Hill KJ, Iannicelli M, Brancati F, Gabriel SB, Russ C, Logan CV, Sharif SM, Bennett CP, Abe M, Hildebrandt F, Diplas BH, Attié-Bitach T, Katsanis N, Rajab A, Koul R, Sztriha L, Waters ER, Ferro-Novick S, Woods CG, Johnson CA, Valente EM, Zaki MS, Gleeson JG. Evolutionarily assembled cis-regulatory module at a human ciliopathy locus. *Science* 2012;355(6071):966-9. PMID: 22282472

Ben-Salem S, Al-Shamsi AM, Gleeson JG, Ali BR, Al-Gazali L. Mutation spectrum of Joubert syndrome and related disorders among Arabs. *Hum Genome Var.* 2014;1:14020. PMID: 27081510

Bizzari S, Hamzeh AR, Nair P, Mohamed M, Bastaki F. Characterization of an Emirati *TMEM138* mutation leading to Joubert syndrome. *Pediatr Int.* 2017;59(1):113-114. PMID: 28102635

## Related CTGA Records

*TMEM138*

## External Links

[http://www.orpha.net/consor/cgi-](http://www.orpha.net/consor/cgi-bin/OC_Exp.php?lng=EN&Expert=2318)

[bin/OC\\_Exp.php?lng=EN&Expert=2318](http://www.orpha.net/consor/cgi-bin/OC_Exp.php?lng=EN&Expert=2318)

<https://ghr.nlm.nih.gov/condition/joubert-syndrome>

## Contributors

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