Transmembrane Protein 138

Alternative Names
TMEM138

Record Category
Gene locus

WHO-ICD
N/A to gene loci

Incidence per 100,000 Live Births
N/A to gene loci

OMIM Number
614459

Mode of Inheritance
N/A to gene loci

Gene Map Locus
11q12.2

Description
TMEM138 encodes a member of the tetraspanin family of mulit-pass transmembrane proteins. Among various protein networks in primary cilia, proteins of the tectonic complex were found to partly play a role in transporting intracellular vesicles to the cilium. *TMEM138* is thought to function as part of this complex by marking post-Golgi vesicles that carry ciliary proteins. *TMEM138*-tagged vesicles and other transmembrane tagged vesicles are tethered in transport to the base of the cilium, a requirement for ciliary assembly and function. Dysfunctional ciliary genes result in various ciliopathies that arise due to absent or underdeveloped cilia.

TMEM138 dysfunction results in autosomal recessive Joubert Syndrome 16 (JBTS16), a neurodevelopmental and multi-visceral disorder characterized by the Molar Tooth Sign (MTS), a mid-hindbrain malformation easily identifiable through an axial brain MRI scan.

Molecular Genetics
TMEM138 is located on the q arm of chromosome 11, it is 14,502 bases long ranging from 61,362,001 to 61,376,502 pter. It contains 5 exons and translates into a 162aa long protein with a molecular weight of 19,262 Da. *TMEM138* is expressed ubiquitously in the cytoplasm and is most abundant in cilia; it is most expressed in the retina. Three alternatively spliced isoforms have been identified. *TMEM138* is aligned with *TMEM216* in a head to tail configuration; both genes flank a conserved regulatory element in the intergenic region, responsible for co-regulating their expression. *TMEM138* and *TMEM216* are thought to be involved in marking relatively distinct post-Golgi vesicles that carry essential ciliary proteins. This tagging is required for ciliary assembly.

Homozygous mutations in *TMEM138* result in Joubert Syndrome 16. The first screening for pathogenic *TMEM138* variants reported 5 unique recurring mutations, including 1 splice site and 4 missense mutations, mainly identified in Arab and Pakistani families.

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 who tested negative for mutations in previously suspected genes. 17 individuals from 3 Emirati families, 1 Omani family, and 2 Egyptian families were reported. Two children from one Emirati family harbored an intronic splice site transition mutation (c.128+5G>A); three children from the second Emirati family exhibited the same

intronic mutation. In the third Emirati family, 3 adults were found to harbor a missense transition mutation (c.380C>T; p.Ala127Val). In the Omani family, 1 infant was found to harbor a different missense transition (c.389A>G; p.Tyr130Cys); 6 siblings are deceased. Lastly, a third missense transition (c.376G>A; p.Ala126Thr) was identified in 1 infant and 1 child, each from separate Egyptian families. All mutations were reported to occur at evolutionarily conserved positions.

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. The Individuals harbored the same missense transversion mutation (c.389A>G; p.Tyr130Cys) described by Lee et al. (2012).

Bizzari S et al., 2017 reported on two Emirati siblings who were diagnosed with Joubert Syndrome 16 (JBTS16). Whole Exome Sequencing identified a previously identified splice site transition mutation in *TMEM138* (c.128+5 G>A). The mutation occurred at a conserved residue 5 nucleotides downstream of the second intron. *In silico* splice site prediction algorithms indicate that this mutation abolished the wild type donor site at intron 2; a stop codon was identified 6 nucleotides downstream of the mutation indicating protein truncation. His unaffected consanguineous parents (1st cousins once removed) are carriers of this mutation.

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

Joubert Syndrome 16
Joubert Syndrome 2
TMEM216

External Links

http://www.genecards.org/cgi-bin/carddisp.pl?gene=TMEM138
https://ghr.nlm.nih.gov/gene/TMEM138#conditions
http://www.proteinatlas.org/ENSG00000149483-TMEM138/tissue

Contributors

Sami Bizzari 07/02/17