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My46 Trait Profile

Joubert syndrome

Joubert syndrome is a genetic condition mainly characterized by a specific brain malformation, low muscle tone, and developmental delays. It can be caused by mutations in any one of many different genes.

Characteristics of Joubert syndrome

Joubert syndrome (JS) is a rare genetic condition characterized by a distinctive brain abnormality (cerebellar and brain stem malformation called the molar tooth sign), low muscle tone (hypotonia), and delays in speech, language, motor, social, and/or thinking skills. These findings are often accompanied by irregular breathing (tachypnea or apnea) and/or abnormal eye movements. Other features may include kidney disease, scarring of the liver, extra fingers and toes (polydactyly), breakdown of the light-detecting layer of the eye (retinal dystrophy), a small gap in the light-detecting layer of the eye (ocular coloboma), a gap in the skull (occipital encephalocele), and hormone abnormalities. These features can vary between and within families. In general, thinking ability in individuals with JS ranges from mildly to severely impaired, but sometimes falls in the normal range.

Diagnosis/Testing

To date, changes or mutations in 19 genes have been found in 50% of individuals with JS: NPHP1, CEP290, AHI1, TMEM67, RPGRIP1L, CC2D2A, ARL13B, INPP5E, OFD1, TMEM216, KIF7, TCTN1, TCTN2, TMEM237, CEP41, TMEM138, C5orf42, TMEM231, and TCTN3. This suggests that there are other genes yet to be identified can also cause JS. These genes make proteins that are often found near or in the primary cilium. The primary cilium is an antenna-like structure extending from most cells that allows cells to react to their environment. These proteins may be required for docking of the cilium to the surface of the cell, as well as for transport of proteins into and out of the cilium. Mutations in these genes cause problems with the formation and function of the cilia. It is not entirely understood why and how the abnormal cilia cause the features seen in JS.

Sometimes, individuals with mutations in certain genes are more likely to have specific physical aspects of the condition, although there are always exceptions. The strongest association is between mutations in the TMEM67 gene, and liver fibrosis and coloboma. Deletion of the NPHP1 gene is the most common cause of nephronophthisis, the type of kidney disease frequently seen in individuals with JS. RPGRIP1L and TMEM216 mutations are also associated with kidney disease, while INPP5E mutations are associated with retinal dystrophy, and CEP290 mutations are associated with both kidney and retinal dystrophy. Mutations in the KIF7 gene have been associated with the absence of the structure that connects the two halves of the brain (i.e., agenesis of the corpus callosum), polydactyly and abnormal bone development.

In females, mutations in one copy of the OFD1 gene typically causes an entirely different disorder called oral-facial-digital syndrome; however, in males, mild mutations in one copy of the OFD1 gene cause JS, sometimes with involvement of the kidney and retina (light detecting part of the eye).

When the genetic cause is known, prenatal diagnosis can be performed by testing DNA from chorionic villous sampling or amniocentesis. When the genetic cause is not known, prenatal diagnosis by ultrasound and MRI is possible.

Management/Surveillance

When infants and children have abnormal breathing, medicines, extra oxygen, or mechanical support (e.g., a

ventilator) may be used to support them. Kidney and liver failure may be treated with medicines, kidney dialysis, and/or transplant. Most individuals with JS receive educational support and physical, occupational, and speech therapies. Many use braces, walkers or sometimes wheelchairs to help with mobility. Sometimes a feeding tube may be required. Surgery may be necessary for polydactyly, drooping of the eyelids or eye crossing (strabismus).

Individuals with JS are at risk for developing blindness, kidney failure and bleeding from liver scarring. Because of these risks, they should be screened regularly for these conditions. Periodic eye exams, kidney, liver and spleen ultrasounds, and special blood tests to test kidney and liver function are recommended. Certain medications should be avoided in individuals with kidney or liver damage.

Mode of inheritance

JS can be inherited in one of two patterns of inheritance: autosomal recessive and X-linked recessive.

Autosomal recessive inheritance:

JS is most commonly inherited in an autosomal recessive pattern. This means that an individual has to inherit two mutations in the same gene (i.e., one from each parent) to be affected with JS. If both parents are carriers of a mutation, they have a 1 in 4 (25%) chance with each pregnancy of having a child with JS.

X-linked recessive inheritance:

Infrequently, JS can also be caused by a mutation in the X-linked OFD1 gene. This follows an X-linked recessive inheritance pattern. This means that in females, both copies of the OFD1 gene must have a mutation, whereas in males, only one copy of the OFD1 gene must have a mutation to be affected with JS.

Risk to family members

The risk to family members depends on the pattern of inheritance.

Autosomal recessive inheritance:

Parents of a child with JS are carriers of JS. If a sibling of a child with JS is unaffected, he/she has a 2 in 3 chance (66%) of being a carrier of JS.

X-linked recessive inheritance:

If a mother is a carrier of JS, each daughter has a 1 in 2 chance (i.e., 50%) of being a carrier and each son has a 1 in 2 chance (i.e., 50%) of being affected with JS.

Special considerations

None

Resources

Joubert Syndrome & Related Disorders Foundation
http://www.jsrdf.org/
Genetics Home Reference: Joubert syndrome
http://ghr.nlm.nih.gov/condition/joubert-syndrome

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