

Genetic Testing and Joubert Syndrome

Genetic disorders, such as Joubert syndrome and other related cerebellar disorders (JSRD), are caused by alterations in a gene. Many genetic disorders, including JSRD, can be caused by changes in several different genes.

What is a Gene?

Within each cell of your body is a unique set of blueprints that determines how your body looks and functions. These blueprints are found within the cell's DNA (deoxyribonucleic acid).

Specific segments of DNA, called genes, contain the instructions for making specific body proteins. One protein may help to determine the color of your eyes while another helps to control a specific chemical reaction within your body. Sometimes, even a small error in one gene can cause severe health problems.

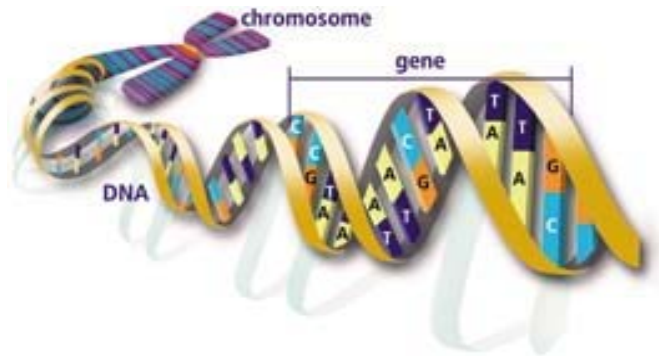


image courtesy of U.S. Department of Energy
Human Genome Program, <http://www.ornl.gov/hgmis>

Genes are found in specific segments of DNA, which is tightly packaged within structures called chromosomes. Every human cell contains 46 chromosomes, arranged in 23 pairs, with one member of each pair inherited from the mother and the other inherited from the father. After conception, these 46 chromosomes duplicate again and again to pass on genetic information to each new cell in the developing child.

What is Genetic Testing?

Genetic tests look for abnormalities in a person's genes, which involves looking directly at the DNA obtained from a person's blood cells, body fluids or tissues. The abnormality can be relatively large — a piece of a chromosome, or even an entire chromosome, may be missing or added. Sometimes the change is very small — as little as one extra, missing or altered chemical base within the DNA strand. Some errors may cause genes to be amplified (too many copies), over-expressed (too active), inactivated or lost altogether. Sometimes pieces of chromosomes become transposed, or switched, to an incorrect location.

Doctors can now pinpoint missing or defective genes for more than 1000 genetic disorders through genetic testing. The type of genetic test needed to make a specific diagnosis depends on the particular genetic condition that a doctor suspects.

Genetic Testing for Joubert Syndrome and Related Disorders

Joubert syndrome and other related disorders are passed down from parents to offspring as autosomal recessive traits. This means that, in order for a child to be affected with a JSRD, both parents must each carry one altered copy of the gene responsible for the disorder. JSRD-affected individuals will have two altered copies of the responsible gene. A mother and father who are both carriers will have a 25% chance of having a child with JSRD in each pregnancy.

In the case of JSRD, scientists look for missing and/or altered copies of the genes known to be responsible for the disorder. As a result of a partnership among researchers studying JSRD, the Joubert Syndrome Foundation & Related Cerebellar Disorders, and PreventionGenetics, a genetics testing company, genetic testing for the five identified JSRD genes is now available to families and can be arranged by a physician. The genes known to cause JSRD are: *AHI1*, *CEP290*, *MKS3*, *NPHP1*, and most recently, *RPGRIP1L*. Additionally, there are more causative genes that are—as yet—still unknown.

Individuals with JSRD found to have mutations in the *AHI1* gene often have impaired vision due to pigment differences in the retina, called retinal dystrophy. Approximately 11% of all JSRD patients would receive a positive test result for mutations in the *AHI1* gene.

CEP290 abnormalities have been identified in some JSRD patients with nephronophthisis and/or retinal dystrophy. Perhaps another 4-10% of all JSRD cases may be a result of alterations to this gene.

MKS3 was identified as a cause of JSRD in early 2007. Alterations in the *MKS3* gene are responsible for both JSRD and Meckel-Gruber Syndrome. These two disorders have overlapping clinical features. Although data is still limited, up to 10% of JSRD cases may be a result of alterations to the *MKS3* gene.

NPHP1 is associated with a progressive form of kidney disease called nephronophthisis. It is estimated that no more than 5% of those with a JSRD would test positive for a deletion in this gene.

The newest gene for JSRD, *RPGRIP1L*, was just identified in the summer of 2007. There is evidence that this gene also causes Meckel-Gruber syndrome. It appears to account for about 5% of all cases of JSRD.

Although researchers are beginning to make connections between abnormalities in each of the aforementioned genes and the symptoms of affected individuals, it is still difficult to determine which gene is involved in a particular patient by their symptoms alone.

Pros and Cons of Genetic Testing

Genetic testing for the JSRD genes is typically done to confirm a diagnosis or to determine if an individual is a carrier for the disorder. A negative test result can, at least, tell doctors where not to look in the future. A positive test result can relieve the uncertainty of “not knowing”, direct a physician toward appropriate treatments, and enable couples to make informed decisions about their reproductive future. Sometimes, the results of genetic testing do not provide a clear answer—and this can be frustrating. As a result, the decision to undergo genetic testing is a very personal one.

Pros:

- Confirm a JSRD diagnosis.
- Individuals can find out whether they are a carrier for JSRD.
- Knowing which gene is abnormal may, especially in the future, indicate specific health problems that a patient is likely to develop and may result in better healthcare management.
- Couples of reproductive age can use the knowledge of their carrier status to make educated decisions regarding their reproductive future.
- Many families and professional geneticists believe that knowledge of the specific genetic causes of JSRD in patients and family members is desirable to allow better understanding of these conditions.

Cons:

- Although genetic tests can identify a particular causative gene, they can't always predict how severely affected the individual will be.
- Genetic testing for JSRD is difficult and costly. Some insurance plans will cover the costs for genetic tests, while others will not. You will have to contact your insurance provider in advance of testing to see if these genetic tests -- which can cost between \$200 and \$6000-- are covered under your plan.
- Sometimes, the results of genetic testing are not definitive. Only one of two causative mutations may be identified in a JSRD gene, or a genetic change of unknown significance may be identified. In this situation, it may be difficult to interpret the results and provide predictive information or prenatal testing options for the family in the future.
- There is a small possibility that the results of genetic testing could be used against you and your family, particularly by employers and insurance companies. Many states have passed legislation to prohibit genetic discrimination, and Congress appears to be close to passing Federal anti-genetic discrimination legislation.
- It is believed that less than 40% of individuals with JSRD will have a mutation identified in one of the 5 known genes. Many of our families are often dealing with troubling uncertainties about their own future and that of their children, as there are no preventive measures or cures for Joubert syndrome. If you decide to pursue genetic testing, the information you receive may not offer the answers that you seek.

Your doctor may refer you to a clinical M.D. geneticist or genetic counselor, as the decision about whether to be tested for JSRD is complex. These professionals are trained to help you weigh the scientific, emotional and ethical considerations that impact this decision. Universities and medical centers often have affiliated geneticists and genetic counselors, or can provide referrals to a counselor or genetics clinic.

For More Information

GeneTests.org (www.genetests.org) provides educational materials, expert-authored publications of specific diseases, and international directories of genetic testing laboratories and clinics.

PreventionGenetics, in Marshfield, WI, offers genetic testing that is available to interested families and can be arranged through a physician, geneticist, or genetic counselor. To see a complete listing of the genetic tests currently available for JSRD, go to www.preventiongenetics.com

The Joubert Syndrome Foundation & Related Cerebellar Disorders (www.jsfrcd.org) is an international network of parents who share knowledge, experience, and emotional support. The JSF&RCD plays an important role in educating physicians and their support teams as well as increasing public awareness of and promoting research in JSRD.

Sources:

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