

## Update on the genetics of Joubert syndrome and genetic testing options

In the past year, there has been a great flurry of genetic discoveries in the field of Joubert syndrome and related disorders (JSRD), with two new causative genes identified. There are now 5 genes in total that are known to cause JSRD. In addition, there are 2 more genes that, although we know their general location within the human genome, have not been discovered yet. One of the challenges in JSRD is that so many different genes can all cause the same condition. However, within an individual family, only one of these genes is likely to cause JSRD, which is due to an alteration in both copies of the same gene in the DNA of an affected child. There are other genetic conditions, such as cystic fibrosis or neurofibromatosis, with only a single causative gene, which makes identifying the specific mutations much easier.

I would like to take this opportunity to describe the 2 new genes discovered in the past year, and then summarize what is known about all the genes identified for JSRD. [For details about the first 3 JSRD genes identified, please see the article on the JSF website ([www.jsfrcd.org](http://www.jsfrcd.org)) linked to “Physician Research” and the news item on “Update on the genes that cause Joubert syndrome” dated 8-5-06.]

The *MKS3* gene was actually identified first in individuals with Meckel-Gruber syndrome (MKS)<sup>1</sup>. This is a condition that can be associated with enlarged kidneys with big cysts, brain malformations known as encephaloceles, and a congenital liver malformation. Some of the MKS fetuses may not survive to be born or may not survive the newborn period. For the most part, the few children with JSRD who have also had mutations in this gene have not had the same appearance as MKS<sup>2</sup>, but have more variable findings. One has had kidney disease and liver fibrosis. We still have much to learn about this gene and its role in JSRD. This is a large gene of 28 exons.

The *RPGRIP1L* gene was first reported this summer by our laboratory and a group based in France<sup>3,4</sup>. This gene has 26 exons in length. There appears to be one mutation that occurs more often in children with JSRD due to this gene, some of whom have developed kidney disease, and others whom have had encephaloceles or extra fingers or toes. Only a few have had retinal disease that impairs vision and may lead to blindness. Some newborns with MKS have also had changes in this gene, but these infants have had more severe symptoms and often, more severe mutations. We think that ~5% of children with JSRD may have changes identified in this gene.

Table: Genes and estimated frequency in individuals with JSRD<sup>5,6</sup>

<u>Locus (genetic region)</u>	<u>Interval size/Gene</u>	<u>Estimated frequency</u>
8q21.13-q22.1	<i>MKS3</i> gene	<10%
16q12.2	<i>RPGRIP1L</i> gene	~5%
6q23	<i>AH11</i> gene	~10%
2q13	<i>NPHP1</i> gene	~1-2%
12q21.3	<i>CEP290</i> gene	~10%
9q34.3	13 cM	?
11 centromere	6 cM	?
TOTAL		<40%

Overall, less than 40% of all families with JSRD will have a mutation identified in one of the 5 known genes. The physical manifestations for children with *AHII* and *NPHP1* gene changes tend to include retinal dystrophy and kidney problems in some individuals. The clinical manifestations for the other 3 genes (*CEP290*, *MKS3*, and *RPGRIP1L*) are more variable and overlap with Meckel-Gruber syndrome. Clearly, other genes remain to be identified, and finding the specific gene in a given family may be complicated. At this time, genetic testing for clinical purposes is available through PreventionGenetics, a genetic testing company based in Wisconsin. This company can perform deletion analysis for *NPHP1*, and full sequence analysis of *AHII*, *MKS3*, *CEP290*, and *RPGRIP1L*. Check with your geneticist and insurance company before pursuing testing for these genes, as it can be expensive if not covered by your policy. (Please see the companion article on “Genetic Testing and Joubert Syndrome” for a description of genetic testing and a discussion of the pros and cons of testing in JSRD.) If the genetic cause of JSRD is known based on testing by PreventionGenetics, and you have worked with our research group, we would appreciate knowing those results, as this helps us understand how the known genes cause JSRD and also helps us find new genes for JSRD.

As always, we appreciate your contributions to our research group to identify the genetic causes of Joubert syndrome and related disorders. We also appreciate the many families who have donated to the JSF & RCD BioBank to advance the cause of research.

Please contact Dr. Parisi at [mparisi@u.washington.edu](mailto:mparisi@u.washington.edu) for more information about the genetics of JSRD. Please contact Dana Knutzen, MS (genetic counselor and research coordinator) at [Dana.Knutzen@seattlechildrens.org](mailto:Dana.Knutzen@seattlechildrens.org) for information about how to participate in research studies. Our toll-free phone number is 1-800-246-6312. Additional information is available on the University of Washington Joubert Center website at <http://depts.washington.edu/joubert/>.

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#### References:

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