

Update on the genes that cause Joubert syndrome

At the recent JSF conference in Irving, Texas, Dr. Melissa Parisi gave an overview of the genetics of Joubert syndrome. Dr. Ian Glass also discussed developments in prenatal diagnosis of Joubert syndrome. In the past few months, a third gene that causes Joubert syndrome and related disorders (JSRD) was discovered. This means that 3 different genes for JSRD have now been identified. In addition, there are 2 other genetic regions where the specific genes have not yet been found. Overall, we know that there will be at least 5 different genes and possibly many more that are associated with JSRD. The table below summarizes this information.

The *AHII* gene is located on chromosome 6. It has been identified as causative in ~11% of families tested in our laboratory. This is a large gene of 28 exons or units of sequence information. Children with JSRD due to mutations in this gene often have retinal dystrophy, a pigmentary difference in the retina that is associated with impaired vision. It may not be apparent at birth. In a few families with genetic changes in *AHII*, the affected children have developed cystic kidney disease in their 20's. We do not know if this is likely to be a common finding or a rare occurrence for individuals with *AHII* mutations. Overall, these individuals will continue to require vision and kidney evaluations.

A few children with JSRD have been found to be missing both copies of the *NPHP1* gene, a medium-sized gene of 20 exons found on chromosome 2. Deletions of the *NPHP1* gene are associated with the progressive kidney disease known as nephronophthisis, which typically develops in children between the ages of 8-20 years. At least one child with an *NPHP1* deletion also developed retinal dystrophy. There may be a distinctive appearance to the molar tooth sign in those with *NPHP1* deletions, but we do not have enough experience to be certain. Children with this form of JS need to have their vision and kidneys monitored. Overall, this appears to be a rare cause of JSRD, as only 1-2% in our series had this as the genetic cause.

The most recent gene for JSRD, *CEP290*, is a very large gene of 55 exons which was identified in some children with nephronophthisis and/or retinal dystrophy. A few of the children with changes in this gene have also been found to have colobomas (defects in the way the eye develops) or encephaloceles (posterior skull defects). Preliminary data suggest that ~4-10% of JSRD may be due to this gene. The *CEP290* protein, along with *NPHP1* and many other proteins, are associated with the primary cilium or "antenna" of the cell, important in cell division, sensing, and development.

Table: Genes and relative frequency in families studied by the University of Washington

<u>Locus (genetic region)</u>	<u>Interval size/Gene</u>	<u>Relative contribution</u>
9q34.3	13 cM	?
11 centromere	6 cM	?
6q23	<i>AHII</i> gene	11%
2q13	<i>NPHP1</i> gene	~2%
12q21.3	<i>CEP290</i> gene	~4%
TOTAL		~17%

Overall, only ~20% of all families with JSRD will have a mutation identified in one of the 3 known genes. In fact, none of the identified genes is associated with polydactyly (extra fingers and/or toes) or with liver fibrosis. Clearly, other genes remain to be identified, and finding the specific gene in a given family may become quite 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*, full sequence analysis of *AH11*, and limited sequencing of *CEP290*. Check with your geneticist and insurance company before pursuing testing for these genes, as it can be expensive if not covered by insurance.

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 for more information about the genetics of Joubert syndrome. Additional information is available on the University of Washington Joubert Center website at <http://joubertsyndrome.washington.edu> where the full text of both the genetics and prenatal diagnosis talks can be downloaded.

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