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## Researchers Identify Joubert Syndrome Genes

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**Overview** Researchers have identified the genes for two different forms of Joubert syndrome, a rare developmental disorder that causes coordination and movement problems and mental retardation in children. The findings allow genetic testing for some forms of the disorder and provide valuable insights about how the human brain develops.

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Researchers have identified the genes for two different forms of Joubert syndrome, a rare developmental disorder that causes coordination and movement problems and mental retardation in children. The findings allow genetic testing for some forms of the disorder and provide valuable insights about how the human brain develops.

In two new studies, reported by Christopher A. Walsh, M.D., Ph.D., and colleagues in the September 2004 issue of *Nature Genetics*,<sup>[1]</sup> and by Joseph G. Gleeson, M.D., and colleagues in the December 2004 issue of the *American Journal of Human Genetics*,<sup>[2]</sup> the two groups of investigators studied families from the Middle East in which the parents were related to each other and had children with Joubert syndrome. The researchers identified mutations in a gene called *AHI1* that caused the disease in these families. Both studies were supported in part by the National Institute of Neurological Disorders and Stroke (NINDS).

The exact function of the *AHI1* gene is not yet known, but it codes for a protein that is strongly expressed in the brain and appears to play an important role in development, especially in brain wiring. Many nerve fibers in children with Joubert syndrome do not cross the midline of the brain as they would in normal development. This sometimes leads to abnormal "mirror movements" in which both limbs move simultaneously. Researchers believe that the *AHI1* protein and other proteins that interact with it may be essential for helping nerve fibers find their way to the correct places during brain development.

Joubert syndrome affects about one in 100,000 children — approximately 40 babies per year in the United States. It includes an absence of the cerebellar vermis, or the midline of the cerebellum, and an unusual brainstem feature called the "molar tooth sign" (because it looks like a tooth) that can be seen in brain scans. There are several forms of Joubert syndrome. Symptoms vary, but they generally include poorly controlled movements and mild to moderate mental retardation. Other symptoms may include seizures, kidney failure, breathing abnormalities, extra fingers or toes, and autism.

"This is a very serious disorder that affects children. Finding this gene allows us to provide more concrete information about the risk of recurrence, and understanding what goes wrong helps us to understand our options in terms of therapy," says Dr. Walsh. "It also gives us a new way to investigate the complex process of neuronal navigation — how nerve fibers find the correct targets."

"This finding allows better diagnosis, and the possibility of prenatal testing and prenatal counseling," says Dr. Gleeson.

"Families want to know if they are at risk of having another affected child." The finding will allow genetic testing for *AHI1* mutations, which will provide valuable information about affected children's prognosis. There is no commercially available genetic test at this time, but the Gleeson and Walsh laboratories are currently testing affected children for mutations on a research basis.

Another NINDS-funded study, published in the July 2004 issue of the *American Journal of Human Genetics*,<sup>[3]</sup> linked some cases of Joubert syndrome with progressive kidney disease to a gene called *NPHP1*. This work, led by Melissa A. Parisi, M.D., Ph.D., of the University of Washington in Seattle, was the first to identify a specific genetic abnormality in Joubert syndrome.

While the form of Joubert syndrome linked to *AHI1* appears to be the most common of the known forms of the disease, studies suggest that *AHI1* and *NPHP1* together account for only a minority of Joubert cases. The genes for other forms of the disease have not yet been found. "It is likely that the majority of genes accounting for Joubert syndrome remain to be identified," says Dr. Parisi. Researchers are working to find those genes. "Ultimately, we hope to provide predictive information for families regarding future health risks for their children with Joubert syndrome, depending on the causative gene," Dr. Parisi says.

The *NPHP1* protein product, called nephrocystin, is structurally similar in some ways to the *AHI1* gene, Dr. Gleeson notes. This suggests that the proteins produced by the two genes may play a similar role, or that they may interact with each other in a way that is important for normal brain development.

Understanding how the *NPHP1* and *AHI1* genes affect brain development also may lead to improved understanding of and potential treatments for mental retardation and other developmental disabilities, Dr. Gleeson suggests. Since children with Joubert syndrome sometimes have autism as well, genes that cause Joubert syndrome may play a role in development of autism and related disorders.

Dr. Walsh's group also examined how the *AHI1* gene differs in humans and other animals to see if it might be important for human evolution. They found that the gene is missing in fruit flies and worms and varies significantly among primates. A portion of the gene is absent in rats and mice but present in animals with bigger brains. This suggests that *AHI1* is one of many genes that played a role in human evolution, he says.

The researchers are continuing to study *AHI1* and *NPHP1* to learn more about how they affect the brain. Dr. Walsh's group is planning to study the *AHI1* gene in an animal model to identify its function and to determine how it affects development of the cerebral cortex and other parts of the brain. The groups led by Dr. Gleeson and Dr. Parisi plan to study more affected families in order to find the Joubert syndrome genes that are still unidentified. This work may help researchers understand more about the biochemical interactions that lead to Joubert syndrome and may make definitive genetic testing available to more people.

The NINDS is a component of the National Institutes of Health within the Department of Health and Human Services and is the nation's primary supporter of biomedical research on the brain and nervous system.

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