Researchers identify fifth gene responsible for Joubert syndrome

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An international study by researchers at Seattle Children's Hospital Research Institute, the University of Washington School of Medicine, and Radboud University in Nijmegen, Netherlands has identified a new genetic cause for Joubert syndrome (JS).

Joubert syndrome is an inherited condition that affects development of the cerebellum and brainstem, the structures in the brain that coordinate movements and regulate basic functions such as breathing, swallowing, heart rate and consciousness.

The study, published in the June 10, 2007 issue of *Nature Genetics*, confirms key information about the genetic changes that cause JS and cellular structures called cilia, conclusively placing JS in a class of recently identified ciliopathic conditions. Though the disease is statistically rare and four other genetic markers have been previously identified, researchers believe these findings are important.

Joubert syndrome can result in developmental delay, poor physical coordination, irregular breathing, visual impairment, kidney failure and extra digits. Diverse symptoms may occur making diagnosis difficult, though patients typically feature a characteristic configuration of the brainstem and cerebellum on magnetic resonance imaging (MRI), where the abnormally developed brain stem resembles the shape of a molar tooth. The researchers' discovery of mutation in the gene (RPGRIP1L) now paves the way for definitive DNA testing that can more conclusively diagnose JS in some patients, and also identify asymptomatic carriers who might unknowingly pass the condition to their future children.

In addition to identifying a fifth gene for JS, the study also sheds light on the role of cilia in this disease and possibly others. Primary cilia are tiny projections on cell surfaces that allow the inside of cells to communicate with their outside environment. Recent research has found that defects in cilia function lead to various newly identified syndromes called ciliopathies. The paper describes a genetic change that prevents interaction between two particular cilia proteins, presumably disrupting cilia function and causing JS. This links JS to other diseases such as Leber congenital amaurosis, Senior-Loken syndrome and nephronophthisis, the most common genetic cause of kidney failure in children. All these conditions share disruptions in the protein networks of cilia. Further, this study exemplifies the power of international collaborative research, an increasingly important trend in biomedical discoveries.

Study findings add substantially to the way JS and other ciliopathies will be identified and understood. "By discovering this gene, we're on the forefront of research changing how we think about brain, retina and kidney development," said Dr. Dan Doherty, co-author on the study, from the Division of Genetics and Developmental Medicine at Seattle Children's Hospital Research Institute. "These advances will lead to better understanding of both normal and abnormal brain development and eventually improved treatments for a variety of diseases."

Source: Children's Hospital and Regional Medical Center of Seattle