



Understanding the Mechanisms Underlying Joubert Syndrome

by Kate Forster

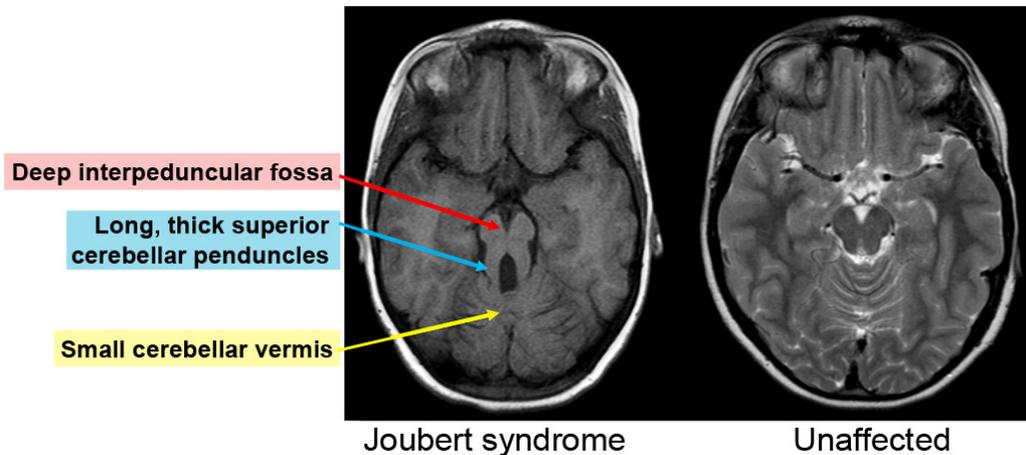
Like so many disorders that have a genetic basis, all of the suspects involved in causing Joubert syndrome—a brain malformation disorder that causes intellectual and developmental disabilities—have yet to be identified, leaving potential points of therapeutic intervention undiscovered. Dan Doherty, M.D., Ph.D., associate professor of pediatrics, and CHDD research affiliate, is working to find new genetic causes of Joubert syndrome and to identify the molecular mechanisms that underlie it. Joubert syndrome is defined by a characteristic brain imaging finding known as the “molar tooth sign,” and symptoms include intellectual disability, decreased muscle tone, difficulties with coordination, and abnormal eye movements and breathing patterns. Individuals with Joubert syndrome can also develop progressive kidney and liver disease. While rare, it is one of a class of disorders known as *ciliopathies*, a group of associated genetic disorders that result in abnormal formation of cilia, the fine hair-like projections outside cells that act as receptors, mediate signaling from the outside world, and tell the cell what to do. Taken together, the combined prevalence of ciliopathies is greater than one in 1,000, and many affected individuals have similar symptoms, including intellectual disability.



Dan Doherty hopes to identify new genetic causes of Joubert syndrome and its underlying mechanisms.

Through the study of Joubert syndrome, Doherty hopes to gain a broader understanding of how the cilium works which, in turn, can help shed light on the other ciliopathies. “The cilium is an incredibly complicated machine,” he said, “and all of the parts have to work together. While the mutations that are involved in each of these disorders differ, they all affect the protein complexes that work together near and in the cilium. So studying Joubert syndrome can really allow us to dissect and understand the different functions of the cilium.”

To identify the different genetic causes of Joubert syndrome, Doherty’s group takes advantage of the fact that both copies of a gene (one from each parent) have to carry mutations to cause the disorder. Right now, his group can identify the genetic mutation that causes Joubert syndrome in 62% of families by using a highly efficient technology developed by Jay Shendure’s lab here at the University of Washington to sequence all of the known Joubert syndrome genes. “We can identify most of the causes by sequencing the coding DNA, which is <3% of the genome that’s used to make the protein building blocks of cells, because most known disease-causing mutations occur in coding DNA.” At least half of the remaining 38% of individuals carry a single mutation in a gene associated with Joubert syndrome. “We hypothesize that many of these individuals have ‘second hits’ in poorly-understood, non-coding DNA in and around genes



The “molar tooth sign” in the brain image on the left indicates the presence of Joubert syndrome.

that determines when and where proteins are expressed. Identifying these non-coding mutations provides an opportunity to help answer one of the most important questions facing human genetics: How do non-coding mutations contribute to human disease?” Bioinformatic analysis resources provided by the CHDD Genetics Core will be instrumental for finding these non-coding mutations in targeted and whole-genome DNA sequence data.

Dissecting the underlying mechanism and broader implications

Doherty hypothesizes that a singular unifying cellular defect is responsible for the brain malformation that defines Joubert syndrome, despite the fact that many different cellular defects have been reported each time a new genetic cause is published. “If you think about it, all the proteins localize to the same part of the cell, and they’re all associated with the same condition, so they should all be involved in the same thing,” said Doherty. To test this hypothesis, he plans to systematically evaluate the cellular characteristics of skin cells donated by patients with Joubert syndrome using advanced microscopy resources available through the CHDD’s Clinical Translational Core. “Once we identify the unifying mechanism underlying Joubert syndrome, we can try to fix it on a cellular level by introducing genes without mutations or treating the cells with candidate medications.” In addition to leading to future treatments, the information gained will provide insights into the basic functions of the cilium and inform animal models for studying Joubert syndrome and other ciliopathies, likely impacting many different diseases that involve the cilium.

Benefits of genetic diagnosis

Doherty also hopes this research highlights the importance of genetic testing for Joubert syndrome. Identifying the genetic cause can clarify the diagnosis when it is uncertain. It can also contribute to the early diagnosis and treatment of complications, since some genes are associated with higher risk of complications than others. In addition, it can define the recurrence risk (25%) and identify families with the rare X-linked form of Joubert syndrome that affects only males.

Understanding the genetic architecture and biological mechanisms underlying Joubert syndrome has important implications both for those with the disorder and for those with other ciliopathies. Elucidating the role of the primary cilium in brain development and function will lead to deeper understanding and treatment of both the rare and the more common ciliopathies.

CHDD is an interdisciplinary center dedicated to the prevention and amelioration of developmental disabilities through research, training, clinical service, and community outreach. CHDD includes the University Center of Excellence in Developmental Disabilities and the Eunice Kennedy Shriver Intellectual and Developmental Disabilities Research Center.

CHDD Outlook

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