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Study finds new gene mutations that lead to enlarged brain size, cancer, autism, epilepsy

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A research team led by Seattle Children's Research Institute has discovered new gene mutations associated with markedly enlarged brain size, or megalencephaly. Mutations in three genes, AKT3, PIK3R2 and PIK3CA, were also found to be associated with a constellation of disorders including cancer, hydrocephalus, epilepsy, autism, vascular anomalies and skin growth disorders. The study, "De novo germline and postzygotic mutations in AKT3, PIK3R2 and PIK3CA cause a spectrum of related megalencephaly syndromes," was published online June 24 in *Nature Genetics*.

The discovery offers several important lessons and hope for the future in medicine. First, the research team discovered additional proof that the genetic make-up of a person is not completely determined at the moment of conception. Researchers previously recognized that genetic changes may occur after conception, but this was believed to be quite rare. Second, discovery of the genetic causes of these human diseases, including developmental disorders, may also lead directly to new possibilities for treatment.

AKT3, PIK3R2 and PIK3CA are present in all humans, but mutations in the genes are what lead to conditions including megalencephaly, cancer and other disorders. PIK3CA is a known cancer-related gene, and appears able to make cancer more aggressive. Scientists at Boston Children's Hospital recently published similar findings related to PIK3CA and a rare condition known as CLOVES syndrome in the American Journal of Human Genetics.

Physician researcher James Olson, MD, PhD, a pediatric cancer expert at Seattle Children's and Fred Hutchinson Cancer Research Center who was not affiliated with the study, acknowledged the two decades-worth of work that led to the findings. "This study represents ideal integration of clinical medicine and cutting-edge genomics," he said. "I hope and believe that the research will establish a foundation for successfully using drugs that were originally developed to treat cancer in a way that helps normalize intellectual and physical development of affected children. The team 'knocked it out of the park' by deep sequencing exceptionally rare familial cases and unrelated cases to identify the culprit pathway." The genes— AKT3, PIK3R2 and PIK3CA—all encode core components of the phosphatidylinositol-3-kinase (P13K)/AKT pathway, the "culprit pathway" referenced by Olson.

The research provides a first, critical step in solving the mystery behind chronic childhood conditions and diseases. At the bedside, children with these conditions could see new treatments in the next decade. "This is a huge finding that provides not only new insight for certain brain malformations, but also, and more importantly, provides clues for what to look for in less severe cases and in conditions that affect many children," said William Dobyns, MD, a geneticist at Seattle Children's Research Institute. "Kids with cancer, for example, do not have a brain malformation, but they may have subtle growth features that haven't yet been identified. Physicians and researchers can now take an additional look at these genes in the search for underlying causes and answers."

Researchers at Seattle Children's Research Institute will now delve more deeply into the findings, with an aim to uncover even more about the potential medical implications for children. "Based on what we've found, we believe that we can eventually reduce the burden of and need for surgery for kids with hydrocephalus and change the way we treat other conditions, including cancer, autism and epilepsy," said Jean-Baptiste Rivière, PhD, at Seattle Children's Research Institute. "This research

truly helps advance the concept of personalized medicine."

Drs. Dobyns, Rivière and team made this discovery through exome sequencing, a strategy used to selectively sequence the coding regions of the genome as an inexpensive but effective alternative to whole genome sequencing. An exome is the most functionally relevant part of a genome, and is most likely to contribute to the phenotype, or observed traits and characteristics, of an organism.

More information: *Nature Genetics* (2012) doi:10.1038/ng.2331

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