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Common brain cyst and neurodevelopmental disorders share genetic drivers

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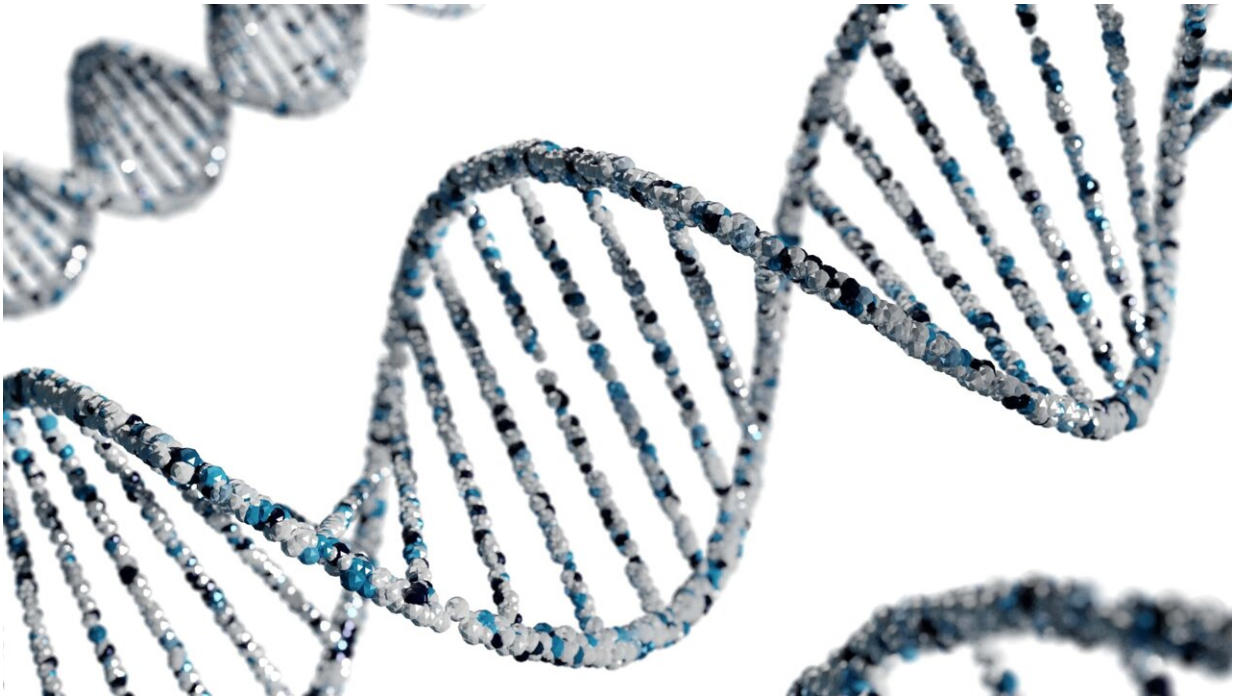

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Often an incidental finding on brain scans looking for trauma or other neurological conditions, arachnoid cysts (ACs) are small, fluid-filled sacs within the arachnoid membrane, one of three layers protecting the brain and spinal cord. They often don't cause noticeable symptoms; however, when they do, patients most commonly report headaches, seizures, developmental delays, and other, often vague neurological

symptoms.

While ACs are the most common type of intracranial brain cyst, prior research has not uncovered the biological drivers behind what forms them or what makes some symptomatic and others seemingly benign. Ultimately, this can make treatment challenging.

In a new Research Briefing published in *Nature Medicine*, researchers at the Yale School of Medicine's Department of Neurosurgery used a multi-omics approach to classify ACs based on genotypic and phenotypic markers. Researchers collected 617 patient-parent (trio) exomes worldwide, amassing the largest trio-based cohort of arachnoid cyst patients to date. Through whole exome sequencing of patients DNA, they have identified seven genes associated with AC formation, all of which have also been associated with other neurodevelopmental disorders in prior research.

The team also used novel analysis techniques and natural language processing of thousands of pages of medical records to group the patients based on the severity of their symptoms (phenotypic markers). This analysis resulted in four distinct AC subclasses.

They were then able to correlate the presence of the identified genetic variants (genotypes) with the severity of symptoms (phenotypes) within each AC class, linking for the first time the genetics of ACs with their clinical presentation. While previously researchers believed the cysts themselves disrupted brain structures and caused symptoms by direct compression of adjacent structures, this new finding suggests that many symptoms associated with arachnoid cysts may come from a shared genetic defect driving both cyst formation and the associated neurodevelopmental abnormalities.

A new application for multi-omics

"We decided to tackle this question not only because ACs are so common and so little is known about their pathobiology, but also because the framework of using classical genomics, integrative genomics, and artificially-intelligence-driven phenomics—what we refer to as 'multi-omics'—has not been applied in this way yet. Having now leveraged it to uncover some of the drivers of ACs, we are excited to apply the model to other enigmatic congenital disorders of the brain and spine," says lead author Adam Kundishora, MD, chief resident of neurosurgery at the Yale School of Medicine.

This research lays the foundation for developing treatment protocols around "symptomatic" and "asymptomatic" ACs. Currently, surgical decision-making can be difficult once an AC has been found, especially if the patient's symptoms are vague or could be attributed to other causes. Additional genetic testing could indicate if patients' symptoms could be coming from generally disrupted brain development and function and thus would likely not benefit from surgical cyst decompression.

Further research is needed to explore the specific effects of the identified genetic variants on the brain. The team is also considering non-genetic and environmental factors that may contribute to AC development.

"Ultimately, we are interested in translating genomic data into pathophysiological insights that have meaningful impact for patients. This study is a solid step in the right direction for ACs," says Kristopher Kahle, MD, Ph.D., adjunct professor of neurosurgery at Yale School of Medicine and director of pediatric neurosurgery at Massachusetts General Hospital and director of the Harvard Center for Hydrocephalus and Neurodevelopmental Disorders.

More information: Epigenomic dysregulation correlates with

arachnoid cyst formation and neurodevelopmental symptoms, *Nature Medicine* (2023). DOI: 10.1038/s41591-023-02239-1