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CONQUER CHIARI
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Genetic Study Points to a Developmental Pathway for Some Chiari Patients

A large new genetic study provides some of the strongest evidence yet that, for a subset of people with Chiari I malformation, the condition may arise from genetic changes that affect development of the cerebellum. Importantly, the people carrying these genetic changes were not necessarily typical of the broader Chiari population. Many also had neurodevelopmental or congenital features: 69% had global developmental delay, more than one-third had macrocephaly or enlarged brain ventricles, and 31% had craniofacial abnormalities. The findings therefore appear most relevant to a particular subgroup of Chiari patients rather than suggesting a single genetic explanation for Chiari as a whole.

Researchers analyzed 1,585 people with sporadic Chiari I—meaning they had no known family history of Chiari—and both of their parents, making this the largest trio-based Chiari genetic study to date. The samples came from several sources, including Massachusetts General Hospital/Harvard, the Yale Centers for Mendelian Genomics, and GeneDx, a large clinical genetic testing laboratory. The researchers also used 1,798 unaffected siblings as a comparison group. The study focused on *de novo* variants, genetic changes that arise in a child but are not present in either parent. The researchers found a striking excess of damaging variants in a family of genes known as CHD genes, which help control how DNA is packaged and how genes are turned on and off during development. Protein-damaging CHD variants occurred about 12 times more often than expected, while predicted loss-of-function variants occurred about 18 times more often than expected. No similar enrichment was seen in the unaffected comparison group.

The biological findings strengthened the genetic results. Several of the implicated CHD genes are active in the developing human cerebellum, particularly in Purkinje cells and inhibitory neurons, with notable activity during fetal development. This supports the idea that disruption of normal gene regulation during cerebellar development can contribute to Chiari in at least some patients.

The authors are careful not to suggest that this is the explanation for all Chiari. Instead, they describe CHD-related changes as one possible mechanism within a much broader picture that may also involve skull-base development, connective tissue, tissue biomechanics, hindbrain growth and posterior fossa crowding.
The findings may eventually have practical implications as well. The authors suggest that exome sequencing could be particularly useful in children with Chiari who also have developmental delay, learning or speech difficulties, autism-related features, low muscle tone, macrocephaly, craniofacial differences, syringomyelia, tethered cord or other congenital abnormalities.

Overall, the study supports the idea that Chiari likely does not have a single underlying cause. In some patients, rare genetic changes affecting brain development may play an important role, while in others different developmental, structural or biomechanical pathways may be involved. Identifying these different pathways could eventually lead to more meaningful subtypes of Chiari and more individualized evaluation and care.

Source: Mehta NH, Allington G, Dennis E, et al. De novo chromatin remodelling variants in sporadic Chiari 1 malformation. Brain. Published online August 25, 2026. doi:10.1093/brain/awag282

Conquer Chiari's research updates highlight and summarize interesting publications from the medical literature while providing background and context. The summaries do contain some medical terminology and assume a general understanding of Chiari. Introductory information and many more research articles can be found in the Conquer Chiari Library.

Conquer Chiari is a 501(c)(3) public charity dedicated to improving the experiences and outcomes of Chiari patients through education, awareness and research.