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Rare functional genetic variants in COL7A1, COL6A5, COL1A2 and COL5A2 frequently occur in Chiari Malformation Type 1

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Purpose

While there is ample evidence that genetics plays a role in some Chiari cases, early research indicates the situation is complex. This study looked for variants of specific genes in a Chiari population compared to published controls and also compared Chiari patients with and without a suspected connective tissue disorder.

Methods

Targeted sequencing of 21 CM1 and Ehlers-Danlos Syndrome candidate genes was performed on saliva samples from 183 unrelated, adult, Caucasian, female CM1 patients. The samples came from both the Chiari1000 project and from a separate study at Duke Medical Center. Subjects were also classified as having suspected connective tissue disorder or not based on self-reported symptoms, already identified EDS, and family history.

Results

In the targeted sequencing analysis, rare variants in six genes (COL7A1, COL5A2, COL6A5, COL1A2, VEGFB, FLT1) were significantly more frequent in CM1 cases compared to public controls. In total, 47% of CM1 cases presented with rare variants in at least one of four significant collagen genes and 10% of cases had variants in multiple significant collagen genes. Moreover, 26% of CM1 cases presented with rare variants in the COL6A5 gene. We also identified two genes (COL7A1, COL3A1) for which the number of rare variants differed significantly between CM1 cases with and without suspected connective tissue disorder.

Conclusions

In summary, nearly half of the Chiari subjects in this study had a rare variant in a collagen gene, and one-fourth had a variant in one specific collagen gene. In addition, differences were found between CMI patients with a suspected connective tissue disorder and those without. Our findings underscore the contribution of rare genetic variants in collagen genes to CM1, and suggest that CM1 in the presence and absence of connective tissue disorder symptoms is driven by different genes. However, the precise roles these genes, and variants, play in the development of CMI is not known.

Genetics Research Glossary

Sources: NCI Dictionary of Genetic Terms; Oxford Dictionary; Wikipedia

Chromosome - *A chromosome is made up of proteins and DNA organized into genes. Each cell normally contains 23 pairs of chromosomes.*

Collagen - *The main structural protein found in skin and other connective tissues.*

Connective Tissue - *Tissue that connects, supports, binds, or separates other tissues or organs.*

DNA - *The molecule inside cells that contains the genetic information responsible for the development and function of an organism.*

Gene - *The basic unit of heredity passed from parent to child. Genes are made up of sequences of DNA and are arranged, one after another, at specific locations on chromosomes.*

Genome - The complete set of genes in a cell or organism.

Targeted Sequencing - Genetic analysis technique focused on specific genes.

Variant - A variation in the most common DNA sequencing (formerly called a mutation).