Key Points

1. One of the most common questions Chiari patients have is whether the disease can be passed from parent to child
2. The number of families with more than one affected member suggest at least some level of a genetic component to Chiari
3. In addition Chiari has been linked to numerous, known genetic conditions
4. Study recruited families with two or more affected persons and examined MRIs and blood samples
5. Analysis of the MRIs showed that posterior fossa volume may be a heritable trait
6. Genetic analysis identified two chromosomes (15 & 9) which may play a role in Chiari genetics
7. Fibrillin-1 is a gene on chromosome 15 known to play a role in 3 genetic disorders which involve misshaped skulls

Definitions

genome - the complete set of genetic information of a living thing

first degree relative - an individual's parent, sibling, or child

morphology - the study of the form and structure of things; in this case refers to the structure of the skull

posterior fossa - depression on the inside of the back of the skull, near the base, where the cerebellum is normally situated

cerebellar tonsils - portion of the cerebellum located at the bottom, so named because of their shape

cerebellum - part of the brain located at the bottom of the skull, near the opening to the spinal area; important for muscle control, movement, and balance

cerebrospinal fluid (CSF) - clear

Zeroing In On A Chiari Gene

November 20, 2006 -- One of the most common, and pressing, questions Chiari patients have is whether the condition is genetic. Adults are often diagnosed in their late 20's or early 30's when they are planning and starting families, and are naturally concerned about passing it on to their children. When children are diagnosed with Chiari, parents often wonder if they will be able to have families of their own when they grow up without having to worry about passing on Chiari.

Unfortunately, we are nowhere near being able to answer those questions. While there is significant evidence that at least some Chiari cases have a genetic component, it is not known what percent are likely to be genetic, what the chances are of the child of a Chiari parent having Chiari, or what gene or genes may be involved.

For years, the Chiari community has noted anecdotally that Chiari tends to run in certain families. In fact, there have been many such case reports in the medical literature. Milhorat's landmark Chiari study noted that 12% of the more than 300 Chiari patients studied had at least one close relative with Chiari and/or syringomyelia.

In addition, over the years Chiari has been linked with numerous genetic conditions. The medical literature contains over 100 reports of Chiari occurring in a person with a known genetic disorder, such as Crouzon and Klippel-Feil. However, it is important to point out that such cases are not the norm, and represent less than one percent of all Chiari cases.

To summarize, Dr. Marcy Speer, a genetic researcher at Duke University, stated in an interview in the first edition of Chiari & Syringomyelia News that enough evidence exists that she is convinced there is some genetic component to Chiari.

Now Dr. Speer, along with a long list of researchers from around the country, have released a study which shows that a key feature of Chiari is highly heritable, and that they are even beginning to zero in on possible locations for a Chiari gene or genes. The study, published recently on-line in the American Journal of Medical Genetics Part A, recruited families with multiple members affected by Chiari and used MRIs and blood samples for the research. While more than 100 patients participated in some aspect only 23 families with 67 affected members participated in both the MRI analysis and complete genetic comparison.

Basing their work on the growing acceptance that Chiari is actually due to a small posterior fossa (the region in the back of the skull where the cerebellum is situated), the researchers used the MRIs to measure a number of specific features associated with the posterior fossa region and compared them among affected family members.

What they found is that while many individual features were not what they term heritable, the overall posterior volume in fact was (see Table 1). Along with one specific feature, the basal angle, the researchers found that statistically it is very likely that the total posterior fossa volume is a trait which can be passed from parent to child. Interestingly, and of significant note, the size of herniation was not found at all to be heritable.

Since Chiari patients have been found in several studies to have small posterior fossas, this finding would seem to imply a mechanism for how Chiari can affect several family members. Namely, that the trait of a small posterior fossa is hereditary and in some cases can lead to tonsillar herniation and Chiari symptoms. The finding that the size of herniation is not hereditary would also seem to support the idea that the primary mechanism is actually the posterior fossa size, and that the cerebellar herniation associated with Chiari is secondary to this. Finally, it is worth noting that this finding is in line with the veterinary research involving the Cavalier King Charles Spaniel which has found a strong hereditary factor involving a small posterior fossa in specific lineages.

Having established the hereditary nature of the posterior fossa volume, the researchers next looked at identifying areas of the human genome which may be involved in this. Through their work, they identified specific areas on two chromosomes (15 & 9) which based on the genes of the affected families might be a factor.

While there are over 300 genes in these regions, the authors point out that one gene in this area in particular, Fibrillin-1, is known to be involved with three genetic conditions which involve mis-shaped skulls. Although far from conclusive, it is a place to start looking with even more Chiari patients.

These results are exciting, but it is important to keep in mind that this research only looked at families with multiple people affected, so the results may not necessarily translate beyond this group to the Chiari population at large. Though much work remains to definitively identify what role genetics play in Chiari, this work, along with the work being funded by Conquer Chiari, provide a good foundation for figuring it out.

liquid in the brain and spinal cord, acts as a shock absorber

Chiari malformation I - condition where the cerebellar tonsils are displaced out of the skull area into the spinal area, causing compression of brain tissue and disruption of CSF flow

decompression surgery - general term used for any of several surgical techniques employed to create more space around a Chiari malformation and to relieve compression

Source

Boyles AL, Enterline DS, Hammock PH, Siegel DG, Slifer SH, Mehltretter L, Gilbert JR, Hu-Lince D, Stephan D, Batzdorf U, Benzel E, Ellenbogen R, Green BA, Kula R, Menezes A, Mueller D, Oro' JJ, Iskandar BJ, George TM, Milhorat TH, Speer MC. Phenotypic definition of Chiari type I malformation coupled with high-density SNP genome screen shows significant evidence for linkage to regions on chromosomes 9 and 15. Am J Med Genet A. 2006 Nov 13; [Epub ahead of print

Table 1
Heritability Of Skull Features

Feature	Heritable
Herniation	N
Foramen Magnum	N
Tentorium	N
Supraocciput	N
Tentorium Angle	N
Clivus	N
Basal Angle	Y
Posterior Fossa Volume	Y
Cranial Volume	N

Note: Y/N refers to whether the skull feature is statistically likely to be heritable, or passed from parent to child

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