

CHG Researchers Intensify Genetic Studies of Chiari Type I Malformation

Recent advancements in genetics have yielded remarkable insight into human health and disease. While few diseases are completely attributable to genetics, it is likely that the next few decades of research will uncover gene variants and genetic mechanisms involved in many more conditions. Thanks to two recent grants and the foresight of the late Dr. Marcy Speer (1959-2007), the Duke Center for Human Genetics (CHG) is poised to begin a promising research agenda aimed at finding the genes involved in Chiari type I malformation (CM1). CM1 is a serious neurological condition in which the cerebellar tonsils — the lower part of the cerebellum — press upon the spinal cord causing a wide range of symptoms including headache, dizziness, and impairment in fine motor skills (1). Often a syrinx, or fluid filled cyst, is also present in the spinal cord resulting in what is called syringomyelia. The clinical presentation of CM1 varies widely from patient to patient and for different subtypes of the disease, complicating both accurate diagnosis and effective treatment. A nuclear magnetic resonance imaging test (MRI) is one of the best diagnostic tools available; the most common treatment is decompression surgery, where part of the lower skull is removed to make more room for the cerebellum (2).

A substantial body of evidence implicates a genetic component in CM1: familial aggregation (i.e., often several members of one family are affected); the frequent co-occurrence of CM1 with other known genetic conditions; and twin studies showing a higher concordance in identical twins compared to fraternal twins (3). In the 1990's, Dr. Speer began a unique biobank of samples from CM1 families, enabling preliminary genetic studies identifying regions of association on chromosomes 9 and 15.

This important research continues at the CHG under the leadership of Drs. Allison Ashley-Koch and Simon Gregory, who aim to collect more patient samples, follow up on the initial findings, and look across the entire genome for additional candidate genes. The latter goal will be accomplished in a genome-wide association study (GWAS) that will test over 600,000 single nucleotide polymorphisms (SNPs) across all the chromosomes. Recent technological advancements have made such experiments possible, whereas a decade ago it would have taken an insurmountable amount of time and resources. A GWAS study is akin to surveying one household on every block across the United States. The hypothesis is that a "hit" (a significant statistical association between the disease and a SNP) will point researchers to the right neighborhood, where they can then go in and survey each house on the street. Called genetic "fine-mapping," this second set of experiments will hopefully zero in on one, or likely several, CM1 candidate genes.

Another key component to this research is assessing how genes are expressed in different CM1 subtypes and in response to surgical treatment. GWAS studies and subsequent fine-mapping describe variation at the level of DNA sequence, while gene expression studies profile how the genetic sequences are expressed as protein products, the molecular machinery of all our cells. (Looking at SNPs is like reading the notes of a musical score; gene expression studies are like hearing the music). Samples from pediatric CM1 patients receiving decompression surgery at Duke University Medical Center will be

profiled for genome-wide expression patterns, both before and after surgery. The goal of these experiments is to identify gene expression signatures that differ among CM1 subtypes, potentially providing a new diagnostic tool. Additionally, predicting surgical outcome based on expression profiles would help guide treatment decisions for future CM1 patients.

CM1 research at the CHG holds remarkable promise for the future of understanding, diagnosing, treating, and maybe one day even curing CM1. If you are interested in participating in the CHG Chiari research study, please contact Heidi Cope at 919-684-0655 or heidi.cope@duke.edu.

References

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- (3) Speer, M. *et al.* (2003). Chiari Type I Malformation With or Without Syringomyelia: Prevalence and Genetics. *Journal of Genetic Counseling*, 12(4), 297-311.