Genetic dissection of Chiari Type I Malformation

Christina A. Markunas,[1] Karen Soldano,[1] Kaitlyn Dunlap,[1] Edgar Asiimwe,[1] Jeffrey Stajich,[1] Heidi Cope,[1] David Enterline,[2] Gerald Grant,[3] Herbert Fuchs,[3] Simon G. Gregory,[1] and Allison E. Ashley-Koch[1]

1) Center for Human Genetics, Duke University Medical Center, Durham, NC; 2) Division of Neuroradiology, *Department of Radiology, Duke University Medical Center, Durham, NC; 3) Division of Neurosurgery, Department of Surgery, Duke University Medical Center, Durham, NC*

Chiari Type I malformation (CMI) is usually diagnosed by the extent of cerebellar tonsillar herniation. Consequently, a clinically heterogeneous population of CMI patients exists that vary with respect to their symptom presentation, response to surgery, presence of associated conditions, and age of onset. As CMI is thought to be influenced by multiple genetic and environmental factors, this clinical heterogeneity is likely due in part to an underlying genetic heterogeneity which can have substantial implications for the design and interpretation of genetic studies. We recently completed a whole genome qualitative linkage screen to identify genomic regions that segregate with disease in CMI multiplex families. Over 500,000 SNPs across the genome were genotyped in 367 individuals from 66 families with at least two individuals presenting with non-syndromic CMI. Following data quality assessment, both two-point and multipoint parametric and nonparametric linkage analyses were conducted. Our initial findings across all 66 families showed minimal evidence for linkage, with no multipoint maximum LOD scores exceeding 2 although several two-point LOD scores exceeded 3 across the various models. Based on these results, two additional approaches were applied to the linkage data in order to reduce potential genetic heterogeneity thus improving power to localize CMI susceptibility genes.

In the first approach, families were stratified into two groups based on a family history of connective tissue disorder (CTD) related symptoms or conditions (e.g., mitral valve prolapse, hypermobility, or aneurysm). Stratified linkage analyses resulted in a marked increase in evidence of linkage to multiple genomic regions. Of particular interest were two significant regions found in the CTD-negative group of families located on chromosome 8 and 12. Both regions harbor genes implicated in the development of Klippel-Feil syndrome (GDF6 and GDF3), which has been reported to co-occur with CMI in roughly 5% of patients. Sequencing efforts are currently underway to screen GDF6 in family members diagnosed with CMI.

The second approach used twenty four cranial morphology measurements derived from the posterior fossa (PF) in order to identify genetically homogeneous subsets of families. Two initial analyses were performed: 1) Heritability was estimated for each PF trait individually, and 2) In order to reduce the dimensionality of the dataset, principal components (PC) analysis was performed and heritability was estimated for the top PCs which reflect more complex representations of the PF. 13/24 individual PF traits and all 6 PCs were found to be significantly heritable ($p<0.05$). Based on these heritability estimates and association with affection status, PF traits across both analyses were prioritized for use in an ordered subset analysis (OSA). The most significant OSA result was observed on chromosome 22 where increased evidence for linkage was found in a subset of families defined by PF height. This genomic region contains a large number of potential candidate genes. One of particular interest is EP300, a histone acetyltransferase that is associated with Rubenstein-Taybi syndrome (RSTS) 2. Interestingly, RSTS1 has been previously reported to co-occur with CMI as well as other craniocervical and spinal cord disorders and is associated with a related gene, CREBBP. We therefore investigated the genomic region containing CREBBP and also found increased evidence for linkage when a similar subset of families was identified using the same trait, PF height. Future work will involve further examination of these genes and other potential biological candidates, as well as the application of additional approaches to reduce genetic heterogeneity.