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CORR Insights®: Are Copy Number Variants Associated With Adolescent Idiopathic Scoliosis?

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Where Are We Now?

Adolescent idiopathic scoliosis (AIS) is a genetically heterogeneous complex condition that affects approximately 3% of the population. Although genome-wide association studies have pointed us towards candidate loci for genetic

causes of this condition, it is evident that these loci do not constitute the majority of AIS heritability. Since copy number variation has been associated with the presence of birth defects, neuropsychiatric disabilities, congenital heart disease, and skeletal disorders such as clubfoot, Buchan et al. theorized that rare copy number variants contribute to the pathogenesis of scoliosis.

In their study, Buchan et al. identified clinically significant copy number variation with a size of 125kb or greater having at least 50 markers using the Affymetrix Genome wide SNP array 6.0 in nine of 143 (6.3%) patients with AIS. These included proximal duplications of 1q21.1 (Thrombocytopenia Absent Radius syndrome region); 2q13, 15q11.2, and 16p11.2 deletions. Trisomy X was identified in two of 114 (1.8%) females with AIS. The 1q21.1

variant appeared to have reduced penetrance. These rare and novel copy number variations were observed with a greater frequency in the AIS population compared to a control population derived from 1079 individuals of European-American ancestry, which included individuals with bipolar disorder and idiopathic clubfoot. It is noteworthy that three of the observed copy number variations are associated with bone phenotypes including 1q21.1 (radial abnormalities), 15q11.2 duplications (hemivertebrae), and Trisomy X (scoliosis).

Where Do We Need To Go?

While this work represents a reasonable initial step in identifying a possible contributory genetic mechanism that may potentially contribute to the pathogenesis of AIS, the data generated from this study also set the stage for future investigations. Although the genomic regions associated with copy number variation in AIS are of interest in this study, caution must be exercised at this early

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stage in demonstrating pathogenic causality. Prior genome-wide association studies have identified *CHD7*, *CHL1*, *LBX1*, and *GPR126* as having statistically significant association with AIS [2, 3]. More recently, rare variants in *FBN1* and *FBN2* have been identified with higher frequencies in patients with AIS, as compared to individuals without scoliosis [1]. The effects of these genes are hypothesized to be mediated via skeletal growth, axonal guidance, somatosensory mechanisms and alterations in connective tissue matrix proteins.

Ideally, future studies would require further evaluation regarding causality and other associations. The study by Buchan and colleagues, as well as other investigations [1–3], could lead to other important questions. Additional investigation needs to be done to better understand the biological basis for copy number variation contribution to AIS, genetic mechanisms through which copy number variations act (dominant versus recessive), and interactions between copy number variation loci and other genes contributing to AIS. Additional areas for future research include understanding environmental and epigenetic influences which mediate AIS

development. The sample size in the current study — while large by “orthopaedic standards” — is relatively small for this purpose, making it difficult to answer these questions. It is likely that other copy number variations in patients with AIS have not yet been identified in larger cohorts. Whether there are genes in the chromosome regions identified by this study contributing to the occurrence of AIS are subject for future investigations. Evidence for pathogenicity of putative candidate genes in model organ or in-vitro systems is needed.

How Do We Get There?

To improve our understanding of the genetic contributions to AIS, much larger consortium-based studies utilizing whole-exome and bioinformatics approaches are necessary. The newly created International Consortium for Scoliosis Genetics should be able to provide a framework for future collaborative multidisciplinary research in scoliosis. I anticipate that future funded research studies will address these questions and provide answers that can help improve the quality of life for

individuals with AIS and their families.

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