Editorial

Genetics of adolescent idiopathic scoliosis in the post-genome-wide association study era

Linlu Zhao¹, Darren M. Roffey²,³, Suzan Chen²

¹Faculty of Health Sciences, University of Ottawa, Ottawa, ON, Canada; ²University of Ottawa Spine Program, The Ottawa Hospital, Ottawa, ON, Canada; ³Clinical Epidemiology Program, Ottawa Hospital Research Institute, Ottawa, ON, Canada

Correspondence to: Suzan Chen. University of Ottawa Spine Program, The Ottawa Hospital, 1053 Carling Avenue, Ottawa, ON K1Y 4E9, Canada. Email: suchen@toh.on.ca.

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Recently, analyses of a genome-wide association study (GWAS) conducted in a Japanese population found several common susceptibility variants associated with adolescent idiopathic scoliosis (AIS) (1-3). The top variants identified from this GWAS reside in genomic regions with potentially etiologically relevant genes and have been replicated across multiple populations and ethnicities. As a result, genes involved in biological pathways that are now viewed as promising targets for downstream functional investigation include abnormal somatosensory function (LBX1) (1), delayed ossification of the developing spine (GPR126) (2), skeletal dysplasia (SOX9) (3) and scoliosis associated with syndromic disease (KCNJ2) (3). One of these variants, a single nucleotide polymorphism (SNP) in the 3′-flanking region of the LBX1 gene (rs11190878) (1), has been consistently replicated in several independent populations (4). Other GWASes have also identified novel AIS-associated variants, with some overlap among the top ranked SNPs, including rs11190878 (Albertsen et al., 2014, ASHG conference abstract) (5).

The clinical validity of the ScoliScore is also currently unclear (7,8).

Given the apparent genetic heterogeneity of AIS, other approaches to identifying susceptibility variants need to be applied. Copy-number variants (CNVs) comprise another type of genetic variation that may contribute to the missing heritability of etiologically complex diseases such as AIS. Accounting for approximately 13% of the human genome, functionally relevant CNVs can alter gene function or regulation and may consequently induce phenotypic changes (9). An exploratory whole-genome study found several CNVs enriched in AIS patients (10). Fortunately, CNVs can be readily detected using existing GWAS SNP microarray data (11).

The lack of functional variant identification may also be due to the presence of rare family-specific mutations with large effects (12). Such family-specific variants may be necessary, but not sufficient, for disease development within individuals in a family; that is, individuals within the family develop AIS when at least one family-specific variant is present in the context of more common variants associated with AIS. This genetic effect has been shown in other diseases, such as asthma (12). With the increasing affordability of next-generation sequencing, whole-exome or whole-genome sequencing strategies should be used to pinpoint these rare variants that segregate within families.

These strategies are but two of many approaches that can be utilized in the search for susceptibility variants and, importantly, precise causal variants to better understand the genetic basis of AIS. The ultimate goal is to translate these genetic findings into clinical practice.
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References