Editorial

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

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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).

Despite the successes of the AIS GWASes, no causal variants have been definitively linked to any of the top gene candidates. The GWAS design, with its focus on common SNPs, is limited in its ability to uncover genetic variants contributing to a disease phenotype, leading to the "missing heritability" problem. Furthermore, the clinical utility of GWAS-identified markers is presently limited. The 53 significantly associated SNPs from a GWAS used in a DNA-based test for the prediction of the risk of curve progression in Caucasians (ScoliScore, Transgenomic, Inc., New Haven, CT) were not replicated in other studies (5,6). 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

1. Takahashi Y, Kou I, Takahashi A, et al. A genome-wide association study identifies common variants near LBX1 associated with adolescent idiopathic scoliosis. Nat Genet 2011;43:1237-40.
2. Kou I, Takahashi Y, Johnson TA, et al. Genetic variants in GPR126 are associated with adolescent idiopathic scoliosis. Nat Genet 2013;45:676-9.
3. Miyake A, Kou I, Takahashi Y, et al. Identification of a susceptibility locus for severe adolescent idiopathic scoliosis on chromosome 17q24.3. PLoS One 2013;8:e72802.
4. Chen S, Zhao L, Roffey DM, et al. Association of rs11190870 near LBX1 with adolescent idiopathic scoliosis in East Asians: a systematic review and meta-analysis. Spine J 2014;14:2968-75.
5. Sharma S, Gao X, Londono D, et al. Genome-wide association studies of adolescent idiopathic scoliosis suggest candidate susceptibility genes. Hum Mol Genet 2011;20:1456-66.
6. Ogura Y, Takahashi Y, Kou I, et al. A replication study for association of 53 single nucleotide polymorphisms in a scoliosis prognostic test with progression of adolescent idiopathic scoliosis in Japanese. Spine (Phila Pa 1976) 2013;38:1375-9.
7. Roye BD, Wright ML, Williams BA, et al. Does ScoliScore provide more information than traditional clinical estimates of curve progression? Spine (Phila Pa 1976) 2012;37:2099-103.
8. Bohl DD, Telles CJ, Ruiz FK, et al. A Genetic Test Predicts Providence Brace Success for Adolescent Idiopathic Scoliosis When Failure is Defined as Progression to Greater Than 45 Degrees. J Spinal Disord Tech 2014. [Epub ahead of print].
9. Stankiewicz P, Lupski JR. Structural variation in the human genome and its role in disease. Annu Rev Med 2010;61:437-55.
10. Buchan JG, Alvarado DM, Haller G, et al. Are copy number variants associated with adolescent idiopathic scoliosis? Clin Orthop Relat Res 2014;472:3216-25.
11. Zhao L, Triche EW, Walsh KM, et al. Genome-wide association study identifies a maternal copy-number deletion in PSG11 enriched among preeclampsia patients. BMC Pregnancy Childbirth 2012;12:61.
12. DeWan AT, Egan KB, Hellenbrand K, et al. Whole-exome sequencing of a pedigree segregating asthma. BMC Med Genet 2012;13:95.

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