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Commentary

Epigenetics for curve progression of adolescent idiopathic scoliosis

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In *EBioMedicine*, Meng et al. reported a genome-wide methylation analysis for curve progression of adolescent idiopathic scoliosis (AIS) (Meng et al. [1]). They examined DNA methylation differences between disconcordant monozygotic (MZ) twins and found decreased methylation at cg01374129 associated with AIS curve progression. This is the first large-scale epigenetic study for AIS and its progression.

AIS is a spinal deformity affecting otherwise healthy children during adolescence. It is a very common disease with a prevalence of 2–4% worldwide; however, its etiology has been unclear. Previous epidemiological and genetic studies indicated AIS is a polygenic disease. We and others have performed genome-wide association studies (GWASs) and identified several loci associated with AIS susceptibility (occurrence) [2–5]. The association of these loci were replicated in multiple cohorts with different ethnic groups [6,7]. Genetic researchers all over the world have gathered and founded a platform for multi-ethnic GWAS meta-analysis [8]. Genomic studies for AIS susceptibility are working well.

In the clinical practice, however, the value of AIS susceptibility loci and genes is limited. Most AIS patients visit hospitals after scoliosis occurred and progressed to a certain degree and only patients with severe or progressive curve require treatment. The main clinician's interest is in AIS curve progression and its prediction. Genomic studies for the curve progression, however, is difficult. A GWAS regarding curve progression needs DNA samples of AIS patients with both progressive and non-progressive curves. Sample size is a critical factor in such GWAS. It is challenging to differentiate progressive and non- progressive AIS and to collect DNA samples from non-progressive AIS. Many studies have suffered from insufficient sample size. Only one study identified a locus associated with AIS curve progression with convincing evidence [9].

Epigenetic analysis may complement genetic analysis. In fact, Mao et al. chose *COMP* encoding cartilage oligomeric matrix protein as a target gene for AIS curve progression and investigated methylation status in its promoter region; high *COMP* promoter methylation was found to be correlated with AIS curve severity [10]. In *EBioMedicine*, Meng et al. recruited two pairs of MZ twins discordant for curve progression as a discovery cohort (Meng et al. [1]). They compared genomic sequence and methylation status between MZ twins and found the association of decreased methylation at site cg01374129 with AIS curve progression. cg01374129 is located at chromosome 8, approximately 1 Mb downstream of *HAS2* (hyaluronan synthase 2). *Has2* plays a critical role in vertebral and intervertebral disc development in mice [11]. The hypomethylation at cg01374129 may relate to curve progression by influencing adolescent spinal growth through altered *HAS2* expression. A further task is the molecular mechanisms: which is a target gene and how does this hypomethylation regulate gene expression?

The accurate prediction method of AIS curve progression has long been awaited; it can reduce negative long-term effects of AIS treatment, such as unnecessary bracing, serial exposures to radiation and cost of care. However, conventional prediction methods using clinical parameters such as the Cobb angle and age at initial visit, sex, and pubertal/growth status, have limited clinical values. Prediction methods using a limited number of associated SNPs have been unsuccessful. Meng et al. attempted to overcome this problem by establishing a prognostic model using the methylation status. It showed a high AUC value of 0.805 in the ROC analysis (Meng et al. [1]). Considering its accuracy, however, it is still insufficient for clinical application.

Although there are several limitations, including sample size, selection of cells to be examined, method of replication, this paper has provided a new insight into the AIS curve progression (Meng et al. [1]). Most AIS studies so far have focused on its genetics, especially common variants detection. In terms of genetics, detection of rare variants and copy-number variations by whole-genome sequencing is certainly a task. A gene-gene interaction analysis is still unexplored and is also required. The next decade is certain to bring an increased focus on epigenetics. This study would make researchers realize its importance and potential to account for the "missing heritability" in AIS GWASs. Further epigenetics analyses such as histone modifications and chromatin accessibility, and their combination with other omics studies such as RNA-seq would be necessary to reach to our ultimate goal of developing the accurate prognostic test for AIS.

Conflict of interest

The authors declare no conflict of interest.

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