

# Current progress in genetic research of adolescent idiopathic scoliosis

Ze Zhang Zhu, Leilei Xu, Yong Qiu

Spine Surgery, Drum Tower Hospital of Nanjing University Medical School, Nanjing 210008, China

Correspondence to: Ze Zhang Zhu, MD. Spine Surgery, Drum Tower Hospital of Nanjing University Medical School, Zhongshan Road 321, Nanjing 210008, China. Email: zhuzezhang@126.com.

**Abstract:** Previous genetic linkage analysis and candidate gene association analysis have unveiled dozens of variants associated with the development of adolescent idiopathic scoliosis (AIS), which however can seldom be replicated in different ethnics. Recently, two genome-wide association studies of AIS performed in Japan revealed that *ladybird homeobox 1 (LBX1)* gene and *G protein-coupled receptor 126 (GPR126)* gene could play a role in the etiopathogenesis of the disease. Since the association between these two genes and AIS were successfully validated in the Caucasian and the Chinese population, *LBX1* gene and *GPR126* gene were the most reliable genetic variants underling the development of AIS.

**Keywords:** Adolescent idiopathic scoliosis; genome-wide association study; *ladybird homeobox 1 (LBX1)*; *G protein-coupled receptor 126 (GPR126)*

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Adolescent idiopathic scoliosis (AIS) is a structural deformity of the spine estimated to affect millions of children with a prevalence of 2-4% (1-3). Commonly understood as a complex disease, AIS is believed to be resulted from the interaction among multiple genetic loci as well as certain environmental factors (4-6). It is possible that genetic factors may be involved in specific aspects of scoliosis including the shape of a scoliosis curve and the risk for curve progression. A number of population studies have documented that scoliosis runs within families and that there is a higher prevalence of scoliosis among relatives of patients with scoliosis than within the general population (7).

In the past decades, genetic linkage analysis and candidate gene association analysis were utilized broadly to reveal the genetic basis underling AIS (7-14). Since year 2000, several genes have been reported to be involved in the etiopathogenesis of AIS, including estrogen receptor estrogen receptor 1 (ESR1) (14), estrogen receptor 2 (ESR2) (9), matrilin 1 (MATN1) (10), melatonin receptor 1B (MTNR1B) (13), tryptophan hydroxylase 1 (TPH1) (11), DOT1L (15), TGFB1 (16) and so on. Seemingly great progress being made to clarify the aetiology of AIS, it should be noted

that validation of these genes in different populations is always challenging. Replication of the associations in other studies with larger sample sizes or different populations is of great importance to validate the results of genetic association studies. Tang *et al.* (17) reported that ESR1 was not associated with the risk of AIS in HongKong. Similarly, Takahashi *et al.* (18) also found no association between polymorphisms of ESR1 and occurrence of AIS in Japan. As for *ESR2*, *TPH1*, *MATN1*, and *MTNR1B* gene, none of them can be successfully validated (19). Recently, we analysed the genotype of TGFB1 in a large cohort of AIS patients and healthy controls from Chinese population, whereas no significant association was found (under submission).

As a powerful tool for the investigation of complex disease, genome-wide association studies (GWAS) was recently applied to the genetic research of AIS (20,21). In 2011, Ikegawa and his fellows performed the first GWAS in Japanese AIS population, and reported that *ladybird homeobox 1 (LBX1)* gene were significantly associated with the occurrence of AIS (21). Two years later, on the basis of previous GWAS data, the group of Ikegawa *et al.* reported another gene, *G protein-coupled receptor 126 (GPR126)*, could

be implicated in the development of AIS (22). Compared with previously reported genetic locus of AIS, variants of *LBX1* and *GPR126* seemed far more promising with regard to their contributions to the development of AIS. The sample size of the GWAS performed by Ikegawa was several times larger than earlier association studies. In the stage of chips experiment, they included a cohort of more than 2,000 patients and controls. And in the validation stage, over 10,000 normal controls were recruited (21). In addition to the large sample size, it is noteworthy that both genes were successfully replicated in other ethnics including southern and northern Chinese Han population and European ancestry (22-24). More importantly, high expression level of *LBX1* was detectable and specific to skeletal muscle and spinal cord of both adult and fetal (21). And *GPR126* was highly expressed in the cartilage of human and the proliferating chondrocytes of the vertebral body of the embryonic mouse (22). Moreover, the functional consequence of *GPR126* was also confirmed by the studies of Ikegawa *et al.* (22). They found that *GPR126* knockdown zebrafish had shorter body lengths and delayed ossification of the vertebrae, as well as slower escape responses, indicating possible neurological defects (22). Taken together, these findings greatly extended the genetic research of AIS, and expanded our understanding on the possible etiology.

It is widely hypothesized that AIS could be induced by abnormal skeletal growth, abnormal somatosensory function and abnormal development of neural system (4). The function of the two AIS-related genes reported by Ikegawa *et al.* appears well coincided with the classical hypothesis of the aetiology of AIS. In mouse, *LBX1* is an important determinant of dorsal spinal neurons and hindbrain somatosensory neurons (25). A recent study reported that *GPR126*-null mice have limb posture abnormalities and growth failure (26). The most significantly associated SNP rs6570507 of *GPR126* gene was also associated with trunk length in a GWAS meta-analysis of height in European populations (27). *GPR126* also functions in nervous system control, and this process may contribute to AIS susceptibility. Several studies have indicated that *GPR126* is essential for myelination, a process necessary for proper nerve conduction velocity (28). To conclude, these observations extraordinarily suggest the possibility that *LBX1* and *GPR126* gene may be involved in the susceptibility of AIS through abnormal spinal development or neural system growth.

Prior to the GWAS performed by Ikegawa *et al.*, Sharma *et al.* performed GWAS of approximately 327,000 SNPs in 419 white AIS families. They found the rs1400180 of

the *CHL1* gene was strongly associated with AIS. It was an interesting finding since *CHL1* encodes an axon guidance protein related to Robo3, the mutations of which can lead horizontal gaze palsy with progressive scoliosis (20). As a well-established AIS susceptibility gene in Caucasian population, however, *CHL1* gene failed to be replicated in Chinese Han population (29). In another GWAS consisted of 196 cases and 401 controls from southern Chinese population, Fan *et al.* (from personal communication) reported two SNPs on one particular chromosome showed marginal significant association (snp1:  $P=1.32 \times 10^{-6}$ , odds ratio =0.52; snp2:  $P=1.23 \times 10^{-5}$ , odds ratio =0.55), both lack of further validation in an enlarged sample of cases and controls. Therefore, for the genetic research of AIS, the following points should be kept in mind to have a sound and reliable result. First, there exists a significant divergence between different populations regarding the association of susceptible genes with pathogenesis of AIS. Second, independent replication study with enlarged sample size is always warranted for the determination of the susceptible gene. Third, population stratification should be well controlled when recruiting the subjects.

## Conclusions

As estimated by Ikegawa *et al.*, variants of *LBX1* and *GPR126* can explain approximately 1% of the trait variance in AIS (22). It is obvious that additional AIS risk factors wait to be discovered. A global meta-analysis of published GWAS data should be helpful for the elucidation of the veiled genetic locus related to AIS. Further functional studies are also necessary to elucidate how the variants in *LBX1* and *GPR126* alter the risk of AIS in humans.

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