

## Genes Associated with Adolescent Idiopathic Scoliosis: A Review

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### Abstract

Adolescent idiopathic scoliosis is considered a multifactorial disease. Numerous altering effects such as age, sex and environment may have significant functions in the phenotypic variation among affected individuals although it is believed to be a complex genetic disease. The expressed phenotype may be due to one or more genes. This article aims to offer several studies, which found genes significantly associated with adolescent idiopathic scoliosis, namely, *LBX1*, *GPR126*, *SOX9* and *KCNJ2*, *melatonin receptor 1B* and *IL-17RC*. Most of the researches were conducted among Asian populations. Though there were many attempts to identify the genetic etiologies of AIS, it has only limited success even there were confirmations obtained for genetic contribution. This calls for a more conclusive study on different ethnic groups. Also to verify these associations, studies that will focus on the underlying mechanisms of the identified genes should be done.

**Keywords:** Idiopathic scoliosis; Adolescent; Scoliosis; Genomic variants

### Introduction

The most common form of scoliosis is adolescent idiopathic scoliosis (AIS). Two to four percent of children between 10-16 year-old have AIS. It is described as a lateral curvature of the spine with a Cobb angle of more than 10 degrees and vertebral rotation. A child's parents usually noticed it when the child is bathing or doing a physical activity. Occasionally, it is early detected on random school screening upon discovery of a waist or rib bump [1]. Several cases of AIS reported that patients do not feel any pain physically till the curves have developed and became more apparent [2]. There are red flags that may indicate a secondary cause for spinal defect and may call for specialty consultation and magnetic resonance imaging. What is interesting about this abnormality is that only 10 percent of adolescents diagnosed with scoliosis have curves that develop and need medical intervention. A large curve magnitude, skeletal immaturity and female gender are the leading risk factors for curve progression. By measuring the curve magnitude using the Cobb method on radiographs and by assessing skeletal growth potential using Tanner staging and Risser grading, one can estimate the possibility of the curve progression [3]. The brace should be administered as a primary treatment if curve progression was verified. In the United States, there were approximately 3,600 hospital discharges for spinal surgery correcting AIS in 2009. The total costs were almost \$514 million though it placed second only to appendicitis among 10-17 year-old children [4]. Worldwide, there are reports of incidences ranging from 0.5% to 10% [5]. This article aims to offer several studies, which found genes significantly associated with adolescent idiopathic scoliosis through genome wide association studies.

### Classification Systems

There are many classification systems made for adolescent idiopathic scoliosis. The first ever classification system was Ponseti classification, which was made by Ponseti and Friedman in 1950's (Table 1) [6]. It was followed by King's classification, which was described in the early 1980's. The five curve types by King were used as the primary means of classifying thoracic AIS curves. This classification was based on principle of selective fusion. Though just recently, Lenke et al. introduced a two-dimensional treatment-based system. Noting some of the limitations of the King classification, it was said to be more reliable and reproducible according to many authors. Miyajima on the other hand, challenged Lenke's new classification system. According to her, the lumbar modifier was not able to distinguish curve types. Moreover, it does not include any clinical information that can alter treatment decisions [7].

### Genetic Factors

The cause of scoliosis is still unknown. Bracing and surgery are the only treatment options. Yet recently, several clinical and genetic studies suggest contribution of genetic factors. Many have tried to identify genes associated with the susceptibility to AIS. Through the use of genome-wide association studies or GWAS, genetic variations were found rapidly across genomes of people associated with the disease. These are as follows:

#### *MATN1*

An association study on parent-offspring trios was performed in 2006 by Montanaro et al. aimed at examining the loci responsible for susceptibility to idiopathic scoliosis not only in single families but in all the population. In the trios components (total of 81 trios in the population), each has a daughter/son which is affected by IS and both parents, the region of *MATN1* gene was amplified and the amplicons

were analyzed after which linkage analysis was performed. They found and identified three microsatellite polymorphisms in the gene consisting of 103 bp, 101 bp and 99 bp respectively. *MATNI*, is localized at lp35 and is primarily expressed in cartilage. It produces cartilage matrix protein, which is linked to cartilage proteoglycans, collagen-dependent and collagen-independent fibrils. Linkage

disequilibrium was detected between the allelic variant 103 bp of the microsatellite in *MATNI* gene. This suggested that it is located in an allelic variant, which should have been related to the cause of mutation of the disease. This study encourages researchers to sequence *MATNI* gene entirely to find out if the 103 bp of the microsatellite marker is directly involved in the progression of idiopathic scoliosis [8].

Curve Type				
	Proximal thoracic	Main thoracic	Thoracolumbar/lumbar	
1	Nonstructural	Structural (major)	Nonstructural	Main thoracic (MT)
2	Structural	Structural (major)	Nonstructural	Double thoracic (MT)
3	Nonstructural	Structural (major)	Structural (major)	Double major (DM)
4	Structural	Structural (major)	Structural (major)	Triple major (TM)
5	Nonstructural	Nonstructural	Structural (major)	Thoracolumbar/lum bar (TL/L)
6	Nonstructural	Structural	Structural (major)	Thoracolumbar/lum bar-main thoracic (TL/L-MT)

**Table 1:**The Lenke classification system of adolescent idiopathic scoliosis [6].

### *LBX1*

In 2011, Takahashi et al. conducted a GWAS and replication study with 1,050 females with adolescent idiopathic scoliosis and 1,474 control subjects. They included only female subjects because school screenings in Japan have shown that prevalence of AIS is almost 10 times greater in females than in males. They have identified a locus at chromosome 10q24.31 that is associated with adolescent idiopathic scoliosis [9]. The single nucleotide polymorphism that appeared to be significant was rs11190870 and is located near *LBX1*, which encodes ladybird homeobox1 [10]. Based on a previous report, *LBX1* is expressed in vertebrates in the dorsal part of the spinal cord and hindbrain, in muscle precursor cells, and in a subpopulation of cardiac neural crest4. Takahashi's group confirmed *LBX1* expression in spinal cord and skeletal muscle. Due to its position, expression and somatosensory function, it is the best candidate to explain the association of chromosome 10q24.31 locus [9].

This was confirmed in a replication study done in an independent southern Chinese population (300 AIS patients and 788 controls) in 2012. The odd ratios they obtained for the association between rs11190870 and AIS risk (1.85 and 1.87) were very close to the first study (1.56). This proposed that the effect size of the risk allele between the two different population, Japanese and southern Chinese population is alike. Meta-analysis of the Chinese and Japanese GWAS results implied that rs11190870 is highly significantly associated with AIS. It was the first SNP associated with AIS that has been finally replicated in another population [11].

Another group led by Gao replicated the study of Takahashi in the Chinese Han population (953: 513 patients and 440 healthy controls) at the end of 2012. They looked at the association between common variants near *LBX1* and AIS, not only SNP rs11190870 but also rs625039 and rs11598564 using a case-control study. All SNPs were found to be associated in AIS predisposition. Believing that disease modifier genes can be used for predicting the development of the disease and would be helpful in early clinical investigation and treatment, a case-only study was further conducted that involved a subgroup of AIS patients (patients who had reached the endpoints of

curve progression without ever having been braced). In terms of the association between *LBX1* and the severity of the spinal curvature, none of the three SNPs were found to be a disease modifier gene. Though they suggested that a more conclusive study, which will include a larger sample size, should be done to confirm this result. Given the number of all replication studies in Chinese Han populations that supported the association of SNP rs11190870 to AIS, more studies involving other ethnic groups should be done [12]. In the United States, only rs11598564 of the three SNP's evaluated was in the top SNPs classified in a current large-scale GWAS [13]. These three SNPs, rs11190870, rs625039 and rs11598564, are also located in the untranslated region of the RNA. Their possible roles are still not well defined though they may act as regulatory elements for *LBX1*, controlling the quality and quantity of *LBX1* mRNA [14,15].

### *GPR126*

Aside from the chromosome 10q24.31, which has offered the most convincing evidence of association with AIS, Takahashi et al. found another susceptibility locus on chromosome 6q24.1 in 2013. Through a stepwise association study including 10,641 X-chromosome SNPs and increased size of replication cohort (1,819 cases and 25, 939 controls), they found the most significantly associated SNP was located in (which encodes G protein-coupled receptor 126), rs6570507. The association was replicated in a further test in Han Chinese and European populations [16]

*GPR126* is an orphan receptor of the adhesion GPCR family [15]. The loss of Sox9, a key regulator of chondrogenesis, was found to decrease the expression of *GPR126* in intervertebral disc in mice [17]. Since there is no study yet that focused on the expression of *GPR126* in skeletal tissues of humans in relation to scoliosis, they assessed the expression of *GPR126* mRNA in various human tissues (bone, cartilage and intervertebral disc) using quantitative RT-PCR. They observed that it was highly expressed in cartilage. In addition, using in-situ hybridization, they analyzed the expression of *GPR126* in mouse spine and detected *GPR126* in proliferating chondrocytes of the vertebral body during the embryonic day. The locus on chromosome 6q24.1, *GPR126*, is a promising candidate for AIS susceptibility. This

is further supported by the studies on zebrafish where the knockdown of the gene caused delayed ossification of the developing spine. A wide-known speculation is that abnormal skeletal growth may induce scoliosis. More studies should be done to reveal how variations in GPR126 increase the risk of AIS in humans [16].

### ***SOX9 and KCNJ2***

Aside from the novel AIS susceptibility loci on chromosomes 10q24.31 and 6q24.1, another locus on chromosome 17q24.3 was identified using a two-stage association study on approximately 12,000 Japanese subjects on the same year by Miyake et al. The p-values on three models (allele model, recessive model and dominant model) were evaluated and rs12946942 on chromosome 17q24.3 showed a significant association with AIS in the recessive model. The rs12946942 genotypes were also found to have a significant association to AIS severity using 1,767 AIS cases. It was followed by replication studies on Japanese and Chinese populations, which gave the report a genome-wide significance [18].

The rs12946942 region is a gene desert. Two of the closest genes include SOX9 and KCNJ2 [19]. SOX9 gene, which was mentioned earlier in the paper, is known to encode a transcription factor involved in chondrogenesis [20]. Mutations in this gene caused campomelic dysplasia (skeletal dysplasia characterized by bowed, long bones, small scapula, tracheobronchial narrowing, sex reversal and kyphoscoliosis) [21]. Variants in the block containing rs12946942 may contribute in scoliosis pathogenesis through the regulation of scoliosis-related tissue-specific expression of SOX9 or other genes [18]. Mutations on the other candidate gene, KCNJ2, resulted to Andersen-Tawil syndrome, a cardiodyrhythmic type of period paralysis. This syndrome is characterized by ventricular arrhythmias, periodic paralysis, facial and skeletal dysmorphism which includes scoliosis [22]. It is also important to note that microdeletions on chromosome 17q24.2 – q24.3 whose deletion area includes KCNJ2 and rs12946942 exhibited skeletal abnormalities such as progressive scoliosis while the same micro-deletion syndrome, which included KCNJ2, but not rs12946942, has not been found to be associated with a scoliosis phenotype [23]. The identified susceptibility locus may contain other candidate causal genes and need to be further studied.

### ***Melatonin Receptor 1B***

Melatonin Receptor 1B gene encodes a melatonin receptor, MT2 protein, one of the membrane associated GPCR belonging to the rhodopsin superfamily [24]. MT2 receptor together with MT1 receptor has been suggested to have a bone remodeling function [25]. A study was done in 2011 on 11 Chinese girls with severe AIS and eight control subjects using intraoperative bone biopsies. An impaired response in proliferation toward melatonin was observed on AIS osteoblasts without MT2 receptor while those with MT2 receptor showed lack of response in proliferation toward melatonin. This is the first study that showed a possible abnormality in MT2 receptor protein in AIS patients. Also, it indicated that AIS patients include a heterogeneous population with different causes of AIS and an evidence for the role of melatonin in the cause and development of the disease [26].

### ***IL-17RC***

A study published in 2012 identified a SNP in the *IL-17RC* gene associated to the susceptibility to and curve severity of AIS. Using polymerase chain reaction restriction fragment length polymorphism

(PCR-RFLP) analysis among 529 AIS Chinese girl patients and 512 healthy age-matched controls, the SNP rs708567 was detected [27] is known to have a central role in regulating inflammation. This implies that IL-17R signaling axis may promote the production of several inflammatory cytokines and increase the activity of metalloproteinases, which has disc degeneration functions [27]. Although the specific influence of SNP rs708567 is still unknown, the study presents an insight to a new susceptibility gene that is associated with AIS.

### **Future Development**

One of the most effective methods for identifying and characterizing genomic variants that cause the predisposition to a multifactorial disease like AIS is the genetic association study. There are many factors that may affect the quality of genetic association. This may include the sample size, stratification of the population, ethnic differences and false-positive associations [28,29]. In this article, most of the studies conducted were among Asian populations. Given the number of genetic variants identified, a genome-wide association studies worldwide is suggested to gather data and comprehensively analyze the genes that are linked to the disease. The next step would be to identify the underlying mechanisms that will lead to the observable clinical features of scoliosis and will be helpful in treating the disease earlier before the curve progression.

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