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Review Article

Etiopathogenesis of adolescent idiopathic scoliosis (AIS): Role of genetic and environmental factors

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Abstract

Adolescent idiopathic scoliosis (AIS) has been known to be related closely to genetic factors. Higher prevalence of AIS among individuals with family history of scoliosis suggesting critical roles of genetic in the pathogenesis of AIS. However, evidence also suggested that environmental factors such as latitude and sun exposure also play a critical role in the pathogenesis of the disease. While genetic factors played an important role in the occurrence of AIS, environmental factors are more likely to affect the progression of the disease. Although the pathogenesis of AIS remains elusive, current knowledge suggests that genetic factors and its interaction with environmental factors are crucial in the development of the disease, explaining differences in clinical characteristics of AIS across the globe. The aim of this review is to summarize the current knowledge of genetic and environmental factors contributing to AIS and their interactions.

Keywords: Adolescent idiopathic scoliosis, pathogenesis, etiology, genetic factor, environmental factor

Introduction

Scoliosis is a term that comes from the Greek "skolios" which means crooked or tilted. In general, scoliosis is divided into two types, idiopathic and non-idiopathic. The diagnosis of idiopathic scoliosis is established if non-idiopathic causes—such as congenital scoliosis, neuromuscular scoliosis, and vertebral malformations—have been ruled out. Adolescent idiopathic scoliosis (AIS), also known as late-onset scoliosis, is a spinal deformity characterized by a lateral curvature of 10° based on a posterior-anterior radiological evaluation in a standing position at the age of 10 to 18 years [1,2]. Approximately 90% of scoliosis is AIS, making it the most common form of scoliosis [3].

The prevalence of AIS ranges from 0.47% to 5.2% globally [3,4]. The prevalence ranges from 0.4 to 2.5% in Asia, 0.4 to 3.9% in North America, 0.7 to 7.5% in Spain, and 1.9% in Middle Eastern countries and Australia [5,6]. The largest cohort study in Hong Kong evaluated the prevalence of scoliosis in children aged from 10 until reaching bone maturity reported that spinal curvature of more than 10° was 2.5% of the total 157,444 students evaluated [6]. Similarly, a smaller study on 784 students aged 9 to 16 years old in Surabaya, Indonesia, reported the prevalence of AIS was 2.93%, in which 2.42% of them were girls and 0.51% were 4 boys [7]. The high prevalence of AIS in the female population has initiated various investigations into the possibility of X-linked inheritance [8,9]. A study in China reported that the risk of developing AIS

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in siblings was 17.7% and an estimated 87.5% was inherited [10]. Recent genetic-epidemiological analyzes have confirmed that scoliosis is a polygenic disease caused by the interaction of some gene loci and the environment [11,12]. Various genes involved in the initiation and evolution of AIS have been identified as causative genes, such as paired box 1 (*PAX1*), ladybird homeobox 1 (*LBX1*), and SRY-box transcription factor 9 (*SOX9*) [13]. The *LBX1* gene, located on chromosome 10q24.31, is the most investigated in various countries. A meta-analysis of seven cohort studies concluded that the *LBX1* gene (rs11190870) was the major locus for suspected AIS in white Asian and non-Hispanic populations especially in female (p=2.94 × 10^{-48}) [14]. Polymorphisms of the *LBX1* gene that are thought to be the locus of AIS in Asian populations have been reported in two previous systematic reviews and meta-analyses [15,16].

Differences in the prevalence of AIS in various regions are thought to be related to geographical location and ethnic differences which are identical to lifestyle differences. Differences in environmental factors such as temperature, humidity, and sunlight influence human biology, including age of menarche [17]. As age of menarche is one of the pathogeneses of AIS, therefore environmental factors indirectly involve in the pathogenesis of AIS. Ethnicity is a potentially important factor to explain genetic variation in AIS cases [18]. Up to this day, knowledge related to the interaction of genetic factors and environmental factors in AIS is still limited [19]. Thus, this review aims to summarize the current understanding of genetic factors contributing to AIS and its interaction with environmental factors.

Definition of idiopathic scoliosis

Idiopathic scoliosis is a three-dimensional deformity of the spine characterized by ≥10° lateral vertebral curvature with rotation of the vertebral column from the sagittal coronal and axial directions for which the exact cause is unknown. Idiopathic scoliosis occurs at the age of 10–18 is referred to AIS [20,21]. Along with the discovery of X-ray technology in the 20th century, the study of scoliosis has vastly grown to this day. The most important word in defining scoliosis is "curve", the term describing a segment of the spine that is normally straight but becomes laterally bent either to the right or to the left in the frontal projection (**Figure 1**).

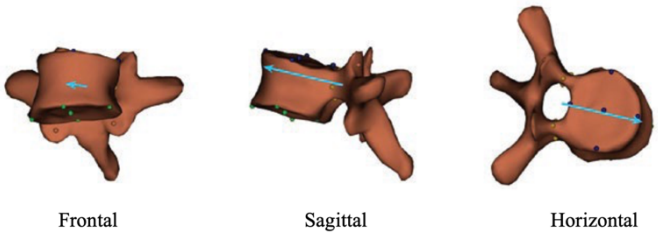

Figure 1. Vector vertebral 3D views of each vertebra of the scoliotic spine. Adopted from Dubousset *et al.* [22].

According to the onset, scoliosis can occur in two periods of time. First, it might occur and develop during the growing period, with progressive torsion, rotation, and tilting of all spinal components. This arises as a result of the growth phase of progressive structural changes and deformation of the vertebral tissue, leading to a type of idiopathic scoliosis in which the deformity of the bones is predominant. The second one is the discogenic cascade that occurs much later in adulthood or as aging progresses. In this second type, a progressive accumulation of vertebrae due to primary disc degeneration is dominant while the bone deformity is secondary [2].

Epidemiology

The prevalence of AIS ranges from 0.47% to 5.2% among the world's population [3,4], with the male to female ratio is about 1:1.5 to 1:3 [8]. Prevalence with higher Cobb angles curves is substantially lower in boys than girls, with the female-to-male ratio increasing up to 7.2:1 on the >40° curve [23]. In general, children aged 10–16 years may have some degree of spinal curvature, although most of it does not require surgical intervention [24]. The prevalence of AIS based on the type of curve varies by gender, in which the prevalence of thoracic curve is 44.06% in men

and 49.10% in women; the prevalence thoracolumbar/lumbar curve is 49.55% in men and 36.09% in women; the rates of double curve is 4.26% in males and 11.10% in females; and the prevalence of double thoracic curves is 2.14% in males and 3.71% in females [25]. A study screening on school children aged 10–15 years in Turkey in 2020 found 369 cases of AIS with a prevalence of 2.3%, with cases with single curvature was 69.3%, double curvature was 29.3%, and triple curvature was 1.4 % [26]. Meanwhile, a study in Sweden found that the prevalence of AIS in women was 3.2% and in men was 0.5% [8].

A 5-year epidemiological study from 2003 to 2007 screening school children aged 11–14 years old in Tokyo found 2,048 cases of Cobb angle 10° with a prevalence of 1.60% and 765 cases of Cobb angle 20° with a prevalence of 0.60%. Meanwhile, in 2011 there were only 177 cases of Cobb angle 10° with a prevalence of 0.14% and 32 cases of Cobb angle 20° with a prevalence of 0.03% [27]. A screening program in China conducted from 2012 to 2013 among elementary, junior, and senior high school students aged 6 to 17 years old found a 2.52% prevalence or 172 scoliosis children with radiographic evidence. Regarding the curve types, 68 students (39.5%) had a thoracic curve, 53 (30.8%) had a thoracolumbar curve, 34 (19.8%) had a lumbar curvature, and 17 (9.9%) had a double curve [28].

In Indonesia, a screening carried out in Surabaya in 2010 found AIS in 23 students or 2.93% (four boys and 19 girls) with Cobb angle of 10°, 15 students (1.91%) had a Cobb angle of 10–19°, 5 students (0.64%) had a Cobb angle of 20–40° and 3 students (0.38%) had a Cobb angle of >40° [7]. A study conducted from 2013 to 2019 at an orthopedic polyclinic in Padang, Indonesia, found 31 AIS patients aged 10–20 years old with an average age of 15.13 years, the female to male ratio was 14.5:1, the average age of menarche was 13.11 years, the direction of deviation of the major curve of scoliosis was dominated by the right direction (83.9%) and the most common curve type was the main thoracic (70.9%) [29].

Etiopathogenesis

Despite growing research on idiopathic scoliosis within the last few years, the etiopathogenesis of AIS remains unclear. This contrasts with neuromuscular and congenital scoliosis, which have a better understood underlying mechanism. Various hypotheses and concepts of AIS etiology involving genetics, central nervous system, biomechanics, metabolic pathways, spinal cord growth, and bone metabolism among others [20].

Gender

Although AIS is a disease that has unknown biological cause, epidemiological studies have consistently identified high heritability and marked sexual dimorphism in AIS, with females having a more than the five-fold greater risk of progressive deformity than males [30]. The risk factor most discussed by researchers is the female gender because AIS patients are dominated by female. Regarding the curvature, the ratio of AIS with 10° curvature was the same between female and male. However, studies showed that as the Cobb angle increases, the female to male ratio increases up to 7.2:1 for Cobb angle 40° [20].

Genetics

Many studies have shown the role of genetics in AIS. A study showed a higher concordance rate in 73% of monozygotic twins compared to 36% of dizygotic twins in AIS heritability [4]. In addition to genetic factors, it is suggested that environmental factors also play a role, as shown between family members diagnosed with AIS and even among monozygotic twins. The phenotypic differences in monozygotic twins could be the result of epigenetic differences that accumulate over time [19].

In addition to genetics, epigenetics has also been suggested to be associated with AIS. Epigenetics—defined as the change in DNA or the paired proteins that does not include changes in the DNA sequence variation—has been suggested to play role gene expression and cell division [4]. A study found 145 genes that might be associated with epigenetic regulation, differently expressed in the osteoblasts of AIS patients [31]. Moreover, a positive methylation on the cartilage oligomeric matrix protein (COMP) promoter resulted in decreased COMP gene expression that

influenced formation of the bone, and was associated with young chronological age and high Cobb angle [32].

Age of menarche

AIS is closely related with puberty, as growth spurt occur during this period and its progression tends to decelerate after reaching skeletal maturity [18]. Previous study suggested that growth spurt usually occurs around the age of 11–13 in females and 13–15 in males [33]. Menarche is an important milestone to determine sexual maturation in adolescent females. Information about age of menarche would help estimating height growth potential and scoliosis prognosis [18,32]. The late age of menarche was reported to be parallel with higher prevalence of AIS. This might be associated with hormonal disturbance involving estrogen, melatonin, and leptin, which all contributes to abnormal pubertal growth that is responsible for curve onset and progression of AIS [32]. Moreover, the age of menarche has been suggested as a meaningful predictor of curve stability. As growth velocity of the spine reach its peak at the onset of menarche, age of menarche suggested no more progression of the spinal curve [17].

The age of menarche and its association with AIS are to some extent influenced by geographical conditions such as latitudes. A study suggested that menarche occurs later in female teenagers living in northern latitudes, while in contrary, the prevalence of AIS decreases as the geographic latitude approaches the equator [18]. Different latitude results in different sunlight exposure, influencing melatonin secretion which is linked to the prevalence of AIS [18,34]. Melatonin, a hormone derived from the amino acid tryptophan, is secreted by the pineal gland and stimulated by darkness. Thus, darkness leads to over production of melatonin while light reduces melatonin production [35]. At the onset of puberty, the hypothalamus resumes a marked pulsatile secretion of gonadotropin releasing hormone (GnRH), resulting in an increased secretion of pituitary gonadotropins (luteinizing hormone (LH) and follicle stimulating hormone (FSH)), particularly during night, which stimulates the gonadal functions. Melatonin indirectly acts on the gonad which reducing the secretion of gonadotropins, particularly LH, and resulting in late onset of sexual maturation which indirectly increase the risk of AIS [36]. However, the role of melatonin in the pathogenesis of AIS has been challenged by some studies showing no increase of scoliosis incidence in children who had lack of serum melatonin after pinealectomy or pineal irradiation [37,38]. Despite the inconclusive role of melatonin in the incidence of AIS, the importance of age of menarche in the pathogenesis of AIS is well established.

Biomechanics

The biomechanical systems of AIS have been depicted as essential or optional to the spinal ebb and flow itself and may impact the beginning and advancement of the spinal arch. The erect human spine communicates different organic and biomechanical processes [20]. In AIS, there is a difference between the growth of the anterior vertebral body and the growth of the posterior elements. The vertebral bodies grow more rapidly than the posterior portions, which results in lordosis. The reduced growth of the hindquarters prevents the centrally located vertebral bodies from growing in height thereby forcing aberrant growths, e.g., twisting, to create space, resulting in rotational lordosis. A recent study has confirmed the theory that lordosis is almost always present in AIS [39]. Through biopsies from AIS patients, the convex side muscles had an increased number of type I fibers than type II, whereas a decreased portion was found on the concave side [40].

Biochemistry

Most cases of AIS occur during adolescence when the pubertal growth spurt occurs [18]. The occurrence of scoliosis in women is almost twice that of men, and this ratio reaches 10:1 for a Cobb angle of 30°. Considering the high prevalence of this disorder in women and the development of scoliosis along with sexual maturation, suggesting an involvement of estrogen and its receptors in the pathophysiology of AIS [41]. Low levels of circulating estrogen also led to decreased osteoblast differentiation, which impacts the stiffness, elasticity, and strength properties of bones, including mineralization [42]. Decreased serum leptin levels in AIS patients has also been suggested to be associated with decreased bone mass [41].

Ethnicity

Several studies have shown an ethnic relationship to the etiology of AIS. A cohort study covering different ethnic groups in five different countries found slight differences between ethnic groups, suggesting that there is no significant heterogeneity in AIS [43]. A study in Singapore in 1985, assessing ethnic relationships with two age groups of AIS patients, found a prevalence of 1.9% among children aged 11–12 years and 3.5% among children aged 16–17 years in Chinese ethnicity, 1.5% among children aged 11–12 years and 1.7% among children aged 16–17 years in Malay ethnicity, and 0.8% among children aged 11–12 years and 1.7% among children aged 16–17 years in Indian ethnicity [44]. Another study also described a higher prevalence of scoliosis in the African (9.7%) than the Caucasian population (8.1%) [23]. Although there were many epidemiological studies on ethnicity and AIS, none has yet explained which ethnicity has the most susceptibility.

The role of genetic factors on the incidence of AIS

Various theories have been developed to explain the pathogenesis of AIS, from the initiation stage to its progression [2]. It has long been known that genetic factors play a role in the pathogenesis of AIS. A twin study provided evidence that genetics is the etiology of AIS. The severity of illness in families might change and sometimes mismatch or pass through generations. It was also possible that more than one gene is involved in the disease [9].

Recent genome-case-control association studies have identified more than 300 single nucleotide polymorphisms (SNPs) that were statistically associated with the development of the AIS curve. AIS is an autosomal complex, polygenic disorder with dominant, recessive, and codominant inheritance patterns [45]. Gene linkage studies, candidate gene approaches, and genome association studies are powerful tools for analyzing the genetic basis of AIS as a polygenic disease [13]. Wise and Ikegawa [30] described genes associated with AIS, on chromosomes 6p, 10q and 18q, after studying a large family of seven affected members. In the following years, other family studies showed that AIS was associated with chromosomes 6, 9, 16 and 17 [46], 17p11 [47], 19p13.37 [48], 8q12 [49], 9q31-q34.2 and 17q25.3-qtel [50], 12p23 [51] and 18q12 [52]. A study in China investigated the association of estrogen receptor gene polymorphisms and they concluded that AIS was associated with the X gene [53].

There are sixteen genes that are mostly reported to be associated with AIS, such as forkhead box A2 *(FOXA2)*, ephrin type-A receptor 4 *(EPHA4)* and SRY-box transcription factor 9 *(SOX9)* [13] (**Table 1**). Recent genomic studies have now identified a genetic role related to the incidence of AIS through research on gene sequencing, particularly targeted bone metabolism, body growth, and development pathways such as ladybird homeobox (*LBX1*), close homolog of L1 (*CHL1*), cuticular protein RR-2 family 126 (*CPR126*), basonuclin 2 (*BNC2*), calmodulin 1 (*CALM1*), matrilin 1 (*MATN1*), and transforming growth factor-beta 1 (*TGFB1*) [54,55].

Table 1. The genes that mostly reported to be associated with adolescent idiopathic scoliosis

Gene	SNP allele	OR (95% CI)	*p*-value
FOXA2, PAX1	rs6137473-G	1.30 (1.19–1.41)	3.00×10^{-8}
PAX1	rs169311-A	1.51(1.28–1.78)	1.25×10^{-6}
PAX1	rs6047663-G	1.22 (1.12–1.34)	2.00×10^{-15}
TNIK	rs9810566-A	1.19 (1.08–1.32)	1.00×10^{-11}
MAGI1	rs7633294-G	1.20 (1.09–1.32)	2.00×10^{-12}
MEIS1	rs7593846-G	1.21 (1.10–1.32)	1.00×10^{-13}
BNC2	rs3904778-G	1.21 (1.14–1.28)	5.00×10^{-8}
BNC2	rs10756785	1.21 (1.14–1.28)	7.00×10^{-10}
LBX1	rs11190870-T	1.61 (1.50–1.73)	5.00×10^{-39}
LBX1 AS1	rs678741-G	1.44(1.37–1.52)	1.00×10^{-36}
BCL2	rs4940576-T	1.35 (1.22–1.48)	2.00×10^{-9}
AJAP1	rs241215-G	1.33 (1.19–1.47)	5.00×10^{-7}
PAX3/EPHA4	rs13398147-T	1.38 (1.23–1.54)	3.00×10^{-8}
GPR126	rs6570507-A	1.23 (1.16–1.3)	7.00×10^{-13}
SOX9, KCNJ2	rs12946942-T	2.21 (1.76–2.77)	6.00×10^{-12}
CDH13	rs4513093-A	1.23 (1.18–0.01)	2.00×10^{-15}

Adopted from Pérez-Machado *et al.* [13]

Another gene, *LBX1*, is also a highly significant gene that could explain its important role in the etiology of AIS leading to spinal curvature and progression to AIS [55,56]. This gene encodes the *LBX1* and is expressed in the central nervous system and skeletal muscle [14]. Many hypotheses explaining the etiology of AIS suggested that central nervous system abnormalities were associated with the incidence of AIS. Central nervous system abnormalities result in impaired somatosensory function and motor adaptation, resulting in asymmetric neuromuscular conditions [57]. This is reinforced by functional studies of patients with AIS that showed abnormalities in postural balance and somatosensory function [58,59].

A meta-analysis of seven cohort studies concluded that the *LBX1* gene rs11190870 was the major locus for suspected AIS in white Asian and non-Hispanic populations, especially in the female [14]. Another study found that rs11190870 which is significantly associated with AIS has been identified through a large-scale genome association study in Japan [15,60]. rs11190870 is present in the 3'-flank region of the *LBX1* gene, encoding *LBX1* on chromosome 10q24.31 [15,60]. *LBX1* is the etiology of scoliosis through abnormal somatosensory function. By damaging sensory areas rather than spinal cord motor areas, suggesting that decreased sensory input may play a role in the development of AIS. Some individuals with AIS have an abnormal somatosensory function. Various neuromuscular disorders are seen in patients with scoliosis such as spastic and diplegia. Thus, *LBX1* is the best candidate to explain the association of the 10q24.31 locus because of its position, expression, and function [60].

Interaction between genetic and environmental factors in AIS

The development of AIS can be divided into two phases: the initiation (onset) phase when the spine curvature starts to form and the progression phase that determines the direction, severity, and outcome of the curvature [10]. Previous studies showed that genetic factors were dominant in the initiation of spinal curvature, but they were poor predictors for curve progression [61]. This hypothesis was supported by the lack association between family history of AIS and curve severity [62]. Moreover, a study on SNP to predict curve progression among AIS patients showed that the test was only good at the identification of patients without curve progression, suggesting its poor potential to predict progression of the curvature in AIS patients [63]. The important role of genetics in the pathogenesis of AIS has been showed in several studies reported higher AIS incidence in people with familial history of AIS, suggesting genetical influence [10,54].

On the other hand, the progression phase is potentially under the environmental influence and genetic effects together with potential epigenetic influence. Many factors are involved in the second phase (progression of the curve), including demographic characteristics (age of onset, sex), growth velocity, bone mineral density [64], mobility and morphology of the spine [65,66], as well as the anthropometric, environmental, and lifestyle factors [67,68]. Environmental factors such as temperature, humidity, and latitude influence the biological process in humans, particularly during puberty. As puberty is closely related with progression of AIS, these environmental factors indirectly affect the progression of the disease [17]. Furthermore, environmental factors such as sun exposure may also affect hormonal changes, especially melatonin, which has been closely linked to AIS [18, 36].

Monozygotic twins have been observed to demonstrate the role of environmental factors in determining complex diseases and phenotypes, including AIS. The concordance rate of AIS in monozygotic twins were reported to be high, up to 0.73–0.92, suggesting the role of genetic in the etiology of AIS [69]. However, a study from the Swedish Twin Registry showed an environmental effect of 0.94 [54], suggesting the role of environmental factors in the etiology of AIS. Another study on monozygotic twin also suggested that curve severity may be affected more by the environment than genetic factors [70]. Last, another monozygotic twin pair concordant for AIS showed that the twins had different apical levels, curve magnitudes, and onset of AIS, which highlight the role of non-genetic (environmental) factors in etiopathogenesis [71].

Conclusion

Despite growing research on spine, the etiology of AIS remains elusive. Most studies suggest genetic factors as the main cause of AIS, yet some others argued that environmental factors also play a significant role in the development of AIS. Current knowledge suggests that genetic factors are crucial in the initiation of AIS, while environmental factors influence the progressivity of the curve. A large observational study comparing these factors across different locations and ethnicities warrants a better understanding of the cause of AIS. Moreover, as the cause of AIS might be different across ethnicity and community, specific screening and prevention programs will be more appropriate instead of a one-for-all screening scheme.

Ethics approval

Not required.

Competing interests

The authors declare that there is no conflict of interest.

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Underlying data

All data underlying the results are available as part of the article and no additional source data are required.

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