

**Original article:**

**INHERITANCE INVOLVED IN THE PATHOGENESIS OF  
IDIOPATHIC SCOLIOSIS**

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**Abstract**

Idiopathic scoliosis is a common cause of spinal deformity in children and adolescents. Although the incidence of the scoliosis is up to 2 %-3 % of the world's population, the pathogenesis is still obscure. Recent evidences show that the disease has a hereditary basis. Clinical manifestations as well as family studies reveal the familial tendency of idiopathic scoliosis, and support that the heredity is an important cause of this disease. Many related genes, such as SNTGI and CHD7, are believed to play a role in the development of idiopathic scoliosis but the underlying mechanism is still not clear. This review focus on the mode of inheritance of idiopathic scoliosis and some related molecules.

**Keywords:** idiopathic scoliosis; genetics

**INTRODUCTION**

Idiopathic scoliosis is a three-dimensional deformity of the spine with lateral curvature combined with vertebral rotation. Frequently the lordosis is increased and the kyphosis is decreased which often affect body equilibrium. The development of scoliosis may be due to different growth rate in the anterior and posterior part of the vertebral column. Subclassification of idiopathic scoliosis is based on the age of presentation into infantile (birth to age 3 years), juvenile (age 3 to 11 years) and adolescent (11 years and older). The incidence of idiopathic scoliosis in the general population ranges from 0.2 % to 3 %, depending on the magnitude of the curve. With a prevalence

of 2 %-3 % in school-aged children, idiopathic scoliosis is the most common form of spinal deformity in humans and poses a significant health burden in the pediatric population (Miller, 2007).

Since the deformity is firstly described by Hippocrates, the diagnosis, cause and treatment of idiopathic scoliosis have been the focus of a great deal of research. Idiopathic forms of scoliosis have been described for centuries, but the etiology has remained a clinical conundrum. There are a number of different proposed etiologies for idiopathic scoliosis, including differences in growth patterns, connective tissue abnormalities, asymmetries in the central nervous system, distribution of melatonin and calmodulin, hormonal variation, ectomor-

phy/spinal slenderness, diet and posture. The hereditary musculoskeletal disorders, such as osteogenesis imperfecta, Marfan syndrome, Stickler syndrome, Ehlers-Danlos syndrome and the muscular dystrophies, can each include scoliosis as a manifestation. Neuromuscular diseases, such as cerebral palsy and myelomeningocele, are associated with the development of scoliosis secondary to muscle imbalance. Paralytic disorders resulting from polio or spinal trauma may lead to a progressive scoliosis. Radiation therapy, tumors and syrinx formation have also been implicated as etiologies of scoliosis (Richards and Vitale, 2008). To date, the genetics underlying idiopathic curvature have not been identified. This is most likely a consequence of several factors, including inconsistent pedigree construction between human studies, an arbitrary consensus threshold for proband curve magnitude that may obscure true heritability, and the lack of a genetic model.

Inheritance of idiopathic scoliosis is generally complex, although some families with apparent Mendelian transmission have been described. One important outcome of understanding the genetics underlying idiopathic curvature would be earlier detection. The genetic complexity of the disease is believed to be due partly to their being controlled by polygenic systems, in which the products of more than one gene interact to produce a phenotype (Armstrong et al., 1982; Miller, 2000). The strong genetic influence in the etiology of the disorder is proven by the twin studies; it shows 73 % concordance in monozygotic and 36 % in dizygotic twins (Weiss, 2007).

### ***Mode of inheritance***

Clinical manifestations as well as family studies reveal the familial tendency of idiopathic scoliosis, and support that the

heredity is an important cause of this disease. Several patients may be usually found from one idiopathic scoliosis family. Harrington (1977) points out that the heritability of this disease is about 27 % from mother to daughters, but the heritability from father to sons is not so obvious. After studying 21 twins with idiopathic scoliosis, Inoue et al. (1998) found that the concordance rate of monozygote twins is 92.3 % (12/13), while dizygous twins maintain the rate of only 62.5 % (5/8). However, the mode of inheritance of idiopathic scoliosis remains dispute.

### ***Autosomal dominant inheritance***

Wynne-Davies (1968) investigated 2000 cases of patients with idiopathic scoliosis, and demonstrated the incidence of the disease decreasing from first-to-second-degree relations, which supported the monogenic inheritance pattern. The concept of monogenic inheritance is that gene was a single hereditary unit, which determines individual's phenotype and character, and delivers from parents to children strictly. Kesling and Reinker (1997) reviewed twins with idiopathic scoliosis, and drew a conclusion that the concordance rate of monozygote twins is approximately 73 % and dizygous twins is 36 %. Because both of the rates are higher than those in general population, he believed the mode of inheritance in some families is autosomal dominant inheritance. Ogilvie et al. (2006) presumed virulence genes were different in different families, but they had a key-gene at least. Since single gene disease is abided by the pattern of Mendelian inheritance, we should study large sample of people to investigate the mode of inheritance, and discover the virulence gene.

### ***X-linked inheritance***

Cowell et al. (1972) noted the paucity of male-to-male transmission in the literature, and reported a pattern of inheritance consistent with that of X-linked inheritance. According to this concept, the incidence and severity of idiopathic scoliosis in male should be much higher than those in female. However, the incidence and severity of idiopathic scoliosis in girls are higher actually. Miller et al. (1998) reported X-linkage as the mode of inheritance of idiopathic scoliosis by using the analytical method of gene linkage, his research showed that a locus on the X chromosome may be involved in the expression of idiopathic scoliosis at least in a portion of these families, and the predisposing genes may exist at X chromosome. Justice et al. (2003) investigated a large group of subjects (202 families, 1198 individuals) by scanning genome and analyzing the genotype, and suggested two potential modes of inheritance: autosomal hereditary and allosomal inheritance in fourteen first degree families. Then he identified a genetic loci in the X chromosome q-arm which predisposed an individual to idiopathic scoliosis by evaluating second and third degree families. The findings of Justice and coauthors were similar to that of Miller's and coauthors, who assumed that idiopathic scoliosis may be a multigenic disease and exists predisposing loci at X chromosome.

### ***Polygenic inheritance***

Although the mode of inheritance has been debated, more and more scholars begin to accept the mode of polygenic inheritance. Individual patients with idiopathic scoliosis appear to have different phenotypic patterns. The results of Riseborough and Wynne-Davies (1973) showed a polygenic pattern of inheritance. In their investigation (2869 individuals), all first-degree

relatives are examined clinically and radiographically, and 81 % of second and third degree relatives are evaluated radiographically. So their results seem to be more reliable compared with Wynne-Davies's experiment. Multiple factor inheritance reveals that the possibility suffering from the disease of each member in a high risk family is not equal. It may be caused by the interaction between the genes, also it may be due to the mutation or polymorphism of key genes, the latter is often affected by the environment. Therefore, it is possible that there are various genetic bases even though the clinical manifestations are similar (Hadley Miller, 2000). Some scholars consider that in a portion of families, there is no apparent key gene, which supports the polygenic inheritance mode; while in other families, the mode is autosomal dominant inheritance.

### ***Screening genetic loci***

Despite many studies have proved the hereditary trait of idiopathic scoliosis, the admitted genetic loci are still unclear. It is not difficult to identify the predisposing loci, but it is not easy to assess whether the loci contain the predisposing genes or not. Some reports usually seek virulence gene by using the linkage analysis. Axenovich (1998) performed linkage analysis in 101 families (788 individuals) by using complex allele segregation analysis. He found the evidence of polygenic inheritance mode, but failed to confirm the location of genetic loci. Recent work by Wise et al. (2000) provided evidences for linkage of familiar idiopathic scoliosis at chromosomes 6p, distal 10q, 4q and 18q with maximum nonparametric LOD scores of 1.42 (P=0.02), 2.55 (P=0.033), 5.08(P=0.015), and 6.33 (P=0.002), respectively. The above authors suggested a limited number of loci predisposing to familial idiopathic scoliosis. Recently, a three

generation family of Italian ancestry with 11 affected individuals had been identified, enabling a locus to be assigned at 17p11 (Salehi et al., 2002). Although Salehi et al. confirmed the linkage of idiopathic scoliosis at chromosomes 17pll, this finding was only based on one family. In a study of multiple members of seven idiopathic scoliosis families, Chan et al. (2002) localized major susceptibility loci in chromosomes 19p13.3, and the minor loci in chromosomes 2q. Miller et al. (2005) investigated 202 families (1198 individuals) and suggested the candidate gene may be located in chromosomes 6, 9, 16 and 17. There are many factors affecting idiopathic scoliosis, such as age, gender and environment, which make the phenotype of virulence gene complicated. Although we have King, Lenke and PUMC classification system, each of them can not include all clinical types of idiopathic scoliosis. We are not sure whether the same type of idiopathic scoliosis has the same hereditary basis. If we can collect the identical type of idiopathic scoliosis and screened genetic loci, we may get new findings.

#### ***Idiopathic scoliosis -related molecules***

From studying the natural history of idiopathic scoliosis, some hypotheses have been proposed, including genetics, biomechanics, dysfunction of neuroendocrine, imbalance of growth and development, and so on. There is genetic susceptibility in idiopathic scoliosis. Mouse mutations have proven to be informative in defining genes that are important in development of complex diseases. Cheng et al. (2007) have identified synteny-defined genes for idiopathic scoliosis. These candidate genes are classified as being involved in intracellular signalling, intracellular signal transduction, encoding extracellular matrix proteins, and involved in extracellular matrix metabolism.

For the past few years, the roles of some genes in the pathogenesis of idiopathic scoliosis have been widely investigated.

#### ***SNTG1***

Mutational analysis of SNTG1 exons in 152 sporadic idiopathic scoliosis patients have revealed a 6-bp deletion in exon 10 of SNTG1 in one patient and a 2-bp insertion/deletion mutation occurring in a polypyrimidine tract of intronic sequence 20 bases in two patients (Giampietro et al., 2003). These changes are not observed in a screen of 480 control chromosomes. Thus, SNTG1 gene has been suggested to affect posture control and being involved in idiopathic scoliosis.

#### ***Aggrecan gene***

Aggrecan is the major component of intervertebral disc matrix proteoglycan. The unbalanced synthesis of disc matrix proteoglycan in vertebrae growth plate is known as one of the cause of idiopathic scoliosis. The expressed disorder of aggrecan gene may be considered as etiologic factor of idiopathic scoliosis, and Qiu and He (2006) deemed the different content of aggrecan in convex side and concave side may be the secondary result after spine scoliosis, also supposed that it may play an important role in the development of idiopathic scoliosis. However, Marosy et al. (2006) found lack of association between the aggrecan gene and familial idiopathic scoliosis.

#### ***CHD7***

In 2007, Gao et al. ascertained a new cohort of 52 families and conducted a follow-up study of genome wide scans, and showed that CHD7 gene polymorphisms are associated with susceptibility to idiopathic scoliosis. The SNP loci associated with idiopathic scoliosis susceptibility are

clearly contained within a 116-kb region encompassing exons 2–4 of the CHD7 gene. Since idiopathic scoliosis mainly affects girls, Inoue et al. (2002) analyzed the correlation between polymorphism of estrogen receptor gene and severity of idiopathic scoliosis, and announced the average Cobb's angle of idiopathic scoliosis patients with genotype XX and Xx is bigger than the xx genotype, also the risk of operation is higher. Some researchers hypothesize that a relative reduction of functional CHD7 in the postnatal period, particularly during the adolescent growth spurt, may disrupt normal growth patterns and predispose an individual to spinal deformity.

### **Hox genes**

Hox genes are transcription factors that are involved in the specification of positional information along the rostrocaudal axis. They represent a subgroup of the homeobox gene family, which contains a 180 bp DNA sequence encoding a DNA-binding domain as part of a "homeoprotein". The Hox family has been studied in great detail in multiple organisms, and homeotic mutations which resemble human dysmorphic syndromes include human synpolydactyly, associated with an in-frame insertion of polyalanine stretches in HOXD13, and human hand-foot-genital syndrome, which is due to a nonsense mutation in HOXA13. Hox genes are expressed in mesodermally and ectodermally derived cells along the body axis (Duester, 2007). A specific "Hox code" defined by Kessel and Gruss determines vertebral anatomy.

### **MesP1 and MesP2**

MesP1 and MesP2 are beta-helix-loop-helix transcription factors that show segmental expression in the presomitic mesoderm. Studies performed in zebrafish have

provided evidence that these genes are involved in the development of the anterior-posterior polarity within the developing somite through interaction with the fibroblast growth factor R and Delta-Notch signaling pathways (Giampetro et al., 2003; Liu et al., 2007)].

### **Pax1**

The Pax1 gene has been shown to be active during sclerotome formation and differentiation (Gorman and Breden, 2007). Pax1 mutations have been identified in undulated mice, suggesting that sclerotome condensation is a Pax1 dependent process. Three mutant alleles of Pax1 have been described in the mouse. All three mutations reduce or eliminate Pax1 gene expression and cause deficient development of the anterior vertebral element. This may lead to scoliosis, split and fused vertebrae, and hypomorphic intervertebral discs. Pax1 appears to be important in specifying ventromedial differentiation of the sclerotome, thus accounting for the vertebral abnormalities seen in the various undulated mutant alleles. The mutant diminutive (dm) which causes decreased viability, decreased body size, macrocytic anemia, extra ribs, vertebral deformations, and short, kinked tails, maps to 82 cM, and may be an additional Pax1 allele. However mutation analysis of Pax1 in dm/dm mice fails to find any coding-region lesions.

### **Mox1**

Mox1 is involved in the subdivision of sclerotomes into a posterior and anterior half. A mouse mutant "rib-vertebrae" (rv) has recently been described by Nacke et al. (2000). Homozygous rv mice have phenotypic features characterized by vertebral and rib defects and urogenital malformations. Mox1 is abnormally expressed. Based on these observations, the rv mutation results

in elongation of the presomitic mesoderm and disruption of the anterior-posterior polarization of somites.

### **BMP-7**

Bone morphogenic protein (BMP) molecules are related to transforming growth factor- $\beta$  and represent a group of osteoinductive cytokines from the bone matrix. Mice that are homozygous for the BMP-7 null allele display various skeletal defects, including lack of fusion of the neural spines of the atlas, twelfth thoracic, and first sacral vertebrae, openings on the sides of the neural arches of the third and fourth thoracic vertebrae, and absence of a lumbar vertebrae. Mutant mice have small or non-existent ossification centers. It has been postulated that the BMP-7 protein is required for the normal ossification process to occur (Grassinger et al., 2007).

### **Wnt3a**

The Wnt3a gene has been localized to mouse chromosome 11 at 32 cM. The human orthologue, Wnt3a, has been mapped to human chromosome 1q42. This gene is a member of a moderate-sized multigene family comprised of at least 12 members in humans and the mouse. It is approximately 53.0 kb long and composed of 4 exons. Genes in this family function both in establishing the body plan in development and as potential oncogenes. The Wnt proteins are relatively insoluble, have affinity for extracellular proteoglycans, particularly heparin sulfate, and are secreted inefficiently. Wnt3a is necessary for generation of the posterior portion of the neuraxis, as knockout mice fail to develop a tailbud and are truncated from a point slightly anterior to the hindlimbs (Giampietro et al., 2003; Dao et al., 2007). A spontaneous mouse mutant, vestigial tail (vt), has a similar but less severe phenotype.

### **Ky**

The Ky gene localizes on chromosome 9 at 56 cM. It encodes a novel muscle specific protein. A GC deletion in codon 24 that leads to a premature stop codon at position 125 has been observed in ky/ky mice. The human Ky orthologue falls into a conserved synteny region on 3q21. Myosin light polypeptide kinase is localized within this region and may possibly be a candidate gene for idiopathic scoliosis (Giampietro et al., 2003; Vargas et al., 2002).

### **Lmx1a**

Lmx1a serves an important function in the specification of dorsal cell fates in the central nervous system and in developing vertebrae. The results of Northern analysis show that Lmx1a has been localized to the roof plate and immediate neighboring structures during early central nervous system development. Lmx1a maps to a conserved synteny region, 1q22-q23, and stimulates transcription of insulin (Chizhikov and Millen, 2004).

### **Fbn-2**

The shaker-with-syndactylism (sy) phenotype is associated with auditory and vestibular defects, fusion of digits and early lethality. A reduction in the caliber of the shafts of long bones and decreased bone density of the long bones of the limbs, girdles, and vertebrae has been observed. Loss of function mutations in Fbn-2 occurring outside of a "conserved neonatal region" has been observed in sy. The association of scoliosis with congenital contractural arachnodactyly supports the candidacy of Fbn-2 for idiopathic scoliosis (Giampietro et al., 2003; Nicoloff et al., 2005). In humans, mutations in Fbn-2 are associated with congenital contractural arachnodactyly.

### **Sim2**

Sim2 belongs to a family of transcription factors characterized by a basic helix-loop-helix-PAS (PER, ARNT, SIM) domain. Sim2 is localized to human chromosome 21q22.2 that shares synteny conservation with the 67.6 region of mouse chromosome 16. The 21q22.2 region is associated with many of the features of Down's syndrome. Sim2 is responsible for midline central nervous system development in the fly. Sim2 mice have idiopathic scoliosis resulting from unequal sizes of ribs and vertebrae. They die shortly after birth because of lung atelectasis and breathing failure. They also have diaphragm hypoplasia, rib protrusions and abnormal intercostal muscle attachments. The expression of Sim2 in the vertebral body, and not the somites, provides evidence for its contribution toward the later stages of vertebral development by regulating their growth (Villemure et al., 2002). It has been suggested that rib overgrowth in Sim2 mice is responsible for the development of idiopathic scoliosis.

### **BPTF**

The bromodomain motive of BPTF is a 110 aminoacid conserved structural region, which is involved in protein-protein interaction, and it can be found in proteins that regulate signal-dependent, non-basal transcription. Malfunction of BPTF in early ontogenesis, together with intense growth rate during adolescence and other environmental factors could influence the development of idiopathic scoliosis. BPTF may play some roles in vertebrate development in some stage of ontogenesis, which if malfunctions may have consequences in later life, particularly in adolescence, when intensive growth can bring to the surface the early developmental inadequacies. The identification of BPTF in the pathomechanism of idiopathic scoliosis, may lead to

better prevention and early identification of the disease (Giampietro et al., 2003; Jones et al., 2000).

### **MTNR1B**

Locating in one of the chromosomal regions linked to idiopathic scoliosis, MTNR1B gene is a potential candidate gene for idiopathic scoliosis. The study by Qiu et al. (2007a) is carried out in 2-stage case-control analysis: 1) initial screening (472 cases and 304 controls) and 2) separate replication test (342 cases and 347 controls) to confirm results in the screening. In the first screening stage, 5 tagSNPs are selected to cover most of the genetic variation in the MTNR1B gene. In the second stage, SNPs showing association in the screening stage are studied in a separate replication sample set to confirm the association. The first stage show a putative association between rs4753426 and idiopathic scoliosis, which is confirmed in the replication sample set. By meta-analysis, the frequency of C allele of this SNP locating in the promoter is significantly higher in the cases than controls. Taken together, the polymorphisms of the promoter of MTNR1B gene are associated with idiopathic scoliosis, but not with the curve severity in idiopathic scoliosis patients.

### **MATN1**

MATN1 is localised at 1p35 and is mainly expressed in cartilage. Montanaro et al. (2006) assessed a linkage disequilibrium between the matrilin-1 (MATN1) gene and the idiopathic scoliosis. The genetic study was conducted on a population of 81 trios, each consistent of a daughter/son affected by idiopathic scoliosis and both parents. In all trios components, the region of MATN1 gene containing the microsatellite marker was amplified by a polymerase chain reaction. As a result, three microsatellite poly-

morphisms, respectively consisting of 103 bp, 101 bp and 99 bp, were identified (Montanaro et al., 2006). ETDT evidence a significant preferential transmission for the 103 bp allele. Thus, the idiopathic scoliosis is associated to the MATN1 gene.

## CONCLUSION

Since idiopathic scoliosis is a common cause of spinal deformity in children and adolescents, many efforts have been made in broad studies, which has demonstrated the complex pathophysiology of this disorder, although the exact etiology of idiopathic scoliosis remains unclear. The consensus is that the disease has hereditary basis, but it is not satisfactory to screen exact genetic loci and definite related genes.

It is likely that different approaches will enable an elucidation of the genetic and environmental basis of idiopathic scoliosis. Since idiopathic scoliosis is due to localized alterations in vertebral body development as opposed to a more widespread distribution of vertebral malformations, a model needs to be developed that incorporates position identity and failure of segmentation. The association of renal, cardiac, skeletal and spinal cord malformations with idiopathic scoliosis may reflect the involvement of different genes that are associated with developmental pathways in several organs (Qiu et al., 2007b). With the identification of additional genes in animal model systems that contribute to different stages of spine development, the list of candidate genes for idiopathic scoliosis will continue to grow. As genes are identified that contribute toward the development of idiopathic scoliosis, allelic mutations in these genes may also be responsible for the development of idiopathic scoliosis. Further research will lead to the identification of the candidate genes involved in the causation

of this disorder. With the development of technology, we firmly believe the cause of idiopathic scoliosis will be eventually eradicated.

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