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Genetics and pathogenesis of scoliosis

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ABSTRACT

Background: Scoliosis is defined as a lateral spine curvature of at least 10° with vertebral rotation, as seen on a posterior-anterior radiograph, often accompanied by reduced thoracic kyphosis. Scoliosis affects all age groups: idiopathic scoliosis is the most common spinal disorder in children and adolescents, while adult degenerative scoliosis typically affects individuals over fifty. In the United States, approximately 3 million new cases of scoliosis are diagnosed annually, with a predicted increase in part due to global aging. Despite its prevalence, the etiopathogenesis of scoliosis remains unclear.

Methods: This comprehensive review analyzes the literature on the etiopathogenetic evidence for both idiopathic and adult degenerative scoliosis. PubMed and Google Scholar databases were searched for studies on the genetic factors and etiopathogenetic mechanisms of scoliosis development and progression, with the search limited to articles in English.

Results: For idiopathic scoliosis, genetic factors are categorized into three groups: genes associated with susceptibility, disease progression, and both. We identify gene groups related to different biological processes and explore multifaceted pathogenesis of idiopathic scoliosis, including evolutionary adaptations to bipedalism and developmental and homeostatic spinal aberrations. For adult degenerative scoliosis, we segregate genetic and pathogenic evidence into categories of angiogenesis and inflammation, extracellular matrix degradation, neural associations, and hormonal influences. Finally, we compare findings in idiopathic scoliosis and adult degenerative scoliosis, discuss current limitations in scoliosis research, propose a new model for scoliosis etiopathogenesis, and highlight promising areas for future studies.

Conclusions: Scoliosis is a complex, multifaceted disease with largely enigmatic origins and mechanisms of progression, keeping it under continuous scientific scrutiny.

Background

The spine is a functionally complex structure. Disorders compromising its integrity can lead to complications in multiple organ systems. Scoliosis is one such condition, where severe curvature may be associated with serious cardiovascular and pulmonary complications, chronic pain, and psychological stress [1–3]. The profound impact of scoliosis on patients' quality of life is becoming increasingly recognized [4,5]. Patients with scoliosis often suffer from body image misperceptions and demonstrate a higher incidence of mood disorders [6]. This broad impact on patients' lives underscores the need for ongoing extensive scientific scrutiny into the etiopathogenesis of scoliosis.

According to the Scoliosis Research Society, the diagnosis of scoliosis involves measuring the Cobb angle, with a threshold of 10° or higher indicating the disease, though significant axial rotation can occur even below this angle [7,8]. The prevalence of scoliosis in the general population is around 2%–3%, with approximately 20% of cases being secondary to another disease [8]. The remaining 80% are cases of idiopathic scoliosis and adult degenerative scoliosis [8]. Idiopathic scoliosis is further subcategorized based on the age of the disease manifestation: infantile (first 3 years of life), juvenile (4–10 years old), and adolescent (10–18 years old). The latter is the predominant form of scoliosis in the pediatric population [9] and is the most common pediatric musculoskeletal disorder, affecting approximately 3% of school-aged children, which amounts to over 29 million children worldwide [10]. Progression

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is more common in girls during puberty and can lead to severe deformities and impaired quality of life if untreated [11]. Such risk is highest before peak growth velocity but decreases sharply after skeletal maturity [12].

In contrast to idiopathic scoliosis, adult degenerative scoliosis develops de novo in patients usually above fifty years of age with no previously detected spine deformity [13]. It is also more prevalent in the female population and is growing in incidence in parallel with the global aging [14]. Intense back and leg pain, leading to spinal dysfunction and disability in patients with adult degenerative scoliosis, can result from uneven muscle strain, facet joint arthritis, or nerve root compression [15].

Management of idiopathic scoliosis generally depends on severity of the curve progression and the symptomatology [9]. It ranges from conservative management with analgesics, orthoses, nerve blocks and physical therapy to possible surgery [16–18].

Fortunately, modern therapeutic interventions are highly successful, significantly improving patients' quality of life [19]. Surgical corrections of scoliotic deformities can be highly effective and improve patient's body image [20]. However, they carry a risk of complications in 5%-25% of cases [21]. Additionally, such surgical interventions result in a large financial burden [22]. In general, treatment of scoliosis has been associated with substantial consumption of healthcare resources [23,24]. Such socioeconomic consequences of scoliosis further highlight the need for improved disease understanding and consequent development of disease prevention strategies.

The current scope of knowledge indicates that idiopathic scoliosis likely results from multiple factors [7,25,26]. The pathogenesis of adult degenerative scoliosis involves a self-reinforcing cycle of asymmetric degeneration of intervertebral discs and facet joints, resulting in unbalanced spinal load distribution and abnormal spinal curvature [27]. However, as with idiopathic scoliosis, the etiopathogenetic mechanisms of adult degenerative scoliosis also remain poorly understood.

Previously, our group conducted a comprehensive literature review on the biological principles driving the development of adult degenerative scoliosis [14]. Building on that study, in this review we explore the evidence on the genetic and pathogenetic factors of both idiopathic and adult degenerative scoliosis. This approach aims to clarify the mechanisms involved in scoliosis, identifying those that are either common to both types or specific to either one. For clarity, the term "idiopathic scoliosis" will refer specifically to adolescent idiopathic scoliosis.

Methods

Literature search and study selection

A comprehensive literature search was conducted to identify studies examining the biological factors, including genetic and developmental aspects, as well as environmental influences on the development and progression of scoliosis. The search focused on studies related to idiopathic scoliosis and adult degenerative scoliosis, with studies on congenital scoliosis excluded, as it is regarded as a distinct category [28] outside the scope of this review.

Databases and search strategy

The databases PubMed and Google Scholar were used for the literature search. Keywords included terms related to "genetic factors in scoliosis," "genetics of scoliosis," "pathogenesis of scoliosis," "biology of idiopathic scoliosis," "biology of adult degenerative scoliosis," "etiology of scoliosis". No time restrictions were applied to the search, allowing for the inclusion of studies published across all years. Only articles published in English were considered.

Genetics of idiopathic scoliosis

The term "idiopathy" is translated from Greek to "a disease of its own kind," referring to a condition that has an unknown cause [29]. This term is particularly relevant in the context of idiopathic scoliosis, where despite numerous pathogenetic theories proposed and extensive research conducted, no single hypothesis has gained universal acceptance, and the debate is continued [30].

The notion that idiopathic scoliosis might be a genetically predetermined disease was proposed over a century ago, and research into its hereditary aspects has been ongoing ever since [31]. Twin studies have been particularly insightful. They have shown that idiopathic scoliosis has a higher genetic correlation in monozygotic twins [73%] than in dizygotic twins [36%], with a noticeable association between disease severity and genetics in identical twins only [32]. Results from the Danish Twin Registry have underscored the strong genetic influence, showing a significantly higher concordance in identical twins [33]. These findings, along with evidence from later-arising genome-wide association studies (GWAS), highlighted the role of genetics in the development of idiopathic scoliosis.

However, not all the identified genetic correlations were found to have an impact on specific forms of curvature [32]. Differences in the progression of idiopathic scoliosis among family members further suggested that the genes modifying its progression are likely distinct from those increasing the disease susceptibility [34].

To facilitate perception, we categorize the identified genes as either idiopathic scoliosis susceptibility genes or genes that are associated with disease severity and progression (Fig. 1). The latter two are combined, considering their interdependence. Namely, severity of scoliosis at the time of diagnosis is a significant predictor of how much the curve might progress. This in part is 1 of the reasons why monitoring and managing scoliosis, especially during periods of rapid growth, is crucial to prevent significant worsening of the spinal curvature. Additionally, we group together a set of genes that have been shown to have a role in both susceptibility and scoliosis progression.

Susceptibility genes

The first GWAS of adolescent idiopathic scoliosis identified a region on chromosome 3p26.3 near the cell adhesion molecule L1 like (CHL1) gene associated with adolescent idiopathic scoliosis risk, although no causal variation was found within CHL1 [35]. The latter encodes a neural cell adhesion molecule that participates in nervous system development [36–38]. Gene LOC642891 with an unidentified function in a proximity to CHL1 was also linked to adolescent idiopathic scoliosis [35]. In the 9q31.2–34.2 interval, SNPs rs4979321 (zinc finger protein 618 [ZNF618] gene), rs891725 (alpha-1-microglobulin/bikunin precursor [AMBP] gene), rs1969944 (paralemmin 2 [PALM2] gene), and rs4836643 (intergenic) showed significant associations with idiopathic scoliosis. These findings suggest that adolescent idiopathic scoliosis risk arises from genetic heterogeneity rather than a single locus [35].

Genome-wide pathway burden analysis of exome sequence data reveals that extracellular matrix (ECM) genes significantly contribute to the polygenic inheritance of idiopathic scoliosis [39]. More broadly, independent studies have identified a group of genes that are functionally linked to the vertebral column structural integrity (COL11A2, GPR126 and PAX1).

Specifically, new coding variants in musculoskeletal collagen genes, particularly collagen type XI alpha 2 chain (COL11A2), increase idiopathic scoliosis risk by more than 2-fold [39]. The G-protein coupled receptor 126 (GPR126 [aka, ADGRG6]) gene within the chromosome 6q24.1 locus was also identified as a candidate for idiopathic scoliosis susceptibility through extensive GWAS analysis, replicated in Japanese, Chinese, and European-ancestry populations [40]. Activated by type IV collagen, GPR126 is crucial for the normal

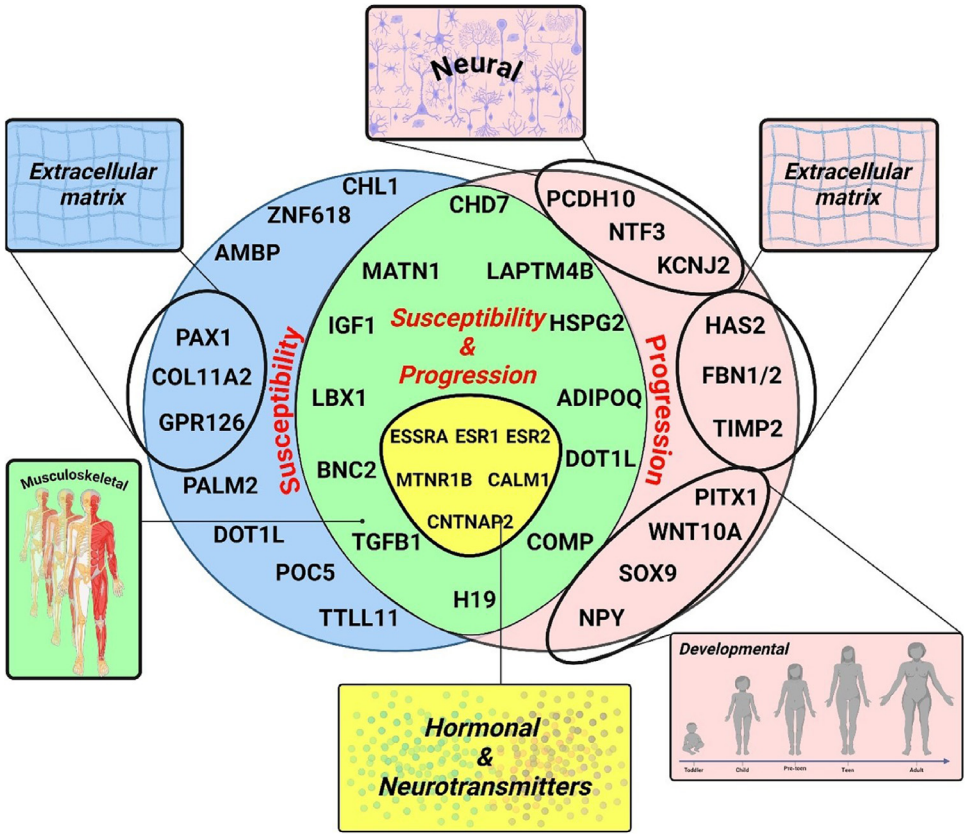

Fig. 1. Genetics of idiopathic scoliosis.

differentiation of promyelinating Schwann cells and proper myelination of axons [41]. Interestingly, variants of GPR126 have also been shown to regulate bone mass through cAMP-CREB signaling pathway [42].

In addition, using a functional fine-mapping strategy, researchers have identified a susceptibility locus for idiopathic scoliosis on chromosome 20p11.22, located downstream of the paired box 1 (PAX1) gene [43]. The PAX1 region has been previously linked to spinal development through research on naturally occurring undulated mouse strains [44]. Collectively, COL11A2, GPR126 and PAX1 may indicate a genetic signature predisposing to spine structural deformities.

Genetic linkage analyses combined with exome sequencing identified a rare missense variant (p. A446T) in the centriolar protein gene POC5 centriolar protein (POC5) that co-occurred with the disease in several families with multiple members affected with idiopathic scoliosis [45]. Using exome sequencing, researchers also identified an insertion, c.1569_1570insTT in the tubulin tyrosine ligase like 11 (TTLL11) gene as 1 of the potentially causative genes for idiopathic scoliosis [46]. Moreover, TTLL11 and POC5 are involved in similar biological processes of cytoskeleton organization and centrioles assembly respectively [47,48]. Both genes may play a role in the pathophysiology of idiopathic scoliosis.

Disease/curve progression genes

In this review of genes associated with the progression of idiopathic scoliosis, we identified 3 rather distinct patterns: genes with neural associations (NTF3, KCNJ2, PCDH10, NPY), genes involved in connective tissue and extracellular matrix homeostasis (FBN1/2, TIMP2, HAS2), and genes associated with spinal embryogenic development (SOX9, PITX1, WNT10A). This patterning may help future research aimed at uncovering the pathogenetic mechanisms underlying the development of idiopathic scoliosis.

Genes with neural associations

Variations in the neurotrophin 3 (NTF3) gene do not correlate with the incidence of idiopathic scoliosis, yet the promoter variation (rs11063714) is linked to the severity of the spinal curvature and influences the effectiveness of brace treatment [49]. This suggests that NTF3 may play a mitigating role in the progression of idiopathic scoliosis. Normally, it promotes nerve growth and survival of neurons [50].

In another study, variant rs12946942 located on chromosome 17q24.3 near potassium inwardly rectifying channel subfamily J member 2 (KCNJ2) gene, has been associated with scoliosis phenotypes [51]. The product of KCNJ2 had been suggested to have a role in establishing action potential waveform and excitability of neuronal and muscle tissues [52,53].

Average methylation of the protocadherin 10 (PCDH10) promoter was higher and gene expression was lower in idiopathic scoliosis patients compared to controls [54]. Additionally, high PCDH10 promoter methylation correlated with the Cobb angle of major curves in idiopathic scoliosis patients [54]. The product of PCDH10 has been shown to be critically involved in formation and maintenance of neural circuits and synapses, and regulations of actin assembly [55].

Genes involved in connective tissue and extracellular matrix homeostasis

Analysis of genetic linkage in eleven families with 52 scoliosis-affected members did not implicate fibrillin 1 (FBN1), elastin, or collagen type I alpha 2 chain (COL1A2) as relevant genes in these cases [56]. Conversely, a genome-wide study examining rare variant burden through exome sequencing identified FBN1 as significantly associated with idiopathic scoliosis [57]. The severity of scoliosis in idiopathic cases was linked to rare variants in FBN1 and FBN2 genes (p=.0012), a finding that was confirmed in a separate Han Chinese cohort (p=.0376) [57]. This indicates that rare genetic variants could serve as predictors for the progression of the spinal curve.

Earlier research indicated a potential link between a promoter polymorphism of the tissue inhibitor of metalloproteinases 2 (TIMP2) gene (rs8179090; −418 bp G/C) and scoliosis progression in a Chinese cohort [58], but this finding was not confirmed in a Japanese study [59]. In more recent studies, four different TIMP2 polymorphisms (rs11077401, rs2376999, rs2277700, and rs4789934) have been associated with an increased risk of developing the progressive form of idiopathic scoliosis [60]. Protein expressed by TIMP2 is a natural inhibitor of the matrix metalloproteinases [61].

In another study, decreased methylation at site cg01374129 of the hyaluronan synthase 2 (HAS2) gene (encodes for an ECM constituent) was linked to an increased curvature, suggesting it could serve as a promising biomarker for distinguishing between patients with and without curve progression [62].

Genes associated with spinal development

In a 2-stage GWAS involving around 12,000 Japanese subjects, researchers have discovered that the common variant rs12946942 is significantly linked to severe idiopathic scoliosis [51]. This variant, located on chromosome 17q24.3 near SRY-Box transcription factor 9 (SOX9), has been associated with scoliosis phenotypes [51]. The product of SOX9 expression was implicated in chondrocyte differentiation toward cartilage formation [63]. The results were also replicated in The Chinese population as well [51]. Furthermore, an international meta-analysis with four ethnically diverse cohorts (2272 severe idiopathic scoliosis cases and 13,859 controls) confirmed this association (combined p=7.23 × 10^-13; odds ratio = 1.36, 95% CI = 1.25–1.49) [64]. In silico analyses indicate SOX9 as the likely gene influencing idiopathic scoliosis curve progression in this region [64].

In another study, hypermethylation of the paired like homeodomain 1 (PITX1) gene promoter in the blood cells of idiopathic scoliosis patients was significantly linked to the Cobb angle of the main curve, indicating a connection to the disease progression [65]. Further, four probes were associated with curve severity: cg02477677 (RARA gene), cg12922161 (LOC150622 gene), cg08826461, and cg16382077 [66]. Promoter regions for WNT10A (WNT signaling) and NPY (bone and energy homeostasis) were prioritized based on methylation concordance in bone, suggesting relevance for bone formation and remodeling [66].

Susceptibility & progression genes

Genes that have been found to contribute both to idiopathic scoliosis susceptibility and progression were found to have common biological involvements (Fig. 1). As such, we identified genes pertinent to the musculoskeletal system (CHD7, IGF1, MATN1, LBX1, BNC2, TGFB1, LAPTM4B, COMP, H19, ADIPOQ, HSPG2, DOT1L) and genes related to hormones and neurotransmitters (ESRRA, ESR1, ESR2, MTNR1B, CALM1, CNTNAP2).

Genes attributable to the musculoskeletal system

The Chromodomain Helicase DNA Binding Protein 7 (CHD7) was the first gene to be associated with idiopathic scoliosis susceptibility [67]. Its role in the etiopathogenesis of CHARGE (Coloboma, Heart defects, Atresia of the nasal choanae, developmental Restriction, Genitourinary abnormalities, and Ear malformations) syndrome, characterized by an increased incidence of scoliosis, suggested a shared underlying etiology with idiopathic scoliosis [67,68]. Research conducted on Polish Caucasian females identified a significant association between the rs1017861 polymorphism in CHD7 and idiopathic scoliosis susceptibility [69]. The rs1017861 and rs4738813 polymorphisms in CHD7 were found to be significantly correlated with the severity and progression of spinal curvature as well [69]. Additionally, in the Chinese Han population, the rs121434341 polymorphism in CHD7 was significantly linked to adolescent idiopathic scoliosis [70]. Furthermore, CHD7 expression has also been positively correlated with bone mineral content, indicating a potential role in the abnormal bone mass observed in patients with this condition [70]. Contrasting these findings, another study that genotyped 22 single nucleotide polymorphisms in the CHD7 gene did not find a statistically significant association with familial idiopathic scoliosis, highlighting the complexity and variability of genetic influences in the development of idiopathic scoliosis [71].

Insulin-like growth factor 1 (IGF-1) is essential for bone growth [72]. A study of 506 Chinese girls with idiopathic scoliosis (Cobb angle >20 degrees) and 227 age-matched controls found that IGF-1 polymorphism affects curve severity but not the onset of scoliosis, suggesting IGF-1 may influence disease severity [73]. However, these results were not replicated in a Japanese cohort, where common single nucleotide polymorphisms in genes for matrilin 1 (MATN1), melatonin receptor 1B (MTNR1B), and tryptophan hydroxylase 1 (TPH1) were also found not to be associated with the idiopathic scoliosis [74].

In contrast, a study of 68 Korean idiopathic scoliosis patients and 35 healthy age- and sex-matched adolescents found that rs5742612 in IGF-1 was associated with both susceptibility to and curve severity in idiopathic scoliosis [75]. In this study, the single nucleotide polymorphism rs2449539 in lysosomal-associated transmembrane protein 4 beta (LAPTM4B) was also found associated with both susceptibility to and curve severity in idiopathic scoliosis [75]. Interestingly, the product of LAPTM4B gene was found to be a negative regulator of transforming growth factor (TGF-β1) [76], which was also independently linked to idiopathic scoliosis [77].

More specifically, the TGFB1 gene allele -509T and genotype -509TT were significantly associated with an increased risk of idiopathic scoliosis in both females and males (p<.01) [77]. Logistic regression revealed a recessive genetic association between the C-509T polymorphism of the TGFB1 gene and idiopathic scoliosis [77]. Additionally, sexual dimorphism was observed: in females, the C-509T polymorphism of the TGFB1 gene was linked to both earlier onset and greater curve severity, but this was not the case in males [77].

Previously, a Japanese study found no significant association with idiopathic scoliosis for matrilin 1 (MATN1) gene, involved in the formation of filamentous networks in the extracellular matrices [74,78]. Likewise, an analysis of MATN1 gene polymorphisms in Turkish individuals using real-time PCR on 53 adolescents with idiopathic scoliosis and 54 healthy adults found no significant differences between the scoliosis and control groups [79]. Conversely, research on Chinese patients identified the tagSNP rs1149048 polymorphism in the MATN1 promoter region as being linked to both susceptibility and progression of idiopathic scoliosis [80]. A recent meta-analysis further confirmed a significant association between the rs1149048 polymorphism and idiopathic scoliosis risk, particularly in the Asian population [81].

A previous study on developing zebrafish implicated basonuclin 2 (BNC2) in the etiology of idiopathic scoliosis by observing a curve development dependent on BNC2 expression levels [82]. Later research on a Chinese population of idiopathic scoliosis patients found that BNC2 gene expression levels were significantly higher compared to controls and strongly correlated with scoliosis curve severity [83].

The polymorphisms rs4794665 in C17orf67 gene and rs12459350 in DOT1L gene were linked to idiopathic scoliosis susceptibility, however, only one of the genotyped SNPs were also correlated with the severity of spinal curvature [84].The product of DOT1L expression is a histone methylator and wad suggested to be involved in protecting cartilage homeostasis [85].

A total of 949 idiopathic scoliosis patients and 976 age-matched healthy controls were recruited for the study, where the SNP rs11190870 near the ladybird homebox 1 (LBX1) gene was linked to both the susceptibility to and progression of idiopathic scoliosis [86]. LBX1 gene product was reported to regulate the muscle precursor cell migration [87]. A meta-analysis of 3 genome-wide association studies, which included 79,211 Japanese individuals, confirmed the association of rs11190870 near LINC01514/LBX1 with idiopathic scoliosis [88].

Additionally, research conducted on the northern Chinese Han population identified two SNPs near LBX1 (rs11190870 and rs1322331) that are associated with an increased risk of idiopathic scoliosis [89].

High cartilage oligomeric matrix protein (COMP) promoter methylation was associated with a high Cobb angle, suggesting it may be a valuable predictor of idiopathic scoliosis susceptibility and curve progression [90]. H19 imprinted maternally expressed transcript (H19) and adiponectin, C1Q and collagen domain containing (ADIPOQ) genes showed inconsistent expression, with lower H19 and higher ADIPOQ levels in concave-sided muscle tissues compared to convex-sided ones [91]. This expression pattern correlated positively with the spinal curve and the age of onset, suggesting a putative role for these genes in both susceptibility and scoliosis progression [91]. Moreover, H19 is located near IGF-2 and has been shown to be involved in osteoporosis development [92]. At the same time, the structure of ADIPOQ gene was founding coding for proteins like collagens X and VIII [93].

The coding variant p.Asn786Ser in the heparan sulfate proteoglycan 2 (HSPG2) gene, encoding a protein that binds to and cross-links many extracellular matrix components, was found to be significantly more prevalent in a larger cohort of idiopathic scoliosis cases than in the control group (p=.024). This suggested an association with the idiopathic scoliosis phenotype [94].

Hormonal and neural genes

In 1978, a prospective study of 26,947 students found a 4.5% incidence of adolescent idiopathic scoliosis, with a female-to-male ratio of 1.25:1 overall and increasing with curve severity [10]. Later, a study of 304 girls with adolescent idiopathic scoliosis found that the XbaI (rs9340799) polymorphism in the estrogen receptor gene was linked with curve progression [95,96]. Girls with XX and Xx genotypes had greater Cobb's angles, a higher risk of a 5-degree curve progression, and a greater likelihood of requiring surgery compared to those with the xx genotype [95,96]. These findings implicated estrogen receptor polymorphisms in curve progression and indicated that DNA analysis could be used to predict this progression.

A study comparing 202 scoliosis patients to 174 healthy controls found that the XbaI (rs9340799) polymorphism of the estrogen receptor gene is linked to idiopathic scoliosis susceptibility in females, with the XX genotype and/or X allele being risk indicators [97]. On the other hand, the PvuII polymorphism showed no association with idiopathic scoliosis risk [97]. However, in a cohort of 540 Chinese girls, no association was found between PvuII and XbaI (rs9340799) polymorphisms of the estrogen receptor 1 and scoliosis susceptibility or curve severity [98]. A meta-analysis of 4 studies (1,827 idiopathic scoliosis cases and 1,253 controls) found no significant association between XbaI (rs9340799) and idiopathic scoliosis(OR 1.09, 95% CI 0.96–1.23, p=.17), suggesting that the XbaI (rs9340799) polymorphism is unlikely to be a susceptibility variant for idiopathic scoliosis predisposition but may be linked to idiopathic scoliosis severity, progression, and treatment [99]. Further, patients resistant to scoliosis brace treatment were linked to the GA genotype and G allele of the estrogen related receptor alpha (ESRRA) gene and the AT genotype and A allele of the tryptophan hydroxylase 1 (TPH1) gene, suggesting that ESRRA and TPH1 are potential genetic markers for predicting brace treatment outcomes [100]. TPH1 gene encodes for an enzyme that is involved in serotonin synthesis, which precedes melatonin synthesis [101].

The AluI site polymorphism of the estrogen receptor 2 (ESR2) gene was linked to Cobb angle severity (AA: 31.9°, AG: 43.2°, GG: 38.9°, p=.002) and differed between moderate (<40°) and severe (≥40°) scoliosis (p=.0011) [102]. While the ESR2 polymorphism was not associated with idiopathic scoliosis predisposition in Caucasian females, it may be linked to curve severity [102]. A missense variant in ESR1 (c.868A>G) and a pathogenic variant in ESR2 (c.236T>C) were identified in idiopathic scoliosis patients with Cobb angles of 41° and 45°, respectively [103]. Both variants showed significantly decreased ability to activate downstream genes, suggesting genetic mutations in ESR1/2 can be associated with idiopathic scoliosis risk [103].

It has been previously reported that calmodulin has an affinity for the estrogen receptor, decreasing its estrogen-binding capacity [104]. This led to the hypothesis that calmodulin's effect on curve progression might be due to the loss of estrogen-binding affinity for the receptor [96]. Researhers investigated the correlation between SNPs in calmodulin 1 (CALM1) and ESR1 genes and double curve idiopathic scoliosis in 67 patients and 100 controls [105]. Significant differences in the polymorphic distribution of rs2234693 in the ER1 gene and rs12885713 and rs5871 in the CALM1 gene were found between idiopathic scoliosis patients and controls. The findings suggest that different SNPs in these genes may be associated with specific idiopathic scoliosis subtypes, particularly double curve idiopathic scoliosis [105].

In a study of 146 idiopathic scoliosis patients and 146 controls, 12 SNPs in the CALM1 gene were analyzed [106]. Three SNPs—rs2300496, rs2300500, and rs3231718—were linked to idiopathic scoliosis predisposition, with no differences found in curve severity or genotype distributions, suggesting CALM1 gene variants can be associated with idiopathic scoliosis susceptibility [106]. In a different study of 55 idiopathic scoliosis patients, calmodulin levels correlated with curve progression and stabilization, indicating potential as a marker for identifying stable and progressive curves [107]. Another study found that idiopathic scoliosis patients had an asymmetric distribution of calmodulin in paraspinal muscles, with higher levels on the convex side and lower levels on the concave side [108]. Interestingly, platelet calmodulin did not reflect the muscle protein values [108].

Contactin-associated protein-like 2 (CNTNAP2) is another gene of interest previously linked to idiopathic scoliosis and later confirmed through a genome-wide association study [35]. CNTNAP2 is also of particular interest, as it participates in axon pathfinding and interacts directly with L1 and Robo class proteins [109]. The latter, when mutated, causes horizontal gaze palsy with progressive scoliosis (HGPPS), a rare disease marked by severe scoliosis [110].

Studying a Chinese population of patients with idiopathic scoliosis, researchers identified interleukin 17 receptor C (IL17RC) gene single nucleotide polymorphism rs708567 associated with both susceptibility and curve progression [111].

Pathogenesis of idiopathic scoliosis

Evolution of erect posture and bipedalism

Modern humans possess a highly mobile lower spine compared to other great apes and short-backed primates, due to unique anatomical features [112] [Fig. 2]. The development of lordosis, enabled by the elongation of the spinal column, aligned the spine over the hip joints in an erect stance [112]. It positioned the center of mass of the head, arms, and trunk over the ground contact point without the need to flex both the hip and knee, as do apes [112–114]. In parallel, ilia and sacrum have broadened and shortened, preventing restrictive contact with the lower lumbar vertebrae [112]. The latter developed a progressive widening of their laminae and increased space between their articular processes [115]. The orientation of human facets became more coronal to resist anterior displacement of L5 at the L5/S1 joint [116]. The mass and cross-sectional area of the erector spinae muscles were reduced [117]. These adaptations, coupled with subtle imbalances in the elongated lumbar spine, may contribute to the rotational instability from which scoliosis originates [118,119]. This might remain subclinical until more severe effects manifest in the spine [112].

The evolutionary drive for bipedality led to significant functional adaptations despite the increased risk of scoliotic deviations and flexion-induced injuries [112]. This suggests that the benefits of upright walking long outweighed potential spinal vulnerabilities. However, over the past 3 million years, primary changes in the human spine and pelvis have focused on lumbar shortening, possibly, among other purposes, to

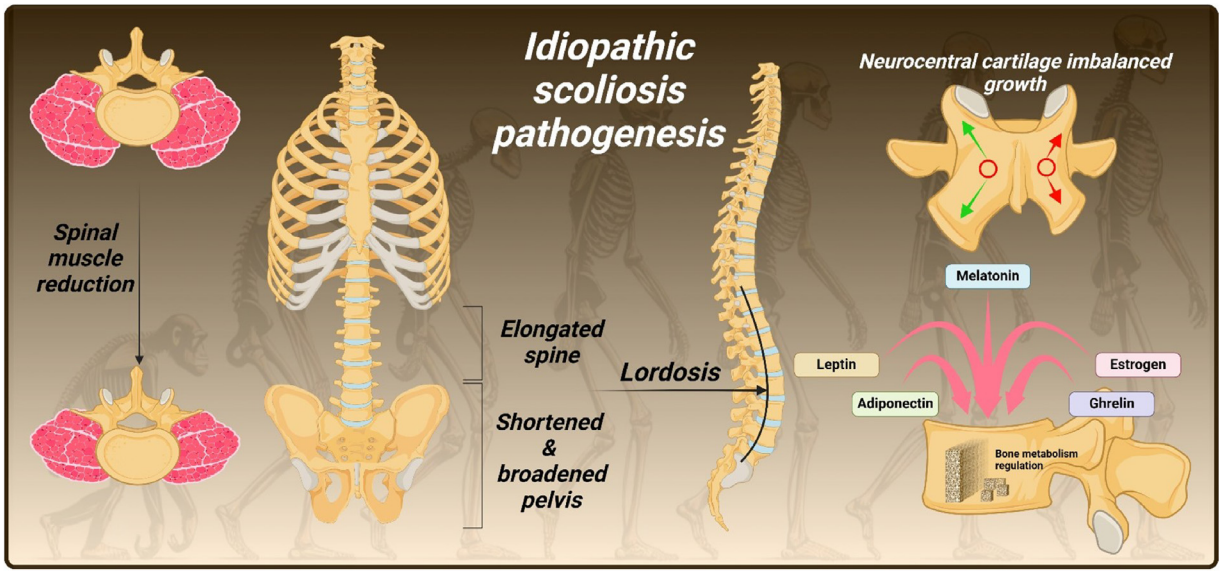

Fig. 2. Pathogenesis of idiopathic scoliosis.

mitigate scoliosis and flexion injuries [112]. Despite this trend towards strengthening the spine, in evolutionary terms these changes are still recent. Consequently, the incomplete adaptation to upright posture and bipedality remains a predisposing factor for the development of scoliotic deformities [120].

Spinal growth and developmental aberrations

Spinal growth is primarily driven by 2 neurocentral joints known as Schmorl's cartilage [121]. The latter are 2 synchondroses that connect each vertebral body to a corresponding semiposterior arch [122]. The asymmetrical development of these cartilages is 1 of the proposed theories behind scoliosis development [120]. This is supported by MRI findings of asymmetrical vertebral pedicles in children with scoliosis and the correlation between intensified joint activity and aggravated idiopathic scoliosis [123,124]. Experimental studies on young pigs show that restricting growth on 1 side of Schmorl's cartilage induces convex scoliosis on the restricted side [125,126]. However, inconsistent results, such as scoliosis on the opposite side of the lesion when electrically sterilized, challenge this theory [127].

Various factors related to abnormal growth and development of the spine contribute to the progression of scoliosis [128]. Some individuals are born with abnormalities in the cartilage of their vertebrae [129,130]. These congenital defects can disrupt normal spinal growth and alignment, contributing to the development and progression of scoliosis [129,130].

Children with scoliosis often experience growth spurts earlier than their peers [128,131]. This rapid growth can exacerbate the spinal curvature because the spine is lengthening faster than it can stabilize. Moreover, during periods of rapid growth, such as puberty, scoliosis tends to worsen. Studies indicate that girls with adolescent idiopathic scoliosis are typically taller and exhibit faster growth rates during puberty than their healthy peers [132,133]. Some researchers have found that during growth phases, the anterior part of the vertebrae can grow more than the posterior part [134]. This uneven growth can cause the vertebrae to become wedged or tilted [135]. The Hueter-Volkmann Law states that compression decelerates both growth whereas traction accelerates [136]. This means that, if the spine starts with a small asymmetry, the differential growth rates will cause this asymmetry to worsen over time.

Anatomical and MRI studies have shown that in structural scoliosis patients, the anterior parts of the spine are longer than the posterior parts, a condition called 'relative anterior spinal overgrowth' (RASO) [137–143]. A similar spinal overgrowth was found in both idiopathic scoliosis and neuromuscular scoliosis patients, suggesting RASO is a general feature of scoliosis rather than a specific cause of idiopathic scoliosis [144]. The anterior-to-posterior length difference correlated with the Cobb angle, indicating RASO may contribute to curve progression [144]. However, RASO's role as a primary cause of adolescent idiopathic scoliosis (AIS) is debated and does not apply to all curve types.

Other researchers suggest disproportional growth between the skeletal and neural systems in idiopathic scoliosis, either due to a short spinal cord or rapid spine growth [140,145,146]. This concept was termed asynchronous neuro-osseous growth [140,145–148]. It was found that in severe AIS, the vertebral column is significantly longer without detectable changes in spinal cord length [149,150]. They suggested that anterior spinal overgrowth stretches the spinal cord and cauda equina, leading to hypokyphosis and thoracic spine deformity, causing scoliosis [149,150].

Finally, the neuromuscular theory of idiopathic scoliosis posited that muscular and nerve imbalances contribute to the condition [151]. Animal studies showed that muscle excision or nerve root division could induce scoliosis, highlighting the role of muscle and nerve integrity in spinal stability [152]. Equilibrial dysfunction at the brainstem level was also suggested, with abnormalities in balance more common in scoliosis patients, correlating with curve severity and resolving with maturity [153]. However, subsequent findings of muscle abnormalities, such as dystrophy and disproportions in muscle fiber types, were inconsistent in their locations, leaving the theory subjected to controversy [154–157].

Bone metabolism regulation

The role of endocrine hormones and bone homeostasis in adolescent idiopathic scoliosis (AIS) is a significant area of research [158]. During adolescence, the rapid changes in hormone levels that regulate growth and development might influence idiopathic scoliosis [158].

The androgen receptor (AR) in bone tissue is concentrated in the growth plate, where androgens stimulate cartilage proliferation and endochondral ossification [159,160]. Idiopathic scoliosis patients have been found to have lower androgen levels than non-AIS patients, suggesting a potential link between androgens and idiopathic scoliosis development [160]. However, research on androgens' role in idiopathic scoliosis pathogenesis is limited, with most studies focusing on estrogen.

Estrogen's involvement in idiopathic scoliosis pathogenesis is viewed from 2 perspectives [158]. One theory suggests that abnormal estrogen levels delay menarche in females, postponing bone development and maturity, thereby increasing the risk of spine deformity [158]. Research supports this theory, identifying significantly lower serum estradiol levels in idiopathic scoliosis patients compared to healthy individuals [161,162]. Low levels of estrogen and delayed menarche can lead to decreased bone mineralization and strength, increasing the risk of bone deformity [163]. Studies of female ballet dancers found that those with delayed menarche were more likely to experience idiopathic scoliosis and stress fractures [164], and that dancers were at a significantly higher risk of developing scoliosis than nondancers of the same age [165].

While the mechanism by which low estrogen indirectly causes idiopathic scoliosis by delaying menarche is plausible, it is important to note that idiopathic scoliosis also occurs in females with normal menarche and in males. In female idiopathic scoliosis patients with normal menarche, estrogen's role is more likely via abnormal bone metabolism and development, increasing the risk of malformations [166].

The second theory suggests that abnormal estrogen levels directly affect bone metabolism and remodeling, leading to improper bone growth and a higher likelihood of developing idiopathic scoliosis [163,167,168]. Supporting this, studies have found that adolescent girls with idiopathic scoliosis exhibit lower bone mineral density and higher bone turnover rates compared to healthy controls [169,170]. Additionally, low bone mineral density in the femoral neck correlates with curve progression [171].

Estrogen and its receptors are widespread in the body, playing roles in various developmental processes. Some studies suggest that estrogen receptors (ERs) might be asymmetrically expressed in the paraspinal muscles of idiopathic scoliosis patients [172]. However, further research did not confirm this, finding no significant difference between idiopathic scoliosis patients and controls [173]. The expression levels of melatonin, estrogen, and other receptors in idiopathic scoliosis paraspinal muscle are very low, implying that estrogen and melatonin likely influence idiopathic scoliosis through their regulatory effects on cartilage and bone development.

Melatonin, an indoleamine regulating biological rhythms, is known to influence bone development [174]. In 1959, it was discovered that chickens developed scoliosis after their pineal gland was removed, suggesting melatonin deficiency might cause idiopathic scoliosis [175,176]. This finding was replicated in bipedal rats [119]. However, subsequent studies showed that adolescents with IS had normal melatonin levels [176,177] and that pinealectomized monkeys did not develop scoliosis [178]. Instead, it was proposed that a dysfunction in melatonin signaling, particularly affecting osteoblasts, could be involved [179]. This led to exploring abnormalities in melatonin signaling pathways.

It was found that the melatonin receptor MT2, but not MT1, showed reduced levels in IS patients, and MT2-related gene polymorphisms were linked to IS [180–182]. Melatonin promotes bone density and mass through MT2 receptors and the MAPK pathway, affecting osteoblast proliferation and differentiation [183]. Further research identified a functional abnormality in the melatonin MT2/PKC signaling pathway in idiopathic scoliosis patients' growth plate chondrocytes, potentially leading to abnormal endochondral ossification [184,185]. Melatonin also reduces osteoclastogenesis and increases osteoclast apoptosis by modulating OPG and RANKL levels, promoting bone formation [186,187]. Therefore, altered melatonin levels and MT2 receptor dysfunction might contribute to the development of idiopathic scoliosis by affecting bone development.

Leptin, ghrelin, and adiponectin play significant roles in the development of scoliosis [158]. Leptin, a hormone produced by adipose tissue, is typically lower in individuals with idiopathic scoliosis despite their low BMI, possibly due to higher utilization and reduced secretion [188,189]. This deficit leads to disrupted muscle and bone development, as leptin is crucial for inhibiting muscle degradation and promoting osteoblast activity [158]. Consequently, the asymmetry and postural imbalances characteristic of scoliosis are exacerbated. Adiponectin, also secreted by adipose tissue, is found at higher levels in idiopathic scoliosis patients [190] and exhibits asymmetric expression in paraspinal muscles [91]. It promotes bone resorption by decreasing OPG and increasing RANKL, potentially resulting in lower bone mass and spinal instability [190,191]. Ghrelin, a hormone from the stomach [192], is elevated in idiopathic scoliosis patients [193] and is linked to scoliosis severity [194]. It affects cartilage and bone development through various signaling pathways, such as ERK/STAT3, and may contribute to abnormal bone mass and cartilage development, exacerbating scoliosis [195–197]. Together, these hormones influence muscle, bone, and cartilage development, playing a pivotal role in scoliosis pathogenesis.

Genetics and pathogenesis of adult degenerative scoliosis

In earlier work, we identified 6 key factors likely contributing to the development and progression of adult degenerative scoliosis: uneven wear of intervertebral discs and facet joints, autophagy-driven angiogenesis and inflammation within the discs, extracellular matrix degradation, bone metabolism abnormalities, muscle loss (sarcopenia), and irregular mechanical stress distribution along the spine [14]. These factors highlight a complex asymmetric degenerative process in the spine with a deviated vertical load axis. This results in disproportional biomechanical pressure, worsening the degeneration and creating a vicious cycle [Fig. 3]. Despite this understanding of its progression, less is known about the origin of adult degenerative scoliosis.

Heritability is 1 key area of research that may help illuminate the manifestation of adult degenerative scoliosis. However, to date fewer genetic factors have been identified in adult degenerative scoliosis compared to other degenerative spine diseases, such as idiopathic scoliosis [198,199]. Nevertheless, several gene groups linked to different pathogenic mechanisms have been reported [Fig. 4].

Angiogenesis and inflammation

One significant group of genes associated with adult degenerative scoliosis pertains to aberrant angiogenesis and inflammation. This group includes cyclooxygenase-2 (COX2), interleukin 6 (IL6), tumor necrosis factor-related apoptosis ligand (TRAIL), and nuclear factor of activated T-cells (NFATC). Previous studies have indicated that COX-2 expression is elevated in degenerative disc disease compared to normal discs, potentially linking it to increased angiogenesis [200,201]. In adult degenerative scoliosis, investigations revealed significantly higher COX-2 levels and lower miR-143 (a COX-2 inhibitor) levels compared to idiopathic scoliosis and control groups further supporting the putative pathogenetic role COX-2 [202].

Another study compared 184 patients with adult degenerative scoliosis to 220 healthy controls, revealing a significant difference in the IL6-572 G/C polymorphism [203]. Additionally, when serum levels of TRAIL and polymorphisms in the TRAIL gene were investigated in patients with intervertebral disc disease, higher serum TRAIL levels in patients with more severe disc degeneration were revealed [204]. The G/C mutation at loci 1525/1595 of the TRAIL gene was also more frequent in patients than in controls [204]. Although no subgroup analysis was conducted for patients with scoliosis, the above evidence suggests TRAIL might also be a contributing factor in adult degenerative scoliosis development [204]. Finally, a genomic study had associated the NFATC gene with adult degenerative scoliosis as well [205]. The product of NFATC gene expression is known to be involved in inducible gene transcription during an immune response [206]. Interestingly, it has also been found to play an important role in osteoclastogenesis and hence, may also be involved in bone remodeling [207].

Aberrant angiogenesis and inflammation have been identified as contributors to the intervertebral disc degeneration [208,209]. Samples from the posterior annulus fibrosus of adult degenerative scoliosis patients showed increased expression of proangiogenic factors like angio-

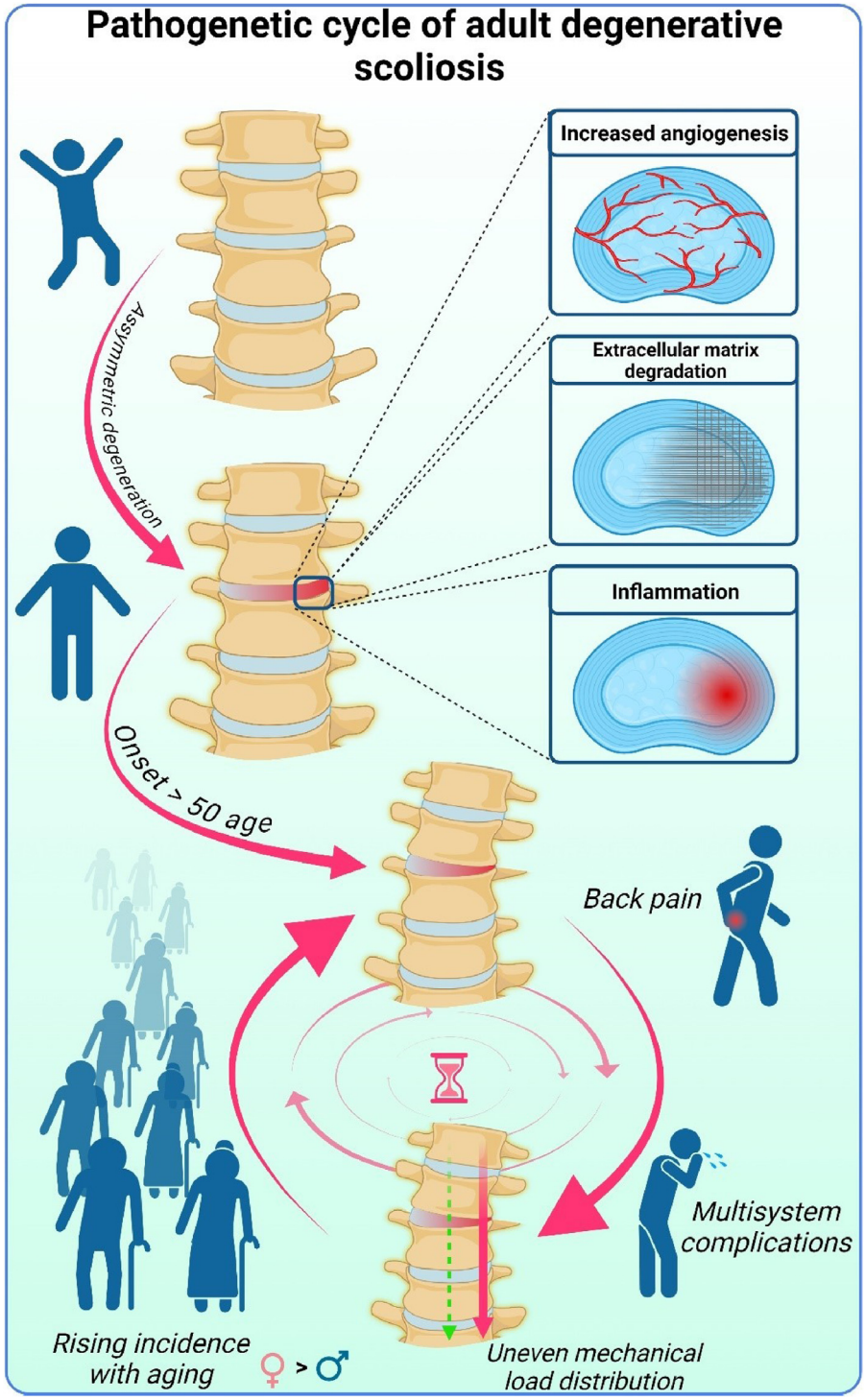

Fig. 3. Vicious cycle of adult degenerative scoliosis.

genin and platelet-derived growth factor B (PDGF-B) [210]. Cells from degenerated discs were found expressing TRAIL and death receptors DR4 and DR5, markers of inflammation that correlated with the disc's degenerative state [211]. Together, aberrant angiogenesis and local inflammation promote extracellular matrix degradation, further driving angiogenesis and perpetuating the degenerative cycle [212].

Extracellular matrix degradation

Extracellular matrix (ECM) disruption is a key factor in the degeneration of intervertebral discs and facet joints [14,213]. Type II collagen, an essential ECM component for the nucleus pulposus and facet joints, plays a crucial role in maintaining their structure. Elevated levels of the C-propeptide of type II collagen (CPII), indicating increased collagen synthesis, have been observed in patients with degenerative lumbar scoliosis [213]. A significant association has been found between the SNP rs2276454 in the collagen type II alpha 1 (COL2A1) gene and adult degenerative scoliosis in Korean patients, underscoring collagen's role in bone homeostasis [214]. This association was further confirmed by comparing 51 adult degenerative scoliosis patients to 235 healthy controls [215]. In the Chinese Han population, single nucleotide polymorphisms rs1337185 in COL11A1 and rs162509 in

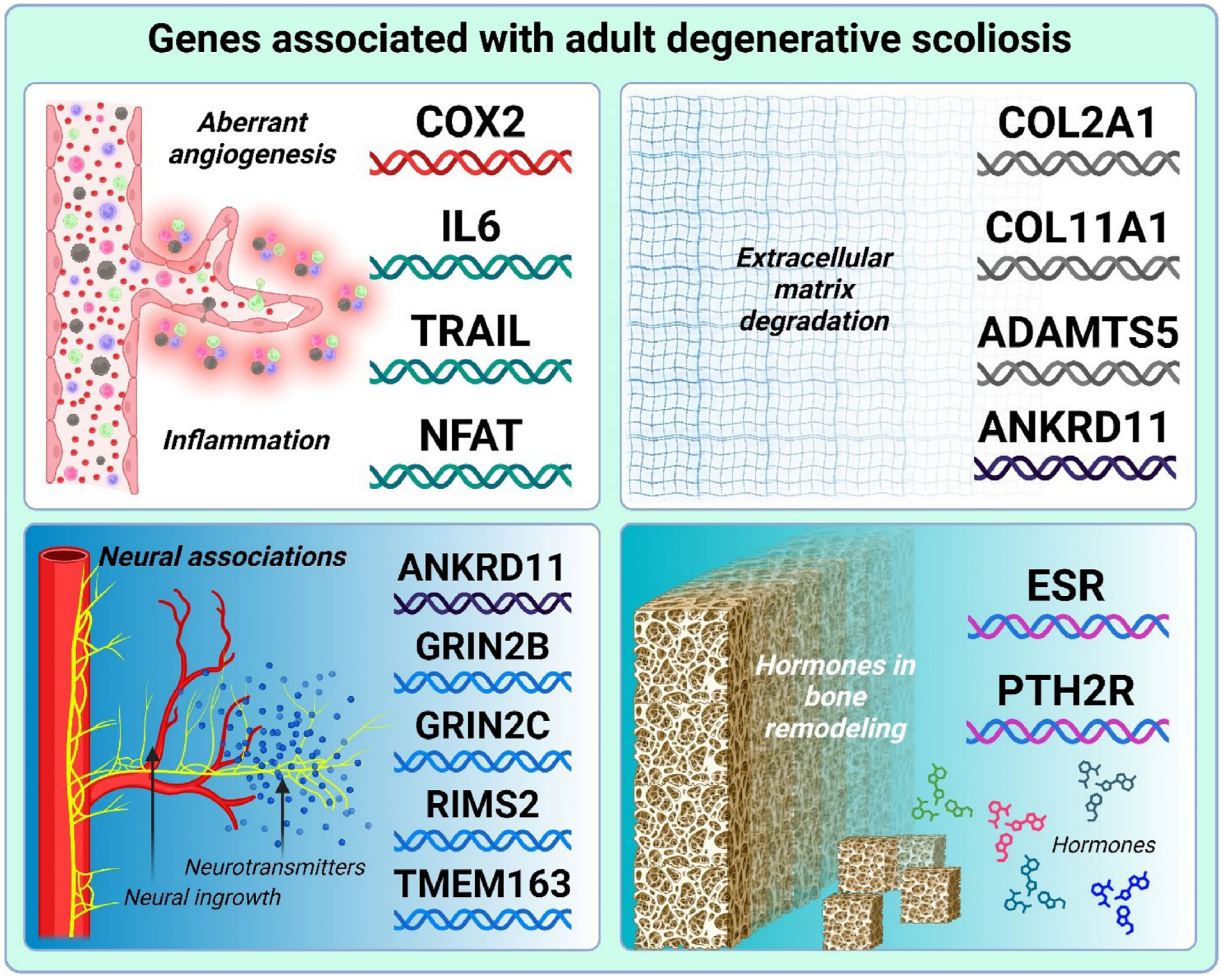

Fig. 4. Genes associated with adult degenerative scoliosis.

ADAMTS5 have been linked to a higher risk of lumbar disc degeneration [216].

Neural associations

A genomic study identified the gene ankyrin repeat domain containing 11 (ANKRD11) as being associated with adult degenerative scoliosis [205]. It is thought to have a role in the proliferation and development of cortical neural precursors [217] and may regulate bone homeostasis [218]. Angiogenesis in intervertebral disc degeneration is thought to be accompanied by neural ingrowth, which has been suggested as the main reason for lower back pain development [219]. Given the presence of N-methyl-D-aspartate (NMDA) receptors in bone cells, researchers examined the genetic link between cSNPs in NMDA receptor genes and adult degenerative scoliosis [220,221]. Although no significant overall association was found [222], specific cSNPs 'in the glutamate ionotropic receptor NMDA type subunit 2C (GRIN2C) gene were linked to larger Cobb angles, and cSNPs in the glutamate ionotropic receptor NMDA type subunit 2B (GRIN2B) gene were associated with greater lateral listhesis within the scoliosis group [221]. However, when the serum proteome profiles of 12 patients with degenerative scoliosis were compared to those of healthy controls, several downregulated proteins were revealed [223]. Among all, isoform 1 of G protein-regulated inducer of neurite outgrowth 1 (GPRIN1) was the most significantly downregulated one [223].

Another study linked an SNP rs10461 in regulating synaptic membrane exocytosis 2 (RIMS2) gene to adult degenerative scoliosis [224]. A genomic study had associated the transmembrane protein 163 (TMEM163) gene, product of which is an integral component of synaptic vesicle membrane, with adult degenerative scoliosis as well [205].

Together, while the precise role of glutamate signaling in degenerative scoliosis remains an intriguing subject of future studies, the existent evidence is supportive of adult degenerative scoliosis having neural associations.

Hormonal influences

Individuals with vertebral compression fractures from osteoporosis, particularly women, face an increased risk of developing scoliotic spine deformities [225]. Women can have up to a 50% lifetime risk of fractures due to bone fragility [226]. Additionally, cartilage is thought to be sensitive to sex hormones [227].

In this context, a notable difference was identified in the Pvu II polymorphism, suggesting that the Pvu II polymorphism may serve as a genetic marker for the prevalence of adult degenerative scoliosis [228]. Additionally, women with degenerative changes in the lumbar spine were found to have a significantly higher frequency of the A-allele of the parathyroid hormone 2 receptor (PTH2R) SNP rs897083 [229]. Although 122 women had adult degenerative scoliosis, no subgroup analysis was performed [229]. Yet, the PTH2R gene variations may contribute to age-related spinal degeneration, potentially leading to adult degenerative scoliosis.

Miscellaneous genes

Proteomic analysis of sera from adult degenerative scoliosis patients identified 11 differentially expressed proteins (Clusterin, CLU cDNA FLJ57622, ALB cDNA FLJ50830, Hypothetical short protein, HLA-A MHC class I antigen [Fragment], ALB 23 kDa protein, Isoform 1 of G protein-regulated inducer of neurite outgrowth 1 [GPRIN1] and Ficolin-3) [230]. Western blot confirmed 2 of these, Clusterin and Ficolin-3, suggesting their potential as biomarkers [230]. Additional analysis of scoliosis patient mesenchymal stem cells revealed differential levels of PIAS2, NDUFA2, and TRIM68, distinct from those in serum [231]. While these proteins may serve as disease biomarkers, further research is needed to validate them across diverse patient populations due to possible environmental and epigenetic influences.

Discussion

Scoliosis affects approximately 2%–3% of the population, translating to an estimated 7–9 million individuals in the United States [232]. Early detection of a progressive curve is crucial for effective treatment of idiopathic scoliosis, as it allows timely intervention. However, significant challenges persist in predicting who will develop scoliosis, understanding the etiological factors, assessing the likelihood of progression, and determining the extent of disease advancement [34]. To this end, genetic testing offers the potential to diagnose idiopathic scoliosis before symptom onset, enabling earlier and more targeted treatments.

Research previously suggested that idiopathic scoliosis may follow autosomal and X-linked dominant inheritance patterns [233]. However, discrepancies in data and the diminishing risk of idiopathic scoliosis across generations indicated a multifactorial inheritance model to be more likely [120]. This model implies a complex interaction between multiple genes and environmental factors, rather than a straightforward hereditary pattern, poising idiopathic scoliosis as a multifaceted disease.

Over time, the methodology for studying the genetics of scoliosis has advanced. Genetic linkage analysis, a widely utilized technique, examines familial cases by analyzing genetic information across generations [234]. This approach identifies genetic markers that consistently co-occur with the disease, pinpointing the chromosome regions likely housing the causative genes. Genetic linkage analysis was the predominant methodology for identifying genetic factors associated with scoliosis. Then followed the emergence of genetic association analysis which focuses on identifying statistical correlations between specific genetic variants—typically single nucleotide polymorphisms (SNPs)—and the presence of diseases in broader populations [1]. This method is particularly useful for complex diseases such as scoliosis, likely influenced by multiple genetic and environmental factors. Each method has its advantages and both have allowed to generate an insight into the genetic factors driving scoliosis development.

Despite the growing interest in the genetics of scoliosis, no specific genetic markers have been identified to date. Research has primarily focused on idiopathic scoliosis, likely because it is the most common form of the condition and typically manifests at a younger age [235]. In contrast, adult degenerative scoliosis generally affects individuals over fifty [13].

Considering different age of scoliosis onset, one may presume the genetic signature that predisposes individuals to scoliosis development is likely different in idiopathic scoliosis vs adult degenerative scoliosis. Supporting this notion, our review identified only the estrogen receptor and collagen genes as common genetic factors in both diseases. In idiopathic scoliosis, abnormal estrogen delays menarche, postponing bone development and maturity [158]. It directly affects bone metabolism and remodeling, leading to improper bone growth and an increased risk of scoliosis [163]. In adult degenerative scoliosis, women can have up to a 50% lifetime risk of fractures due to bone fragility [225,226]. Thus, while estrogen-related genetic changes increase susceptibility to both IS and ADS, they do so via distinct mechanisms.

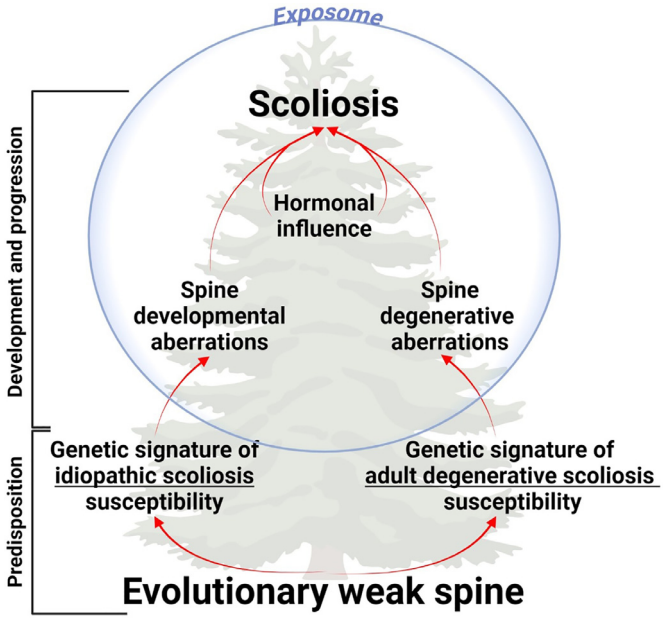

Fig. 5. The etiopathogenetic tree of scoliosis.

Another shared feature of idiopathic scoliosis and adult degenerative scoliosis is the development of spinal asymmetry, though the underlying mechanisms differ significantly as well. In idiopathic scoliosis, the most widely accepted mechanism is the asymmetrical activity of the neurocentral cartilage [120]. This uneven growth pattern leads to spinal curvature and has led to therapeutic suggestions, such as targeting the growth of neurocentral cartilage with thoracic pedicle screw instrumentation [236].

Conversely, in adult degenerative scoliosis, asymmetry arises primarily from the uneven degeneration of intervertebral discs [14]. This degeneration is thought to be driven by a combination of aberrant angiogenesis and chronic inflammation, which together perpetuate the degradation of the extracellular matrix [14]. These processes contribute to the uneven wear and tear of the intervertebral discs, resulting in spinal asymmetry. However, unlike in IS, where the sequence of pathogenic events is relatively well theorized, the reason why these degenerative processes become asymmetric in the aging spine leading to adult degenerative scoliosis, remains unclear.

Further, we propose a new tree-like model of scoliosis etiopathogenesis, which depicts multiple layers of disease susceptibility and progression [Fig. 5]. The first layer involves an evolutionarily maladaptive spine, predisposing humans to spinal deformities and serving as a common predisposition for both types of scoliosis. The second layer, consisting of distinct genetic signatures, differentiates the pathogenetic trajectories of idiopathic and adult degenerative scolioses. Influenced by hormonal changes and exposomal factors, these genetic factors lead to aberrations in spinal development and intervertebral disc degeneration, resulting in idiopathic and adult degenerative scolioses, respectively.

The term exposome was coined by Christopher Wild in 2005 to represent a compilation of all environmental, lifestyle, behavioral and social factors that may contribute to disease development and/or progression [237]. Studies on monozygotic twins have previously highlighted the significant role of environmental factors in idiopathic scoliosis [238]. However, research on the role of exposomal factors in idiopathic scoliosis has not been gaining momentum. It has been suggested to be due to an excessive emphasis on the genetic aspect of the disease.

Among the new evidence is recognition of epigenetic regulations as bridges between the exposome and the inner pathogenetic mechanisms. It has been shown to reflect the early life environmental influ-

ences [239]. Continued research in this direction may help shedding more light on the origin of the process that eventually lead to idiopathic scoliosis development.

Studies on the exposomal factors for adult degenerative scoliosis have been more prevalent in identifying the risk factors for the disease. As such, bone mineral density <−1.85g/cm2, body mass index >25.57 kg/m2, and sagittal vertical axis >3.98cm were suggested to be potential risk factors for degenerative scoliosis [240]. A body mass index [BMI] over 25 kg/m^2 is linked to a higher risk of degenerative lumbar scoliosis [241]. Excess weight is associated with more frequent falls, sarcopenia, and the production of proinflammatory cytokines like IL-6 and TNF-α, which contribute to increased osteoclastogenesis and bone loss [242–244]. Conversely, a high BMI is also associated with higher bone mineral density (BMD), indicating stronger bones [245]. This paradox can be partially explained by mechanical loading and strain, as well as estrogen production by adipocytes, which enhances bone formation and reduces resorption [246]. The net effect of these conflicting influences of obesity on degenerative scoliosis remains unclear. Therefore, further research is needed to understand the precise roles of physical activity and obesity in the development and progression of adult degenerative scoliosis.

Understanding these distinct pathogenetic mechanisms is crucial, as it could inform more targeted treatments for each type of scoliosis. In idiopathic scoliosis, interventions might focus on modulating the growth and development of spinal structures during critical periods, whereas in ADS, therapies could aim at mitigating the degenerative processes and inflammation that contribute to disc asymmetry. Despite the differences, both conditions underscore the complexity of spinal asymmetry and the need for continued research to fully elucidate these mechanisms.

Conclusion

Despite major advancements and success in therapy of scoliosis, the disease continues to affect large populations both among children and adults. In the case of adult degenerative scoliosis, the global trend toward aging is alarming, since it portends a rise in disease prevalence. Given these considerations, it is imperative to refine predictive and preventive strategies to enhance the diagnosis and treatment of scoliosis. To do so, more studies are needed to better understand the etiology and pathogenesis of scoliosis.

Summary

This comprehensive review explores the genetic factors and multifaceted pathogenesis of idiopathic and adult degenerative scoliosis, proposing a new model for scoliosis etiopathogenesis and highlighting future research directions.

Declaration of competing interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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