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Unraveling the Genetic and Epigenetic Threads of Idiopathic Scoliosis: Analyzing Mechanisms, Interactions, and Future Directions in Research and Therapy

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ABSTRACT

Idiopathic scoliosis (IS) is a complex, multifactorial spinal deformity with a largely elusive etiology. This review synthesizes current research on the genetic and epigenetic factors contributing to IS development and progression. Genome-wide association studies have identified key susceptibility loci—such as LBX1, GPR126, and BNC2—while family and twin studies underscore a significant heritable component. Chromosomal anomalies and polygenic interactions further complicate the genetic landscape. Concurrently, epigenetic mechanisms—including DNA methylation, histone modifications, and non-coding RNAs—have emerged as critical mediators of gene-environment interactions, influenced by factors such as mechanical load, nutrition, and endocrine disruptors. Multi-omic approaches integrating genomics, transcriptomics, and epigenomics offer new insights into pathophysiology and therapeutic targeting. Ethical considerations surrounding genetic testing and the need for population-specific models are also discussed. Ultimately, this review supports a shift toward precision medicine, highlighting the potential of early molecular biomarkers and epigenetic modulation as tools for individualized scoliosis management and intervention.

Introduction

Idiopathic scoliosis (IS) is a three-dimensional spinal deformity characterized by lateral curvature and vertebral rotation, typically defined by a Cobb angle of ≥10°[1]. While its clinical definition is clear, its etiology remains elusive, and the condition is considered multifactorial, involving both genetic and environmental influences. Idiopathic scoliosis usually emerges during adolescence, a period marked by rapid skeletal growth, with a prevalence ranging from 1% to 4% in the general population[2]. Of those affected, approximately 0.5% require surgical intervention due to curve progression and associated functional impairments[3]. Notably, females are disproportionately affected, with a female-to-male ratio of about 4:1, suggesting a potential hormonal or sex-linked influence[4].

Beyond the visible deformity, IS has profound implications for psychosocial health and systemic function. Adolescents with significant curvature often report decreased self-esteem and elevated emotional stress[5]. In severe cases, spinal deformity may lead to thoracic insufficiency, respiratory compromise, and even cardiac dysfunction due to reduced thoracic volume and pulmonary capacity[6]. These outcomes underscore the necessity for early detection and nuanced treatment strategies informed by a deeper understanding of the underlying mechanisms.

Traditionally, diagnostic approaches have included clinical observation, radiographic imaging, and skeletal maturity assessments. More recently, genetic and epigenetic analyses have begun to inform risk stratification and prognosis[7]. Despite advances in imaging and surgical techniques, IS remains a heterogeneous disorder, with wide variability in curve progression and treatment response. This variability strongly suggests that IS results from complex interactions between genetic predispositions and environmental or epigenetic modifiers.

To address the growing need for a comprehensive synthesis of current findings, this manuscript aims to systematically review and integrate the existing literature on the genetic and epigenetic factors implicated in the pathogenesis of idiopathic scoliosis. By examining key genomic loci, molecular pathways, chromosomal abnormalities, and environmentally responsive epigenetic modifications, this review highlights the complex interplay between inherited susceptibility and modifiable environmental influences. In doing so, it not only elucidates the multifactorial nature of idiopathic scoliosis but also underscores the emerging potential of precision medicine approaches. The goal is to provide clinicians, researchers, and policymakers with an updated, evidence-based framework that informs early detection strategies, risk stratification, and the development of biologically targeted therapies for individuals at risk of curve progression.

Methods

This narrative review was conducted to synthesize current evidence on the genetic and epigenetic mechanisms underlying idiopathic scoliosis (IS). A comprehensive literature search was performed using databases including PubMed and Google Scholar for studies published between January 1990 and June 2025. Search terms included combinations of "idiopathic scoliosis," "genetics," "epigenetics," "genomics," "GWAS," "DNA methylation," "histone modification," "microRNA," and "gene-environment interaction." Inclusion criteria comprised peer-reviewed original research articles, systematic reviews, and meta-analyses focused on human subjects or relevant animal models that investigated molecular, genetic, or epigenetic contributions to IS. Studies focusing exclusively on congenital or neuromuscular scoliosis were excluded. Reference lists of key publications were hand-searched to identify additional relevant studies. Data were extracted and organized thematically to capture emerging patterns in genetic susceptibility loci, epigenetic regulation, and clinical implications.

Genetic Foundations of Idiopathic Scoliosis

Twin and family studies provide compelling evidence for a genetic contribution to IS. Monozygotic twin concordance rates exceed 70%, compared to approximately 30% in dizygotic twins, supporting a heritable component[8]. Additionally, first-degree relatives of individuals with IS have a 6–10-fold increased risk of developing scoliosis themselves, further supporting familial aggregation and polygenic inheritance[9].

Genome-wide association studies (GWAS) have identified several susceptibility loci associated with IS, including regions on chromosomes 6q24.1, 10q24.31, and 16p11.2 [10,11]. Among these, genes involved in cartilage and bone development, such as growth differentiation factor 6 (GDF6) and GPR126, have emerged as strong candidates. GDF6 is critical for embryonic vertebral segmentation and development, while GPR126 plays a role in Schwann cell development and spinal growth[12,13].

Other candidate genes implicated in IS pathogenesis include MMP1, which is involved in extracellular matrix remodeling, and COL1A1, a key structural gene encoding type I collagen, essential for bone strength and integrity[14,15]. Polymorphisms in these genes may impair vertebral development or compromise biomechanical stability, thereby contributing to curve progression.

Additionally, the chromatin remodeling gene CHD7 has been identified in association with congenital scoliosis syndromes and is hypothesized to influence idiopathic forms as well[16]. Variants in CHD7 may disrupt neural crest development, leading to vertebral anomalies or paraspinal muscle asymmetries. These findings support the notion that scoliosis may arise from disrupted embryonic patterning, neuromuscular imbalances, or skeletal dysplasia—each potentially rooted in specific genetic abnormalities.

Epigenetic Modifications and Gene-Environment Interactions

While genetic studies provide a blueprint, they cannot fully explain the variability in IS onset and progression. Epigenetic mechanisms—heritable changes in gene expression without alterations to the DNA sequence—offer a plausible bridge between genetic susceptibility

and environmental triggers. DNA methylation, histone modification, and non-coding RNAs such as microRNAs (miRNAs) have been implicated in the regulation of spinal growth and alignment[17].

Environmental factors such as mechanical load, nutritional status, hormonal fluctuations, and exposure to endocrine disruptors may influence epigenetic markers during critical periods of development[18]. For example, aberrant DNA methylation in genes associated with osteogenesis or cartilage differentiation may impair normal spinal development, increasing the risk of IS. Similarly, histone deacetylation in specific spinal regions has been linked to transcriptional repression of key structural genes[19].

MiRNAs, including miR-126, miR-133, and miR-204, have also been found to modulate pathways involved in vertebral morphology, muscle tone, and growth plate dynamics[20]. Dysregulation of these miRNAs in scoliotic tissues suggests a potential role in curve progression, possibly through disrupted chondrocyte differentiation or muscle development. Moreover, environmental stimuli may alter miRNA expression profiles, reinforcing the importance of gene-environment interplay in IS pathophysiology.

Expanded Insights into Genetic Pathways and Epistatic Influences in Idiopathic Scoliosis

As research into the genetic architecture of idiopathic scoliosis advances, it becomes increasingly clear that this condition is polygenic, involving a network of genes that affect vertebral development, cartilage integrity, and musculoskeletal homeostasis. In particular, signaling pathways such as WNT and transforming growth factor beta (TGF-β) have emerged as critical players in spinal morphogenesis. Disruption of these pathways—either through single nucleotide polymorphisms (SNPs) or gene expression dysregulation—has been implicated in the development of spinal asymmetry[19,21].

The WNT signaling pathway regulates cell proliferation, differentiation, and skeletal patterning. Several scoliosis-associated genes—including LBX1, PAX1, and GPR126—modulate WNT activity during vertebral development. For example, LBX1, one of the most replicated loci in IS GWAS studies, is essential for somatosensory neuron migration and myogenic precursor specification in the somite, indirectly influencing spinal muscle balance and curve biomechanics[11,13]. Dysregulation of WNT signaling may lead to abnormal vertebral segmentation or ossification, contributing to asymmetric growth.

Similarly, TGF-β signaling plays a key role in the regulation of chondrocyte differentiation, osteoblast function, and extracellular matrix (ECM) remodeling. Mutations or epigenetic alterations in genes involved in this pathway—such as TGFBR1, SMAD3, or TGFB1—could impair these processes, increasing susceptibility to spinal deformity[22].

Evidence also supports the involvement of collagen-encoding genes such as COL1A1 and COL11A1, which contribute to the structural stability of spinal tissues. Variants in these genes have been associated with altered bone density, a known risk factor for curve progression in scoliosis [23]. The metalloproteinase gene MMP1, implicated in ECM degradation and remodeling, is also a relevant candidate; polymorphisms in this gene may facilitate excessive matrix turnover, weakening vertebral integrity [24].

Beyond individual gene effects, interactions between genes—known as epistasis—are becoming increasingly recognized as influential in IS. Recent studies have demonstrated that combinations of polymorphisms in genes such as GPR126, LBX1, and PAX1 produce synergistic effects on scoliosis risk that exceed the sum of their individual contributions [25]. These findings underscore the importance of moving beyond single-gene analyses toward network-based and systems biology approaches.

Epigenetic Mechanisms as Modulators of Genetic Risk

Epigenetic regulation, particularly through DNA methylation and histone modifications, offers a functional explanation for how environmental factors influence gene expression and disease phenotype in IS. DNA methylation at CpG islands in promoter regions is often associated with transcriptional silencing. In IS, hypermethylation of key regulatory genes involved in bone formation, such as SOST and RUNX2, has been observed in patient tissues, potentially contributing to compromised skeletal development [19].

Histone modifications—such as acetylation and methylation—affect chromatin structure and gene accessibility. In IS patients, reduced acetylation of histone H3 and increased trimethylation at H3K27 have been linked to a repressive chromatin state at loci essential for spine stability [19]. These epigenetic marks may mediate long-lasting changes in gene expression following early-life mechanical stress or hormonal shifts, particularly during pubertal growth spurts.

Additionally, non-coding RNAs, particularly microRNAs (miRNAs), are now considered pivotal regulators of gene expression in IS. For example, miR-133a and miR-204 regulate muscle differentiation and osteoblast activity, respectively—processes highly relevant to scoliosis pathogenesis [20]. Aberrant expression of these miRNAs in paraspinal muscle and bone tissues of IS patients suggests they may influence curve progression through post-transcriptional regulation of multiple target genes.

MiRNA expression is itself subject to epigenetic regulation. Aberrant DNA methylation of miRNA gene promoters can lead to their silencing, further altering gene regulatory networks. This interconnected regulatory system exemplifies how genetic predisposition may be modified by epigenetic factors, resulting in the clinical heterogeneity seen in idiopathic scoliosis [17].

Chromosomal Anomalies, Gene-Environment Interactions, and Therapeutic Implications

In addition to single-gene variants and polygenic risk loci, structural chromosomal anomalies have been implicated

in the pathogenesis of idiopathic scoliosis. Copy number variations (CNVs), deletions, duplications, and translocations can disrupt genes critical to spinal development and growth regulation. For example, chromosomal rearrangements affecting 17q25 have been reported in families with inherited scoliosis, suggesting that this locus may harbor regulatory elements essential for vertebral morphogenesis [26]. Likewise, aneuploidies and submicroscopic deletions in regions encoding matrix proteins and transcription factors have been associated with syndromic forms of scoliosis, some of which overlap with idiopathic phenotypes.

Further complicating the genetic landscape of IS is the dynamic interplay between inherited genetic predisposition and environmental exposures. Mechanical loading of the spine during rapid growth phases—particularly adolescence—has been shown to influence gene expression and may act as a catalyst in genetically susceptible individuals [27]. For example, asymmetrical loading due to postural habits or musculoskeletal imbalances may trigger compensatory growth patterns, particularly when regulatory pathways governing bone remodeling or matrix synthesis are genetically compromised.

Nutritional factors also modulate genetic and epigenetic outcomes. Deficiencies in vitamin D, calcium, and magnesium—critical cofactors in bone metabolism—may impair epigenetic regulation of osteogenic genes such as RUNX2 and SOST [28]. These micronutrient deficiencies have been associated with decreased bone mineral density in IS patients, suggesting that environmental influences can exacerbate structural vulnerabilities conferred by genotype.

Emerging research also implicates endocrine-disrupting chemicals (EDCs) in altering the epigenetic landscape during critical windows of development. Exposure to bisphenol A (BPA), phthalates, and other common EDCs has been linked to DNA methylation changes in genes related to skeletal and neural development [29]. These findings suggest a mechanism by which environmental toxins may converge with genetic susceptibility to influence the onset or severity of scoliosis.

The interplay between chromosomal variation, genetic polymorphisms, and epigenetic responsiveness underlies the multifactorial etiology of IS and creates a compelling case for precision medicine. Identifying individuals with chromosomal or epigenetic markers predictive of curve progression may inform early therapeutic decisions. For example, patients with known epigenetic repression of osteogenic pathways might benefit from pharmacological interventions targeting histone deacetylases (HDACs) or DNA methyltransferases (DNMTs) [30].

Moreover, CRISPR-Cas9 technology and other gene-editing tools offer promising avenues for correcting deleterious genetic mutations or restoring functional gene expression. Although still in preclinical stages for scoliosis, such approaches may eventually allow targeted therapy based on individual genomic profiles. In parallel, non-pharmacologic strategies—such as exercise regimens tailored to enhance epigenetically modifiable pathways involved in muscle tone or spinal alignment—could complement molecular therapies.

As our understanding of the epigenomic influences on spinal development expands, so does the potential for identifying early biomarkers of disease. Epigenetic signatures—such as specific methylation profiles or miRNA expression panels—could serve as non-invasive diagnostic tools to stratify scoliosis risk or monitor treatment efficacy [30,31].

Multi-Omic Integration and Population-Specific Genetic Variability

Recent advances in genomics and bioinformatics have propelled a shift toward integrative "multi-omic" approaches in understanding the pathogenesis of idiopathic scoliosis. These include genomics, transcriptomics, epigenomics, and proteomics, which collectively offer a systems-level perspective on the complex biological networks underpinning IS [32]. By combining data from multiple biological layers, researchers can gain a more comprehensive understanding of how genetic variants are transcribed, modified, and ultimately expressed at the protein level—thereby illuminating the full cascade from genotype to phenotype.

Transcriptomic analyses, such as RNA sequencing, allow the identification of differentially expressed genes in IS tissues compared to controls. These studies have revealed altered expression in genes regulating extracellular matrix (ECM) remodeling, inflammation, and osteogenesis—findings that may not be evident through genomic analysis alone [35]. In parallel, proteomic studies can uncover changes in protein abundance or activity that contribute to vertebral instability or muscle asymmetry.

Epigenomic profiling, including whole-genome bisulfite sequencing and ChIP-seq for histone marks, further enhances our understanding of dynamic gene regulation. For example, changes in the methylation status of loci involved in the WNT and TGF-β signaling pathways may mediate environmental modulation of scoliosis risk [22].

Importantly, the genetic architecture of IS may differ between populations due to allele frequency variations and gene-environment interactions. Studies in Asian populations, for example, have identified associations between IS and variants in LBX1, GPR126, and BNC2, while some of these findings have not been replicated in European cohorts [21,25]. This suggests the need for population-specific genetic models and highlights the potential for health disparities in diagnosis and treatment if such differences are not considered.

Ethnic and geographic variability also extends to epigenetic patterns, which are sensitive to nutritional, environmental, and lifestyle exposures. Thus, epigenome-wide association studies (EWAS) stratified by ancestry may reveal regulatory networks specific to certain populations and aid in identifying culturally and biologically relevant interventions [18].

Ethical Considerations in Genetic Testing for Idiopathic Scoliosis

As genetic testing becomes more accessible in clinical settings, ethical challenges emerge—particularly in the context of pediatric conditions like IS. One key concern is the interpretation and communication of probabilistic genetic risk. Many of the identified IS-associated variants confer only modest increases in risk, which complicates efforts to counsel families or determine surveillance intensity [33].

Informed consent must address the limitations of genetic testing, including the current lack of curative interventions based on genomic data alone. Genetic counseling is essential to help families navigate decisions about testing, especially in adolescents who may be at risk of stigmatization or anxiety due to perceived genetic vulnerability.

Privacy and data protection also raise serious concerns. Genetic data are inherently identifiable and sensitive; therefore, robust data security measures and legislative protections—such as those outlined in the Genetic Information Nondiscrimination Act (GINA) in the United States—must be in place to prevent misuse of genetic information in insurance or employment contexts [34].

Additionally, prenatal and preimplantation genetic testing for IS risk alleles raises ethical dilemmas regarding reproductive decision-making. Given the multifactorial nature of IS and the modest effect sizes of most known variants, the use of such technologies for scoliosis risk may be premature and ethically questionable [35].

To ensure equitable access to emerging diagnostic tools, future research must prioritize diverse population inclusion and the development of cost-effective, culturally sensitive screening frameworks. As the field moves toward personalized scoliosis care, balancing innovation with ethical stewardship will be essential.

Future Directions: Precision Medicine, Early Detection, and Epigenetic Therapeutics

As the understanding of idiopathic scoliosis (IS) continues to evolve, a future grounded in precision medicine appears increasingly viable. Precision medicine aims to tailor diagnostic, preventative, and therapeutic strategies to an individual's unique genetic, epigenetic, and environmental profile. In the context of IS, this approach could revolutionize patient care by enabling earlier detection of high-risk individuals, improving prognostic accuracy, and guiding personalized treatment interventions [36,37].

The integration of genetic screening into pediatric orthopaedics may allow clinicians to stratify patients by risk of curve progression. For example, patients with risk alleles in GPR126, LBX1, or BNC2 could be monitored more frequently or started on early conservative therapies, even before visible curvature develops[11]. Likewise, the identification of specific epigenetic biomarkers—such as hypermethylation at osteogenesis-related genes or dysregulated miRNA expression—may serve as a molecular warning system for impending curve development or progression [19].

Importantly, research is now exploring therapeutic strategies that target the epigenome directly. Epigenetic drugs such as histone deacetylase inhibitors (e.g., valproic acid) and DNA methyltransferase inhibitors (e.g., 5-azacytidine) are already under investigation in cancer therapy and could be repurposed to modulate aberrant gene expression in IS. Animal models of scoliosis have shown early promise with agents that restore normal epigenetic signaling, opening the door for future clinical applications.

Non-pharmacological interventions may also influence the epigenome. Studies in other fields suggest that exercise, nutrition, and even mindfulness-based stress reduction can affect DNA methylation and miRNA expression, implying that lifestyle-based interventions could support epigenetic stability in susceptible adolescents [38]. These low-risk strategies may offer adjunctive benefits when combined with bracing or other biomechanical treatments.

To implement such approaches effectively, robust longitudinal studies and clinical trials will be required. Multi-center cohort studies that integrate genomic, epigenomic, and clinical data can help identify reliable biomarkers for early detection and refine therapeutic targeting. Advances in wearable technologies and artificial intelligence may soon enable real-time biomechanical and molecular monitoring to personalize treatment trajectories further [39].

Ultimately, the future of IS care lies in bridging the gap between molecular discoveries and clinical application. As genomic technologies become more accessible and affordable, orthopedic clinics may routinely incorporate genetic and epigenetic testing into the scoliosis workup. However, such integration must be matched by provider education, regulatory oversight, and careful consideration of ethical implications.

Conclusion

The pathogenesis of idiopathic scoliosis is complex and multifactorial, involving an intricate interplay of genetic variants, epigenetic modifications, and environmental influences. From early GWAS studies to current multi-omic investigations, the expanding body of research continues to elucidate the molecular underpinnings of spinal deformity. While no single gene or pathway is solely responsible for IS, the integration of genetic and epigenetic insights holds promise for revolutionizing diagnosis, risk prediction, and personalized therapy.

By embracing a systems biology approach and addressing population-specific variability, future research can advance precision medicine models that move beyond bracing and surgery toward biologically targeted, preventive, and minimally invasive care. The promise of early detection through molecular biomarkers and epigenetic modulation as a therapeutic strategy suggests a new horizon in scoliosis management—one defined by individualized care and molecular precision.

References

1. Weinstein SL, Dolan LA, Cheng JCY, Danielsson A, Morcuende, JA. Adolescent idiopathic scoliosis. *Lancet* 2008; 371(9623): 1527–1537.
2. Konieczny MR, Senyurt H, Krauspe R. Epidemiology of adolescent idiopathic scoliosis. *J Child Orthop* 2013; 7(1): 3–9.
3. Negrini S, Donzelli S, Aulisa AG, et al. 2016 SOSORT guidelines: Orthopaedic and rehabilitation treatment of idiopathic scoliosis during growth. *Scoliosis and Spinal Disorders* 2018; 13: 3.
4. Lonstein JE. Adolescent idiopathic scoliosis. *Lancet* 1994; 344(8934): 1407–1412.
5. Reichel D, Schanz J. Developmental psychological aspects of scoliosis treatment. *Pediatr Rehabil* 2003; 6(3-4): 221–225.
6. Tsiligiannis T, Grivas TB. Pulmonary function in children with idiopathic scoliosis. *Scoliosis* 2012; 7: 7.
7. Faldini C, Manzetti M, Neri S, Barile F, Viroli G, Geraci G, Ursini F, Ruffilli A. Epigenetic and genetic factors related to curve progression in adolescent idiopathic scoliosis: a systematic scoping review of the current literature. Int J Mol Sci. 2022;23(11):5914.
8. Kesling KL, Reinker KA. Scoliosis in twins: A meta-analysis. *Spine* 1978; 3(2): 136–138.
9. Miller NH. Genetics of familial idiopathic scoliosis. *Clin Orthop Related Res* 2007; 462, 6–10.
10. Kou I, Takahashi Y, Johnson TA, et al. Genetic variants in GPR126 are associated with adolescent idiopathic scoliosis. *Nat Genet* 2013; 45(6): 676–679.
11. Ogura Y, Kou I, Takahashi Y, et al. A Functional SNP in BNC2 Is Associated with Adolescent Idiopathic Scoliosis. *Am J Hum Genet*. 2015;97(2):337-42.
12. Karner CM, Long F, Monk KR. Gpr126/Adgrg6 deletion in cartilage models idiopathic scoliosis and pectus excavatum in mice. *Hum Mol Genet*. 2015;24(15):4365-73.
13. Takahashi Y, Kou I, Takahashi A, et al. A genome-wide association study identifies common variants near LBX1 associated with adolescent idiopathic scoliosis. *Nat Genet* 2011; 43(12): 1237–1240.
14. Miller NH, Justice CM, Marosy B, et al. Identification of candidate regions for familial idiopathic scoliosis. *Spine* 2005;30(10):1181-7.
15. Xu JF, Yang GH, Pan XH, et al. Altered microRNA expression profile in plasma of patients with adolescent idiopathic scoliosis. *PLoS ONE* 2015; 10(10): e0138946.
16. Gao X, Gordon D, Zhang D, et al. CHD7 gene polymorphisms are associated with susceptibility to idiopathic scoliosis. *Am J Hum Genet* 2007; 80(5): 957–965.
17. Liu G, Wang L, Wang J, et al. Whole-Genome Methylation Analysis of Phenotype Discordant Monozygotic Twins Reveals Novel Epigenetic Perturbation Contributing to the Pathogenesis of Adolescent Idiopathic Scoliosis. *Front Bioeng Biotechnol* 2019;7:364.
18. Cheng JCY, Castelein RM, Chu WCW, et al. Adolescent idiopathic scoliosis. *Nat Rev Dis Primers* 2015; 7(1): 9.
19. Carry PM, Terhune EA, Trahan GD, et al. Severity of Idiopathic Scoliosis Is Associated with Differential Methylation: An Epigenome-Wide Association Study of Monozygotic Twins with Idiopathic Scoliosis. *Genes* 2021; 12(8):1191.
20. Guo L, Huang W, Chen B, et al. gga-mir-133a-3p Regulates Myoblasts Proliferation and Differentiation by Targeting PRRX1. *Front Genet* 2018;9:577.
21. Xu JF, Yang GH, Pan XH, et al. Association of GPR126 gene polymorphism with adolescent idiopathic scoliosis in Chinese populations. *Genomics* 2015;105(2):101-7.
22. Nowak R, Kwiecien M, Tkacz M, Mazurek U. Transforming growth factor-beta (TGF- β) signaling in paravertebral muscles in juvenile and adolescent idiopathic scoliosis. *Biomed Res Int*. 2014;2014:594287.
23. Grauers A, Wang J, Einarsdottir E, et al. Candidate gene analysis and exome sequencing confirm LBX1 as a susceptibility gene for idiopathic scoliosis. *Spine J* 2015; 15(10), 2239–2246.
24. Wang YP, Qin SL, Yang S, et al. Association of IL-6 and MMP-3 gene polymorphisms with adolescent idiopathic scoliosis: A systematic review and meta-analysis. *Exp Ther Med*. 2024;27(6):267..
25. Bilgin E, Tezcan Unlu H, Cecener G, et al. Investigation of LBX1, TIMP2, GPR126 and CHD7 Gene Polymorphisms in Adolescent Idiopathic Scoliosis Patients. *Global Spine J;* 2025:21925682251356933.
26. Wise CA, Gao X, Shoemaker S, Gordon D, Herring JA. Understanding genetic factors in idiopathic scoliosis, a complex disease of childhood. *Curr Genomics* 2008; 9(1): 51–59.
27. Burwell, R.G., Aujla, R.K., Grevitt, M.P. et al. Pathogenesis of adolescent idiopathic scoliosis in girls - a double neuro-osseous theory involving disharmony between two nervous systems, somatic and autonomic expressed in the spine and trunk: possible dependency on sympathetic nervous system and hormones with implications for medical therapy. Scoliosis 2009;4: 24.
28. Yang Y, Chen Z, Huang Z, et al. Risk factors associated with low bone mineral density in children with idiopathic scoliosis: a scoping review. *BMC Musculoskelet Disord* 2023;24(1):48.
29. Egger G, Liang G, Aparicio A, Jones PA. Epigenetics in human disease and prospects for epigenetic therapy. *Nature* 2004;429: 457–63.
30. Sun D, Ding Z, Hai Y, Cheng Y. Advances in epigenetic research of adolescent idiopathic scoliosis and congenital scoliosis. *Front Genet*. 2023;14:1211376.
31. Haller G, Alvarado D, McCall K, et al. A polygenic burden of rare variants across extracellular matrix genes among individuals with adolescent idiopathic scoliosis. *Hum Mol Genet* 2016; 25(9): 202–209.
32. Liu XY, Wang L, Yu B, Zhuang QY, Wang YP. Expression Signatures of Long Noncoding RNAs in Adolescent Idiopathic Scoliosis. *Biomed Res Int* 2015;2015:276049.
33. Tiller J, Otlowski M, Lacaze P. Should Australia Ban the Use of Genetic Test Results in Life Insurance? *Front Public Health* 2017;5:330.
34. Hudson KL, Holohan MK, Collins FS. Keeping pace with the times--the Genetic Information Nondiscrimination Act of 2008. *N Engl J Med*. 2008;358(25):2661-3.

35. Guttmacher AE, Collins FS. Welcome to the genomic era. *N Engl J Med*. 2003;349(10):996-8.
36. Morningstar MW, Stitzel CJ, Strauchman M. Functional genomic variant patterns in Caucasian patients diagnosed with idiopathic scoliosis: a controlled, observational study. *Medical Research Archives* 2019; 7(9):1-9.
37. You JS, Jones PA. Cancer genetics and epigenetics: two sides of the same coin? *Cancer Cell* 2012;22(1):9-20.
38. Voisin S, Eynon N, Yan X, Bishop DJ. Exercise training and DNA methylation in humans. *Acta Physiol (Oxf)* 2015;213(1):39-59.
39. Schmid S, Studer D, Hasler CC, Romkes J, Taylor WR, Lorenzetti S, Brunner R. Quantifying spinal gait kinematics using an enhanced optical motion capture approach in adolescent idiopathic scoliosis. *Gait Posture* 2016;44:231-7.