Exploring the association between specific genes and the onset of idiopathic scoliosis: a systematic review

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Abstract

Background: Idiopathic Scoliosis (IS) is the most common spinal deformity in adolescents, accounting for 80% of all spinal deformities. However, the etiology remains uncertain in most cases, being identified as Adolescent Idiopathic Scoliosis (AIS). IS treatments range from observation and sport to bracing or surgery. Several risk factors including sex and familiarity, have been linked with IS. Although there are still many uncertainties regarding the cause of this pathology, several studies report a greater incidence of the defect in families in which at least one other first degree relative is affected. This study systematically reviews the available literature to identify the most significant genes or variants related to the development and onset of IS.

Methods: The research question was formulated using a PIOS approach on the following databases: Medline, Embase, Cinahl, Scopus, Web of Science and Google Scholar. The search was performed from July to August 2021, and articles from the inception of the database to August 2021 were searched.

Results: 24 of the 919 initially identified studies were included in the present review. The 24 included studies observed a total of 16,316 cases and 81,567 controls. All the considered studies stated either the affected gene and/or specific SNPs. CHD7, SH2B1, ESR, CALM1, LBX1, MATN1, CHL1, FBN1 and FBN2 genes were associated with IS development.

Conclusions: Although association can be found in some candidate genes the field of research regarding genetic association with the onset of IS still requires more information.

Keywords: Scoliosis, Idiopathic scoliosis, Early onset, Genetic, Diagnosis

Background

Idiopathic Scoliosis (IS) is the most common spinal deformity in adolescents, accounting for 80% of all spinal deformities. However, the etiology remains uncertain in most cases, being identified as Adolescent Idiopathic Scoliosis (AIS) [1, 2]. Diagnosis of IS begins with a complete physical examination that starts with inspecting shoulder and flank asymmetry. Clinical evaluation is of fundamental importance for the efficacy of the treatment [3]. According to the Scoliosis Research Society classification, scoliosis could be divided into early (EOS) or late-onset; the latter is usually identified with AIS. EOS is characterized by its appearance in children before ten years [4, 5]. It is a complex and highly variable condition, with several etiologies, manifestations, and associations [6]. EOS accounts for less than 1% of the total
scoliotic cases and, several conditions including genetic syndromes and neurological diseases, could explain its onset [3, 6]. Among these conditions, VACTERL syndrome is notably associated with congenital scoliosis. Other pathologies also appear to be related to the onset of EOS, in particular neuromuscular disorders (syringomyelia or myelomeningocele), connective tissue disorders (Marfan Syndrome) and metabolic conditions (osteogenesis imperfecta) [3]. AIS presents in patients older than 10 years of age with a global incidence of 3% [7]. Despite the high incidence of cases worldwide, AIS etiology remains unclear [8]. IS treatments range from observation and sport, to bracing or surgery [1, 3, 9]. In the latter approach the procedure aims to stop curvature progression before reaching a severe spinal curvature identified when the Cobb Angle is greater than 90° and that could reduce cardio-pulmonary function. Bracing is another procedure which aims to achieve halting or reduction of curvature progression but acts using external compressive forces [10]. Despite being a non-invasive approach, contrarily to surgery, bracing is not free from side effects, as it has proven to produce a reduced lung volume accompanied by increased effort during breathing [10].

Several risk factors such as sex and familiarity, have been linked with IS [7]. Moreover, variation in the distribution of the disease in different countries has been reported [11]. However, the precise etiology of this condition remains unknown, and no clear genetic or environmental factors have been directly associated with IS. Although there are still many uncertainties regarding the cause of this pathology, several studies report a greater incidence of the defect in families in which at least one other first degree relative is affected; this information has been supported by twin studies [7, 12]. According to these studies, it is possible to hypothesize that there may be a relevant genetic contribution to the development of IS [13].

IS management is strictly related to the time of presentation and the value of the Cobb angle. The study by Weinstein et al. indicated bracing as an effective AIS treatment option in the case of non-surgical scoliosis (<45° of Cobb angle). Another study by Hans-Rudolf Weiss reported that patients not treated for IS in the early stages of the disease (skeletal maturity and >45°) tended to have worse outcomes compared to ones treated early [14].

Therefore, an early diagnosis and treatment could reduce the risks of intervention; furthermore, these improvements could lead to a decrease in the overall rate of complications in case of surgery.

Genetic tests could diagnose IS before the beginning of characteristic symptoms, allowing early diagnosis and treatment. To our knowledge, however, few studies investigated specific genes related to IS onset. In the light of these considerations, the importance of refining strategies to predict and prevent the disease is evident and may be crucial to diagnosis and treatment.

This study systematically reviews the available literature to identify the most significant genes or variants related to the development and onset of IS.

### Methods

#### Study Selection

The research question was formulated using a PIOUS-approach: Patient (P); Intervention (I); Outcome (O) and Study Design (S). This systematic review aims to study the association (O) between patients that have developed IS (P) and specific genes, identified through genetic screening. Literature in which patients affected with IS were genetically tested (I) for mutations in genes of interest was reviewed. The following study designs were included (S): Randomized Controlled Trials (RCT) and Non-Randomized (NRCT) as Prospective (PS), Retrospective (RS), Case series (CS), Case–Control (CC), and Cohort (CS) studies.

#### Inclusion Criteria

Only articles published in English were screened. Peer-reviewed articles of each level of evidence according to Oxford classification were considered. Only studies reported on affected genes in the onset of IS in patients were included.

#### Exclusion Criteria

Technical notes, letters to editors, instructional courses or studies that did not include genetic testing of patients were excluded. Studies with a sample size smaller than 10 patients were considered not eligible for the present study. Studies with missing or incomplete data were also excluded. The analysis did not include degenerative, syndromic, and neurological scoliosis.

#### Search

A systematic review was performed using the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines. Medline, EMBASE, Scopus, CINAHL and CENTRAL bibliographic databases were searched using the following string: (((diagnosis) AND ((genetic) OR (genome))))) AND (((scoliosis) AND (((adolescent) OR (idiopathic)) OR (early-onset))) OR (late-onset))). Keywords were used both isolated and combined. Additional studies were searched among reference lists of selected papers and systematic reviews.
The search was performed by two authors (A.G. and M.M.) from July to August 2021 and articles from the inception of the database to August 2021 were searched.

**Data Collection Process**
Two independent reviewers performed data collection (A.G. and M.M.), and differences were reconciled by mutual agreement. Any disagreement was resolved upon consultation of a third reviewer (S.D.S.). Firstly, title and abstract screening were performed, and then selected texts were reviewed in full text. The PRISMA flowchart, seen in Fig. 1, reported the inclusion and exclusion of reviewed articles.

**Data Items**
General study characteristics extracted included: primary author, year of publication, country, type of study, level of evidence, sample size (cases and controls), affected gene, statistical association (expressed by p-value or odds ratio), diagnostic method, type of scoliosis (early or late-onset).

**Risk of Bias**
The non-randomized control studies included in this review were assessed for the possibility of bias using the Risk of Bias in Non-Randomized Studies of Interventions (ROBINS-I) tool by Cochrane. Cochrane’s Risk of Bias 2 (RoB 2) tool was used to test for bias in randomized control studies. The scoring was performed by the authors A.G. and M.M. independently, and any disagreement was resolved by a third author S.D.S.

**Results**

**Study Selection**
The search resulted in 919 records identified, which went down to 917 after duplicate removal. Of the 917 records, 850 were excluded during title/abstract screening, leaving 67 articles for the full-text assessment. After the full-text...
assessment, 43 articles were not considered eligible for the study: some did not provide relevant information for the present review (n = 36) or provided insufficient data on the genes of interest (n = 2); one study was excluded because it included less than 10 participants and one article was not available in English. Thus, 24 studies were included for qualitative synthesis. Due to different identified genes in the collected data, a meta-analysis could not be performed.

Study Characteristics
The 24 included studies observed a total of 16,316 cases and 81,567 controls. The high number of controls compared to cases is mostly accounted by Kou et al., who utilized three large genome wide association studies (GWAS) that included 73,884 controls compared to 5,327 cases.

All the considered studies stated either the affected gene and/or specific single nucleotide polymorphisms (SNPs). Of the 23 studies 15 stated SNPs of the affected gene [2, 8, 12, 15–26], seven of these also presented the risk allele and/or genotype [15, 16, 18, 21, 23, 25, 26]. Of those that didn't report the related SNPs, three specified affected gene locus only[1, 7, 27], one stated the specific variant of the affected gene[28], two specified affected gene locus and deletion or insertion, and/or risk allele[4, 29], one stated copy number variant (CNV) of affected gene and corresponding duplication or deletion[9], and one stated risk allele genotype of the affected gene[30].

In regards to statistical data extracted, 11 studies included only the p-value[1, 2, 7, 9, 18–20, 24–26, 28], 11 included both p-value and odds ratio[8, 12, 15–17, 21–23, 27, 30, 31], and two provided neither [4, 29]. In the case of absent p-value and/or odds ratio the item was not assessed, and the studies were used to identify other possible genes of interest.

Of the selected studies, the following levels of evidence and study designs were included: 10 level III case–control studies[2, 16, 19, 20, 23–25, 27, 29, 30], seven level III cohort studies[1, 4, 7, 8, 15, 17, 21], three level III case–control cohort studies[9, 12, 31], three level III case–control association studies[18, 22, 26], one level IV cross-sectional study[28]. The study characteristics are reported in Table 1.

Gene and allele association
All data discussed in the following section are reported in Table 2.

Region 19p13
Alden et al. [1] evaluated four markers of region 19p13: D19S591, D19S1034, D19S922, and D19S714 with a statistically significant association (p < 0.005). Marker D19S1034 specifically has the strongest statistical association, suggesting that it may be more critical in the development of IS compared to the others.

CNV 16p11.2
Four of the included studies reported on CNV 16p11.2, Buchan et al. reported on various deletions and duplications; however, the proximal duplication 1q21.1 was the only one that showed a significant correlation to the onset of IS given its p-value of 0.0057 [9].

Sadler et al. focused on gene SH2B1 with a 16p11.2 distal deletion and duplication [7], which seems to be the only alteration related to IS onset.

In two other studies, Takeda et al. and Zhao et al. identified a 16p11.2 deletion [4, 17, 29] in relation to the TBX6 gene, and both did not specify the statistical association.

CHD7
Borysiak et al. focused on three SNPs of the CHD7 gene. However, only rs101786 demonstrates a statistical association [15]. These values suggest a strong association between the recessive model of rs101786 and IS development.

TBX6
Kou et al. identified a specific SNP, of gene TBX6 rs1978060, with a statistically significant association between gene modification and IS onset [17].

ESRs
Estrogen Receptor Genes (ESRs) may be related to IS, specifically ESR1 and ESR2. In the three tested SNPs, Wang et al. reported a significant association for the missense variant in ESR1 and another missense variant in ESR2 [16, 28]. Zhao et al. reported similar results ESR1 founding a significant relation to SNP rs2234693 [24] and IS. Wu et al. looked at Pvull and XbaI polymorphisms of the ESR gene and nine possible genotypes. They found that PpXX had a statistically significant correlation with the onset of IS [30]. However, in the study by Kotwicki et al., no association between IS and ESR2 was found. These data points hint at an association between estrogen receptor gene modifications and the onset of IS, despite Kotwicki et al. data showing no association.

SNP rs12885713.
Another associated SNP is rs12885713 of the CALM1 gene, which Zhao et al. found a p-value of 0.034 [24].

LBX1
The LBX1 gene was identified in three included studies [17, 18, 20]. All three studies identified rs11190870 as a significant SNP. In Takashi et al., no significant statistical
| Author, year     | Country   | Type of study, level of evidence | DNA extraction protocol                                                                 | Age of IS onset                  | Associated pathology                        |
|------------------|-----------|---------------------------------|----------------------------------------------------------------------------------------|----------------------------------|---------------------------------------------|
| Alden, 2006      | USA       | Cohort study, Level 3           | Standard Purification Protocols                                                         | Early Onset                      |                                             |
| Borysiak, 2020   | Poland    | Cohort study, Level 3           | AsyPrep Blood Genomic DNA Mini-prep Kit                                                 | Late Onset                       |                                             |
| Buchan, July 2014| USA       | Case–control cohort study, Level 3 | Isolation Kit for Mammalian Blood or Oragene1 Purifier                                 | x                                | Trisomy X, 1.8% (2/114)                     |
| Buchan, May 2014 | USA, China| Case–control cohort study, Level 3 | Genome Analyzer IIX or HiSeq 2000 sequencer SureSelect Human All Exon 38 Mb and 50 Mb kits or TruSeq Exome Enrichment kit | x                                | Marfan Syndrome                            |
| Kotwicki, 2014   | Poland    | Case–control study, Level 3     | PCR restriction fragment length polymorphism (PCR–RFLP)                                 | x                                |                                             |
| Kou, 2019        | Japan     | Cohort study, Level 3           | Sequenom MassARRAY SNP genotyping platform                                             | x                                |                                             |
| Liu, 2017        | China     | Case–control association study, Level 3 | Single base primer extension assay                                                      | x                                |                                             |
| Moon, 2013       | South Korea| Case–control study, Level 3    | PCR                                                                                     | 1–3 years of age (4)            | 10–16 years of age (78)                     |
| Nikolova, 2016   | Bulgaria, Japan| Case–control study, Level 3  | PCR                                                                                     | x                                |                                             |
| Ogura, 2013      | Japan     | Retrospective cohort study, Level 3 | Invader Assay                                                                           | x                                |                                             |
| Sadler, 2019     | USA       | Cohort study, Level 3           | IDT xGen Exome Panel V1 capture on Illumina HiSeq 4000 paired-end reads                | x                                |                                             |
| Sharma, 2011     | USA       | Case–control cohort study, Level 3 | Genotyped on Illumina Human CNV370-Quad arrays                                          | x                                |                                             |
| Takahashi, 2018  | Japan     | Case–control study, Level 3     | PCR-based Invader assay                                                                 | x                                |                                             |
| Takeda, 2017     | Japan     | Case–control study, Level 3     | TaqMan real-time quantitative PCR, Microsatellite analysis, Sanger sequencing             | x                                | Vertebral malformations                     |
| Wang, 2008       | China     | Cohort study, Level 3           | PCR                                                                                     | x                                |                                             |
| Wang, 2020       | China     | Cross-sectional study, Level 4  | Whole-exome sequencing                                                                  | x                                |                                             |
| Wu, 2006         | China     | Case–control study, level 3     | PCR, Electrophoresis                                                                    | x                                |                                             |
| Xu, 2015         | China     | Retrospective case control study, Level 3 | TaqMan SNP Genotyping Assay                                                            | x                                |                                             |
| Xu, 2020         | China     | Case–control association study, Level 3 | Genome DNA Extraction with QIAGEN kit, Sanger Sequencing (10%), Exon Sequencing (192) | x                                |                                             |
association was found; however, in Kou et al. and Liu et al., the association was statistically significant [17, 18].

**MATN1**

While two studies both tested for the MATN1 gene, one for the 1p35 marker and the other for rs1149048, both reported no statistically significant association [19, 27].

**CHL1**

Moon et al. and Sharma et al. identified rs10510181, an SNP of the CHL1 gene; however, the two studies showed a discrepancy in p-value [12, 19]. While Moon et al. found no association, Sharma and colleagues reported a p-value of 0.021, suggesting an association between this SNP and IS development.

FBN1 and FBN2.

Buchan et al. gave p-value and odds ratio for FBN1 only, FBN2 only, FBN1 or FBN2: the p-value and OR were 0.0041 and 4.2, 0.0307 and 3.0, and 0.00054 and 3.5 respectively [9]. These values all highlight a strong association between the affected gene and the development of scoliosis.

**Quality of Evidence**

Upon assessment using the ROBINS-I tool, the risk of bias for 11 of the studies was considered "low", while 13 were found to have a "moderate risk of bias." "Bias due to missing data" was the most common bias domain, followed by "bias due to selection of participants". Most of the studies were similar in design and did not precisely describe the enrollment criteria of the participants (Fig. 2).

No Randomized Clinical Trials were not considered eligible; therefore, the RoB-2 tool was not used.

**Discussion**

Idiopathic Scoliosis is a multifactorial condition, and the present study focuses on exploring whether specific genetic mutations or polymorphisms could influence its onset [32, 33]. Understanding the genetic basis of this disease may lead to early diagnosis and treatments.

The CALM1 gene, along with CALM2 and CALM3, are genes that code for calmodulin, a calcium receptor protein involved in various cellular processes, including cell differentiation, cell proliferation, and cytoskeletal architecture and function, and metabolic homeostasis [34]. This gene, and more directly calmodulin, has previously been associated with the development of IS and has been shown to play a role in musculoskeletal development [35]. Furthermore, the results showed a positive correlation between a specified SNP of this gene and IS onset [24].

The studies by Buchan [9] and Sadler [7], identified CNV 16p11.2 as having a positive correlation with the onset of scoliosis. The 6p11.2 distal deletion includes the SH2B1 gene involved in leptin and insulin signalling and has been shown to have a polymorphic effect on obesity [7, 36]. More specifically, this gene promotes leptin signalling by stimulating Janus kinases 1 and 2 [36]. A specific study reported the risk of scoliosis as 1.5 times higher in the underweight group compared to both healthy and overweight groups [7, 37]. A study also reported that IS patients had lower leptin levels in serum compared to the control group, a parameter often found in severely underweight patients [37]. This data suggests that there may be involvement of the SH2B1 gene in IS onset thanks to its involvement in leptin signalling, and perhaps its polymorphic effects on weight regulation [7, 36].

Furthermore, data seems to support the idea that distal regions may exert regulatory effects on proximal regions of the CNV, including the TBX6 gene [7]. This is
Table 2  Primary author, year of publication, affected gene, frequency in cases and statistical association of the included studies

| Author, year   | Affected gene                      | Sample size | Frequency in cases | Statistical association |
|----------------|------------------------------------|-------------|--------------------|-------------------------|
| Alden, 2006    | Chromosome 19p13: D19S591, D19S1034, D19S922, D19S714 | 703/495     | Not Reported/Not Reported | 0.0233*/0.0366*/0.0018(singlepoint)*/0.042(multipoint)*/0.035* |
|                | Cases                  | Controls    | Cases              | Controls              | P value    | Odds ratio |
| Borysiak, 2020 | Gene: CHD7 rs1017861    | 211/83 (%)  | rs1017861          | rs1017861             | rs1017861  | 2.4 (1.5–3.8) |
|                | G: A:AG:GG:GA:A          |             | 87.7/12.3          | 74.6/25.4             | Alleles: 0.0001 | 3.3 (0.9–12.7) |
|                | AA:rs4738824            |             | rs4738824          | rs4738824             | Dominant Model: 0.4 (0.2–0.6) |
|                | G: A:AG:GG:GA:A          |             | 81.8/18.3          | 79.5/20.5             | Recessive Model: 2.1 (0.6–7.9) |
|                | AA:rs4738813            |             | rs4738813          | rs4738813             | Alleles: 0.53 | 0.99 (0.44–2.25) |
|                | T: C:TC:TT:CT:CC:       |             | 68.7/31.2          | 69.3/30.7             | Dominant Model: 0.47 | 0.96 (0.58–1.59) |
|                |                     |             | 48.2/51.8          | 49.4/50.6             | Recessive Model: 0.84 |
| Buchan, July 2014 | CNV: 16p11.2(1q21.1 duplication (proximal), 2q13 duplication, 15q11.2 deletion, 15q11.2 duplication, 16p11.2 duplication) | 143/1079 (n) | 3/1 | 0.0057* |
|                | 1q11.2 duplication (proximal) |             | 1/7                | 1.0316               |
|                | 2q13 duplication         |             | 1/4                | 0.4639               |
|                | 15q11.2 deletion         |             | 1/5                | 0.5269               |
|                | 15q11.2 duplication      |             | 1/2                | 0.3118               |
| Buchan, May 2014 | FBN1                  | 323/493 (n) | 13/311             | 5/489                | 0.0041* | 4.2 |
|                | FBN2                  |             | 11/316             | 5/427                | 0.0307* | 3.0 |
|                | FBN1 or FBN2           |             | 24/304             | 10/425               | 0.000546* | 3.5 |
| Kotwicki, 2014 | Gene ESR2 C/T rs12561120, A/G rs4986938, A/G rs1256049 | 248/243       | Not Reported/Not Reported | 0.1716 | 0.02646–1.886 (0.6234–1.276) | 1.557 |

Table 2 (continued)

| Author, year | Affected gene | Sample size | Frequency in cases | Statistical association |
|--------------|---------------|-------------|-------------------|-------------------------|
|              |               | Cases       | Controls          | P value | Odds ratio |
| Kou, 2019    | LOC101928078: | 5327        | 73,884            |          |            |
|              | rs141903557   |             |                   |          |            |
|              | MTMR11: rs11205303 |     |                   |          |            |
|              | ARF1: rs12029076 |     |                   |          |            |
|              | TBX1: rs1978060 |     |                   |          |            |
|              | LINC02378/MIR3974: | |                   |          |            |
|              | rs2467146     | 0.042       | 0.38              | 0.019   | 1.62 x 10^-10* |
|              | CSMD1: rs11787412 | 0.019      | 0.013             | 0.019   | 3.15 x 10^-9*  |
|              | KIF24: rs188915802 | 0.54        | 0.51              | 0.54    | 9.10 x 10^-9*  |
|              | BCKDHB/FAM46A: | 0.54        | 0.51              | 0.54    | 2.30 x 10^-8*  |
|              | rs658839      | 0.74        | 0.72              | 0.74    | 2.92 x 10^-8*  |
|              | CREB5: rs160335 | 0.33        | 0.31              | 0.33    | 3.56 x 10^-8*  |
|              | NT5DC1: rs482012 | 0.11        | 0.10              | 0.11    | 3.66 x 10^-8*  |
|              | LOC101927021/UNCX: | 0.11       | 0.10              | 0.11    | 4.40 x 10^-8*  |
|              | rs11341092    | 0.82        | 0.79              | 0.82    | 2.01 x 10^-8*  |
|              | PLXNA2: rs7011903 | 0.66        | 0.56              | 0.66    | 3.51 x 10^-9*  |
|              | AGMO/MEOX2:   | 0.48        | 0.43              | 0.48    | 2.19 x 10^-17* |
|              | rs397948882   | 0.46        | 0.42              | 0.46    | 1.35 x 10^-11* |
|              | FTO: rs12149832 | 0.58        | 0.55              | 0.58    | 1.45 x 10^-11* |
|              | LINC01514/LBX1: | 0.51        | 0.47              | 0.51    | 8.69 x 10^-9*  |
| Liu, 2017    | Gene: LBX1    | 180         | 182               | (n)     | (n)         |
|              | rs11190870    | 150         | 195               |          |            |
|              | allele: C     | 210         | 169               |          |            |
|              | allele: T     | 182         | 138               |          |            |
|              | rs1322331     | 178         | 226               |          |            |
|              | allele: T     | 20          | 26                |          |            |
|              | allele: G     | 340         | 336               |          |            |
|              | rs4917933     | 124         | 155               |          |            |
|              | allele: A     | 236         | 209               |          |            |
|              | allele: G     | 13          | 22                |          |            |
|              | rs625039      | 347         | 342               |          |            |
|              | allele: A     | 13          | 22                |          |            |
| Moon, 2013   | CHL1          | 35          | 68                | (Allele) | (n)         |
|              | rs10510181    | 30          | 40                |          |            |
|              | DSCAM         | 24          | 33                |          |            |
|              | rs2222973     | 22          | 23                |          |            |
|              | LAPTMB4       | 22          | 25                |          |            |
|              | rs2449359     | 17          | 19                |          |            |
|              | FOXB1         | 16          | 17                |          |            |
|              | rs1437480     | 12          | 15                |          |            |
|              | CBLN4         | 12          | 15                |          |            |
|              | rs448013      | 10          | 12                |          |            |
|              | RRAGC         | 10          | 12                |          |            |
|              | rs10493083    | 10          | 12                |          |            |
|              | BRIP1         | 10          | 12                |          |            |
|              | rs1695692     | 10          | 12                |          |            |
|              | MATN1         | 10          | 12                |          |            |
|              | rs1149048     | 10          | 12                |          |            |
|              | MTNR1B        | 10          | 12                |          |            |
|              | rs4753426     | 10          | 12                |          |            |
|              | IGF1          | 10          | 12                |          |            |
|              | rs5742612     | 10          | 12                |          |            |
| Author, year | Affected gene | Sample size | Frequency in cases | Statistical association |
|-------------|---------------|-------------|--------------------|------------------------|
|             |               | Cases | Controls | Cases | Controls | P value | Odds ratio |
| Nikolova, 2016 | Gene: IL-6 | 105 | 210 | (%) | (%) | <0.0001* | |
|             | rs1800795 | (G = Risk Allele) | | GG: 51.0 | CG: 44.8 | CC: 10.5 | G: 70.5% | 0.84 (0.36–1.94) | |
| Ogura, 2013 | rs7613792 | 2117 | Not Reported | Not Reported | 0.66 | 1 | 0.99 (0.23–4.15) | 1 |
|             | rs16902899 | | | | 1 | N/A | | |
|             | rs2700910 | | | | | | | |
|             | rs10787096 | | | | | | 1 | 1.39 (0.31–6.24) | |
|             | rs1558729 | | | | | | 1 | N/A | |
|             | rs17635546 | | | | | | 1 | N/A | |
| Sadler, 2019 | Gene: SH2B1 | 1197 | 1664 | (n) | (n) | Dup: 0.42 | |
|             | 1q21.1 | | | | | Del: 0.07 | |
|             | 2q13 | | | | | Del: 0.56, Dup:1 | |
|             | 15q11.2 | | | | | Del: 0.42 | |
|             | 15q13.3 | | | | | Del: 0.66 | |
|             | 16p13.11 | | | | | Del: 0.42, Dup: 0.66 | |
|             | Distal 16p11.2 | | | | | Del: 0.18 | |
|             | Proximal 16p11.2 | | | | | | | |
|             | HNPP/CMT1A | | | | | | | |
|             | 17q12 | | | | | | | |
|             | DiGeorge/VCFS | | | | | | | |
| Sharma, 2011 | Gene: CHL1 | 375 | 444 | (n) | | S: 0.43 | |
|             | rs1400180 | | | | | Del: 0.07 | |
|             | rs9754850 | | | | | Del: 0.56, Dup:1 | |
|             | rs9754552 | | | | | Del: 0.42 | |
|             | rs10510181 | | | | | Del: 0.66 | |
| Takahashi, 2018 | Gene: LBX1 | 2191 | | (n) | | TT: 818 | |
|             | rs11190870 | | | | | TC: 865 | |
|             | | | | | | CC: 177 | |
| Takeda, 2017 | Gene: TBX6 | 94 | | (n) | | SSS: 5 | |
|             | 16p11.2del | | | | | Del: 1 | |
|             | c.699G>A | | | | | Del: 1 | |
|             | c.156delG | | | | | Del: 1 | |
|             | c.935_936insGA | | | | | Del: 1 | |
|             | c.333G>T | | | | | Del: 1 | |
| Wang, 2008 | Gene: TPH1 | 103 | 108 | SS | (%) | 0.0003* | 2.909 |
|             | Allele A of rs10488682 | | | | | 7.9 | |
|             | A/A homozygote genotype | | | | | 9.9 | |
|             | | | | | | 15.7 | 39.8 | |
| Wang, 2020 | Missense variant in ESR1 (c.868A>G) | 113 | | Not Reported | Not Reported | 0.026* | 0.014* |
|             | Missense variant in ESR2 (c.236 T>C) | | | | | | | |
| Wu, 2006 | PvuII, XbaI polymorphisms of Estrogen Receptor Gene | 174 | 202 | (n), (%) | (n), (%) | 0.53 | 1.29 |
|             | PPXX | | | | | 13, 7.47 | |
|             | PXX | | | | | 13, 7.47 | |
|             | PPXX | | | | | 14, 8.05 | |
|             | PpXX | | | | | 18, 9.40 | |
|             | PpXX | | | | | 21, 10.40 | |
|             | PpXX | | | | | 28, 13.86 | |
|             | PpXX | | | | | 32, 15.84 | |
|             | PpXX | | | | | 17, 9.77 | |
|             | ppXX | | | | | 11, 5.56 | |
|             | ppXX | | | | | 12, 6.07 | |
|             | ppXX | | | | | 15, 7.82 | |
|             | ppXX | | | | | 18, 9.09 | |
especially significant because TBX6 is related to somite development critical to the axial skeleton [38]. TBX6 compound inheritance has also been shown to lead to congenital vertebral malformations in humans and mice [39], which was the associated pathology reported by Takeda and colleagues [29]. The TBX6 gene was also targeted for testing independently by Takeda et al. and Zhao et al. Unfortunately, these studies did not provide statistical comparisons [4, 29].

Kotwicki, Wang, and Wu et al. looked at estrogen receptors genes, but only the latter two found significant statistical association [16, 28, 30]. These data points reflect the controversial role of estrogen in IS. Estrogen’s role in growth regulation and adaptation has been a target for therapy, especially in adolescents, but these therapies have come with their criticisms [35]. Furthermore, in a study performed by Rusin et al., an asymmetric expression of ESR2 in deep paravertebral muscles was discovered to favor the side of convexity of the spinal curve in IS patients, supporting the idea of a correlation between estrogen and IS [40]. Unfortunately, it is not yet clear whether these findings are causes or consequences of the onset of IS [33].

Three studies focused on the LBX1 gene [17, 18, 20], with two of them finding statistically significant associations with the onset of IS [15, 16]. LBX1 mutations have been linked to disruption of paraspinal development, which is regulated by the WNT/beta-catenin pathways.

| Author, year | Affected gene | Sample size | Frequency in cases | Statistical association |
|--------------|---------------|-------------|-------------------|------------------------|
| Xu, 2015     | allele G of rs12618119; allele A of rs9945359; allele T of rs4661748; allele C of rs4782909 | 990 1188 | 55 (5%) 40 (4%) 46.5 (5%) 22.6 (19.4%) 15.6 (47.4%) 42.4 | <0.001* 1.29 |
| Xu, 2020     | Gene: SLC39A8 rs11097773 | 192 192 | (G = Risk Allele) | 0.01* 0.486 |
| Yilmaz, 2012 | MCM6 (6p21); MATN1 (1p35); VFR (12q13.1) | 54 53 | (n), (%) | 0.97 1.16 (0.3–4.0) |
| Zhao, 2009   | Gene: CALM1 rs12885713; rs5871; Gene: ER1 rs223469 | 67 100 | (n), (%) | 0.034* 0.061 0.014* |
| Zhao, 2020   | Gene: TBX6 16p11.2del | 447 | (n) | Not Reported |
| Zhou, 2012   | Gene: IL-17RC allele G of rs708567; GG genotype | 529 512 | 55 (96) 59 (44) 41 (30.6) | 0.028* 0.023* |
| Zhu, 2014    | Gene: SOCS3 rs4969168 | 398 367 | (n) | 0.087 A: 0.835 |

* Case: Control risk allele frequencies; $Case: Control risk allele frequencies; $5$ percentage of patients and controls with variant gene/deletion; $5$ number of patients with variant gene/deletion; * $p < 0.05$
| Study             | D1 | D2 | D3 | D4 | D5 | D6 | D7 | Overall |
|------------------|----|----|----|----|----|----|----|---------|
| Alden, 2006      | +  | -  | +  | +  | +  | +  | +  | -       |
| Borysiak, 2020   | +  | +  | +  | -  | +  | +  | +  | -       |
| Buchan, July 2014| +  | +  | +  | -  | +  | +  | +  | -       |
| Buchan, May 2014 | -  | +  | +  | -  | +  | +  | +  | -       |
| Kotwicki, 2014   | +  | +  | +  | +  | +  | +  | +  | +       |
| Kou, 2019        | +  | +  | +  | +  | -  | +  | +  | +       |
| Liu, 2017        | +  | +  | +  | -  | +  | +  | +  | -       |
| Moon, 2013       | +  | +  | -  | +  | -  | +  | +  | -       |
| Nikolova, 2016   | +  | -  | +  | +  | -  | +  | +  | -       |
| Ogura, 2013      | +  | +  | +  | +  | +  | +  | +  | +       |
| Sadler, 2019     | +  | +  | +  | +  | -  | +  | +  | -       |
| Sharma, 2011     | +  | +  | +  | +  | +  | +  | +  | +       |
| Takahashi, 2018  | +  | +  | +  | +  | -  | +  | +  | -       |
| Takeda, 2017     | +  | -  | +  | +  | -  | +  | +  | -       |
| Wang, 2008       | +  | +  | +  | +  | +  | +  | +  | +       |
| Wang, 2020       | +  | +  | +  | +  | +  | +  | +  | +       |
| Wu, 2006         | +  | +  | +  | +  | +  | +  | +  | +       |
| Xu, 2015         | +  | +  | +  | +  | +  | +  | +  | +       |
| Xu, 2020         | +  | +  | +  | +  | -  | +  | +  | -       |
| Yilmaz, 2012     | +  | +  | +  | +  | +  | +  | +  | +       |
| Zhao, 2009       | +  | +  | +  | +  | -  | +  | +  | -       |
| Zhao, 2021       | +  | +  | -  | +  | +  | +  | +  | -       |
| Zhou, 2012       | +  | +  | +  | +  | +  | +  | +  | +       |
| Zhu, 2014        | +  | +  | +  | +  | +  | +  | +  | +       |

Domains:
- D1: Bias due to confounding.
- D2: Bias due to selection of participants.
- D3: Bias in classification of interventions.
- D4: Bias due to deviations from intended interventions.
- D5: Bias due to missing data.
- D6: Bias in measurement of outcomes.
- D7: Bias in selection of the reported result.

Judgement:
- Low
- Moderate
function and motor adaptation leading to the asymmetry in the CNS may impair somatosensory system (CNS) could predispose to AIS [43]. The studies reported that abnormalities in the central nervous system (CNS) could impair somatosensory function and motor adaptation leading to the asymmetry of the neuromuscular condition [43].

The LBX1 gene, beyond playing a role in embryological muscle development also specifies distinct neuronal subtypes in the spinal cord [42]. LBX1 expression creates a distinction between two neuronal classes generated in the dorsal spinal cord and functions as a selector gene in the fate determination of somatosensory relay neurons [42]. When gait parameters of IS patients were investigated, somatosensory dysfunction showed an impact on dynamic balance control, which may play a role in etiology. Unfortunately, this is another instance where it is unclear whether it is a cause or consequence of IS onset [42].

However, both LBX1 and CHL1 influence the CNS and have both been statistically associated with IS onset.

Data on genetic correlations with IS onset would benefit from some standardizing measures, including more consistent reporting of odds ratio and p-value as statistical measures, a standardized measure for reporting allele frequency, clearer inclusion and exclusion criteria for participants, and more participant data, including sex, age of IS onset, and ethnicity. These measures could improve the quality of preliminary data and allow for a more in-depth and accurate exploration of the genetic correlations with IS onset and facilitate comparison across different studies.

Limitations

The present review has some limitations. The study did not collect data from randomized control trials and included some low-quality studies.

Secondly, the meta-analysis of results could not be performed due to the heterogeneity of the collected data. Only English-language articles were included, limiting the number of eligible articles. Most of the included studies did not distinguish between early-onset and late-onset scoliosis. This is a limitation because the information on the age of onset may have been relevant in understanding the function of the identified genes, or possibly allowed for discrimination between genes identified in early and late-onset.

Another important point to mention is that due to the complexity of this topic contradicting data was sometimes found when searching for genetic correlations to the onset of IS likely due to its complex and multifactorial nature. The discrepancy between Moon et al. and Sharma et al. results regarding the same gene serves as an example.

Furthermore, the present study does not consider the ethnicity of patients and consequentially the possible genetic differences between ethnic groups in relation to the onset of IS. Although more literature on the subject is required studies have reported differences in the prevalence of IS across various races [44, 45]. For example, a retrospective study by Kebaish et al. found that the prevalence of scoliosis was higher in whites (11.1%) compared to African Americans (6.5%) [44]. However, this parameter was not considered because it was not reported in included studies. The lack of data on ethnicity highlights the need to include this parameter in future studies.

Conclusions

Several studies show an association between the development of scoliosis and specific genes, SNPs, CNVs and markers. Therefore, identifying genes directly linked to the onset of scoliosis would represent a turning point in the diagnosis and treatment of this condition. However, it is not possible to draw a conclusion, due to the lack of high-quality evidence. For this reason, more numerous and higher-quality studies are needed.

Abbreviations

AIS: Adolescent Idiopathic Scoliosis; CS: Case series; CC: Case–Control; CS: Cohort studies; CNV: Copy number variant; EOS: Early onset scoliosis; ESRs: Estrogen Receptor genes; GWAS: Genome wide association studies; IS: Idiopathic Scoliosis; NRCT: Non-Randomized Controlled Trials; PS: Prospective studies; RCT: Randomized Controlled Trials; RS: Retrospective studies; SNPs: Single nucleotide polymorphisms.

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