Review Article

The Role of Melatonin Receptor Genes and Estrogen Receptor Genes in the Pathogenesis of Adolescent Idiopathic Scoliosis: A Systematic Review

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Abstract

Objective: Adolescent idiopathic scoliosis (AIS) is the most common spinal deformity affecting healthy children. Genetic factors are thought to play a role in the etiology of this condition, along with other factors. The occurrence of the condition in twins, its early onset, and its familial predilection all support the possibility of an underlying genetic cause. This article aims to review the published studies that looked at the association of estrogen and melatonin receptor (*ESR* and *MTNR*) genes with the pathogenesis of AIS, to serve as a guide for future work and opportunities in this field. **Methods:** The following databases were searched: Cochrane, PubMed, Medline, Ovid, ProQuest, and ScienceDirect using relative keywords. The analysis included 14 studies. **Results:** Of 312 identified studies, only 14 studies (nine for *ESR* gene and five for *MTNR* gene) met our inclusion criteria. Only one study found an association between AIS susceptibility and *xbal* polymorphism on *ESR1* gene. *MTNR* genes were found to be associated with AIS occurrence in large populations or when synergizing with other gene single-nucleotide polymorphisms. *MTNR* gene studies showed no relation with curve severity, and none of them considered curve progression, whereas five *ESR* gene studies considered curve progression and severity. Due to the different gene loci examined in various studies, pooled analysis of the results was not possible. **Conclusion:** We reviewed the genetic association of *ESR* and *MTNR* genes. Several studies found supporting evidence for both genes and their association with AIS, despite conflicting results. Further studies on different genes and different ethnic backgrounds are needed.

Keywords: Adolescent idiopathic scoliosis, estrogen receptor genes, genetics, melatonin receptor genes, pathogenesis

Introduction

Significant advances have been made in the past decades in the field of medicine in general and in identifying the genes responsible for particular diseases, which have led to specific therapy targeted at the affected gene(s). The same approach was used in the field of orthopedics, for example, in osteoarthritis, a disease that affects a large number of elderly population worldwide, where microRNAs are believed to play a role in chondrogenesis and osteoarthritis pathogenesis.[1] Another condition that affects millions of people; degenerative disc disease and various genes were studied and were found to have single-nucleotide polymorphism (SNPs) supporting the idea that up to 75% of intervertebral disc degeneration is thought to be genetically related.[2] Identifying the genes responsible for a particular disease forms the basis for gene therapy. Many studies have been published on the pathogenesis of adolescent idiopathic scoliosis (AIS), a relatively common condition, affecting 2%–4% of adolescents,[3] with a higher prevalence in females,[4] but its main cause remains unknown. There are many theories concerning the pathogenesis of AIS; these include genetic predisposition,[5-7] abnormal growth, hormonal disturbance, biomechanical factors,[8,9] and developmental neuromuscular dysfunctions.[10] Although

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one factor cannot explain all the clinical characteristics of AIS, the genetic factor seems to play a significant role in its pathogenesis.

Several studies also suggested that the causation of AIS is multifactorial and is strongly associated with genetics as it can be found in different members of the same family.[11,12] A recent Swedish study of twins estimated that overall genetic effects accounted for 38% of the observed phenotypic variance.[13] Of testing 30 candidate genes, 18 unique loci were identified suggesting that AIS might be due to genes segregating in populations.[14] Although not yet confirmed, it is suggested that AIS is a complex genetic trait influenced by multiple predisposing factors.[15] Of the multiple factors that play a role in the pathogenesis of AIS, the genetic factors are the most widely studied with conflicting results.

Various genes were studied to locate the gene(s) with the strongest association with AIS, which will later be of great value to identify those at risk of developing the disease or maybe developing a therapy for AIS at the genetic level.[16,17] Estrogen receptor *(ESR)* genes and melatonin receptor *(MTNR)* genes are among the most studied genes in the pathogenesis of AIS with variable results. The purpose of this systematic review is to look at the association of *ESR* and *MTNR* genes with the pathogenesis of AIS, emphasizing the strength, weakness, and results of each publication and to serve as a guide for future work and opportunities in this field. In addition to being two of the most extensively studied genes, we choose *ESR* and *MTNR* genes because curve pathogenesis in AIS patients coincides with growth and adolescence.[14] In females, the high estrogen produced in early puberty is extremely important in regulating the growth of the skeleton and maintaining the mass and strength of bone.[18] *ESR* gene has been shown to be expressed in both human osteoblasts and osteoclasts, and mutations of the *ESR1* gene were shown to reduce bone density and delay skeletal growth in affected humans.[12,19-26] Moreover, the female-to-male ratio ranges from 1.5:1 to 3:1 and increases substantially with increasing age.[27] The female-to-male ratio rises with the severity of the curve from 1.4:1 in curves from 10° to 20° up to 7.2:1 in curves >40°.[27] This supports the hypothesis that any mutation affecting the pathway modulating estrogen effect can lead to disturbance in bone growth and maturation. This hypothesis has driven many to study the association of SNPs in the *ESR* genes and AIS etiology.

In an experimental pinealectomy by Thillard in 1959 on newborn chicken, chicken with low melatonin levels developed a spinal deformity similar to scoliosis in humans.[28] This has led many studies to investigate melatonin levels in AIS patients.[29] However, no significant difference in melatonin levels was found between patients and controls.[30] This suggested that AIS in humans may be caused by another component of the melatonin signaling pathway. Theories suggesting melatonin dysfunction as a cause for abnormal skeletal growth were tested,[31] along with the *MTNR* gene as candidates for AIS etiology.

We aim to review the published studies that looked at the association of *ESR* and *MTNR* genes with the pathogenesis of AIS, emphasizing the strength, weakness, and results of each publication and to serve as a guide for future work and opportunities in this field.

Materials and Methods

This systematic review was confirmed to the Preferred Reporting Items for Systematic Review and Meta-Analyses guidelines.

Search strategy

Cochrane, PubMed, Medline, Ovid, ProQuest, and ScienceDirect databases were searched for case–control studies that examined the association between *ESR* gene or *MTNR* gene and AIS. Published articles from 1966 up to February 19, 2017, using the following keyword search string: (Adolescent idiopathic scoliosis OR familial idiopathic scoliosis) AND (estrogen receptor gene OR melatonin receptor gene) were identified. Reference lists of included studies were inspected for additional relevant studies. Furthermore, language restriction was applied (only English language), and no publication date restrictions were applied.

Study selection

Search results were screened independently by four reviewers. Disagreements between reviewers were resolved by discussion until consensus was reached. Level 1 screening consisted of evaluating all available information returned by the electronic search (e.g., abstract, title, and keywords). Level 2 screening consisted of evaluating full-text reports for studies deemed potentially eligible after Level 1 screening or for which insufficient information was available to determine eligibility (e.g., no abstract).

Inclusion and exclusion criteria

The selected studies met the following inclusion criteria: (1) case–control study; (2) English language; (3) AIS diagnosed based on clinical and/or radiological examination; and (4) investigated and reported an association between *ESR* gene or *MTNR* gene and AIS. The following are the exclusion criteria: (1) reviews or case reports that were not case–control studies; (2) articles written in a language other than the English language; (3) articles looking at signaling pathway or not directly studying the gene receptors; and (4) duplicate publications.

Methodological quality assessment

The methodological quality of the studies was assessed independently by two reviewers, using a modified version of the Newcastle-Ottawa Scale (NOS) for observational studies (case–control). Disagreements between reviewers were resolved by discussion until consensus was reached. Studies with a score of 5 or higher were deemed satisfactory and considered of high methodological quality.

Results

Study inclusion and characteristics

Figure 1 provides a summary of the study identification and selection process. A total of 312 studies were identified. After scanning the titles and abstracts, 27 full-text articles were assessed for eligibility. Of those, only 14 studies with a total of 10,187 participants (5344 patients/4843 controls) met the inclusion criteria. The characteristics of nine studies examining the association between different loci of the *ESR* genes and AIS are shown in Table 1. Four studies were conducted in Chinese populations, two in Japanese populations, two in Caucasian populations, and one in an Italian population. Six of the nine studies recruited only female cases and controls, while the other three studied recruited cases at a female-to-male ratio of approximately 7.5:1.

Table 2 shows the characteristics of five studies examining the association of different loci of the *MTNR* genes and AIS. Two studies were conducted in Chinese populations, another two were conducted in Caucasian populations, and one study was conducted in a Japanese population. Four of the five studies recruited only female cases. One study recruited 47 families with a total 177 individuals (113 affected/64 not affected). Reporting quality of the included studies was comparatively distinct, but sufficient information was presented to allow for proper assessment of the methodology. All studies assessed using the NOS were of excellent methodological quality, apart from some concerns.

Predisposition

Of the nine studies that looked into the association of *ESR* genes polymorphisms and AIS, five studies thought of *ESR* gene as a predisposing factor to AIS.

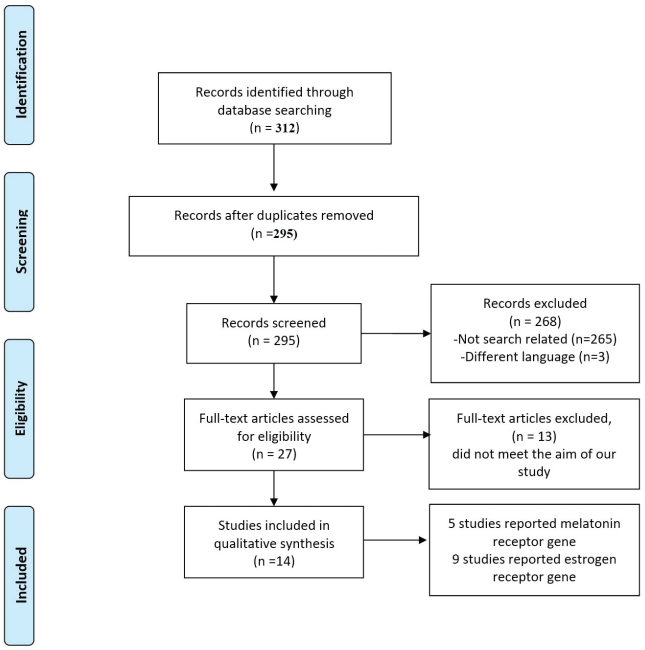

Figure 1: Flow diagram of the study identification and selection process

In a Chinese study by Wu *et al*., significant polymorphism in *xbal* was found in AIS patients compared to controls.[37]

Both Janusz *et al*. and Takahashi *et al*. found no association between the polymorphism of *xbaI* and the incidence of AIS.[35,36] Furthermore, Esposito *et al*. considered *xbaI, pstI, stuI,* and *mseI* polymorphisms on *ESR1* and did not find >1 mutation per sample.[33]

AlwNI, a locus on *ESR2* gene, was thought to play a part of curve predisposition; no association was found in Takahashi *et al*.'s study.[35]

Peng *et al*. studied the polymorphism of G-protein coupled receptor gene (*GPER*), another novel receptor of estrogen, and its association with curve onset; no association was found.[32]

Of the five studies that looked into *MTNR* genes polymorphisms as a potential factor in the etiology of AIS, three articles studied the polymorphism of rs4753426 in *MTNR1B* gene and its association with AIS. Morocz *et al*. studied the *MTNR1B* gene polymorphism among other genes of other receptors and hormones in Hungarians with AIS, and no association was found between *MTNR1B* polymorphism and the risk of AIS. However, a combination of leptin (*LEP*) and *MTNR1B* gene enhances the susceptibility of AIS.[39] The fact that two or more of predisposing genetic variants of AIS-related factors can be synergistic is foreseeable, giving the complexity of the disease.

A two-stage Chinese study of the same SNP among other four SNPs resulted in a significant association between rs4753426 in *MTNR1B* gene and predisposition to AIS, after a meta-analysis of the two. Another SNP (rs741837) in the promoter region was also marginally associated with the occurrence AIS.[41]

A replication study on a larger Japanese sample of 798 AIS patients found no significant association between the alleles frequency of the SNP and the predisposition in AIS patients.[40]

Qiu *et al*. found no association between rs2119882 in *MTNR1A* gene polymorphism and the occurrence of AIS.[38]

A linkage analysis by Morcuende *et al*. on 47 Canadian families with AIS found no relation between variant genetic polymorphisms of the *MTNR1A* gene and the expression of AIS phenotype.[12]

To summarize, only one study found an association between AIS susceptibility and *xbal* polymorphism on *ESR1* gene. Other studies showed no association. *MTNR* genes were found to be associated with AIS occurrence only in large population studies or when synergizing with other gene polymorphisms.

Severity

Eight of the nine studies about *ESR* gene polymorphism and its association with AIS considered *ESR* gene as a factor affecting curve severity.

Table 1: Study characteristics on the association between estrogen receptor gene single-nucleotide polymorphism and adolescent idiopathic scoliosis

Study	Gene	Genotyping method	Cobb angle	Case characteristics	Control characteristics	Result
Peng *et al*.[32]	GPER	TaqMan-based genotyping assay	>15°	*n*=389 AIS cases (336 females and 53 males) Chinese population	*n*=338 controls (289 females and 49 males) Chinese population	rs3808351: Related to curve severity (*P*=0.004) rs10269151: Related to curve severity (*P*=0.048) rs426655s3: Related to curve severity (*P*=0.028)
Esposito *et al*.[33]	ESR1 (alpha) XbaI, PstI, StuI, MseI	PCR-RFLP	Not mentioned	*n*=174 AIS cases Italian population	*n*=104 controls Italian population	rs9340799: No relation PstI, StuI, MseI: No relation
Kotwicki *et al*.[34]	ESR2 (beta)	PCR-RFLP	Not mentioned	*n*=248 female AIS cases Caucasian (polish) population	*n*=243 female controls Caucasian (Polish) population	rs4986938: related to severity (*P*=0.002) rs1256120: No relation rs1256049: No relation
Takahashi *et al*.[35]	ESR1 (alpha) XbaI ESR2 (beta) AlwNI	PCR-based invader assay	>15°	*n*=798 female AIS cases Japanese population	*n*=637 female controls Japanese population	rs9340799: No relation rs1256120: No relation
Tang *et al*.[15]	ESR1 (alpha) XbaI, PvuII	PCR-RFLP	>20°	*n*=540 female AIS cases Chinese population	*n*=260 female controls Chinese population	rs9340799: No relation rs2234693: No relation
Janusz *et al*.[36]	ESR1 (alpha) XbaI, pvuII	PCR-RFLP	>10°	*n*=287 AIS female cases Caucasian population	*n*=182 female controls Caucasian population	rs9340799: No relation rs2234693: No relation
Zhao *et al*.[10]	ESR1 (alpha) PvuII	PCR-RFLP	>30°	*n*=67 AIS cases (60 females and 7 males) Chinese population	*n*=100 controls (75 females and 25 males) Chinese population	rs2234693: Relation to double curve, cobb angle >40°, and thoracic curve, (*P*=0.014, 0.0128, 0.0184 respectively)
Inoue *et al*.[20]	ESR1 (alpha) XbaI, pvuII	PCR-RFLP	>10°	*n*=304 AIS female cases Japanese population		rs9340799: relation to severity, thoracic curve, double curve and progression (*P*=0.002, 0.036, 0.007, 0.01 respectively) rs2234693: No relation
Wu *et al*.[37]	ESR1 (alpha) XbaI, pvuII	PCR-RFLP	>20°	*n*=202 AIS cases (185 females and 7 males) Chinese population	*n*=174 controls (154 females and 20 males) Chinese population	rs9340799: relation to curve severity (*P*<0.001) rs2234693: no relation

GPER: G-protein coupled receptor, ESR: Estrogen receptor, PCR: Polymerase chain reaction, RFLP: Restriction fragment length polymorphism, AIS: Adolescent idiopathic scoliosis

Table 2: Study characteristics on the association between melatonin receptor gene single-nucleotide polymorphism and adolescent idiopathic scoliosis

Study	Gene	Genotyping method	Cobb angle	Case characteristics	Control characteristics	Result
Morcuende *et al*.[12]	MTNR1A	PCR-SSCP	>30°	*n*=113 AIS female cases Caucasian population	*n*=64 female controls Caucasian population	No relation
Qiu *et al*.[38]	MTNR1A	PCR-RFLP	>10°	*n*=226 AIS female cases Chinese population	*n*=277 female controls Chinese population	rs2119882: No relation
Mórocz *et al*.[39]	MTNR1B	PCR-RFLP	>45°	*n*=126 AIS cases Hungarians population	*n*=197 controls Hungarians population	rs4753426: No relation
Takahashi *et al*.[40]	MTNR1B	PCR-SSCP	>15°	*n*=798 AIS female cases Japanese population	*n*=1239 female controls Japanese population	rs4753426: No relation
Qiu *et al*.[41]	MTNR1B	PCR-RFLP	>20°	Stage I (*n*=472 female AIS cases) Stage II (*n*=342 female AIS cases) Chinese population	Stage I (*n*=304 female controls) Stage II (*n*=347 female controls) Chinese population	rs4753426: Relation with curve predisposition, not severity

PCR: Polymerase chain reaction, SSCP: Single strand conformation polymorphism, RFLP: Restriction fragment length polymorphism, AIS: Adolescent idiopathic scoliosis, MTNR: Melatonin receptor

In 2002, a Japanese study by Inoue *et al*. found a significant association between the *xbaI* polymorphism and curve severity but no association in *pvuII* polymorphisms.[20] Same results were found in 202 Chinese AIS patients in a study by Wu *et al*.[37] On the other hand, *pvuII* polymorphism affected curve severity significantly in a study by Zhao *et al*., but *xbaI* did not.[10] Janusz *et al*. and Takashi *et al*. found no association between curve severity and the polymorphism of *xbaI*.[35,36] Similarly, in a larger Chinese study, 540 cases of AIS were studied for SNPs in *xbaI* and *pvuII*, and no association was found with curve severity.[15]

Kotwicki *et al*. found a significant association between *AluI* (rs4986938) site on *ESR2* polymorphism and curve severity but not with *AlwNI* (rs1256120) and *RsaI* (rs1256049).[34]

The same *AlwNI* was thought to play a part in curve severity along with the *ESR1* by Takashi's study; no association was found.[35]

Peng *et al*. found an association between the polymorphism of *GPER* and curve severity.[32]

Three out of the five articles about *MTNR* gene polymorphisms studied its association with curve severity in AIS. Qiu *et al*. and Takahashi *et al*. found no association between rs2119882 polymorphism on *MTNR1A* gene and curve severity in AIS patients.[38,40] A two-stage study by Qiu *et al*. considered rs4753426 locus among other four loci on the *MTNR1B* gene. None of the SNPs was related to curve severity in AIS patients.[41] A replication study by Takahashi *et al*. found no significant association between the alleles frequency of the SNP and curve severity in AIS patients.[40]

To summarize, most of the studies on *ESR* genes polymorphisms included in this review found an association with curve severity in AIS patients in different loci of the genes. None of the studies of *MTNR* genes showed association with severity.

Progression

Progression is defined as >5° increase in Cobb angle from the initial assessment.[42]

Five of the estrogen studies concluded that ESR gene polymorphism as a factor affecting curve progression in AIS patients. Inoue *et al*. found an association between *xbal* and curve progression, but there was no association with *pvull*.[20] These results could not be replicated in a study by Tang *et al*., who found no association between *xbaI* and *pvuII* with curve progression.[15] Similarly, both Janusz *et al*. and Takashi *et al*. found no association between the *xbal* polymorphism and curve progression.[35,36]

A polish study by Kotwicki *et al*. found a significant association between *AluI* (rs4986938) site on *ESR2* polymorphism and curve progression but not with *AlwNI* (rs1256120) and *RsaI* (rs1256049).[34] The same *AlwNI* was also investigated by Takahashi *et al*., and no association was found.[35]

None of the studies about *MTNR* genes polymorphisms considered the progression of AIS.

Discussion

Despite extensive research to know the etiology of AIS, it remains obscure. It is estimated that >30 genes have been studied as candidate genes contributing to susceptibility, severity, and progression of AIS.[14] Among them are the genes responsible for the connective tissue in bone structure. These include genes encoding fibrillin, elastin, collagen I, and collagen II. Studies have shown no association between these genes and AIS.[43-45] Matrilin, a gene encoding matarlin protein (cartilage matrix protein) involved in the formation of filamentous networks in the extracellular matrices of various tissues, including bone matrix, have been found to be associated with AIS in Italian and Chinese studies.[12,42,46] However, a larger Japanese cohort study of (789 cases/1239 controls) found no association.[40]

Matrix metalloproteinase (*MMP-3)* is an enzyme, which degrades fibronectin, laminin, collagens III, IV, IX, and X, and cartilage proteoglycan. The gene encoding this enzyme and their inhibitors (tissue inhibitors of metalloproteinases) have been studied for the association with AIS. *MMP-3* was associated with AIS in a small Italian study.[47] However, neither the association was detected in a larger Chinese study,[48] nor was it directly associated with AIS in a Hungarian sample.[39]

Other sets of genes that were considered are those responsible for bone metabolism, most commonly interleukin 6 (IL-6), leptin (LEP), Bone morphogenetic protein 4 (BMP 4). These genes were studied in a Hungarian sample, along with the *MTNR* 1B gene. No association was found between independent SNPs and AIS.[39] However, *IL-6* was found to be associated with AIS predisposition in a small Italian study.[47] Neither this was confirmed either in a larger Chinese cohort study,[48] nor the previously mentioned Hungarian study.[39] In the same Hungarian sample, Morocz *et al*. found a synergistic effect of paired SNPs on the risk of AIS formation.

In a small Chinese study, calmodulin 1 receptor gene (*CALM1*) was associated with the predisposition of a double curve.[49]

In a Japanese study with a sample of 304 females with AIS, Vitamin D receptor (*VDR*) gene was not associated with the progression of AIS.[20] However, in a Korean study, it was found that *VDR* is associated with low bone mineral density and double curve formation.[50]

In a case-only Korean study, receptor activator of nuclear factor-κB (*RANK*), now known as tumor necrosis factor receptor superfamily member 11a (NFKB) activator (*TNFRSF11A*), as well as a *RANK* ligand , was not associated with AIS.[51] The same study found an association between osteoprotegerin, now known as tumor necrosis factor receptor superfamily member 11B (*TNFRSF11B*), and low bone mineral density.

To summarize, studies of genes responsible for connective tissue and bone metabolism that showed association with AIS were small studies that may have been underpowered. Larger studies of the same genes were not able to replicate the

same results. Further studies with larger samples and different races are required to determine which genes play a role in the etiology of AIS.

Although proper case selection was done in all the included studies, only five studies selected controls from the community,[34,38-41] and other studies either recruited controls from the hospital or did not mention further details about controls. This makes it difficult to assess for selection bias. Population stratification could confuse the genetic associations by making false associations. No population stratification was mentioned in any of the 14 studies [Supplement Tables 1and 2].

It is apparent that the effort to know the genetic etiology and progression of AIS was distributed toward different directions. Over time, studies were directed towards genes showing more promising results. And even then, researchers have tried to search for different loci in the same gene. A pooled analysis of different studies is only possible if they considered the same locus of a specific gene. Since this review included both *ESR* genes and *MTNR* genes, there are a large number of loci that cannot be pooled together. Nonetheless, six out of the nine studies about *ESR* genes considered *xbal* as a potential locus for predisposition, severity and progression. Another locus that was considered in five out of the nine *ESR* genes studies is *pvull*. Each locus can undergo pooled analysis separately. A systematic review and meta-analysis of the famous *xbal* and *pvull* loci on the *ESR1* gene was carried by Yang in 2014. The review included five Asian articles[10,15,35,37,49] and a Polish article[36] concluded no obvious association between *xbal* and *pvull* and the risk of developing AIS.[52] Another systematic review was done analyzing four studies about the *xbal* association to the risk of developing AIS. No association was found.[15,35-37] Of note, the *xbal* could be associated with severity and progression of the curve rather than being a predisposing locus.[53]

Zhao *et al*. did a systematic review and meta-analysis involving a locus in the *ESR2* (rs1256120). Three studies of Chinese,[49] Japanese,[35] and Caucasian[34] populations were analyzed and concluded that the rs1256120 is neither a predisposing factor nor a disease-modifying gene.[54]

As for the *MTNR* genes associated with AIS, three studies about *MTNR1B* gene considered rs4753426 as a potential predisposing locus for AIS. A systematic review and meta-analysis carried by Yang *et al*. included four out of the five *MTNR* studies found a significant association between a rs4753426 polymorphism in the *MTNR1B* gene and AIS,[38-41] especially in the Asian population.[55]

The same locus was considered with another locus from the *MTNR1B* (rs4753426) in another systematic review of Asian and Caucasian populations in five studies. The study found no obvious association between the two loci and the risk of developing AIS.[56]

Studies included in this review were confined in certain geographical areas. The Chinese population studied in six of the fourteen articles, followed by Caucasians and then Japanese populations. Only one study included Italian population. To our knowledge, there are no studies about *ESR* genes or *MTNR* genes association with AIS in Saudi Arabia. Al-Othman *et al*. recruited 100 AIS girls and their parents and healthy siblings for genetic analysis of three different markers (D19S216, D19S894, and DS1034) on chromosome 19p13.3., and the marker DS1034 was significantly associated with AIS patients and their fathers.[57]

A weakness of the current review is our inability to perform pooled analysis of the results due to the heterogeneity of the studied gene receptors in various studies. We thought despite this weakness, including all relevant studies would help us gather more information about the predisposition, curve severity, and progression with these receptors genes.

Conclusion

The exact cause of AIS remains unknown, despite years of research looking at the multiple potential causative factors. The strong familial predisposition to the condition along with the findings in twin studies favors the role of genetics in the pathogenesis of AIS. Out of the many genes that have been studied, *ESR* and *MTNR* genes are two of the most studied genes with the most promising results. In this article, we reviewed the genetic association of *ESR* and *MTNR* genes. While *ESR* genes show more promising results, *MTNR* studies were insufficient. Moreover, the studies showed inconsistent results. More studies need to be conducted on the two receptors genes, in similar approaches.

Only specific region samples have been studied, most commonly in Southeastern Asia. Larger populations with different ethnic backgrounds should be studies as different results may be obtained. To our knowledge, there were no studies conducted in Saudi Arabia on *ESR* or *MTNR* genes. Candidate loci and other loci in these two genes should be studied on Saudi population.

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Nil.

Conflicts of interest

There are no conflicts of interest.

Authors' contributions

SAB designed the study, set inclusion and exclusion criteria and key words, conducted research, reviewed titles and abstracts, helped in reviewing included articles and wrote the initial and final draft. BFA helped in study design, set inclusion and exclusion criteria and key words, conducted research, helped in screening, assessed the methodological quality of the included articles, helped in writing the initial and final draft. AKH conducted research, helped in article screening, assessed the methodological quality of included articles, helped in writing the initial and final draft. TME conducted research, helped in article screening helped in writing the initial and final draft. SMF helped in study design, revised included articles,

helped in writing the initial draft, and provided logistic support. All authors have critically reviewed and approved the final draft and are responsible for the content and similarity index of the manuscript.

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