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Review Article

Association of estrogen receptor gene polymorphisms and idiopathic scoliosis: a meta-analysis

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Abstract: Idiopathic scoliosis (IS) is considered to be a multifactorial disease. There is some controversy regarding whether estrogen receptor (ESR) gene is associated with IS susceptibility. A systematic search in PubMed, EMBASE, and Cochrane CENTERAL database until the end of October 2015 were carried out. Pooled odds ratios (ORs) with 95% confidence intervals (CIs) were calculated using random or fixed effects model. Newcastle-Ottawa scale was used to evaluate the methodological quality, and Stata 11.0 was used to analyze data. The associations between XbaI, PvuII, AlwNI polymorphisms and IS susceptibility were investigated. Seven eligible case-control studies were included in our meta-analysis. The final results showed that no significant difference was detected in all genetic models in any of the three polymorphisms. In conclusion, this meta-analysis found a lack of significant association between any of the three estrogen receptor gene polymorphisms and IS risk. Additional high quality studies are still necessary to assist with this finding.

Keywords: Estrogen receptor, gene, polymorphism, SNP, idiopathic scoliosis

Introduction

Idiopathic scoliosis (IS), the most common spinal deformity in adolescents, is a complex, three-dimensional structural deformity of the spine [1]. Using a Cobb angle greater than 10° as the diagnostic criterion, the prevalence of IS was reported to range from 1% to 3% in adolescents [2, 3]. Without timely treatment, IS can lead to significant functional limitations and cosmetic problems.

Though a number of studies have investigated IS, the exact etiology of IS remains unknown. Some hypotheses have been proposed that IS is associated with abnormal growth, hormonal disturbance, and developmental neuromuscular dysfunction [4-6]. Currently, according to the most accepted view, IS is considered to be a multifactorial disease [7]. As a higher prevalence of IS exist in families than in the general population, genetic factors are also believed to play a contributing role [8].

In all evaluated genes, much attention has been paid to the estrogen receptor (ESR) gene, which belongs to the nuclear receptors superfamily of transcription factors [9]. ESR1 and ESR2 are two types of receptors that estrogen hormones can act through. In the ESR1 gene, XbaI polymorphism (rs9340799) and PvuII polymorphism (rs2234693) are two single-nucleotide polymorphisms (SNPs) that have been described to reveal an association with IS susceptibility [10, 11]. Association of the ESR2 gene polymorphisms has also been reported, and AlwNI polymorphism (rs1256120) is supposed to be an important SNP associated with IS [12].

Despite of various studies on the association of the ESR gene polymorphisms with IS susceptibility, these investigations have not yielded any conclusive evidence. Sometimes, a single study may be unable to detect a true association due to the relatively small sample size. Meta-analysis, on the other side, can increase the statistical power of the association analysis and obtain more precise estimates of effect by pooling the results of several studies. To our knowledge, no meta-analysis has comprehensively assessed the associations of ESR1 gene XbaI,

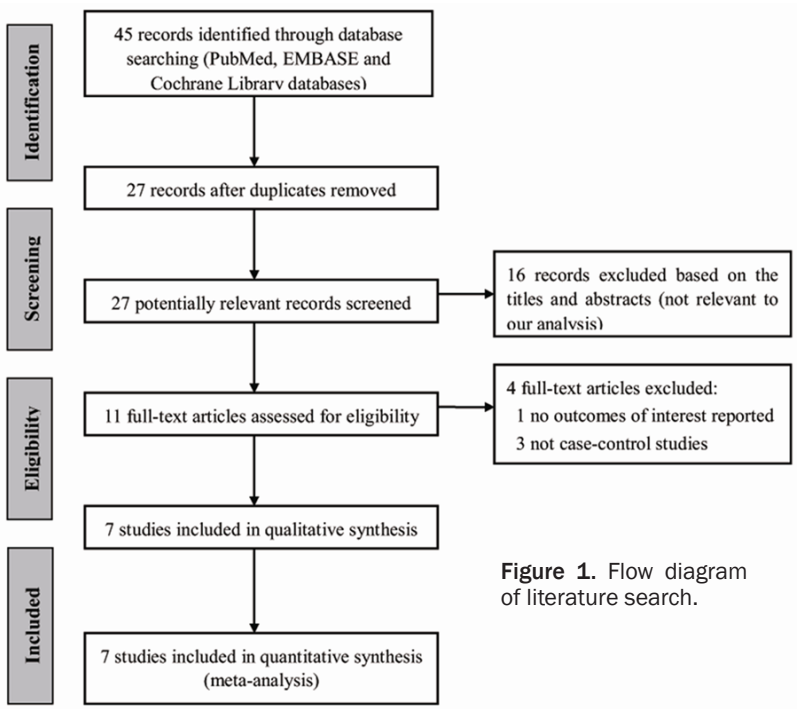

Figure 1. Flow diagram of literature search.

plication of previous publications; (b) comment, review or editorial; (c) studies without detailed data. If the same population was reported in several publications, we retained only the most informative article or complete study to avoid duplication of information.

Data extraction and quality assessment

The following contents were collected: name of first author, year of publication, country, ethnicity, genotyping methods, subject characteristics, number of cases and controls, genotype frequency in cases and controls.

PvuII, and ESR2 gene AlwNI polymorphisms with the risk of IS. Therefore, to derive the currently available evidence on association of the SNPs in ESR genes and IS, we conducted this systematic review and meta-analysis.

Methods and materials

Identification of eligible studies

A systematic search in PubMed, EMBASE, and Cochrane CENTERAL database until the end of October 2015 were carried out by two independent investigators. The following search terms were used: (idiopathic scoliosis) AND (XbaI OR PvuII OR AlwNI OR polymorphism) AND estrogen. The search was limited to human subjects and English-language. The reference of retrieved studies and recent reviews were manually searched until no additional articles could be identified.

Inclusion and exclusion criteria

Studies in this meta-analysis should meet the following inclusion criteria: (a) case-control design; (b) IS diagnosed on the basis of clinical and/or radiological examination; (c) investigating the association between XbaI, PvuII, AlwNI polymorphisms and IS; (d) providing detail frequencies of genotype. Exclusion criteria: (a) du-

The quality of the included studies was evaluated using a modified version of the Newcastle-Ottawa Scale (NOS) [13]. The quality score ranges from 0 to 9, and studies with a score of 5 or higher were considered as high methodological quality.

Data extraction and quality assessment were performed independently by two authors. Any disagreements were resolved by discussion and consensus.

Statistics analysis

The association strength between XbaI, PvuII, AlwNI polymorphisms and IS were measured by odds ratios (ORs) with 95% confidence intervals (CIs). The possible association between the ESR1a XbaI A/G polymorphism and the risk of IS was evaluated according to allele contrast (G versus A), co-dominant (GG versus AA, and GA versus AA), dominant (AG+GG versus AA), and recessive (GG versus AG+AA) models; the strength of association between the ESR1 PvuII T/C, the ESR2 AlwNI T/C polymorphisms and IS susceptibility was evaluated according to allele contrast (C versus T), co-dominant (CC versus TT, and CT versus TT), dominant (TC+CC versus TT), and recessive (CC versus TC+TT) models,

Table 1. General characteristics of studies included in this meta-analysis

Author	Year	Country	Ethnicity	Cobb angle (range)	Gender	Case	Control	Method	Mutations reported	Quality
Tang [10]	2006	China	Asian	NR	Female	540	260	PCR-RFLP	XbaI, PvuII	7
Wu [11]	2006	China	Asian	25-125	Female and male	202	174	PCR-RFLP	XbaI, PvuII	6
Zhang [12]	2009	China	Asian	12-135	Female and male	218	140	PCR, DHPLC	AlwNI	7
Zhao [17]	2009	China	Asian	30-90	Female and male	67	100	PCR-RFLP	PvuII	5
Takahashi [16]	2011	Japan	Asian	NR	Female	798	637	PCR-based invader assay	XbaI, AlwNI	6
Janusz [15]	2013	Poland	Caucasian	10-114	Female	287	182	PCR-RFLP	XbaI, PvuII	7
Kotwicki [14]	2014	Poland	Caucasian	10-114	Female	248	243	PCR-RFLP	AlwNI	7

NR, not reported; PCR, polymerase chain reaction; RFLP, restriction fragments length polymorphism analysis; DHPLC, denaturing high-performance liquid chromatography.

Table 2. Frequency of genotypes and the results of Hardy-Weinberg equilibrium test

Study ID		Case			Control			P_H
XbaI (rs9340799)		GG	GA	AA	GG	GA	AA	
Tang [10]	2006	36	176	328	18	85	157	0.40
Wu [11]	2006	54	76	72	26	66	82	0.13
Takahashi [16]	2011	24	248	526	20	196	421	0.89
Janusz [15]	2013	50	141	96	29	92	61	0.84
PvuII (rs2234693)		CC	CT	TT	CC	CT	TT	
Tang [10]	2006	93	246	201	30	128	102	0.56
Wu [11]	2006	39	92	71	40	70	64	0.06
Janusz [15]	2013	66	144	77	47	93	42	0.95
AlwNI (rs1256120)		CC	CT	TT	CC	CT	TT	
Zhang [12]	2009	36	105	77	10	55	75	0.99
Takahashi [16]	2011	99	368	331	79	306	252	0.64
Kotwicki [14]	2014	164	74	10	159	77	7	0.81

P_H, *P* for Hardy-Weinberg equilibrium.

respectively. Hardy-Weinberg equilibrium (HWE) was evaluated for each study by chi-square test in control groups, and $P < 0.05$ was considered a significant departure from HWE.

The heterogeneity was tested by a chi-square-based Q statistic test. The effect of heterogeneity was quantified by using an I^2 value as well as a *P* value. If the I^2 value was > 50% and $P < 0.10$, this suggested that an obvious heterogeneity existed, and ORs should be pooled by random effect model; otherwise, the fixed effect model was used. To explore the reliability of the results, we also performed a sensitivity analysis by excluding relatively low-quality studies and re-analysed the results.

Potential publication bias was detected by Begg's funnel plots, and $P < 0.05$ was judged as statistically significant. All statistical analyses were performed using STATA, version 11.0 (StataCorp, College Station, TX).

Results

Search results

A total of 45 records were selected from databases, but 38 records were excluded, of which 18 were duplicate ones, 16 were not relevant to our study, 3 were not case-control study, and 1 had no interested outcomes. Finally, 7 eligible case-control studies were included in our meta-analysis [10-12, 14-17]. **Figure 1** provides a summary of the study identification and selection process.

Study characteristics

The main characteristics of each study are shown in **Table 1**. Of these studies, 5 [10-12, 16, 17] were conducted in Asia, and 2 [14, 15] were in Europe. Different genotyping methods were utilized including polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP), polymerase chain reaction (PCR), denaturing high-performance liquid chromatography (DHPLC), and PCR-based invader assay. Four studies [10, 14-16] recruited only female in cases and controls, whereas the other 3 studies [11, 12, 17] included both male and female in studies. About the NOS scale, 4 studies [10, 12, 14, 15] scored 7, 2 studies [11, 16] scored 6, and 1 study [17] scored 5. All studies were of high quality.

Table 2 shows the frequency of genotypes and results of Hardy-Weinberg equilibrium test. No deviation from HWE was detected in the control subjects in any of the studies.

Main results

Association of XbaI polymorphism and IS susceptibility: Four studies reported the associa-

Table 3. Results on the association between the single nucleotide polymorphisms and idiopathic scoliosis

ESR gene polymorphisms	No. of studies	Pooled OR	LL 95% CI	UL 95% CI	*P* value	Effect model	Q-test (*P*)	I^2 (%)
XbaI (rs9340799) in ESR1 gene								
Allelic contrast (G/A)	4	1.12	0.91	1.38	0.30	Random	0.03	65.5
Co-dominant model (GA/AA)	4	1.03	0.89	1.21	0.69	Fixed	0.75	0
Co-dominant model (GG/AA)	4	1.25	0.81	1.93	0.31	Random	0.09	54.5
Dominant model (GG+GA/AA)	4	1.07	0.92	1.24	0.41	Fixed	0.22	31.9
Recessive model (GG/GA+AA)	4	1.25	0.95	1.64	0.11	Fixed	0.15	44.4
PvuII (rs2234693) in ESR1 gene								
Allelic contrast (C/T)	4	0.91	0.71	1.17	0.46	Random	0.03	66.9
Co-dominant model (CT/TT)	3	0.99	0.79	1.24	0.91	Fixed	0.59	0
Co-dominant model (CC/TT)	3	1.04	0.66	1.63	0.88	Random	0.10	55.8
Dominant model (CC+CT/TT)	3	1.01	0.82	1.25	0.92	Fixed	0.54	0
Recessive model (CC/CT+TT)	3	1.04	0.67	1.60	0.87	Random	0.07	63.2
AlwNI (rs1256120) in ESR2 gene								
Allelic contrast (C/T)	3	1.19	0.80	1.76	0.38	Random	< 0.01	85.1
Co-dominant model (CT/TT)	3	1.12	0.64	1.97	0.70	Random	0.02	75.6
Co-dominant model (CC/TT)	3	1.34	0.56	3.24	0.51	Random	< 0.01	80.2
Dominant model (CC+CT/TT)	3	1.18	0.61	2.26	0.62	Random	< 0.01	83.4
Recessive model (CC/CT+TT)	3	1.23	0.81	1.87	0.34	Random	0.06	64.2

ESR, estrogen receptor; OR, odds ratio; LL, lower limit; UL, upper limit; CI, confidence interval.

tion between XbaI polymorphism and the susceptibility to IS. Significant heterogeneity was identified by Q-test in allelic contrast (G/A) and co-dominant model (GG/AA), and random effect model was used. Other genetic models used fixed effect model. Overall, no significant association was identified in any genetic model (C versus G, OR = 1.12, 95% CI 0.91-1.38, *P* = 0.30; GA versus AA, OR = 1.03, 95% CI 0.89-1.21, *P* = 0.69; GG versus AA, OR = 1.25, 95% CI 0.81-1.93, *P* = 0.31; GG+GA versus AA, OR = 1.07, 95% CI 0.92-1.24, *P* = 0.41; GG versus GA+AA, OR = 1.25, 95% CI 0.95-1.64, *P* = 0.11) (**Table 3**).

Association of PvuII polymorphism and IS susceptibility: There were 4 studies reported the association between PvuII polymorphism and the risk of IS, but only 3 studies were available for analyzing genotypes. Significant heterogeneity was identified in allelic contrast (C/T), co-dominant model (CC/TT) and recessive model (CC/CT+TT), and random effect model was used. Other genetic models used fixed effect model. Overall, no significant association was identified in any genetic model (C versus T, OR = 0.91, 95% CI 0.71-1.17, *P* = 0.46; CT versus TT, OR = 0.99, 95% CI 0.79-1.24, *P* = 0.91; CC versus TT, OR = 1.04, 95% CI 0.66-1.63, *P* = 0.88; CC+CT versus TT, OR = 1.01, 95% CI 0.82-1.25, *P* = 0.92; CC versus CT+TT, OR = 1.04, 95% CI 0.67-1.60, *P* = 0.87) (**Table 3**).

Association of AlwNI polymorphism and IS susceptibility: Three studies investigated the association between AlwNI polymorphism and the susceptibility to IS. Significant heterogeneity was identified in all contrasts. Thus, only random effect model was used. As a result, no significant association was identified in any genetic model (C versus T, OR = 1.19, 95% CI 0.80-1.76, *P* = 0.38; CT versus TT, OR = 1.12, 95% CI 0.64-1.97, *P* = 0.70; CC versus TT, OR = 1.34, 95% CI 0.56-3.24, *P* = 0.51; CC+CT versus TT, OR = 1.18, 95% CI 0.61-2.26, *P* = 0.62; CC versus CT+TT, OR = 1.23, 95% CI 0.81-1.87, *P* = 0.34) (**Table 3**).

Sensitive analysis and publication bias

The exclusion of one study [17] with NOS score of 5 did not affect the statistical significance of any meta-analysis outcomes. Publication bias was not assessed owing to the limited number of included studies (< 10).

Discussion

Although the cause of IS remains unknown, most theories suggest that it is multifactorial with a strong genetic background [8, 18]. It is well known that even a minor variation in deoxyribonucleic acid could have enormous effect on the expression of different target genes and thus lead to the susceptibility of some diseases. In recent years, a series of studies evaluated the association between the ESR gene polymorphisms and IS susceptibility. But the results obtained were inconsistent or controversial [11, 15]. In this meta-analysis, 7 eligible studies were identified and analyzed. The final results showed that no significant difference was detected in all genetic models in any of the three SNPs, which means that we cannot demonstrate a significant association between XbaI, PvuII, AlwNI polymorphisms and IS yet.

In the ESR1 gene, 2 SNPs were described to be associated with IS. XbaI polymorphisms is one of the most commonly studied SNP in ESR1 gene, and various studies indicated that XbaI polymorphism was associated with the development of many diseases, such as Alzheimer's disease [19], breast cancer [20], endometriosis [21] and endometrial cancer [22]. In 2002, Inoue et al. reported that the XbaI polymorphism is associated with curve severity of IS [23]. Several years later, the study conducted by Wu et al. firstly reported a statistically significant association between XbaI polymorphism and IS risk. They also concluded that XbaI polymorphism was associated with curve severity and abnormal growth of patients with IS [11]. However, subsequent studies with larger sample sizes were unable to replicate this initial finding [15, 16]. In this meta-analysis, we pooled several results from eligible studies, and a significant association could not be found, which means that XbaI polymorphism is not a likely susceptibility locus for IS.

PvuII polymorphism is another important SNP site in ESR1, and it was also thought to be associated with many diseases [22, 24, 25]. Zhao et al. described association of PvuII polymorphism with double curve severe scoliosis in the Chinese population [17], whereas in other studies, the Pvu II site polymorphism did not show association with IS [15]. After all, previous studies did not make a definite conclusion. Based on the results of our meta-analysis, we cannot demonstrated that PvuII polymorphism is associated with the susceptibility of IS yet.

An important SNP in ESR 2 gene is AlwNI. In 2009, Zhang et al. analyzed it in Chinese population. They evaluated 218 patients with IS versus 140 healthy controls and found significant over-representation of the C allele and CC genotype in patients compared with controls. The CC genotype was associated with height 160 cm or more, with Cobb angle 30° or more and with menarche age 12 years or more [12]. However, their conclusion is based on a relatively small number of patients. In the present meta-analysis, a non-significant association was found, suggesting that there is a lack of association between AlwNI and IS.

Reporting quality among the included studies was comparatively lacking, but sufficient information was presented to allow an assessment of overall methodological quality. Based on the reported information, all included studies assessed with NOS score were of high methodological quality. The exclusion of one study [17] with NOS score of 5 did not affect the statistical significance of any meta-analysis outcomes, which means that the results were reliable to some extent.

Despite a lack of direct association with IS predisposition, there is some mixed evidence indicate that the SNPs may contribute to the curve severity of IS [23, 26]. We also cannot determine if these SNPs had other effects on the onset of disease. Potential functional roles of these SNPs and their impact on IS severity need to be explored in future studies.

This meta-analysis was conducted in a strict and comprehensive process, but there are still some potential limitations that should be noticed. First, patients included in this meta-analysis had different baseline characteristics, such as initial Cobb angle, genotyping methods and quality of study, which may lead to heterogeneity and affect the results eventually. Second, potential for selection bias cannot be adequately assessed, as case selection was not well described in some included studies and control selection was described in less detail compared to cases. This methodological flaw decreased the quality of studies to some extent although the overall quality of these studies was high. Third, both Asian and Caucasian were investigated by previous investigators. However, we did not clearly distinguish them and make a further subgroup analysis because of the relatively small numbers of studies in both subgroups. Consequently, the

quantitative results of this review should be interpreted with caution.

Despite the limitations mentioned above, this study is clinically valuable to some extent. The present systematic review provides a comprehensive examination of available evidence on the association between XbaI, PvuII, AlwNI polymorphisms and IS. Meta-analysis found a lack of significant association between any of these SNPs and IS risk. Considering the limitations listed above, additional high quality studies are still necessary to assist with this finding.

Disclosure of conflict of interest

None.

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