Association of ESRα Xbal A > G, ESRα PvuII T > C and ESRβ AlwNI T > C Polymorphisms with the Risk of Developing Adolescent Idiopathic Scoliosis: A Systematic Review and Genetic Meta-analysis

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Abstract

Several association studies of genes polymorphisms on estrogen receptors-α and β with respect to adolescent idiopathic scoliosis (AIS) have been published in the past two decades. However, the association with AIS, especially among different ethnic subgroups, still remains controversial. Thus, we investigated these inconclusive data by performing a meta-analysis to systematically evaluate the association.

A literature search was conducted in the PubMed, ISI Web of Science, EMBASE, SCOPUS, EBSCO, Cochrane Library, China National Knowledge Infrastructure (CNKI) and Wanfang databases until January 20, 2018. The strength of relationship was assessed using odds ratios (ORs) and 95% confidence intervals (95%CIs).

A total of 12 case–control studies with 4,304 cases of AIS and 3,123 controls met our criteria. The pooled ORs indicated that the ESRα Xbal A > G, ESRα PvuII T > C and ESRβ AlwNI T > C polymorphisms were not significantly associated with the risk of developing AIS in the overall analysis. However, we found a significant association between the ESRα Xbal A > G polymorphism and AIS under the homozygote model (GG versus AA; OR = 1.448, 95%CI: 1.052–1.993; p = 0.023).

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The present meta-analysis suggests that the ESRα Xbal A > G, ESRα PvuII T > C and ESRβ AlwNI T > C polymorphisms may not be associated with the risk of developing AIS in the overall analysis. However, ESRα Xbal A > G might have an influence on the susceptibility to develop AIS among Asians. Considering the limited sample size and ethnicity, further larger studies are needed to provide a more precise estimation of the associations.

Resumo

Vários estudos de associação entre os polimorfismos genéticos dos receptores de estrogénio α e β e a escoliose idiopática da adolescência (EIA) foram publicados nas últimas duas décadas. No entanto, a associação com a EIA, especialmente entre diferentes subgrupos étnicos, continua a ser controversa. Assim, o presente estudo investigou esses dados inconclusivos realizando uma metanálise para avaliar sistematicamente essa associação.

Uma pesquisa bibliográfica foi realizada nas bases de dados PubMed, ISI Web of Science, EMBASE, SCOPUS, EBSCO, Cochrane Library, China National Knowledge Infrastructure (CNKI) e Wanfang até 20 de janeiro de 2018. A força de associação foi avaliada usando razões de probabilidades (RPs) e intervalos de confiança de 95% (ICs95%).

Um total de 12 estudos de caso-controle, com 4.304 casos de EIA e 3.123 controles, atenderam aos critérios de inclusão do presente estudo. As RPs combinadas indicaram que os polimorfismos ESRα Xbal A > G, ESRα PvuII T > C e ESRβ AlwNI T > C não estavam significativamente associados ao risco geral de desenvolvimento de EIA. No entanto, observou-se uma associação significativa entre o polimorismo ESRα Xbal A > G e a EIA sob o modelo homozigótico (GG versus AA; RP = 1,448; IC95%: 1,052–1,993; p = 0,023).

Palavras-chave
► escoliose idiopática
► receptores estrogênicos
► polimorfismo
► metanálise

Introduction

Adolescent idiopathic scoliosis (AIS) is a clinically significant disorder with high heritability that affects between 2% and 4% of the world population.1 It is estimated that AIS affects up to 3% of all children, and its onset occurs after the age of 10.2 The pathogenesis of AIS is poorly understood.3 It seems that the cause of AIS is complex, and the possible etiology includes genetic factors, hormones and metabolic dysfunction, abnormal growth, and environmental and lifestyle factors.4 Out of all these factors, the genetic factors are widely well documented. Dominant autosomal and dominant X-linked inheritance have been described for the etiology of AIS, but most AIS families have complex and non-Mendelian inheritance.5,6 Further efforts to understand the genetic basis of AIS have focused on genome wide association and candidate gene studies. Population studies of index patients and their families have shown that 11% of first-degree relatives are affected, as are 2.4% and 1.4% of second- and third-degree relatives respectively.7

Many previous studies have focused on the identification of genes involved in the onset and evolution of AIS, such as melatonin receptor 1B (MTNR1B), ladybird home-box1 (LBX1), tryptophan hydroxylase1 (TPH1), aryalkylamine N-acetyltransferase (AA-NAT) and basonuclin2 (BN2) and, among them, the LBX1 gene is widely investigated.4,8

Because AIS develops during puberty and it is more common among females, both forms of the estrogen receptors (ESRα and ESRβ) have been implicated as candidate genes.3,4

Though the functional implications of the selected ESRα Xbal (A/C), ESRα PvuII (T/C) and ESRβ AlwNI (C/T) polymorphisms are still not fully elucidated, it has been suggested that intrinsic changes in the ERSα sequence may modify the expression or affinity of this receptor by estrogen.9 Therefore, we have conducted the current meta-analysis to better understand the association between the polymorphisms of the ESRα and ESRβ genes and AIS using human and animal-based studies.

Materials and Methods

Literature Search Strategy

The present meta-analysis was conducted and reported in accordance with the Preferred Reporting Items for Systematic
reviews and Meta-analyses (PRISMA) guidelines. We performed a search in the Medline, ISI Web of Science, EMBASE, SCOPUS, EBSCO, Cochrane Library, China National Knowledge Infrastructure (CNKI), and Wanfang databases covering all articles published until January 20, 2018. These searches were conducted using the following keywords: scoliosis, AIS, ESR1, ESRα, ESRβ, estrogen receptor, -351 A > G, XbaI, rs9340799, rs9340799, PvuII, rs2234693, AlwNI, and rs1256120, gene or allele, genotype, mutation, variant, variation, polymorphism. We evaluated potentially relevant publications by examining their titles and abstracts, and all of the studies matching the eligible criteria were retrieved. All eligible studies were examined carefully, and their references were checked for other relevant publications. If more than one article had been published by the same author using the same case series, we selected the study in which the most individuals were investigated. In addition, no restrictions were placed on language, and only published studies with full-text articles were included.

Inclusion and Exclusion Criteria
The studies included in the current meta-analysis had to meet all of the following criteria: a) evaluation of the ESRα XbaI (A/G), ESRα PvuII (T/C) and ESRβ AlwNI (C/T) polymorphisms and the risks of developing AIS; b) case–control studies; and c) sufficient published data to estimate an odds ratio (OR) with a 95% confidence interval (95%CIs). The exclusion criteria were as follows: a) researches not related to AIS; b) population studies; c) summaries, comments, case reports, letters, and reviews; d) duplicates of previous publications; and e) studies with no sufficient data provided.

Data Extraction
Two investigators extracted the data independently, and the results were reviewed by a third investigator. From each study, the following items were noted: name of the first author, year of publication, country, number of cases and controls, gene polymorphisms, minor allele frequencies (MAFs), and deviation from the Hardy–Weinberg equilibrium (HWE) of the control group. If there were any disagreements, they were solved by discussion and consultation with another researcher.

Quality Assessment
The quality assessment of the included studies mostly agreed with the confirmation of the HWE for the genotype distribution of the ESRα XbaI (A/G), ESRα PvuII (T/C) and ESRβ AlwNI (C/T) polymorphisms in the controls. If the studies deviated from the HWE in the controls, they were defined as low-quality studies. Conversely, studies with the genotype distribution of the ESRα XbaI (A/G), ESRα PvuII (T/C) and ESRβ AlwNI (C/T) polymorphisms in the controls in accordance with the HWE (p > 0.05) were defined as high-quality studies.

Statistical Analysis
The strength of the association between the ESRα polymorphism and the risk of developing AIS was measured by ORs, whereas a sense of the precision of the estimate was provided by the 95%CIs. The ESRα XbaI (A/G) polymorphism and the susceptibility to develop AIS was evaluated using allelic (G versus A) and genotypic comparisons of codominant (GG versus AA and GA versus AA), dominant (GG + GA versus AA), and recessive (GG versus GA + AA) genetic models, in which the G allele was considered the risk allele. The ESRα PvuII (T/C) and ESRβ AlwNI (C/T) polymorphisms were evaluated according to the allele (C versus T), homozygote (CC versus TT), heterozygote (TC versus TT), dominant (TC/CC versus TT), and recessive (CC versus TC/TT) models respectively. The genetic model evaluated for the OR of the polymorphism was a dominant model. Cochrani’s Q statistic was used to formally test for heterogeneity. The heterogeneity was considered significant when p < 0.01 in the Q statistic. The percentage variability of the pooled OR attributable to heterogeneity among studies was quantified with the I² metric, which is independent of the number of studies in the meta-analysis, and considers values between 0% and 100%, with higher values denoting a greater degree of heterogeneity 33 (I² = 0–25%: no heterogeneity; I² = 25–50%: moderate heterogeneity; I² = 50–75%: great heterogeneity; I² = 75–100%: extreme heterogeneity).10,11 The random-effects model (DerSimonian–Laird method) or fixed-effects model (Mantel–Haenszel method) were used to calculate pooled effect estimates in the presence or absence of heterogeneity. The HWE was assessed by Fisher exact test.12 The sensitivity was assessed by changing the effect models. A statistic alteration in the significance indicated that the results were unstable.13 In addition, one-way sensitivity analysis was also used to assess the stability of the results by omitting one of the studies each time. The publication bias was assessed by visual inspection of funnel plots, in which the standard error of log(OR) of each study was plotted against its log(OR). The publication bias was qualitatively assessed by making Begg funnel plots, and it was quantitatively evaluated by the Egger test. Values of p < 0.05 were considered representative of statistically significant publication bias. In addition, an asymmetric plot indicated a possible publication bias.11 Subgroup analyses were performed according to sample size, ethnicity, source of control, family history status and genotyping method separately. All statistical analyses were performed with the Comprehensive Meta-Analysis (CMA, Biostat, Englewood, NJ, US) software, version 2.1. All p-values in the meta-analysis were two-sided, and p-values < 0.05 were considered significant.

Results
Characteristics of the Included Studies
The present study met the requirements of the PRISMA statement (Fig. 1). In the initial screening, we have identified 174 publications in the database searches, and 98 publications were excluded after we read the titles due to the high rate of repetition of articles in different databases. After eliminating the duplicates, 64 articles were excluded after we screened the titles, abstracts and full texts because they were inconsistent with our inclusion criteria. Finally, 7 eligible case–control studies with a total of 2,377 cases and 1,770 controls were
The characteristics of the included studies are summarized in Table 1. The studies were published between 2006 and 2014, and were performed in China, Japan and Poland. The distribution of the ethnic groups among these seven studies was as follows: in 2 studies with 535 cases and 425 controls, the subjects were Caucasian, and in 5 studies with 1,842 cases and 1,982 controls, the subjects were Asian.

The genotype distributions among the controls of all studies followed the HWE, except for two studies on XbaI (rs9340799) and one study on PvuII (rs2234693). Therefore, according to the quality criteria, there were five high-quality studies and two low-quality studies.

ESRα XbaI A > G polymorphism

In total, 5 case–control studies with 1,927 cases and 1,353 controls investigated the association of ESRα XbaI A > G with the risk of developing AIS. Overall, the present meta-analysis suggested that there was no significant association between the ESRα XbaI A > G polymorphism and the risk of developing AIS (G versus A, OR = 1.071, 95% CI: 0.879–1.209, p = 0.497; GA versus AA, OR = 1.032, 95% CI: 0.821–1.229, p = 0.965), and the recessive models (CC versus CT + TT, OR = 1.034, 95% CI: 0.808–1.322, p = 0.792). In the subgroup analyses by ethnicity, there was no significant association between the ESRα XbaI A > G polymorphism and the risk of developing AIS among Asians under the homozygote model (GG versus AA, OR = 1.448, 95% CI: 1.052–1.993, p = 0.023).

ESRα PvuII T > C polymorphism

In total, 4 case–control studies with 1,129 cases and 714 controls investigated the association of the ESRα PvuII T > C polymorphism with the risk of developing AIS. The pooled results based on all included studies did not show a significant association between the ESRα PvuII T > C and the risk of developing AIS under the allele (C versus T, OR = 1.018, 95% CI: 0.888–1.166, p = 0.800), the heterozygote (CT versus TT, OR = 0.969, 95% CI: 0.804–1.234, p = 0.874), the homozygote (CC versus TT, OR = 1.045, 95% CI: 0.789–1.383, p = 0.760) (<Fig. 2B>), the dominant (CC + CT versus TT, OR = 1.605, 95% CI: 0.821–1.229, p = 0.968), and the recessive models (CC versus CT + TT, OR = 1.034, 95% CI: 0.808–1.322, p = 0.792). In the subgroup analyses by ethnicity, there was no significant association between the ESRα PvuII T > C polymorphism and

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*[Fig. 1] Flow diagram of the study selection process.*
### Table 1 Main characteristics of studies included in the meta-analysis

| First author | Country (ethnicity) | Case/Control | Gender | Cases | Control | Genotypes | Alleles | Genotypes | Alleles | MAFs | HWE |
|--------------|--------------------|--------------|--------|-------|---------|------------|---------|------------|---------|------|------|
| Wu et al. | China (Asian) | 202/174 | Overall | 72 | 82 | AA | 66 | GA | 220 | 184 | 0.339 | 0.042 |
| | | | Female | 64 | 72 | AG | 70 | GA | 198 | 172 | 0.340 | |
| | | | Male | 8 | 10 | GG | 6 | G | 22 | 12 | 0.325 | |
| Tang et al. | China (Asian) | 540/260 | Female | 328 | 157 | TT | 176 | TC | 832 | 248 | 0.232 | 0.173 |
| Zhao et al. | China (Asian) | 100/100 | Female | 58 | 55 | CC | 34 | TC | 150 | 50 | 0.295 | 0.010 |
| Takahashi et al. | Japan (Asian) | 798/637 | Female | 526 | 421 | TT | 248 | TC | 1300 | 296 | 0.185 | 0.645 |
| Janusz et al. | Poland (Caucasian) | 287/182 | Female | 96 | 61 | TT | 141 | TC | 333 | 241 | 0.559 |
| Wu et al. | China (Asian) | 202/174 | Overall | 71 | 64 | AA | 92 | GA | 234 | 170 | 0.431 | 0.017 |
| | | | Female | 65 | 57 | AA | 84 | 55 | 36 | 156 | 40 | 0.431 | |
| | | | Male | 6 | 7 | TT | 8 | 7 | 20 | 14 | 0.425 | |
| Tang et al. | China (Asian) | 540/260 | Female | 201 | 102 | TT | 249 | TC | 648 | 432 | 0.361 | 0.284 |
| Zhao et al. | China (Asian) | 100/100 | Female | 31 | 50 | CC | 51 | TC | 113 | 31 | 0.44 | 0.883 |
| Janusz et al. | Poland (Caucasian) | 287/182 | Female | 77 | 42 | CC | 144 | TC | 298 | 276 | 0.513 | 0.758 |
| AlwNI (rs1256120) | | | | | | | | | | | |
| Zhang et al. | China (Asian) | 202/174 | Overall | 36 | 10 | TT | 105 | TC | 177 | 259 | 0.732 | 0.984 |
| | | | Female | 30 | 5 | TC | 85 | TT | 145 | 207 | 0.750 | |
| | | | Male | 6 | 5 | CC | 20 | TT | 32 | 52 | 0.7083 | |
| Takahashi et al. | Japan (Asian) | 798/637 | Female | 99 | 79 | CC | 368 | CC | 566 | 1030 | 0.6358 | 0.347 |
| Kotwicki et al. | Poland (Caucasian) | 248/243 | Female | 164 | 159 | TT | 74 | TT | 10 | 402 | 94 | 0.1872 | 0.521 |

Abbreviations: MAFs, minor allele frequencies; HWE, Hardy–Weinberg equilibrium.
the risk of developing AIS under all five genetic models (→ Table 2).

**ESRβ AlwNI C > T Polymorphism**
A total of 3 case–control studies with 1,248 cases and 1,054 controls were selected to estimate the association of the ESRβ AlwNI C > T polymorphism and the susceptibility to develop AIS. As a result, no statistically significant association was found in any of the genetic models (C versus T, OR = 1.072, 95% CI: 0.946–1.215, p = 0.276; CT versus TT, OR = 0.896, 95% CI: 0.705–1.139, p = 0.370; CC versus TT, OR = 0.950, 95% CI: 0.266–3.386, p = 0.937; CC + CT versus TT, OR = 1.374, 95% CI: 0.758–2.493, p = 0.295 (→ Fig. 2C); CC versus CT + TT, OR = 1.032, 95% CI: 0.857–1.242, p = 0.739); (→ Fig. 2).

**Heterogeneity and Sensitivity Analyses**
The heterogeneity was not significant for the ESRα Xbal A > G, ESRα PvuII T > C and ESRβ AlwNI T > C polymorphisms in most genetic models, which suggested that the polymorphisms were not the source of heterogeneity among the studies (→ Table 2). The sensitivity analyses by sequential omission of any individual study, one at a time, or by omitting studies in which the genotype distributions in the healthy controls significantly deviated from the HWE, did not materially alter the pooled ORs, indicating that the results were stable.

**Publication Bias**
The Begg funnel plot and the Egger tests were performed to estimate the publication bias of the studies regarding the

| Polymorphism | Genetic model | Type of model | Heterogeneity (H) | Odds Ratio (OR) | Publication bias |
|--------------|---------------|---------------|------------------|----------------|-----------------|
| **Xbal (rs9340799)** | | | | | |
| Overall | G versus A | Random | 61.79 | 0.033 | 1.071 | 0.879–1.304 | 0.679 | 0.497 | 0.806 | 0.949 |
| | GA versus AA | Fixed | 0.00 | 0.869 | 1.037 | 0.889–1.209 | 0.466 | 0.641 | 0.806 | 0.401 |
| By ethnicity | | | | | | |
| Asian | G versus A | Random | 71.18 | 0.015 | 1.079 | 0.834–1.396 | 0.580 | 0.562 | 1.000 | 0.950 |
| | GA versus AA | Fixed | 0.00 | 0.765 | 1.048 | 0.888–1.236 | 0.552 | 0.581 | 0.308 | 0.359 |
| **PvuII (rs2234693)** | | | | | |
| Overall | C versus T | Fixed | 5.54 | 0.365 | 1.018 | 0.888–1.166 | 0.253 | 0.800 | 1.000 | 0.472 |
| | CT versus TT | Fixed | 0.00 | 0.788 | 0.996 | 0.804–1.234 | –0.033 | 0.973 | 0.734 | 0.903 |
| | CC versus TT | Fixed | 34.62 | 0.204 | 1.045 | 0.789–1.383 | 0.305 | 0.760 | 1.000 | 0.608 |
| | CC + CT versus TT | Fixed | 0.00 | 0.548 | 1.005 | 0.821–1.229 | 0.044 | 0.965 | 0.308 | 0.574 |
| | CC versus CT + TT | Fixed | 45.60 | 0.138 | 1.034 | 0.808–1.322 | 0.263 | 0.792 | 1.000 | 0.767 |
| **AlwNI (rs1256120)** | | | | | |
| Overall | T versus C | Fixed | 0.00 | 0.476 | 1.075 | 0.917–1.260 | 0.889 | 0.374 | 1.000 | 0.398 |
| | TC versus CC | Fixed | 0.00 | 0.813 | 1.044 | 0.819–1.330 | 0.345 | 0.730 | 1.000 | 0.714 |
| | TT versus CC | Random | 90.86 | <0.001 | 0.950 | 0.266–3.386 | –0.896 | 0.370 | 0.296 | 0.078 |
| | TT + CT versus CC | Random | 84.41 | 0.002 | 1.374 | 0.758–2.493 | 1.047 | 0.295 | 0.296 | 0.212 |
| | TT versus TC + CC | Fixed | 0.00 | 0.391 | 1.032 | 0.857–1.242 | 0.333 | 0.739 | 1.000 | 0.970 |

Abbreviations: 95%CI, 95% confidence interval; AIS, adolescent idiopathic scoliosis.

Table 2 Meta-analysis on the association of the ESRα Xbal (A > G), ESRα PvuII (T > C) and ESRβ AlwNI (C > T) polymorphisms with the risk of developing AIS
association between the susceptibility to develop AIS and the ESRα XbaI A>G, ESRα PvuII T>C and ESRβ AlwNI C>T polymorphisms. The shape of the funnel plot did not reveal any evidence of obvious asymmetry for the polymorphisms under any of the genetic models. Furthermore, the p-values of the Egger tests were higher than 0.05, providing statistical evidence of the symmetry of the funnel plots. However, the results of the Egger tests showed evidence of publication bias for the ESRα PvuII T>C polymorphism in Asians under the dominant model (CC + CT versus TT; $p_{\text{Egger}} = 0.296$, $p_{\text{Egger}} = 0.041$); (► Fig. 3).

**Discussion**

The pathogenesis of AIS is a complex process. It is known that genetic factors play an important role in the susceptibility to develop AIS. However, most of the molecular mechanisms leading to AIS development are still unknown. Gene mutations in various loci have been identified by genetic studies, and a genetic basis for the AIS pathogenesis has been established. Although many epidemiological studies have been conducted to assess the roles of the ESRα and ESRβ polymorphisms and the risk of developing AIS in different populations, the results have been inconclusive. The ESRα and ESRβ gene polymorphisms have been linked to a higher risk of developing different conditions. The human ERα gene is located on chromosome 6q25, it extends for more than 140 kb, and includes 8 exons. The most studied polymorphisms in this gene are the PvuII T>C and XbaI A>G in intron 1, 397 bp and 351 bp upstream of exon 2 respectively. The gene that encodes ESRβ is located on chromosome 14q23, and the potential association of the single-nucleotide polymorphisms (SNPs) in ESRβ (Rsal G>A, Alul A>G and AlwNI C>T) and disease have not been studied previously.

The current updated meta-analysis, including 12 eligible studies with a total of 4,304 AIS cases and 3,123 controls, provides a comprehensive examination of the evidence currently available on the associations of the ESRα and ESRβ polymorphisms with the susceptibility to develop AIS. The results suggested that the polymorphisms in question had no significant association with the risk of developing AIS. The present meta-analysis is consistent with previous meta-analyses by Chen et al, Yang et al (ESRα XbaI and ESRα PvuII) and Cao et al (ESRβ AlwNI), who found negative
results for the association between the ESRα and ESRβ polymorphisms and the risk of developing AIS. However, Inoue et al.22 and Wu et al.14 reported a significant association between the ESRα XbaI A > G and ESRα PvuII T > C polymorphisms and the risk of developing AIS. In 2016, Cao et al.4 reported that there was no significant association between the ESRα XbaI A > G and ESRα PvuII T > C polymorphisms and the risk of developing AIS in a total population analysis. However, for the comparison with the study by Cao et al.4 the subgroup analysis by ethnicity was also performed. In the present meta-analysis, we found that the ESRα XbaI A > G polymorphism was associated with the risk of developing AIS in Asians under the homozygote model (GG versus AA, OR = 1.448, 95%CI: 1.052–1.993, p = 0.023). The discrepancy between ethnicity subgroups may be due to the limited studies in Europe, since only one study was conducted among subjects of Caucasian ethnicity. Therefore, we performed a stratified analysis only on the Chinese population (Asians). Our data revealed that the XbaI G allele was a risk factor in the Chinese population. Unlike the ESRα XbaI polymorphism, no significant difference was found in the ESRα PvuII T > C polymorphism allele or genotype distribution among AIS patients and healthy individuals.

In the current meta-analysis, a fixed-effects or a random-effects models were used based on the heterogeneity testing. The differences in the studied populations with different genetic backgrounds and variations in sample selection and environmental exposures may result in heterogeneity.28–30 Our meta-regression analysis also showed that ethnicity in case groups and control groups significantly contributed to the heterogeneity. When limiting the analysis to the studies within the HWE, the result was not altered, suggesting that the present meta-analysis is robust and credible. Moreover, we performed a sensitivity analysis according to sample size and leave-one-out cross validation to determine whether the change in the inclusion criteria by removing one study each time did not materially affected the original results.

There are some limitations to the present meta-analysis. First, the sample size was comparatively small and had insufficient statistical power for the association to be estimated. Second, we have included only studies published in English and Chinese; therefore, publication bias may have occurred. Third, the greatest proportion of statistical power was provided by Asians. There were not enough studies in Caucasians, which limited the statistical power. No study from other parts of the world was found, such as Africa and Latin America. This suggests a partial result that is only relevant to the Asian and Caucasian subgroups. Fourth, in interpreting the results, we should mention that, as with other complex traits, the risk of developing AIS may be modulated by several other genetic markers and candidate genes besides the ESRα and ESRβ genes. Therefore, further investigations on the haplotypic effect of the polymorphisms and the study of multiple polymorphisms in different genes are necessary. Finally, due to the unavailability of other detailed information, our results were based on single-factor estimates without adjustments for other risk factors. Further evaluations of the risk of developing AIS should pay more attention to the potential gene–gene, gene–environment interactions, and even the interactions of different polymorphism of the ESRα and ESRβ genes and other loci.

**Final Consideration**

In summary, the present meta-analysis suggests that the ESRα XbaI (A/G), ESRα PvuII (T/C) and ESRβ AlwNI (C/T) polymorphisms are not associated with an increased risk of developing AIS. However, ESRα XbaI A > G might have an influence on the susceptibility to develop AIS among Asians. Based on the aforementioned limitations, it is critical that large, well-designed studies are performed to re-evaluate the potential associations of the ESRα and ESRβ gene polymorphisms with other candidate gene polymorphisms and the risk of developing AIS.

Conflict of Interests
The authors have no conflict of interests to declare.

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