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Impact of *ESR1* Gene Polymorphisms on Migraine Susceptibility

A Meta-Analysis

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Abstract: An increasing number of studies have explored genetic associations between the functionally important polymorphisms in estrogen receptor 1 (*ESR1*) gene and migraine susceptibility. The previously reported associations have nevertheless been inconsistent.

The present work incorporating the published data derived from 8 publications was performed to assess the impact of these polymorphisms on incident migraine. Strength of the genetic risk was estimated by means of an odds ratio along with the 95% confidence interval (OR and 95% CI).

From the results, we found individuals who harbored the 325-GG genotype, compared with those harboring the CC genotype or CG and CC combined genotypes, had almost 50% greater risk of migraine. The same genetic models showed notable associations in subgroups of Caucasians and migraine with aura (MA). For 594G>A, a moderately increased risk of migraine was seen under AG versus GG. The AA + AG versus GG model, however, showed a borderline association with migraine. Subgroup analyses according to ethnicity and subtype of migraine provided statistical evidence of significantly increased risk of migraine in Caucasians and of a marginal association with MA, respectively. Both 325C>G and 594G>A polymorphisms showed no major effects either in males or in females.

Based on the statistical data, we conclude some of the *ESR1* gene polymorphisms may have major contributions to the pathogenesis of migraine in Caucasian populations.

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Abbreviations: CI = confidence interval, *ESR1* = estrogen receptor 1, MA = migraine with aura, MO = migraine without aura, OR = odds ratios.

INTRODUCTION

Migraine is a common and disabling type of primary headache disorder comprising 2 major subgroups: migraine with aura (MA) and migraine without aura (MO).[1] Heredity, polluted environment, and hormonal factors individually or jointly confer susceptibility to this genetically complex disease. Due to numerous severe consequences, the genetic basis of migraine has received intensive attention in the past decades.[2,3] In addition to a panel of genes ranging from *SCN1A* to *ATP1A2*,[4–6] several genes located on chromosome 19 and chromosome 1 have been implicated in studies concerning familial hemiplegic migraine that is a rare autosomal dominant subtype of MA.[7–9] Although multiple low penetrance, modifying genes have been identified, knowledge on the genetic foundation of migraine remains limited. Therefore, further studies are necessary.

The polymorphic estrogen receptor 1 (*ESR1*) gene at human chromosome 6q25.1 has 8 exons and 7 introns and spans about 300 kb in length.[10] *ESR1* (corresponds to ER alpha) as a functional estrogen receptor and a nuclear transcription factor controls the actions of many endogenous steroid hormones, such as 17beta-estradiol or E2, and is expressed in many cell types of metazoans.[11] It also stimulates proliferation and differentiation of mammary epithelial tissue by cooperating with other estrogen receptors. Significant associations related to genetic variability in *ESR1* gene have been reported in a wide range of sex steroid hormone-related cancers, including prostate cancer, breast cancer, endometrial cancer, and ovarian carcinoma.[12–15]

In the hormone binding region of *ESR1* gene, there lies a C to G substitution polymorphism (325 C>G). The exon 4 polymorphism, along with the exon 8 594G>A and Pvu IIC>T, has been speculated to have major impact on migraine which is a hormone-regulated disorder. However, the extensive research fail to reach a consensus with respect to the inherent susceptibility to migraine associated with *ESR1* gene polymorphisms.[16–21] The small numbers and varying populations of the published studies may partially account for the controversial results. The most important reason that promotes us to perform the present meta-analysis is the less reliable discoveries of an earlier analysis as a result of overlapped data[22] and the new information from recent publications.[21,23] This study therefore aimed to provide compelling evidence such that we could better understand the molecular pathogenesis of migraine in association with *ESR1* polymorphisms.

MATERIALS AND METHODS

Identification and Selection of The related Studies

Embase (http://www.embase.com), PubMed (http://www.ncbi.nlm.nih.gov/pubmed), Web of Science (http://isiknowledge.com), and China National Knowledge Infrastructure (www.cnki.net) databases were thoroughly searched by 2

independent investigators to identify potential studies addressing the association between at least one of *ESR1* polymorphisms being investigated and migraine susceptibility. The terms "polymorphism," "polymorphisms," "estrogen receptor," "*ESR1*," "rs1801132," "rs2228480," "rs2234693," "325C>G," "594G>A," "Pvu IIC>T," and "migraine" were used. Online searches were completed in March 2014. The missing data (the data that we failed to identify during the electronic search) were obtained by reviewing the citations of review articles and all eligible studies.

The major criteria for inclusion were an independent study based on a case–control or cohort design; evaluated the association between *ESR1* polymorphism of interest and migraine susceptibility; provided genotype frequencies in full detail which assisted to successfully calculate odds ratios (ORs) and 95% confidence intervals (CIs); and only study with the largest sample size was included in case of 2 or more studies containing the same series of patients.

Data Extraction

From each study, the following data were independently extracted by the same 2 investigators using a standardized form: first author's last name, year of publication, study country, ethnicity, genotyping assay, allele and genotype frequencies, and gender distribution between migraine, MA, MO patients, and controls. Disagreements were resolved through discussion with a 3rd investigator.

Statistical Analysis

On the basis of data on 2811 patients and 2565 control subjects, ORs with 95% CIs were calculated to assess the association between *ESR1* polymorphisms and migraine risk assuming distinct genetic models. The ORs were summarized either with the fixed-effects model or the random-effects model according to the P values of between study heterogeneities, which was initially tested by Cochran Q test.[24] $P < 0.05$ represented presence of significant heterogeneity. The I^2 statistics was then quantified to evaluate the proportion of variance across studies ($I^2 < 50\%$ low heterogeneity, $I^2 = 50\%$–75% large heterogeneity, and $I^2 > 75\%$ extremely large heterogeneity).[25] The fixed-effects model (Mantel-Haenszel method) was performed in the case of $P > 0.05$ or $I^2 < 50\%$, and vice versa.[26,27] Stratified analyses according to ethnicity (Caucasian, Asian), gender, and subdivision of migraine (MA, MO) were performed to evaluate the potential source of heterogeneity. To determine the influence of each study on the overall estimate, sensitivity analysis was performed by omitting the single studies one by one and recalculating their ORs. Publication bias was evaluated by the use of a funnel plot and Egger test.[28,29] Deviation of genotype frequencies in control subjects from Hardy-Weinberg equilibrium was tested by using the Chi-square goodness of fit. All statistical analyses were carried out by STATA version 12.0 (Stata Corporation, College Station, TX). Significance level was defined at $P < 0.05$.

RESULTS

The Characteristics of Included Studies

Figure 1 shows the selection process of studies ultimately used in the meta-analysis. A total of 23 potentially relevant records were identified through databases and other sources, and 12 records were fist removed, including 6 obviously irrelevant articles and 6 articles mistakenly believed to contain
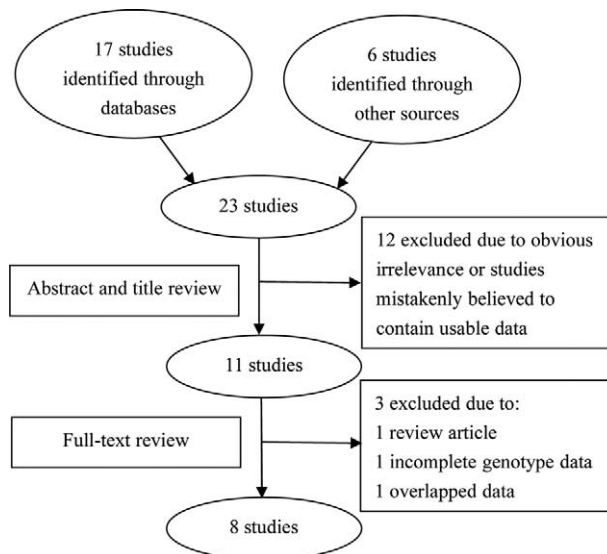

FIGURE 1. Flow chart showed the process for eligible study identification.

usable data. We further evaluated eligibility of the remaining 11 articles through reviewing the full texts, of which 1 article was an overview of migraine and genetic polymorphisms;[30] 1 had the same study population with the other updated by the same author;[31] and 1 did not report detailed genotype frequency of *ESR1* polymorphisms.[32] Finally, 8 articles were included in this meta-analysis.[16–21,23,33] As described in Table 1, Caucasian subjects were used in most studies and only 1 study for 594G>A showed deviation from Hardy-Weinberg equilibrium. For 325C>G, five studies provided detailed data for migraine, 5 for MA, 4 for MO, 3 for male and female. With respect to 594G>A, there were 6 studies available for migraine, 6 for MA, 5 for MO, 4 for male and female. Moreover, a total of 3 studies were analyzed to assess the effects of Pvu IIC>T on migraine risk.

Meta-Analysis Results

A summary of the meta-analysis results on the association between the polymorphisms at *ESR1*, and migraine risk is displayed in Table 2.

325C>G Polymorphism and Migraine Risk

As no significant heterogeneity was detected across the studies ($P > 0.05$), the ORs were hence pooled with the fixed-effects model. By combining the data from each study, we found the GG genotype was associated with a 51% increased risk of migraine as compared with the CC genotype (GG vs CC: OR = 1.51, 95% CI = 1.15–1.99, $P_h = 0.313$) (Figure 2). When using the GG versus CG + CC genetic model, we obtained an OR of 1.52 (95% CI = 1.16–1.98, $P_h = 0.212$). In the stratified analysis by ethnicity, increased risk of migraine was observed in Caucasians (GG vs CC: OR = 1.63, 95% CI = 1.20–2.22, $P_h = 0.317$; GG vs CG + CC: OR = 1.63, 95% CI = 1.21–2.21, $P_h = 0.196$), but not in Asians. Further stratified analyses according to subtype and gender showed a notable increase in the risk of MA, while no significant associations were seen in subgroups of MO, male and female.

TABLE 1. Characteristics of Migraine Studies Included in the Meta-Analysis

First Author/ Publication Year	Study Country	Ethnicity	MA Case (Control), M/F	MO (Case/ Control), M/F	Case (Control), M/F	Method	Cases/ Controls	HWE *P*-Value
325C>G								
Colson 2006	New Zealand	Caucasian	– (–)	– (–)	64/167 (60/189)	PCR-RFLP	231/249	0.32
Kaunisto 2006	Finland	Caucasian	– (–)	– (–)	180/718 (220/700)	MassARRAY	896/888	0.06
Oterino 2008	Spain	Caucasian	46/152 (109/263)	41/117 (109/263)	89/267 (108/266)	RT-PCR	356/372	0.31
Corominas 2009	Spain	Caucasian	– (–)	– (–)	47/153 (–)	PCR-SSCP	210/210	0.72
Ghosh 2012	India	Asian	28/78 (67/133)	72/156 (67/133)	100/234 (67/133)	PCR-SSCP	334/200	0.07
594G>A								
Colson 2004	New Zealand	Caucasian	36/103 (57/167)	21/64 (57/167)	57/167 (57/167)	PCR-RFLP	224/224	0.14
Colson 2004	New Zealand	Caucasian	30/191 (36/224)	6/33 (36/224)	36/224 (36/224)	PCR-RFLP	260/260	0.88
Kaunisto 2006	Finland	Caucasian	– (–)	– (–)	180/718 (220/700)	MassARRAY	898/900	0.45
Oterino 2006	Spain	Caucasian	42/155 (90/142)	39/131 (90/142)	81/286 (90/142)	RT-PCR	367/232	0.02
Corominas 2009	Spain	Caucasian	– (–)	– (–)	47/153 (–)	PCR-SSCP	210/210	0.29
Ghosh 2012	India	Asian	28/78 (67/133)	72/156 (67/133)	100/234 (67/133)	PCR-SSCP	334/200	0.78
Pvu IIC>T								
Colson 2006	New Zealand	Caucasian	– (–)	– (–)	64/167 (62/140)	PCR-RFLP	231/202	0.61
Huo 2011	China	Asian	– (–)	– (–)	9/32 (14/30)	PCR-RFLP	41/44	0.90
Ghosh 2012	India	Asian	28/78 (67/133)	72/156 (67/133)	100/234 (67/133)	PCR-SSCP	334/200	0.16

F = female, HWE = Hardy-Weinberg equilibrium, M = male, MA = migraine with aura, MO = migraine without aura, PCR-RFLP = polymerase chain reaction-restriction fragment length olymorphism, PCR-SSCP = PCR-single strand conformation polymorphism, RT-PCR = real time-PCR,

594G>A Polymorphism and Migraine Risk

Meta-analysis of 594G>A polymorphism provided statistical evidence for an intermediate association with migraine (AG vs GG: OR = 1.14, 95% CI = 1.01–1.28, P_h = 0.290) (Figure 3). We also found a borderline association among the individuals harboring both AA and AG genotypes (AA + AG vs GG: OR = 1.13, 95% CI = 1.00–1.26, P_h = 0.216). Subgroup analyses by ethnicity showed significant elevations in Caucasians. When data were restrained to MA, we only found a marginal association. No major effects were seen in males or females when data were stratified by gender.

Pvu IIC>T Polymorphism and Migraine Risk

Three studies looking at Pvu IIC>T polymorphism and migraine risk were analyzed in this meta-analysis. We did not find any evidence of a significantly increased risk of migraine under the genetic models tested.

Substantial heterogeneity was detected in the meta-analysis of 594G>A polymorphism under AA versus GG (P = 0.053, I^2 = 0.542). Sensitivity analyses by sequentially deleting the independent studies identified Colson et al (2004, the follow-up study) influenced the interstudy homogeneity. We then excluded this outlier and found a drastic drop in heterogeneity (P = 0.287, I^2 = 0.201), with the combined effects not notably affected (data not shown).

Publication bias was checked by the funnel plots and Egger test. Figures 4 and 5 show the symmetric funnel plots for 325C>G and 594G>A, respectively. The symmetry was confirmed by performing the Egger test (P = 0.686 under CG vs CC, P = 0.130 under AG vs GG).

## DISCUSSION

Migraine has a multifactorial background. However, the importance of genetic factors in the pathogenesis of migraine becomes increasingly highlighted in recent years.[34,35] Many molecular and cellular processes, such as cell growth and differentiation, are critical for many physiological and pathophysiological outcomes, including neuronal function.[36] The human *ESR1* gene encoding ERs is functionally involved in these processes, suggesting a potential association between *ESR1* and neurological diseases, including migraine. The susceptibility of 325C>G polymorphism in the hormone binding region of *ESR1* gene was primarily reported in a Spanish population[20] and this positive association was subsequently replicated in an updated study.[18] In contrast, other epidemiological studies in which subjects were also of Caucasian descent failed to replicate it and showed evidence that there was no role of 325C>G polymorphism in inherited susceptibility to migraine.[16,17,19] Likewise, mixed and contradictory evidence has shown in the studies of 594G>A or Pvu IIC>T polymorphisms. A plausible reason for the considerable controversy may relate to the sample size and ethnic group differences. Other factors, such as methods used for genotype determination and

TABLE 2. Results of Meta-Analysis for *ESR1* Polymorphisms and Migraine Risk

Study Groups	Case/Control	GG vs CC		GG + CG vs CC		GG vs CG + CC		CG vs CC	
		OR (95% CI)	P_h/I^2	OR (95% CI)	P_h/I^2	OR (95% CI)	P_h/I^2	OR (95% CI)	P_h/I^2
325C>G									
All	2027/1919	1.51 (1.15, 1.99)	0.313/0.159	1.06 (0.94, 1.19)	0.873/0	1.52 (1.16, 1.98)	0.212/0.315	1.02 (0.90, 1.16)	0.763/0
Ethnicity									
Caucasian	1693/1719	1.63 (1.20, 2.22)	0.317/0.151	1.07 (0.95, 1.22)	0.795/0	1.63 (1.21, 2.21)	0.196/0.360	1.03 (0.90, 1.18)	0.618/0
Asian	334/200	1.10 (0.59, 2.05)	—	1.00 (0.75, 1.33)	—	1.13 (0.62, 2.06)	—	0.99 (0.73, 1.34)	—
Subdivision									
MA	1427/1919	1.59 (1.17, 2.15)	0.503/0	1.08 (0.95, 1.23)	0.851/0	1.58 (1.18, 2.13)	0.376/0.054	1.04 (0.91, 1.19)	0.720/0
MO	563/1031	1.29 (0.83, 2.01)	0.382/0.021	1.01 (0.83, 1.23)	0.841/0	1.30 (0.85, 2.01)	0.330/0.125	0.98 (0.79, 1.21)	0.808/0
Gender									
Male	251/236	0.78 (0.35, 1.72)	0.544/0	0.98 (0.70, 1.36)	0.758/0	0.74 (0.34, 1.59)	0.456/0	1.00 (0.70, 1.42)	0.597/0
Female	670/585	1.59 (0.99, 2.54)	0.263/0.252	1.15 (0.93, 1.41)	0.488/0	1.56 (0.99, 2.48)	0.251/0.276	1.11 (0.89, 1.39)	0.515/0
594G>A		*AA vs GG*		*AA + AG vs GG*		*AA vs AG + GG*		*AG vs GG*	
All	2293/2026	1.25 (0.80, 1.95)	0.053/0.542	1.13 (1.00, 1.26)	0.216/0.292	1.19 (0.90, 1.57)	0.170/0.356	1.14 (1.01, 1.28)	0.290/0.189
Ethnicity									
Caucasian	1959/1826	1.36 (0.83, 2.22)	0.055/0.567	1.17 (1.04, 1.33)	0.197/0.318	1.24 (0.93, 1.66)	0.139/0.423	1.19 (1.04, 1.35)	0.672/0
Asian	334/200	0.73 (0.30, 1.77)	—	0.82 (0.58, 1.15)	—	0.80 (0.33, 1.93)	—	0.81 (0.57, 1.16)	—
Subdivision									
MA	1640/2026	1.34 (0.79, 2.26)	0.041/0.568	1.13 (1.00, 1.28)	0.197/0.318	1.28 (0.95, 1.73)	0.102/0.455	1.14 (0.99, 1.30)	0.250/0.245
MO	597/1126	1.02 (0.62, 1.67)	0.848/0	1.08 (0.89, 1.32)	0.427/0	0.93 (0.57, 1.52)	0.971/0	1.10 (0.90, 1.36)	0.395/0.020
Gender									
Male	274/250	1.11 (0.25, 4.88)	0.046/0.625	1.14 (0.83, 1.57)	0.417/0	0.95 (0.23, 3.99)	0.051/0.613	1.19 (0.84, 1.67)	0.589/0
Female	912/666	1.57 (0.69, 3.59)	0.018/0.704	1.17 (0.97, 1.41)	0.175/0.395	1.43 (0.66, 3.09)	0.027/0.672	1.16 (0.95, 1.42)	0.230/0.304
Pvu IIC>T		*TT vs CC*		*TT + CT vs CC*		*TT vs CT + CC*		*CT vs CC*	
All	606/446	1.15 (0.82, 1.61)	0.196/0.387	1.06 (0.88, 1.29)	0.646/0	1.06 (0.77, 1.44)	0.141/0.490	1.07 (0.86, 1.34)	0.721/0

P_h: P value for heterogeneity from Q-test; significant results are marked in bold.
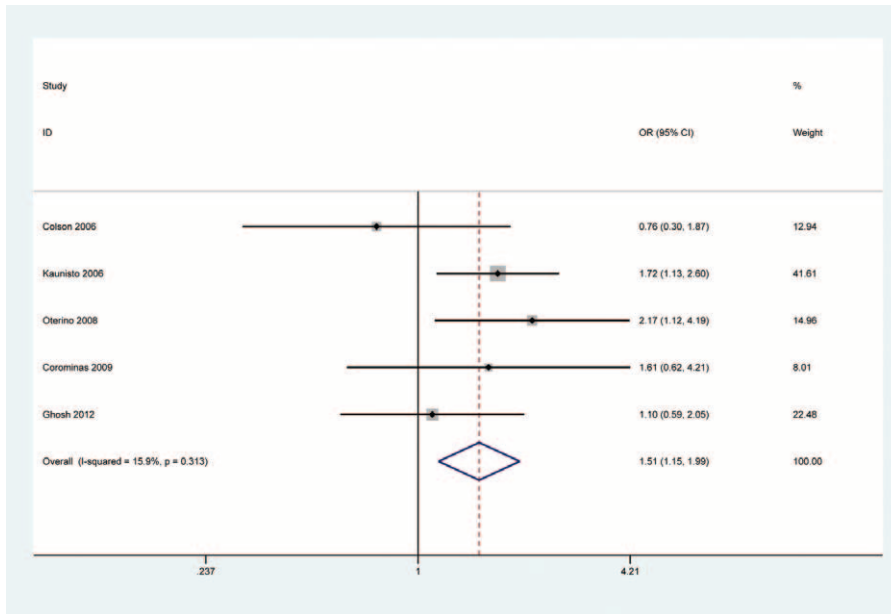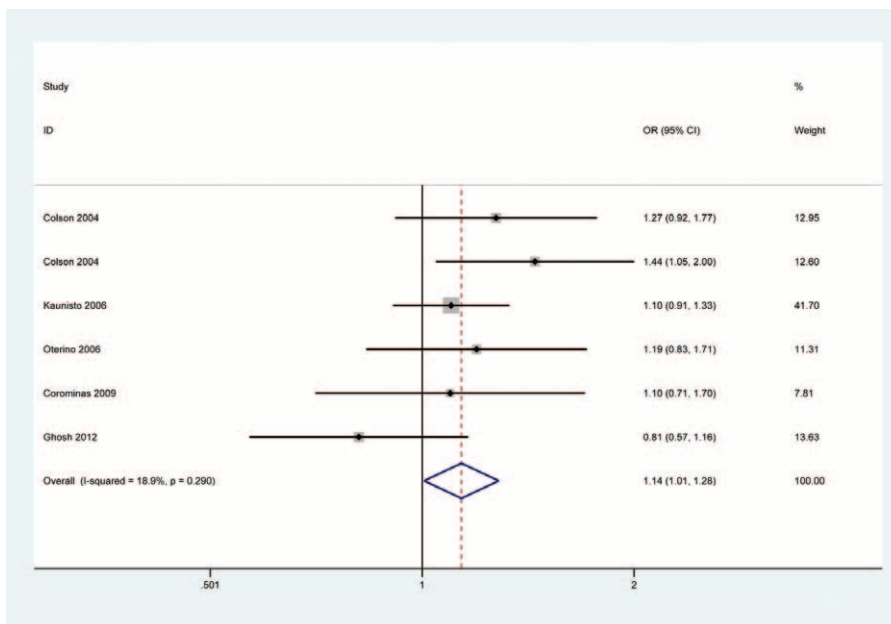
FIGURE 2. Forest plot showed the results of the association between *ESR1* 325C>G and overall migraine risk (GG vs CC). The result indicated that there was an association between *ESR1* 325 C>G and increased migraine risk. Fixed-effect model was used. *ESR1* = estro-estrogen receptor 1.

the threshold defined for subject enrollment, may interfere with the statistical power and thus lead to less reliable results.

The association of *ESR1* gene polymorphisms and migraine risk has been examined by a previous meta-analysis.[22] The results suggested significantly increased risk of migraine, MA and MO in relation to *ESR1* 325C>G and *ESR1* 594G>A. In the present meta-analysis of data from 8 epidemiological and molecular studies, we also found a notable

increase in risk of both migraine and MA for 325C>G and in risk of migraine only for 594G>A. Differently, no statistical evidence was indicated supporting a significant association with MO. We additionally found strong evidence of elevated susceptibility to migraine in Caucasians for *ESR1* 325C>G and 594G>A. In the earlier work, certain factors may have biased the results. For example, overlapped data were included[20] and recently published information was missed,[21,23]

FIGURE 3. Forest plot showed the results of the association between *ESR1* 594G>A and overall migraine risk (AG vs GG). The result indicated that there was an association between the *ESR1* 594G>A and increased migraine risk. Random-effect model was used. *ESR1* = estrogen receptor 1.
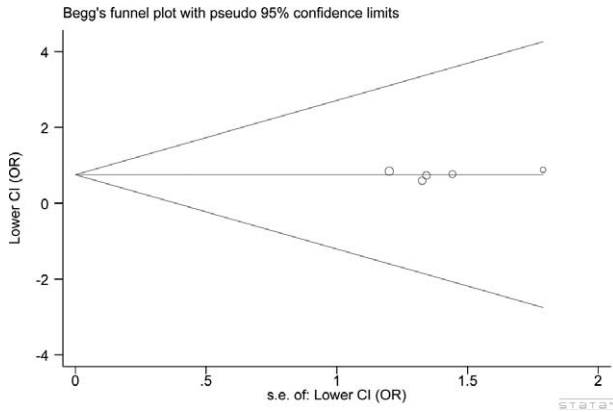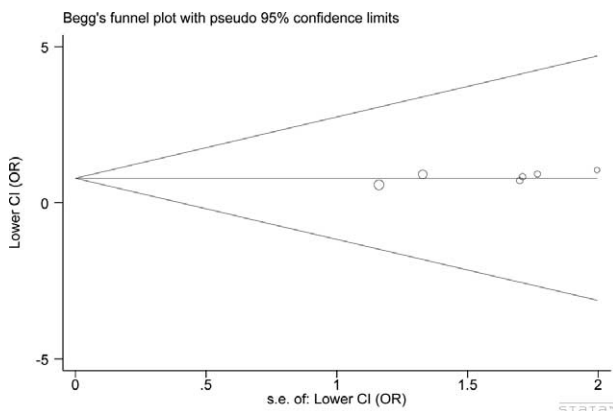
FIGURE 4. Funnel plots of *ESR1* 325C>G and migraine risk (CG vs CC). *ESR1* = estrogen receptor 1.

which might together result in false positive estimations as observed in MO.

In the stratified analysis by ethnicity, increased risk of migraine was suggested in Caucasian populations, while no effect modification was indicated in Asians. We found the minor allele frequency of 325C>G polymorphism is differentially distributed in the 2 studied populations. The G allele frequency of Caucasians (22.4%) is remarkably lower compared with Asians (36.6%). Nevertheless, the A allele frequency of 594G>A between Caucasians and Asians is almost the same (21.9% vs 19.4%). Therefore, the null association in Asians seems more likely to attribute to the widely different genetic background and the small number of subjects analyzed in each analysis. To identify the exact role of the 2 sequence variants played in various ethnic groups, it is worthwhile to perform an enormously large study in future.

In addition, we found that the risk of developing migraine did not differ between men and women. This may contradict other findings. It has been estimated that of the general population, accounting approximately 6% for men and 18% for women.[37,38] The incidence rate of migraine is higher among women during their fertile-period life span, because fluctuating hormones of the ovarian cycle are specific migraine triggers.[39,40] Theoretically, women appear to be more susceptible

to migraine compared with men. Hence, the findings implicated in this work require further investigation and identification.

As yet, no analysis is comparable with the current wok in terms of the number of samples. Moreover, pooled summary estimates from this meta-analysis are relatively easier to interpret, because the studies included are generally homogeneous. However, several limitations should be concerned. First, the results of the present meta-analysis could be better convinced if a larger study was conducted. Certain findings, especially those in each subgroup, are still indefinitive and remain to be further validated. Second, although thorough literature searches were conducted, we cannot rule out the possibility that some literature covered in the databases we did not search may have missed, which has more or less exerted effects on the current outcomes. Finally, exogenous risk factors along with their interactions with modifier genes are widely accepted as important components in the progression of many common diseases. Such analyses, particularly in a rather sufficient study group, should be carried out to identify the effects.

In conclusion, based on data from molecular and epidemiological studies, our meta-analysis suggested that exon 4 325C>G and exon 8 594G>A polymorphisms of the *ESR1* gene conferred increased susceptibility to migraine. Consistent with this finding, stratified analyses by ethnicity and subtype showed significant associations in Caucasians and MA for 325C>G, and in Caucasians only for 594G>A. The gene-to-gene and gene-to-environment interactions should be taken into consideration in future larger studies to provide precise effect estimations.

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FIGURE 5. Funnel plots of *ESR1* 594G>A and migraine risk (AG vs GG). *ESR1* = estrogen receptor 1.

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