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GENETICS

Association between estrogen receptora gene (ESR1) PvuII (T/C) and XbaI (A/G) polymorphisms and premature ovarian failure risk: evidence from a meta-analysis

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Abstract
Background and aims Genetic factors are important in the pathogenesis of Premature ovarian failure (POF). Notably, estrogen receptor-a (*ESR1*) has been suggested as a possible candidate gene for POF; however, published studies of *ESR1* gene polymorphisms have been hampered by small sample sizes and inconclusive or ambiguous results. The aim of this meta analysis is to investigate the associations between two novel common *ESR1* polymorphisms (intron 1 polymorphisms PvuII-rs2234693: T.C and XbaI-rs9340799: A.G) and POF.
Methods A comprehensive search was conducted to identify all studies on the association of *ESR1* gene polymorphisms with POF up to August 2014. Pooled odds ratio (OR) and corresponding 95 % confidence interval (CI) were calculated using fixed-or random-effects model in the meta-analysis.
Results Three studies covering 1396 subjects were identified. Pooled data showed significant association between *ESR1* gene PvuII polymorphism and risk of POF: [allele model: Cvs. T, OR=0.735, 95%CI: 0.624~0.865, p=0.001; co-dominant models: CCvs.TT, OR=0.540, 95%CI: 0.382~0.764, p=0.001, CTvs.TT, OR=0.735, 95%CI: 0.555~0.972, p=0.031; dominant model: CT+CCvs.TT, OR=0.618, 95%CI: 0.396~0.966, p=0.035; recessive model: CCvs.TT+CT, OR=0.659, 95%CI: 0.502~0.864, p=0.003]. Subgroup analyses showed a significant association in all models in Asian population, but no significant association in any model in European population. For the XbaI polymorphism, overall, no significant association was observed under any genetic models. However, under dominant model, *ESR1* gene XbaI polymorphism is significantly association with risk of POF in Asian population.
Conclusion The present meta-analysis suggests that *ESR1*gene PvuII polymorphism is significantly associated with an increased risk of POF. And *ESR1*gene XbaI polymorphism is not association with risk of POF overall. However, under dominant model, *ESR1*gene XbaI polymorphism is significantly association with risk of POF in Asian population. Further large and well-designed studies are needed to confirm the association.

Keywords Estrogen receptor alpha gene · Polymorphism · Premature ovarian failure · Meta-analysis

Meirong He and Jingcheng Shu contributed equally to this study and should be considered as co-first authors.

Capsule In a case-control study comprising 478 women with POF and 918 women without the disease. For the PvuII polymorphism, we were able to demonstrate that there were significant association observed under all genetic models, overall and in Asian population. However,for the XbaI polymorphism,overall, no significant association was observed under any genetic models. But *ESR1* gene XbaI polymorphism is significantly association with risk of POF under dominant model in Asian population.

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Introduction

POF is defined as a cessation of ovarian function with low estrogen level and elevated gonadotrophins before the age of 40 [1], and results in amenorrhea, infertility, and other systemic consequences (such as Cardiovascular disease, osteoporosis, and so on) because of sex-steroid deficiency [2]. Which affects approximately 1 % of women of reproductive age [3]. It is characterized by the absence of menstruation for a period longer than 6 months (secondary amenorrhea), but it can occur before menarche, leading to primary amenorrhea [4–7].

Although many etiologies are suggested as the cause of POF including genetic, autoimmune and metabolic causes, amongst others [8–10], the etiology remains unknown in a

large proportion of cases. It is well known that follicular growth and maturation occurs by the synergic influence of the hormones estrogen, FSH and LH on the ovary [11]. Considering that initial follicular pool size and the rate of follicular depletion are associated with the age of menopause, genetic variants in sex hormone receptor genes could affect the risk of POF. Studies on female α-ER knockout mice showed anovulation and completed infertility suggesting the importance of ER-α in reproduction [12].

Two ER subtypes exist in humans, including estrogen receptor-α (ER-α) and estrogen receptor-β (ER-β), encoded by *ESR1* and *ESR2* gene [13], respectively. Estrogen acts through ER-α at the hypothalamus-hypophysis-ovarian (HPO) axis to stimulate the release of gonadotrophins to regulate folliculogenesis, and through ER-β in the ovary to enhance follicular development [14]. Intron 1 of the *ESR1* gene contains two common single-nucleotide polymorphisms (SNPs) at Pvu II (−397 T/C, rs2234693, NM_000125.3:c.453-397 T>C) and Xba I (−351 A/G, rs9340799, NM_000125.3:c.453-351A>G) restriction enzyme sites. Recently, several studies on the association between *ESR1* Pvu II (−397 T/C, rs2334693) and Xba I (−351 A/G, rs9340799) polymorphisms and POF risk among different populations including Chinese Han population. However, with relatively small sample sizes, and in Chinese Han population these former studies provided limited information and could not draw a convincing conclusion. Therefore, in this study, a meta-analysis was performed on previous reports to assess the association between the *ESR1* gene Pvu II (−397 T/C, rs2334693) and Xba I (−351 A/G, rs9340799) polymorphisms and the risk of POF .

Materials and methods

Patient and control recruitment

The diagnostic criteria for POF following the definition include at least 4 months of amenorrhea before the age of 40 years, with high serum FSH levels (40 CIU/l). All the patients were assessed clinically for complete medical and gynecological history, including the menstrual history, menopausal age, serum FSH levels (two times at 1-month interval), LH levels, TSH levels and for any history of autoimmune disease and mental retardation. Patients with endocrinopathies, autoimmune disorders or chromosomal abnormalities (determined by G-banded karyotype analysis) or with a past history of hysterectomy, pelvic surgery, and chemotherapy were excluded from the study.

Search strategy

A comprehensive electronic search of Pubmed、Ovid、Chinese National Knowledge Infrastructure (CNKI), and Chinese Biomedical Literature Database (CBM) and WanFang Database published up to August 2014. Literature searches were performed by an expert using the following key words and MeSH terms: “Premature ovarian failure” or “POF”, “estradiol receptor alpha” or “ER alpha” or “*ESR1*” or “estrogen receptor 1” and “genetic polymorphism” or “genetic variants” or “single nucleotide polymorphisms”.

Inclusion and exclusion criteria

Studies included in our meta-analysis had to meet the following criteria: (a) population-based case–control or cohort study focusing on associations of *ESR1* PvuII and/or XbaI polymorphisms with POF; (b) the papers offered the size of the samples, source of controls, distribution of alleles, genotypes, or other information that could help us calculation of odds ratio (OR) with 95 % confidence interval (CI); (c) the following criteria for diagnosing POF were used [15]: >4 months of amenorrhea and two serum FSH levels of >40 mIU/ml in a women aged <40 years. (d) published in the English or Chinese language. While the major reasons for exclusion of studies were as follows: (a) insufficient or error data; (b) lack of control-group or genotype distribution is deviation from the test of Hardy–Weinberg equilibrium (HWE) in controls; (c) studies were meta-analyses, letters, reviews or editorial articles; (d) when multiple publications reported on the same or overlapping data, we used the most recent or largest population as recommended by Little et al. [16].

Data extraction and quality assessment

All data from included studies were extracted independently by two investigators (He and Shu) using a piloted data standardized form (any disagreement were resolved through discussion and, when necessary, adjudicated by a third reviewer). The following data elements were extracted from the studies: first author, year of publication, origin of country, ethnicity of subjects, deviation fromHWE in controls, source of controls, genotyping method, distribution of alleles and genotypes in case and control groups.

Statistical analysis

The association of *ESR1* gene PvuII/XbaI polymorphism with the POF susceptibility were estimated by calculating odds

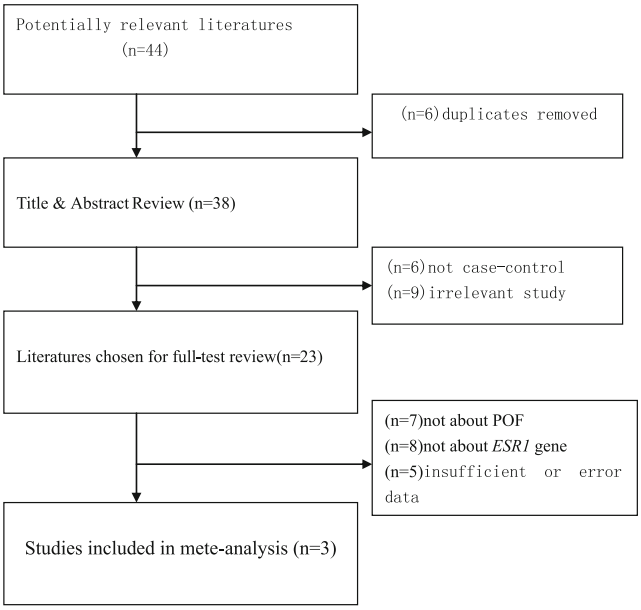

Fig. 1 Flow chart of the study selection process

ratios (ORs) with the corresponding 95 % confidence intervals (CIs) under all genetic models. Data analysis was performed using STATA Software (version 12.0, Stata Corp.). P <0.05 was considered statistically significant. Five comparison models for the PvuII/XbaI polymorphism were evaluated: an allele model (T vs. C/ A vs. G), a co-dominant model (TT vs. CC and CT vs. CC / AA vs. GG and AA vs. AG), a recessive model (TT+CT vs. CC / AA+AG vs. GG), and a dominant model (TT vs. CT+CC/AA vs. GG+GA).

The between-study heterogeneity was examined by Q statistic test. *P* value <0.1 was considered statistically significant [17]. When *P* value >0.10 and I^2<50 %, the between-study heterogeneity was not significant, we used the fixed-effects (Mantel–Haenszel) model, otherwise, the random-effects (DerSimonian–Laird) model was used to calculate the data. In the subgroup analysis, we evaluated the effect of the PvuII/XbaI polymorphism on the susceptibility to POF in the different populations stratified by geographic location (Asian and European).

Sensitivity analysis was performed by sequentially removing an individual study each time to check whether any single study could bias the overall estimate [18]. The potential publication bias was investigated using Begg' funnel plot and Egger's regression test [19]. *P*<0.05 was regarded as statistically significant. In our meta-analysis, the *P* value for the control population in HWE was calculated by a Chi-square test again. The HWE was considered statistically significant, when the *P* value was less than 0.05 [20].

Results

Three studies that met the inclusion criteria were included in the meta-analysis [21–23]. The detailed selection process is illustrated in Fig. 1. The characteristics of the extracted information from each article are summarized in Table 1. Among the eligible studies, a total of 1396 subjects (478 POF cases, 918 healthy controls) were included for this meta-analysis, two were performed in Asia, one was performed in Europe, respectively. All the genotype frequencies in the control populations were in agreement with HWE.

Quantitative synthesis of data

The relationship between *ESR1* gene PvuII/XbaI polymorphism and the risk of POF were explored through 3 case–control studies including 1396 subjects (478 cases, 918 controls). For the PvuII polymorphism, overall, there were significant association observed under all genetic models [allele model:Cvs.T, OR=0.735, 95%CI: 0.624~0.865, p=0.001; co-dominant models: CCvs.TT, OR=0.540, 95%CI: 0.382~0.764, p=0.001, CTvs.TT, OR=0.735, 95%CI: 0.555~0.972, p=0.031; dominant model: CT+CCvs.TT, OR=0.618, 95%CI: 0.396~0.966, p=0.035; recessive model: CCvs.TT+CT, OR=0.659, 95%CI: 0.502~0.864, p=0.003]. (Figure 2). When the subgroup analysis was categorized into Asian and European populations, significant association were observed between *ESR1* gene PvuII polymorphism and the risk of POF under all genetic models in the Asian (Table. 2). However, there were no significant association in any model in the European populations (Table. 2).

For the XbaI polymorphism, overall, no significant association was observed under any genetic models [allele model:Gvs.A, OR=1.090, 95%CI: 0.746~1.591, p=0.656; co-dominant models: GGvs.AA, OR=0.790, 95%CI: 0.510~1.225, p=0.293, GAvs.AA, OR=1.257, 95%CI: 0.721~2.191, p=0.420; dominant model: GG+GAvs. AA, OR=

Table 1 Main characteristics of individual studies in the meta-analysis of the *ESR1* gene PvuII/XbaI polymorphism and POF

Author	Country	Geographic location	age of case	age of control	Sample size		HWE
					Case	Control	
Li	Serbia	European	34.2±8.6	33.6±11.1	197	547	0.586
Lipeng	China	Asian	30.05±4.10	29.61±3.74	155	150	0.476
Yoon	Korea	Asian	27.5±9.0	30.14±3.38	126	221	0.357

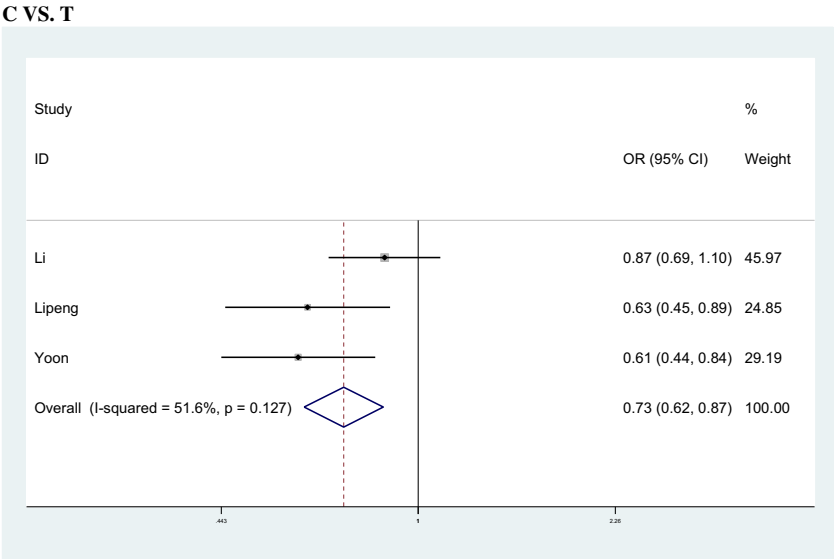

Fig. 2 Meta-analysis of the association between *ESR1* PvuII (T/C) polymorphisms and the risk of POF under allele model (C vs. T)

1.186, 95%CI: 0.706~1.993, p=0.519; recessive model: GGvs.AA+GA, OR=0.789, 95%CI: 0.520~1.196, p=0.264] (Fig. 3). In the subgroup analysis by ethnicity (Asian and European population), a significant association was observed between *ESR1* gene Xbal polymorphism and the risk of POF under dominant model (GG+GAvs.AA, OR=0.458, 95%CI: 0.325~0.722, p=0.001) in Asian populations. However, there were no significant association in any model in the European populations. The overall and subgroup results are displayed in Table 3.

Sensitivity analysis

Sensitivity analysis, after removing one study at a time, was performed to evaluate the stability of the results. For the *ESR1*

Table. 2 Results of the relationship between the meta-analysis of the *ESR1* gene PvuII polymorphism and POF

Comparison	Population	N	Sample Size		Test of association				M	test of heterogeneity		
			Case	Control	OR[a]	95%CI[b]		P_{OR}		x^2	Pvalue [c]	I^2(%)
C vs. T	overall	3	956	1836	0.735	0.624	0.865	0.001	F	4.13	0.127	51.6
	asian	2	562	742	0.620	0.491	0.782	0.001	F	0.03	0.871	0.0
	european	1	394	1094	0.870	0.690	1.096	–	–	–	–	–
CC vs. TT	overall	3	246	370	0.540	0.382	0.764	0.001	F	4.21	0.122	52.54
	asian	2	148	190	0.359	0.212	0.610	0.001	F	0.00	0.956	0.0
	european	1	98	280	0.751	0.471	1.198	0.001	–	–	–	–
CT vs. TT	overall	3	364	562	0.735	0.555	0.972	0.031	F	3.30	0.192	39.5
	asian	2	207	249	0.552	0.363	0.893	0.005	F	0.02	0.889	0.0
	european	1	157	413	0.933	0.637	1.367	0.031	–	–	–	–
CT+CC vs. TT	overall	3	478	818	0.618	0.396	0.966	0.035	R	4.67	0.097	57.2
	asian	2	281	371	0.458	0.325	0.722	0.001	F	0.12	0.732	0.0
	european	1	197	547	0.873	0.609	1.251	0.035	–	–	–	–
CCVS.TT+CT	overall	3	478	818	0.659	0.502	0.864	0.003	F	1.51	0.469	0.0
	asian	2	281	371	0.566	0.392	0.819	0.002	F	0.15	0.701	0.0
	european	1	197	547	0.785	0.527	1.169	0.003	–	–	–	–

a, OR odds ratio

b, 95 % confidence interval

c, Pvalue for heterogeneity based on Q test

M model of meta-analysis, *F* fixed-effects model, *R* random-effects model

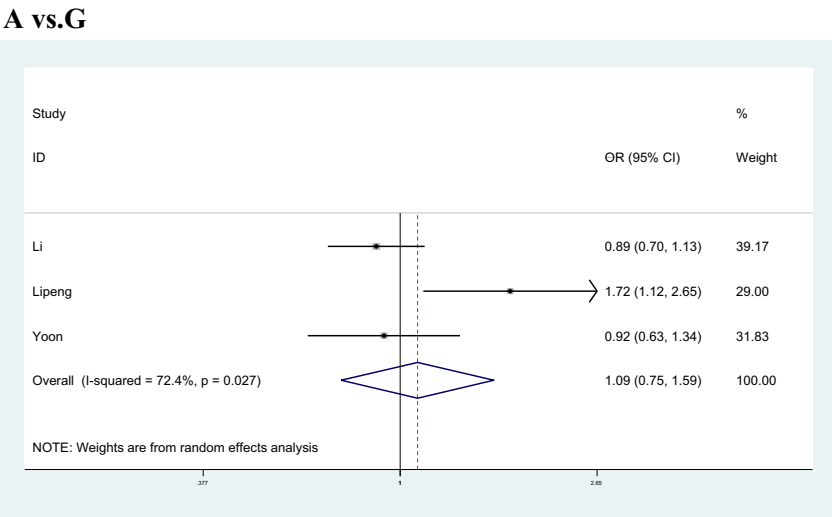

Fig. 3 Meta-analysis of the association between *ESR1* XbaI (A/G) polymorphisms and the risk of POF under allele model (A vs. G)

gene PvuII /XbaI polymorphisms, when successively excluded one study (data not shown), the estimated pooled odd ration remains unchangeable. Sensitivity analysis indicated that our results are reliable and stable.

Publication bias diagnostics

We conducted a Begg's funnel plot and Egger's regression test to strengthen further the confidence level in the results. The funnel plot did not reveal evidence asymmetry, which suggested there was no obvious publication bias and Egger's test also showed that there was no statistical significance for the evaluation of publication bias under the allele model T vs. C / A vs. G (Fig. 4).

Discussion

The role of sex steroid hormones in reproductive function, especially estrogen, has for long been studied and positive

Table 3 Results of the relationship between the meta-analysis of the *ESR1* gene XbaI polymorphism and POF

Comparison	Population	N	Sample Size		Test of association				M	test of heterogeneity		
			Case	Control	OR[a]	95%CI[b]		P_{OR}		x^2	Pvalue[C]	I^2(%)
G vs. A	Overall	3	956	1836	1.090	0.746	1.591	0.656	R	7.26	0.027	72.4
	Asian	2	562	742	1.250	0.677	2.306	0.475	R	4.59	0.032	78.2
	European	1	394	1094	0.888	0.699	1.128	–	–	–	–	–
GG vs. AA	Overall	3	288	558	0.790	0.510	1.225	0.293	F	0.19	0.909	0.0
	Asian	2	183	266	0.873	0.388	1.963	0.743	F	0.11	0.744	0.0
	European	1	105	292	0.935	0.659	1.327	–	–	–	–	–
GA vs. AA	Overall	3	444	819	1.257	0.721	2.191	0.420	R	9.37	0.009	78.6
	Asian	2	171	354	1.498	0.606	3.703	0.382	R	6.58	0.01	84.8
	European	1	173	465	0.935	0.659	1.327	–	–	–	–	–
GG+GA vs. AA	Overall	3	478	918	1.186	0.706	1.993	0.519	R	8.99	0.011	77.8
	Asian	2	281	371	0.458	0.325	0.722	0.001	F	0.12	0.732	0.0
	European	1	197	547	0.892	0.640	1.244	–	–	–	–	–
GGVS.AA+GA	Overall	3	478	918	0.789	0.520	1.196	0.264	F	0.00	1.000	0.0
	Asian	2	281	371	0.794	0.355	1.776	0.574	F	0.00	0.986	0.0
	European	1	197	547	0.787	0.483	1.281	–	–	–	–	–

a, OR odds ratio

b, 95 % confidence interval

c, *P* value for heterogeneity based on Q test

M model of meta-analysis, *F* fixed-effects model, *R* random-effects model

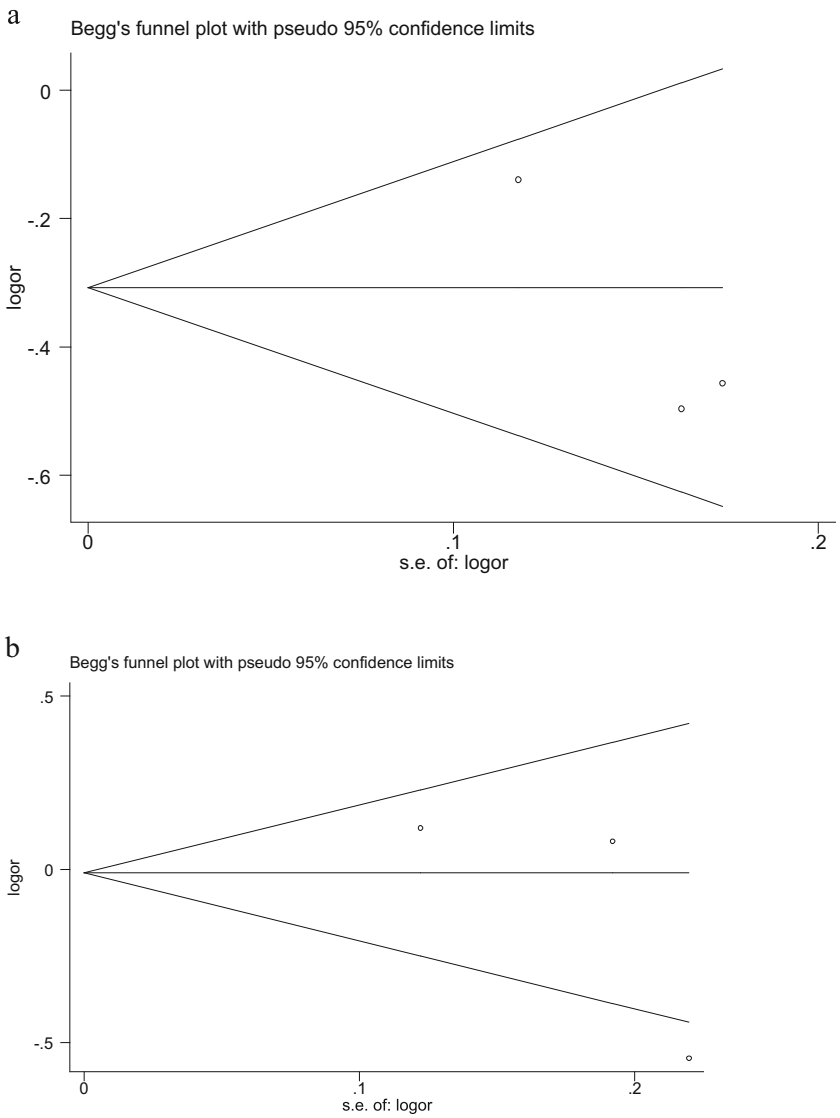

Fig. 4 Begg's funnel plot of publication bias on the association between *ESR1* PvuII (T/C) (**a**) and XbaI (A/G) (**b**) polymorphisms and the risk of POF under allele model in the overall populations

correlations have been found by diverse groups and gynecological diseases [24–27]. Indeed, studies with *ESR1* knockout mice showed important evidences of reproductive impairment as anovulation and complete infertility in the absence of this gene [12].

Human *ESR1* gene is located on chromosome 6q25.1, wild-type *ESR1* gene length of 140 kb, and consists of eight exons separated by seven introns. Study indicated that the *ESR1* is a major mediator of the atheroprotective effect of estrogen on animal and human [28]. When ERs bind to estrogen, a conformational change ensues that enables the homodimerization of the complex, allowing for binding to estrogen response elements and subsequently altering the expression of relevant target genes, and the result that thereby regulating the growth, reproduction, differentiation and function of many target organs, including the breast tissue, cardiovascular system, nervous system, bone tissue, liver, and so on. Recently, several studies have focused on the *ESR1* rs2234693 and rs9340799 polymorphisms with risk of POF. In fact, the results were inconclusive. Such as study by Liu [21] the *ESR1* rs2234693 and rs9340799 polymorphisms were significantly association with POF, but study by LI.J [22], no significantly association with POF in both the *ESR1* rs2234693 and rs9340799 polymorphisms. However, study by Yoon SH [23], their results have demonstrated that the genetic variation in *ESR1* gene (PvuII polymorphism) is associated to POF risk. Therefore, we decided to perform a meta-analysis of all eligible case–control studies on POF risk in order to reveal a more accurate relationship between the PvuII and XbaI polymorphisms of the *ESR1* gene and risk of POF.

To our knowledge, this is the first meta-analysis which comprehensively assessed the associations between the *ESR1* rs2234693 and rs9340799 polymorphisms and risk of POF in different populations. Three studies covering 1396 subjects were identified. Pooled data showed significant association between *ESR1* gene PvuII polymorphism and risk of

POF: [allele model:Cvs.T, OR=0.735, 95%CI: 0.624~0.865, p=0.001; co-dominant models: CCvs.TT, OR=0.540, 95%CI: 0.382~0.764, p=0.001, CTvs.TT, OR=0.735, 95%CI: 0.555~0.972, p=0.031; dominant model: CT+CCvs.TT, OR=0.618, 95%CI: 0.396~0.966,p=0.035; recessive model: CCvs.TT+CT, OR=0.659, 95%CI: 0.502~0.864, p=0.003]. Subgroup analyses showed a significant association in all models in Asian population, but no significant association in any model in European population. For the XbaI polymorphism, overall, no significant association was observed under any genetic models. However, under dominant model, *ESR1*gene XbaI polymorphism is significantly association with risk of POF in Asian population.

Few studies have focused on *ESR1* XbaI polymorphisms associated with age at menopause or POF. However, the X allele of XbaI was reported to be related to increased bone mineral density, reduced risk of osteoporosis, and cardiovascular diseases, which suggest higher levels of estrogen [29–33]. So, we hypothesize a series of mechanisms for POF and ER genetic polymorphisms: (1) Estrogen binds to ERs in reproductive tissues, such as the ovaries, uterus, and vagina [34]. The low activity gene encoding protein leads to the low of activity of ERs, and then estrogenic action in the tissue may be weak; (2) Continuous weak estrogenic effect in the reproductive tissue, especially the ovaries, may have a negative feedback on the pituitary gland, especially follicle stimulating hormone (FSH) secretion; (3) FSH, in turn, can accelerate the rapid depletion of the ovarian follicles, leading to the development of POF because of ovarian dysfunction. To clarify the exact mechanisms between ER genes and POF.

We used a fixed-effects or a random-effects model in our analysis of the studies based on heterogeneity testing (Table 2). For the XbaI polymorphism, all the comparison models revealed large heterogeneity between the studies for the overall populations and the Asian subgroup. Differences in the studied populations with different genetic backgrounds and variations in sample selection and environmental exposures may result in these heterogeneities. Our meta-regression analysis also showed that the ethnicity in case groups and control groups significantly contributed to the heterogeneity.

Begg's funnel plot and Egger's test did not show any evidence of significant publication bias in all the comparison models. Sensitivity analysis indicated that none of the studies study influenced the results of this meta-analysis. So, the results of our study can be interpreted with a high confidence level.

Limitation

We acknowledged that there were some limitations in our study. First, sample size in our study was comparatively small and had insufficient statistical power to detect the association. Second, the effect of gene-gene and gene-environment interactions was not considered in this meta-analysis. Third, in the current meta-analysis study, two were performed in Asia, one was performed in Europe, but not from Africa and North America et al. Fourth, this meta-analysis was based on unadjusted estimates, whereas a more precise analysis could be obtained if all individual raw data were available. Thus, we hope that these issues will be considered in future by the related researchers.

Conclusions

In conclusion, although these limits, the results of our meta-analysis strongly suggests that *ESR1* gene PvuII polymorphism was significant associated with an increased risk of POF. And *ESR1* gene XbaI polymorphism is not association with risk of POF overall. But, *ESR1*gene XbaI polymorphism was significantly association with risk of POF in dominant model in Asian population. In the future, well-designed studies are performed to re-evaluate the potential associations between *ESR1*gene polymorphisms with other candidate gene polymorphisms and POF risk..

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Conflict of Interest The authors declare that they have no competing interests with respect to the authorship and/or publication of this article.

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