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*Estrogen receptor 1 Pvu*II and *Xba*I polymorphisms and susceptibility to Alzheimer's disease: a meta-analysis

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ABSTRACT. The aim of this study was to explore whether estrogen receptor 1 (*ESR1*) *Pvu*II and *Xba*I polymorphisms are associated with susceptibility to Alzheimer's disease (AD). We conducted a meta-analysis of the associations between AD and *ESR1 Pvu*II and *Xba*I polymorphisms as well as haplotypes of the *ESR1 Pvu*II and *Xba*I polymorphisms. A total of 1359 patients and 1387 controls from 9 studies on the *ESR1 Pvu*II polymorphism and 1525 patients and 1575 controls from 8 studies on the *ESR1 Xba*I polymorphism were included in this meta-analysis. Gender-specific meta-analysis showed an association between the *ESR1 PP+Pp* genotype and AD in males (OR = 0.302, 95%CI = 0.100-0.914, P = 0.034), but not in females. No association was observed between AD and the *ESR1 Xba*I X allele (OR = 1.114, 95%CI = 0.868-1.429, P = 0.397). However, country-specific meta-analysis identified an association between AD and the *ESR1 X* allele in Japanese (OR = 1.386, 95%CI = 1.055-1.822, P = 0.019), but not Chinese or Italian populations. Meta-analyses results indicated an association between the PP/XX haplotypes and AD in Chinese

population (OR for PP/XX *vs* others = 2.758, 95%CI = 1.750-4.346, P = 1.2 x 10^{-6}). This meta-analysis showed associations between the *ESR1 Pvu*II polymorphism and AD susceptibility in males, between AD risk and the *ESR1 Xba*I polymorphism in the Japanese population, and between the PP/XX haplotype and AD susceptibility in the Chinese population.

Key words: Alzheimer's disease; Estrogen receptor; Polymorphism; Meta-analysis

INTRODUCTION

Alzheimer's disease (AD) is a complex, progressive, and irreversible neurodegenerative disease of the brain. AD is characterized by the accumulation of the amyloid-β (Aβ) protein and neurofibrillary tangles in the brain (Boada et al., 2012a). Although the etiology of AD has not been determined, a genetic component of susceptibility to AD has been established by some case-control, twin, and family studies.

Estrogen induces synaptogenesis, acts as a neuroprotective agent, regulates neurotransmission in the central nervous system (CNS), and is associated with cognitive symptoms (Szego et al., 2011). Estrogen may inhibit the formation of the Aβ protein and protect against Aβ protein-induced neuronal death (Szego et al., 2011), however AD may be more prevalent in women, attributed in part, to estrogen (Bachman et al., 1992). Thus estrogen is considered to play a role in the pathogenesis of AD (Xing et al., 2013). Estrogen action is mediated through estrogen receptors 1 (ESR1) and 2 (ESR2). The *ESR1* gene, located on chromosome 6q25.1, is expressed in the brain, predominantly in the hypothalamus and amygdale (Xing et al., 2013). *ESR1* polymorphisms located in intron 1, *Pvu*II (rs2234693) and *Xba*I (rs9340799), may be in linkage disequilibrium (LD) with regulatory polymorphisms that affect *ESR1* expression or disease susceptibility genes. The *ESR1 Pvu*II and *Xba*I polymorphisms have been the most intensively studied in association with susceptibility to AD and whether *ESR1*gene plays a role in the pathogenesis of AD (Xing et al., 2013).

Published results on the genetic association of ESR1 polymorphisms are controversial and inconclusive. While some reports have shown associations between these *ESR1* polymorphisms and AD, others found no such association (Ji et al., 2000; Maruyama et al., 2000; Lambert et al., 2001; Lin et al., 2003; Monastero et al., 2006; Porrello et al., 2006; Usui et al., 2006; Dresner-Pollak et al., 2009; Ma et al., 2009; Boada et al., 2012b; Deng et al., 2013). This discrepancy may be due to sample size, statistical power, ethnicity, gender, clinical heterogeneity, or a combination of these factors. Meta-analysis is a powerful tool to overcome the drawbacks of small sample size and inadequate statistical power from genetic studies of complex traits. To overcome the limitations of individual studies, we carried out a meta-analysis (Lee and Nath, 2005; Lee et al., 2005, 2006) to determine whether the *ESR1 Pvu*II and *Xba*I polymorphisms are associated with susceptibility to AD.

METHODS

Identification of eligible studies and data extraction

Using MEDLINE and EMBASE citation databases, we performed a literature search

to identify articles published up to October 2013 that examined associations between *ESR1* polymorphisms and AD. Combinations of key words such as "estrogen receptor 1", "*ESR1*", "polymorphism", "Alzheimer's disease", and "AD" were entered as Medical Subject Heading terms and text words. References in the studies identified were used to identify additional studies not indexed by the electronic databases. Inclusion criteria were as follows: 1) case-control study design, 2) original data, 3) genotype or allele data to calculate odds ratios (ORs), and 4) studies in which the genotype distribution in the controls was not consistent with the Hardy-Weinberg equilibrium (HWE), because such deviations in HWE among controls suggests the possibility of bias during control selection or genotyping errors. The following information was extracted from each study identified: author, year of publication, ethnicity and country of the study population, demographics, and number of cases and controls for each *ESR1* polymorphism. Allele frequencies were calculated from the corresponding genotype distributions.

Evaluation of statistical associations

A chi-square test was used to determine whether observed genotype frequencies conformed to HWE. Point estimates of risks, ORs, and 95% confidence intervals (CIs) were estimated for each study. Cochran's Q-statistic was used to assess intra- and inter-study variation or heterogeneity. I^2 values ranged between 0 and 100%, representing the proportion of inter-study variability attributable to heterogeneity rather than chance (Higgins and Thompson, 2002). I^2 values of 25, 50, and 75% were nominally assigned as low, moderate, and high estimates, respectively. The fixed-effects model assumed that a genetic factor had the same effect on AD susceptibility across all studies investigated and that variations between studies were caused by chance alone. The random-effects model assumed that different studies had substantial diversity and assessed intra-study sampling error and inter-study variance (DerSimonian and Laird, 1986). A comprehensive meta-analysis program (Biostat Englewood, NJ, USA) was used for analysis. Study power was computed as the probability of detecting an association between the *ESR1* polymorphisms and AD at a significance level of 0.05, assuming an OR of 1.5 (small effect size). Power analysis was performed using the G*Power statistical program (http://www.psycho.uni-duesseldorf.de/aap/projects/gpower).

Evaluation of heterogeneity and publication bias

Meta-regression was performed to examine the potential source of heterogeneity observed in the meta-analysis. Sensitivity analysis was also performed to assess the influence of each individual study on the pooled OR by omitting each individual study. We evaluated publication bias using Egger's linear regression test, which measures funnel plot asymmetry using a natural logarithmic scale of ORs. When asymmetry was indicated, we used the trim and fill method to adjust the summary estimate for the bias observed.

RESULTS

Studies included in the meta-analysis

We identified 135 studies by electronic and manual search, of which 16 studies were selected for a full-text review on the basis of the title and abstract details (Isoe-Wada et al.,

1999; Ji et al., 2000; Maruyama et al., 2000; Lambert et al., 2001; Lin et al., 2003; den Heijer et al., 2004; Pirskanen et al., 2005; Monastero et al., 2006; Porrello et al., 2006; Usui et al., 2006; Boccardi et al., 2008; Dresner-Pollak et al., 2009; Ma et al., 2009; Goumidi et al., 2011; Boada et al., 2012b; Deng et al., 2013). After full-text review, seven studies were excluded, of which 4 did not contain genotype data for *ESR1* polymorphism (den Heijer et al., 2004; Pirskanen et al., 2005; Boccardi et al., 2008; Goumidi et al., 2011), 2 contained data on control genotype deviated from HWE (Maruyama et al., 2000; Boada et al., 2012b) and 1 study contained duplicate data (Isoe-Wada et al., 1999). Thus, a total of 9 studies (Ji et al., 2000; Lambert et al., 2001; Lin et al., 2003; Monastero et al., 2006; Porrello et al., 2006; Usui et al., 2006; Dresner-Pollak et al., 2009; Ma et al., 2009; Deng et al., 2013), corresponding to 1359 patients and 1387 controls, met all the inclusion criteria and were considered for the *ESR1 Xba*I polymorphism meta-analysis (Table 1C). Of these, 8 studies corresponding to 1525 patients and 1575 controls were also included in the *ESR1 Pvu*II polymorphism meta-analysis (Table 1B). The statistical power of the studies ranged from 23.6 to 68.1% and none had statistical power exceeding 80%.

Table 1. Characteristics of studies used in the meta-analysis.

Clinical characteristics								
Citation	Country	Population	Gender (Female, %)		Age at examination (means ± SD)		Onset age (means ± SD)	
			Case	Control	Case	Control	Case	Control
Deng et al., 2013	China	Clinic	66.5	66.5	67.3 ± 7.2	66.4 ± 9.1	NA	NA
Ma et al., 2009	China	Community	84.3	75.5	81.4 ± 6.7	73 ± 6.3	NA	NA
Dresner-Pollak et al., 2009	Israel	Community	NA	NA	83.5 ± 7.3	81.0 ± 7.1	NA	NA
Monastero et al., 2006	Italy	Clinic	65.1	65.1	73.7 ± 8.0	72.9 ± 7.9	70.8 ± 8.0	NA
Porrello et al., 2006	Italy	Clinic	56	53	75 ± 7	71 ± 10	NA	NA
Usui et al., 2006	Japan	Clinic	54.1	35.8	69.110.7	62.8 9.0	NA	NA
Lin et al., 2003	China	Community	73.1	50.4	791.4	NA	NA	NA
Lambert et al., 2001	UK	Clinic	61	53	67.9 ± 12.5	62.6 ± 14.9	64.6 11.8	NA
Ji et al., 2000	Japan	Clinic	NA	NA	78.6 ± 8.2	75.5 ± 5.5	NA	NA

*ESR1 Pvu*II polymorphism												
Citation	Ethnicity	Numbers		Case			Control			HWE	Association P[a]	Power (%)[b]
		Case	Control	PP	Pp	pp	PP	Pp	pp			
Deng et al., 2013	Asian	236	236	46	123	67	53	127	56	0	0.241	58.4
Ma et al., 2009	Asian	219	215	24	113	82	34	110	71	0	0.162	54.9
Dresner-Pollak et al., 2009	Jewish	118	68	181*			86*			0	0.006	27.5
Porrello et al., 2006	European	131	109	23	62	46	24	45	40	0	0.750	34.0
Usui et al., 2006	Asian	205	92	43	91	71	19	41	32	0	0.957	40.6
Lin et al., 2003	Asian	30	128	7	17	6	19	56	53	0	0.035	34.1
Lambert et al., 2001	European	186	405	36	96	54	77	200	128	0	0.639	68.1
Ji et al., 2000	Asian	234	134	59	114	61	21	61	52	0	0.004	48.3

*ESR1 Xba*I polymorphism												
Citation	Ethnicity	Numbers		Case			Control			HWE	Association P[a]	Power (%)[b]
		Case	Control	XX	Xx	xx	XX	Xx	xx			
Deng et al., 2013	Asian	236	236	22	93	121	35	105	96	0	0.009	58.4
Ma et al., 2009	Asian	228	234	21	84	123	22	99	113	0	0.328	57.5
Dresner-Pollak et al., 2009	Jewish	118	68	177*			80*			0	0.001	27.5
Monastero et al., 2006	European	158	172	18	92	48	33	98	41	0	0.064	44.3
Porrello et al., 2006	European	131	109	15	61	55	14	48	47	0	0.976	34
Usui et al., 2006	Asian	205	92	18	59	128	2	36	54	0	0.700	40.6
Lin et al., 2003	Asian	29	125	6	9	14	8	32	85	0	0.006	23.6
Lambert et al., 2001	European	186	405	21	88	77	43	197	165	0	0.998	68.1
Ji et al., 2000	Asian	234	134	23	90	121	6	41	87	0	0.006	48.3

SD, Standard deviation; NA, Not available; UK, United Kingdom; HWE, Hardy-Weinberg equilibrium; 0, control genotype in HWE; [a]Allelic association; [b]Assuming an odds ratio of 1.5 (small effect size) at a level of significance of 0.05, *Allele number.

Meta-analysis of the *ESR1 Pvu*II polymorphism and AD

No association was observed between AD and the *ESR1 Pvu*II P allele in the combined study subjects (OR = 1.135, 95%CI = 0.920-1.401, P = 0.238) (Table 2, Figure 1). Country-specific meta-analysis indicated no association between the *ESR1* P allele and AD in either Chinese (OR = 0.999, 95%CI = 0.700-1.424, P = 0.993) or Japanese (OR = 1.272, 95%CI = 0.823-1.966, P = 0.279) population (Table 2). *ESR1* polymorphism data in both, males and females, was presented in 2 studies (Lambert et al., 2001; Lin et al., 2003). Gender-specific meta-analysis of results from these studies indicated no association between the *ESR1* P allele and AD in females (OR = 1.496, 95%CI = 0.724-3.091, P = 0.277) or males (OR = 1.187, 95%CI = 0.821-1.716, P = 0.363) (Table 2). However, meta-analysis using dominant model showed an association between the *ESR1 Pvu*II polymorphism and AD in males (OR = 0.302, 95%CI = 0.100-0.914, P = 0.034), but not in females.

Table 2. Analysis of the association between the *ESR1 Pvu*II polymorphism and AD.

Polymorphism	Population	No. of studies	Test of association			Test of heterogeneity		
			OR	95%CI	P	Model	P	I^2
P *vs* p	Overall	8	1.135	0.920-1.401	0.238	R	0.002	69.2
	Chinese	3	0.999	0.700-1.424	0.993	R	0.035	70.5
	Japanese	2	1.272	0.823-1.966	0.279	R	0.061	71.4
	Female	2	1.496	0.724-3.091	0.277	R	0.052	73.4
	Male	2	1.187	0.821-1.716	0.363	F	0.340	0
p *vs* P	Overall	8	0.88	0.714-1.087	0.238	R	0.002	69.2
	Chinese	3	1.001	0.702-1.428	0.993	R	0.035	70.5
	Japanese	2	0.786	0.509-1.215	0.279	R	0.061	71.4
	Female	2	0.669	0.324-1.381	0.277	R	0.052	73.4
	Male	2	0.843	0.583-1.218	0.363	F	0.340	0
PP *vs* Pp + pp (Recessive)	Overall	7	0.990	0.803-1.220	0.923	F	0.157	35.4
	Chinese	3	0.836	0.602-1.160	0.283	F	0.233	31.3
	Japanese	2	1.398	0.930-2.102	0.108	F	0.168	47.2
	Female	2	1.152	0.668-0.987	0.611	F	0.196	40.0
	Male	2	0.704	0.389-1.273	0.245	F	0.617	0
PP + Pp *vs* pp (Dominant)	Overall	7	1.117	0.856-1.458	0.416	R	0.044	53.6
	Chinese	3	1.024	0.603-1.739	0.929	R	0.048	66.9
	Japanese	2	1.364	0.773-2.407	0.284	R	0.098	63.4
	Female	2	1.899	0.667-5.403	0.229	R	0.076	68.2
	Male	2	0.302	0.100-0.914	0.034	R	0.061	71.5
PP *vs* pp	Overall	7	0.928	0.729-1.180	0.541	F	0.100	43.5
	Chinese	3	0.781	0.541-1.127	0.187	F	0.421	0
	Japanese	2	1.525	0.939-2.478	0.088	F	00175	45.6
	Female	2	2.062	0.479-8.874	0.331	R	0.072	69.0
	Male	2	1.427	0.663-3.070	0.363	F	0.357	0

ESR1, estrogen receptor 1; HWE, Hardy-Weinberg equilibrium; F, fixed model; R, random model.

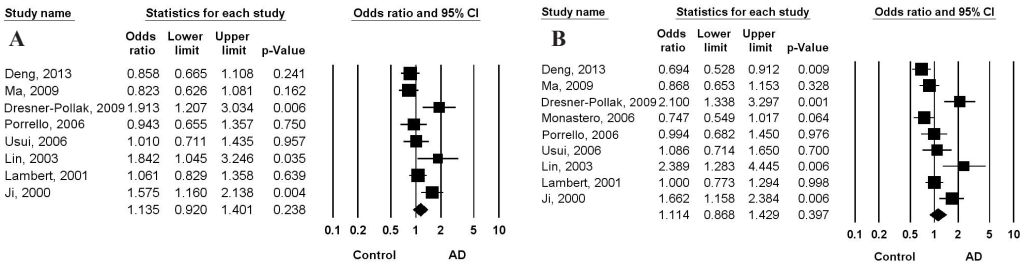

Figure 1. ORs and 95%CIs of individual studies and pooled data for the allelic association between AD and *ESR1 Pvu*II (**A**) and *Xba*I (**B**) polymorphisms in all subjects.

Meta-analysis of *ESR1 Xba*I polymorphism and AD

Meta-analysis of the combined study subjects showed no association between AD and the *ESR1 Xba*I X allele (OR = 1.114, 95%CI = 0.868-1.429, P = 0.397) (Table 3, Figure 2).

However, country-specific meta-analysis identified an association between AD and the *ESR1 Xba*I X allele in Japanese (OR = 1.386, 95%CI = 1.055-1.822, P = 0.019), but not in either Chinese or Italian population (Table 3). Gender-specific meta-analysis indicated no association between the *ESR1* X allele and AD in both, males and females (Table 3).

Table 3. Analysis of the association between AD and the *ESR1 Xba*I polymorphism.

Polymorphism	Population	No. of studies	Test of association			Test of heterogeneity		
			OR	95%CI	P	Model	P	I^2
X *vs* x	Overall	9	1.114	0.868-1.429	0.397	R	0.000	78.3
	Chinese	3	1.040	0.618-1.750	0.884	R	0.002	84.3
	Japanese	2	1.386	1.055-1.822	0.019	F	0.131	56.1
	Italian	2	0.838	0.660-1.064	0.147	F	0.131	56.1
	Female	2	1.309	0.956-1.792	0.094	F	0.119	58.8
	Male	2	1.780	0.554-5.714	0.333	R	0.067	71.6
x *vs* X	Overall	9	0.898	0.700-1.152	0.397	R	0.000	78.3
	Chinese	3	0.962	0.571-1.619	0.884	R	0.002	84.3
	Japanese	2	0.721	0.549-0.948	0.019	F	0.131	56.1
	Italian	2	1.193	0.940-1.515	0.147	F	0.131	56.1
	Female	2	0.764	0.558-1.047	0.094	F	0.119	58.8
	Male	2	0.562	0.175-1.804	0.333	R	0.067	71.6
XX *vs* Xx + xx (Recessive)	Overall	8	1.127	0.722-1.757	0.599	R	0.007	63.77
	Chinese	3	1.138	0.479-2.704	0.770	R	0.016	75.7
	Japanese	2	2.768	1.263-6.067	0.011	F	0.485	0
	Italian	2	0.653	0.402-1.061	0.085	F	0.342	0
	Female	2	1.469	0.770-2.801	0.243	F	0.809	0
	Male	2	4.525	0.352-58.13	0.246	R	0.017	82.4
XX+ Xx *vs* xx (Dominant)	Overall	8	0.973	0.752-1.258	0.835	R	0.012	61.3
	Chinese	3	0.929	0.550-1.570	0.784	R	0.024	73.2
	Japanese	2	1.229	0.617-2.450	0.557	R	0.038	76.7
	Italian	2	0.158	0.603-1.223	0.397	F	0.295	88.9
	Female	2	1.658	0.674-4.081	0.271	R	0.091	65.0
	Male	2	1.115	0.651-1.908	0.692	F	0.606	0
XX *vs* xx	Overall	8	1.130	0.675-1.892	0.643	R	0.002	69.3
	Chinese	3	1.105	0.399-3.064	0.848	R	0.005	81.2
	Japanese	2	3.018	1.362-6.687	0.007	F	0.722	0
	Italian	2	0.621	0.362-1.063	0.082	F	0.224	32.3
	Female	2	1.623	0.822-3.025	0.163	F	0.548	0
	Male	2	3.590	0.424-30.41	0.241	R	0.048	74.4

ESR1, estrogen receptor 1; F, fixed model; R, random model.

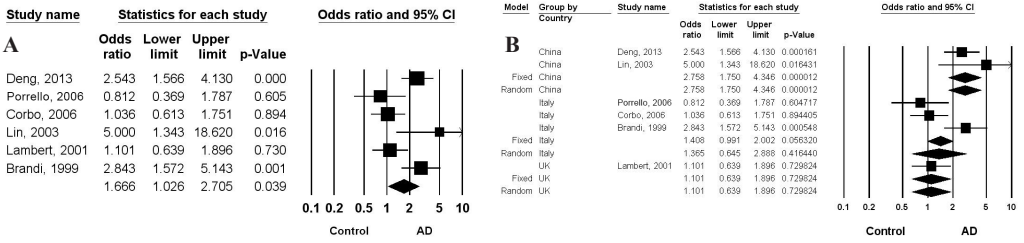

Figure 2. ORs and 95%CIs of individual studies and pooled data for the allelic association between AD and the *ESR1 Pvu*II-*Xba*I haplotype in all subjects (**A**) and in each country group (**B**).

Meta-analysis of *Pvu*II-*Xba*I haplotype and AD

Meta-analyses of the *Pvu*II-*Xba*I haplotype showed a significant association between the PP/XX haplotypes and AD (OR for PP/XX *vs* others = 1.666, 95%CI = 0.026-2.705, P = 0.039; OR for PP/XX *vs* pp/xx = 2.071, 95%CI = 1.150-6.368, P = 0.023) (Table 4). Country-specific meta-analysis indicated an association between the PP/XX haplotypes and AD Chinese (OR for PP/XX *vs* others = 2.758, 95%CI = 1.750-4.346, P = 1.2 x 10^{-6}; OR for PP/XX *vs* pp/xx = 14.66, 95%CI = 6.729-31.95, P < 1.0 x 10^{-8}), but not in Italian population (Table 4).

Table 4. Analysis of the association between AD and the *Pvu*II-*Xba*I haplotype.

Polymorphism	Population	No. of studies	Test of association			Test of heterogeneity		
			OR	95%CI	P	Model	P	I^2
PP/XX *vs* others	Overall	6	1.666	1.026-2.705	0.039	R	0.004	71.6
	Chinese	2	2.758	1.750-4.346	1.2 x 10^{-6}	F	0.344	0
	Italian	3	1.365	0.645-2.888	0.416	R	0.014	76.7
	Female	2	1.526	0.797-2.924	0.203	F	0.613	0
	Male	2	5.569	0.349-88.90	0.224	R	0.043	75.5
PP/XX *vs* pp/xx	Overall	6	2.071	1.150-6.368	0.023	R	0.000	86.1
	Chinese	2	14.66	6.729-31.95	<1.0 x 10^{-8}	F	0.613	0
	Italian	3	1.535	0.735-3.206	0.254	R	0.036	69.9
	Female	2	1.953	0.957-3.985	0.066	F	0.294	9.28
	Male	2	7.887	0.240-259.1	0.246	R	0.049	74.2

ESR1, estrogen receptor 1; F, fixed model; R, random model.

Heterogeneity, meta-regression, sensitivity analysis, and publication bias

Inter-study heterogeneity was observed in meta-analyses of the *ESR1 Pvu*II and *Xba*I polymorphisms and PP/XX haplotypes (Tables 2 and 3). Meta-regression showed that sample size (P = 0.013), but not ethnicity (P = 0.534), and publication year (P = 0.162) had a significant impact on the heterogeneity in the *ESR1 Pvu*II polymorphism. Sensitivity analysis showed that no individual study significantly affected the pooled OR. Egger's regression test showed evidence of publication bias in the meta-analyses of the *ESR1 Pvu*II and *Xba*I polymorphisms (Egger's regression test P values = 0.085, 0.017). However, the adjusted ORs by the trim and fill technique were not significantly changed.

DISCUSSION

In the present study, we conducted a country- and gender-specific meta-analyses of the associations between the *ESR1 Pvu*II and *Xba*I polymorphisms and AD susceptibility. We found an association between the *ESR1 Pvu*II polymorphism and AD susceptibility in males, and an association between AD risk and the *ESR1 Xba*I polymorphism in the Japanese population. We also detected an association between the PP/XX haplotype of the *ESR1 Pvu*II and *Xba*I polymorphisms and AD susceptibility in the Chinese population.

ESR1 polymorphisms may have a functional significance. Maruyama et al. (2000) found that *ESR1 Pvu*II and *Xba*I polymorphisms showed a weak enhancer activity, where the activity was higher in the x allele than in the X allele. Herrington et al. (2002) suggested that the P allele underlines a functional myb transcription factor-binding site that could alter the transcription, stability, or structure of the *ESR1* transcript and the subsequent *ESR1* protein.

There is also a possibility that *ESR1 Pvu*II and *Xba*I polymorphisms may be in LD with disease susceptibility genes.

The difference in the associations across countries, even within the same ethnic group remains unexplained. This could be due to unknown environmental factors and not ethnicity but country-related genetic factors. It is also unclear why a weak association of these polymorphisms and AD was observed in men in particular, in the different populations analyzed. This could be due to different levels of production and the effects of estrogen among men and women. However, we cannot rule out the possibility of false-positive type I error, due to the small number of studies included in this meta-analysis. Therefore, further studies with a large sample size are recommended.

Our study has several limitations. First, heterogeneity and confounding factors might have distorted the analysis. Second, it would have been interesting to evaluate the association between *ESR1* polymorphisms and clinical features of AD, but this was not possible because of the limited data.

In conclusion, this meta-analysis shows that the *ESR1 Pvu*II polymorphism is associated with AD susceptibility in males, and that *ESR1 Xba*I polymorphism is associated with AD risk in the Japanese population. In addition, the PP/XX haplotype is associated with AD susceptibility in the Chinese population. These data support that the *ESR1 Pvu*II and *Xba*I polymorphisms play a role in susceptibility to AD.

Conflicts of interest

The authors declare no conflict of interest.

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