Neuroscience Letters 574 (2014) 41–46

Contents lists available at ScienceDirect

Neuroscience Letters

journal homepage: www.elsevier.com/locate/neulet

Meta-analysis of *Pvu*II, *Xba*I variants in *ESR1* gene and the risk of Alzheimer's disease: The regional European difference

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HIGHLIGHTS

- We conducted a meta-analysis on *ESR1* polymorphisms with the risk of AD under different genetic models.
- The *Pvu*II variant, but not *Xba*I polymorphism, was associated with AD in Caucasians.
- The regional European difference was found in the *Pvu*II polymorphism in AD.
- No relationships were found for the *ESR1* polymorphisms and AD risk in Asians.

ARTICLE INFO

Article history:
Received 1 February 2014
Accepted 7 May 2014
Available online 22 May 2014

Keywords:
Alzheimer
ESR1
Variants
Meta analysis
Geographical region

ABSTRACT

The *Pvu*II and *Xba*I polymorphisms of *ESR1* gene have been reported in the Alzheimer's disease (AD) studies. However, whether these *ESR1* genetic variants can contribute to the risk of AD remains controversial. Herein, we conducted a meta-analysis to clarify the association between *ESR1* polymorphisms and the occurrence of AD. Articles were identified by systematic searches in PubMed, Google scholar and Wan Fang Med Online database. The combined odds ratios (OR) and 95% confidence intervals (CI) were calculated within different inherited models. Publication bias tests, subgroup analyses and sensitive analyses were also performed. Overall, the *Pvu*II variant was negatively associated with AD in the Caucasian population (pp vs PP+Pp, OR 0.86, 95%CI (0.76, 0.96)). However, there was a poor association between *Xba*I polymorphism and AD in European populations. In particular, *Pvu*II variant was found significantly associated with a decreased AD risk in South European samples (pp vs PP+Pp, OR 0.86, 95%CI (0.75, 0.98)). This meta-analysis indicated that regional European differences of *ESR*1 *Pvu*II polymorphism in the association with the occurrence of AD, which need to be further identified, especially in South European countries.

1. Introduction

Afflicting about 30 million people globally [1] and as the most common cause of senile dementia, Alzheimer's disease (AD) now represents a worldwide growing clinical challenge [2]. AD is characterized by senile plaques and neurofibrillary tangles in the brain, consequently distinct memory loss and progressive cognitive function deficit in clinical features. Approximately 70% of AD risk is attributable to genetic factor [3].

There are emerging evidences suggesting that the estrogen-signaling pathway is contributable to AD (see reviews [4–6]). Estrogen could exert an important neuroprotective effect which is dependent on the activation of the nuclear estrogen receptor alpha and beta [6]. The estrogen associated gene polymorphisms [7], especially estrogen receptor 1(*ESR1*) single-nucleotide polymorphisms (SNP) [8] are reported to increase risk for AD. The *ESR1* gene encodes for estrogen receptor alpha and is located on chromosome 6q25.1. *Pvu*II (rs2234693, C>T) and *Xba*I (rs9340799, A>G) are the most studied restriction fragment length polymorphisms in the *ESR1* gene. The P or p and X or x are commonly used for *Pvu*II and *Xba*I, respectively, and the capital letter refers to the absence of the restriction site [7]. Earlier studies had shown that *Pvu*II and *Xba*I polymorphisms in *ESR1* gene played a role in the susceptibility to AD [9,10]. However, contrasting results were also reported from researches on the association between *ESR1* SNPs and AD [10,11].

Recent investigations suggested that the AD relationship of genetic variants in several genes [12–14] differed between populations from different European geographical regions. There was also an evidence of differences in socio-demographic and clinical features among AD patients from various European countries [15]. Accordingly, we conducted a meta-analysis to estimate the corre-

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http://dx.doi.org/10.1016/j.neulet.2014.05.017
0304-3940/

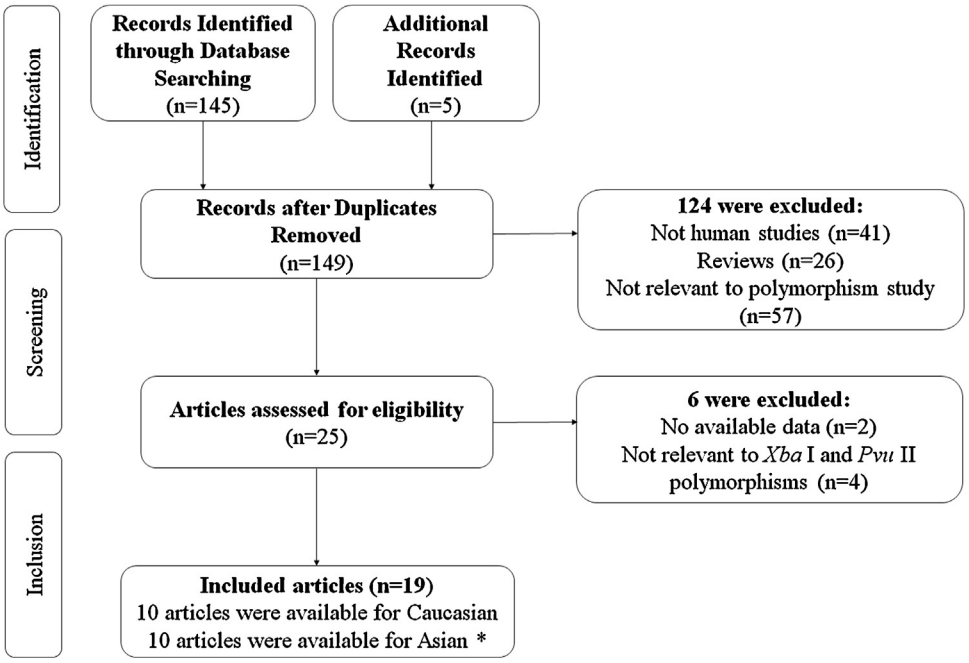

Fig. 1. Flow diagram to select articles for the AD related *ESR1* variants in the current meta-analysis. *One article was performed in both Caucasians and Asians

lation of *Pvu*II and *Xba*I SNPs with the risk of AD in Caucasians and different European geographical regions.

2. Methods

2.1. Search strategy

All available articles were approached by searching in PubMed, Google scholar and Wan Fang Med Online database up to January 2014. Language was not restricted. "Alzheimer's disease", "AD", "*ESR1*", "estrogen receptor alpha", "polymorphism" or "variant" were used as keywords. Potential studies were further identified by title and abstract review. Bibliographies of relevant articles were also reviewed to obtain additional studies.

2.2. Inclusion criteria and data extraction

The retrieved studies was selected when match the inclusion criteria: (1) a case-control study design; (2) available data of desired genotype distribution; (3) clinical diagnosis of AD; (4) available information on races or countries; (5) the most recent studies or largest subjects were selected from the repeated or overlapped publications; (6) studies were relevant to the *Pvu*II and *Xba*I SNPs. Animal studies, reviews, case reports, duplicated publications were excluded from the analysis. The following data were extracted from related studies: name of first author, year of publication, country or location, genotypic distribution numbers and frequency of relevant alleles within subjects and controls.

2.3. Statistical analysis

A meta-analysis was performed according to published methods with modifications [16,17]. In overall analysis, pooled odds ratio (OR) and 95% confidence interval (CI) were calculated within: allele model, dominant model, recessive model and homozygote comparison model. Heterogeneity was estimated and significant heterogeneity was assigned as the combination of I squared >50% and presence of 10% level of significance [16,17]. Random effects model in Mantel–Haenszel model was utilized when significant heterogeneity presented, otherwise, fixed effects model was used.

As relevant studies were from UK, Finland, Sweden, Spain and Italy, subjects were further divided into North European and South European subsets to conduct a subgroup analysis. No evidence of publication bias was concluded if $p > 0.05$ in both Egger's plot and Begg's tests. Sensitive analysis was performed by excluding studies deviating from Hardy–Weinberg equilibrium (HWE) in control group [18] when the value of chi-squared >3.84 (equals to $p < 0.05$). All statistical analysis was conducted by STATA/SE 11.0 (Stata Corporation, College Station, TX).

3. Results

3.1. Summary of study characteristics

Our main interest is the impact of *ESR1* polymorphisms on AD risk in European populations. We also conducted another meta-analysis in Asian population (see Section 4 and the supplementary data).

19 articles met the inclusion criteria were involved in the meta-analysis, in which 9 articles were conducted in Europe, the other 9 belonged to Asia. The rest one studies combined both Caucasian and Asian data. The selections in each step are shown in the Fig. 1.

When extracting data, a total of 11 and 10 case-control studies were selected for the relationship between *ESR1 Pvu*II [9–11,19–24], *Xba*I [9–11,20–23,25] genotype and risk of AD in Caucasians, respectively. 2581 cases and 2884 controls were included within the studies about *Pvu*II polymorphism in European population. In addition, 1533 in subject vs 1683 in control group were involved for *Xba*I variant in Caucasian studies. When Caucasian samples were subset by European geographical regions, 5 and 6 studies were produced for *Pvu*II polymorphism in North and South European, respectively. Whereas, there were 6 and 4 related studies in North European and South European for *Xba*I variant, respectively. The basic characteristics of *Pvu*II and *Xba*I related studies in European populations are shown in Tables 1 and 2.