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Research article

Association of KIBRA polymorphism with risk of Alzheimer's disease: Evidence based on 20 case-control studies

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ABSTRACT

Kidney and brain expressed protein (KIBRA) has been demonstrated to play an important role in episodic memory by genome-wide association study (GWAS). Since memory impairment is a typical clinical feature of AD, KIBRA has been considered to be a candidate gene for AD. Previous case-control association studies on KIBRA SNP rs17070145 have yielded inconsistent results. Thus, this study aimed to assess the risk of KIBRA polymorphism for sporadic AD via meta-analysis. A total of 7 articles including 20 case-control studies were included in this study. Results showed that rs17070145 had a significant association with AD risk in the homozygote comparison model (OR = 1.23; 95%CI = 1.07, 1.41), and the dominant model (OR = 1.14; 95%CI = 1.02, 1.26). In the subgroup analysis by ethnicity, an increased risk was detected in the homozygote comparison model and the dominant model among Caucasians, as well as in the homozygote comparison model and recessive model among Asians. Notably, in the subgroup analysis by age, a borderline increased risk was detected in the Old subgroup under the dominant model (OR = 1.19; 95%CI = 1.00, 1.43), but not in the Young subgroup. Results of the present meta-analysis indicated that KIBRA polymorphism rs17070145 might increase the risk of sporadic AD, especially among Caucasians, Asians and elders.

1. Introduction

Alzheimer's disease (AD), a neurodegenerative disease, is the most common form of dementia in the elderly [5]. The clinical characteristics of AD are the memory impairment and the behavioral and cognitive deficits [1]. Previous studies showed that the incidence of AD elevated with age. For instance, the incidence of AD is 1% for 65–69 year-old populations, while 50% for 85–95 year-old populations [10]. Thus, AD has become an important public health problem [18]. However, the mechanisms of AD are still unclear.

It has been found that epidemiological factors, such as overweight and obesity, cigarette smoking, dietary habits, intake of aluminum in drinking water and diabetes, may contribute to the risk of AD [12]. Moreover, genetic factors may play an important role in the pathogenesis of AD [14]. The relationship between genetic factors, such as presenilin 1 (PSEN1), presenilin2 (PSEN2) and β-amyloid precursor protein (APP) and the occurrence of the early-onset familial AD (EOAD) had been reported [4]. Nevertheless, compared with EOAD, the pathogenesis of late-onset AD (LOAD) in genetic susceptibility seems to be more complicated. Although only the association of Apolipoprotein E epsilon 4 (APOEε4) with AD risk has been convincingly replicated [3], decades of clinical and epidemiological studies involving multiple genes regarding AD risk have also been reported. Because the mechanisms of AD are complex multiple-gene involved processes, additional genetic and environmental factors influencing the AD susceptibility need to be identified.

KIBRA, a protein mainly expressed in the kidney and brain, whose functions are still being characterized, are involved in multiple biological processes in the brain [8,24], such as synaptic function, vesicular transport and synaptic plasticity [24]. As reported, KIBRA is highly expressed in memory-related regions of the brain and hippocampus [13]. The association between KIBRA rs17070145 and episodic memory has been demonstrated in genome-wide association study (GWAS) [21] in 2006, with replications in follow-up studies and a meta-analysis [19]. Meanwhile, since memory impairment is a typical clinical feature of AD, KIBRA genetic variation seems to play a role in the susceptibility to AD.

Previous studies have been conducted on the association of KIBRA polymorphism with sporadic AD risk, with the conclusions inconsistent. Whether KIBRA variation is a risk factor for AD remains uncertain.

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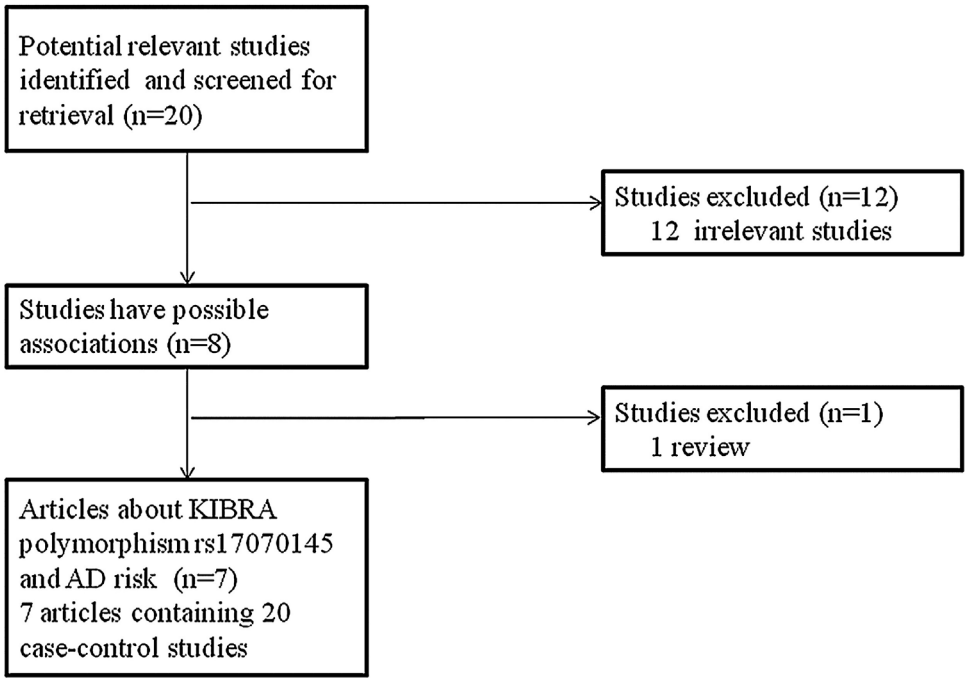

Fig. 1. Flow chart of literature screening for this meta-analysis.

Table 1
Characteristics of Studies Included in the Meta-Analysis.

Series	Publication Year	Number of Cases (Male/Femal)	Number of Controls (Male/Femal)	Mean Age, Year (Cases/Controls)	Age Range	Ethnicity	Country
Li et al(AlzGene)	2008	753(316/437)	736(265/471)	77.8/73.4	Mixed	Caucasian	Canda
Rodríguez	2009	391(133/258)	428(137/291)	75.7/80.5	Mixed	Caucasian	Spain
Corneveaux, US	2008	849(NA/NA)	492(NA/NA)	NA	Mixed	Caucasian	USA
Corneveaux, Germany	2008	219(NA/NA)	113(NA/NA)	NA	Mixed	Caucasian	Germany
Corneveaux, Norway	2008	143(NA/NA)	97(NA/NA)	NA	Mixed	Caucasian	Norway
Corneveaux, Netherlands	2008	16(NA/NA)	12(NA/NA)	NA	Mixed	Caucasian	Netherlands
Hayashi	2010	346(110/236)	375(170/205)	75.2/75.5	Mixed	Asian	Japan
Mayo_AA_OLD	2011	75(NA/NA)	104(NA/NA)	NA	Old	Afro-American	USA
Mayo_JS_OLD	2011	229(NA/NA)	248(NA/NA)	NA	Old	Caucasian	USA
Mayo_RS_OLD	2011	271(NA/NA)	610(NA/NA)	NA	Old	Caucasian	USA
Mayo_AUT_OLD	2011	318(NA/NA)	103(NA/NA)	NA	Old	Caucasian	USA
Mayo_NCRAD_ OLD	2011	154(NA/NA)	86(NA/NA)	NA	Old	Caucasian	USA
Mayo_AA_YOUNG	2011	42(NA/NA)	138(NA/NA)	NA	Young	Afro-American	USA
Mayo_JS_ YOUNG	2011	357(NA/NA)	340(NA/NA)	NA	Young	Caucasian	USA
Mayo_RS_ YOUNG	2011	269(NA/NA)	747(NA/NA)	NA	Young	Caucasian	USA
Mayo_AUT_ YOUNG	2011	259(NA/NA)	254(NA/NA)	NA	Young	Caucasian	USA
Mayo_NCRAD_ YOUNG	2011	546(NA/NA)	123(NA/NA)	NA	Young	Caucasian	USA
Wang_OLD	2013	536(NA/NA)	320(NA/NA)	NA	Old	Asian	China
Wang_YOUNG	2013	254(NA/NA)	476(NA/NA)	NA	Young	Asian	China
Kawai	2015	397(174/223)	154(71/83)	77.7/64.0	Mixed	Asian	Japan

NA = not available. As described in the articles, the age range was divided as follows: Caucasian (Young: 60–80 years, Old: > 80 years), Afro-American (Young: 60–74 years, Old: > 74 years), Asian (Young: 65–74 years, Old: > 74 years). Characteristics of the study from Li et al. were obtained from AlzGene database (http://www.alzgene.org).

Therefore, in the present study, a quantitative meta-analysis of published studies was carried out to obtain a more convincible conclusion of this association.

2. Materials and methods

2.1. Literature search strategy

The relevant studies published up to October 2016 were identified using a systematic search in the databases, including Medline, Embase, Ovid, and CNKI databases, with no language and country limitations. Combinations of the following keywords were used for searching: KIBRA; polymorphism; mutation; variant and Alzheimer's disease. All searched studies were retrieved.

2.2. Inclusion criteria

The following criteria were used in the inclusion of literature: i) studies focused on the association of KIBRA polymorphism with AD risk; ii) case-control or cohort designed; iii) sufficient information accessible [e.g. data on sample size for each research group, odd ratios (ORs), the 95% confidence intervals (95% CIs), and genotypes]; iv) AD diagnosed according to the criteria set by the World Health Organization. Accordingly, the exclusion criteria of this study were listed as follows: i) different study design; ii) duplicated literature, reviews, or animal studies; iii) unavailability of important information for data extraction.