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Meta-analysis of the insulin degrading enzyme polymorphisms and susceptibility to Alzheimer's disease

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HIGHLIGHTS

- Insulin degrading enzyme polymorphisms (rs3758505, rs1832196) and AD risk.
- No significant association was found in the polymorphisms and AD risk.
- To define potential gene-gene interactions.

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ABSTRACT

The association between insulin degrading enzyme (IDE) gene polymorphisms and Alzheimer's disease (AD) risk has been widely reported, but results were somewhat controversial. To assess the association between IDE polymorphisms and AD risk, a meta-analysis was performed. We systematically reviewed relevant studies retrieved by PubMed, Embase, AlzGene, CNKI and Web of Science. Finally, 8 articles were identified for rs3758505 polymorphism and 5 for rs1832196 polymorphism. The pooled ORs were performed for all the four genetic models. Subgroup analysis was also performed by ethnicity. Results suggested that rs3758505 polymorphism was unlikely to be associated with genetic susceptibility of AD based on the current published studies. However, for the rs1832196 polymorphism, significant association with AD was found by the dominant model in overall and subgroup analysis. However, larger scale association studies are necessary to further validate the association of IDE polymorphisms with sporadic AD risk and to define potential gene–gene interactions.

1. Introduction

Alzheimer's disease (AD) is the most common cause of dementia in the elderly, with an annual incidence of approximately 3% in the 65–74 year age group, increasing to almost 50% in those >85 years of age [5]. Alzheimer's disease (AD) is a neurodegenerative disorder characterized by senile plaques containing β-amyloid protein (Aβ) and neurofibrillary tangles (NFT) rich in hyperphosphorylated tau protein [13]. Aβ exerts a primary role in the cascade of events, which leads to neuronal death in AD [3]. IDE is a functional AD candidate gene because it encodes the insulin degrading enzyme, which has been shown to degrade Aβ [10,14,24,25,27] and to influence brain Aβ levels in vivo [11,12,18].

The first evidence that IDE might be involved in Aβ42 degradation was found by Kurochkin and Goto in 1994, who demonstrated that purified rat IDE efficiently degrades synthetic Aβ42 in vitro [14]. IDE, also known as insulysin, insulin protease or insulinase, is a 110 kDa zinc-dependent metalloprotease, which is coded by a 122 kb spanning, ubiquitously expressed gene on the distal region of the human chromosome 10q [15]. Except its primary target insulin, IDE competitively hydrolyzes multiple proteins [14,30]. In addition to its role in insulin catabolism, IDE has been found to degrade β-amyloid (Aβ)40 and 42 and the amyloid precursor protein (APP) intracellular domain and to eliminate Aβ42 neurotoxic effects [20]. Subsequently, it was shown that an IDE-like activity from soluble and synaptic membrane fractions of postmortem human brain both degrade Aβ42 peptides [17,23,25]. Three studies showed an association between IDE polymorphism and AD [2,3,9].

However, the results of these genetic studies remain controversial, with some studies unable to identify any association with AD [4,22,26].

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2. Materials and methods

2.1. Search strategy

A comprehensive search strategy was conducted towards the electronic databases including PubMed, Embase, AlzGene, CNKI and Web of Science databases using the following terms: 'insulin degrading enzyme', 'IDE', 'polymorphism', 'dementia', 'Alzheimer's disease' and 'AD'. An upper date limit of October 2012 was applied and we used no lower date limit. The language was restricted to English and Chinese. Reference lists of the identified articles were also examined and the literature retrieval was performed in duplication by two independent reviewers. When more than one of the same patient population was included in several publications, only the most recent or complete study was included in the meta-analysis.

2.2. Inclusion criteria

We reviewed titles and abstracts of all citations and retrieved literatures. The following inclusion criteria were used for the literature selection: (1) the outcome was AD and there were at least two comparison groups, e.g. AD vs. healthy controls; (2) determined association between AD and IDE polymorphisms; genotype or allele frequencies were available; (3) AD diagnosed according to clinical confirmation, the diagnostic and statistical manual of mental disorders (DSM) criteria, or the National Institute of Neurological Disorders and Stoke–Alzheimer Diseases and Related Disorders Association (NINCDS-ADRDA) criteria; (4) case–control design; and (5) Family-based studies were excluded. When genotype frequency was not reported, we contacted the author to get the relevant information by e-mail.

2.3. Data extraction

Data were extracted from each study by two reviewers independently according to the pre-specified selection criteria. Decisions were compared and disagreements about study selection were resolved by consensus or by involving a third reviewer. The following information was extracted from the literatures: first author, year of publication, country of origin, ethnicity of the population studied, mean age of AD patients, definition of cases, matching criteria of controls in all groups. If data from any of the above categories were not reported in the primary study, items were treated as 'not applicable (NA)'. Different ethnic descents were categorized as Asian and Caucasian.

2.4. Statistical analysis

Crude ORs with their 95% CIs were used to assess the strength of association between the IDE gene polymorphisms at rs3758505, rs1832196 and Alzheimer's disease risk. The pooled ORs were performed for all the four genetic models. Subgroup analysis was also performed by ethnicity for rs3758505 and rs1832196 polymorphisms. Heterogeneity assumption was assessed by chi-square based *Q*-test and *I*-squared test. The heterogeneity was not considered significant when $p > 0.05$. With lack of heterogeneity among studies, the pooled OR estimate of the each study was calculated by the fixed effects model [15]. Otherwise, the random effects model [7] was used. Possible publication bias was tested by begg's funnel plot and egger's test. The departure of frequencies of IDE polymorphisms from expectation under Hardy–Weinberg equilibrium (HWE) was assessed in controls. All statistical tests were conducted with STATA software package (version 11.0, College Station, TX). A p value of 0.05 for any test was considered to be statistically significant.

3. Results

3.1. Study characteristics

3.1.1. rs3758505 polymorphism

Our final eligible studies about the association of rs3758505 with sporadic AD included nine case–control studies with 2707 AD cases and 2835 controls (Table 1) published from 2001 to 2009 [1,2,6,8,16,19,21,28,31]. The sample sizes of the AD case group

Table 1
Association between individual study characteristics and IDE gene polymorphisms.

First author	Year	Country	Ethnicity	Diagnosis criteria	Age (mean ± SD)	Onset age of AD	Male (%) cases/controls	Genotyping
Zuo	2009	China	Asian	NINCDS-ADRDA	NA	70.3 ± 9.8	NA	RFLP
Vepslinen	2007	Finland	Caucasian	NINCDS-ADRDA	NA	72 .0 ± 7.0	115/177	Sequencing
Mueller	2007	Germany	Caucasian	NINCDS-ADRDA	66.4 ± 12.7	69.24 ± 9.4	164/83	MALDI-TOF
Marlowe	2006	USA	Asian	NINDS-ADRDA DSM-IIIR	81.78 ± 5.2	72.29 ± 6.33	NA	Pyrosequencing
Cellini	2005	Italian	Caucasian	Published guidelines	NA	72.3 ± 4.9	NA	NA
Nowotny	2005	USA	Caucasian	NINCDS/ADRDA	NA	77.1 ± 7.0	198/194	Pyrosequencing
Bian	2004	China	Asian	NINCDS/ADRDA	NA	74.58 ± 0.0	NA	RFLP
Edland	2003	USA	Caucasian	NINCDS/ADRDA	NA	NA	23/36	RFLP
Abraham	2001	UK	Caucasian	NINCDS-ADRDA	NA	72.5 ± 6.5	NA	RFLP
Bjork	2007	Sweden	Caucasian	NINCDS-ADRDA	NA	78.9 ± 7.4	508/421	Hybridization
Ozturk	2006	USA	Caucasian	NINCDS/ADRDA	76.57 ± 5.7	>60	337/–	Pyrosequencing
Ertekin-Taner	2004	USA	Caucasian	NA	NA	>59	NA	TaqMan

First author	Matching criteria of controls	APOE ε4 + cases/controls	Samples size (cases/controls)	Polymorphisms investigated
Zuo	Age, gender	112/29	357/331	rs3758505
Vepslinen	Age, gender, ethnic	NA	370/454	rs3758505
Mueller	Age, gender, ethnic	NA	444/269	rs3758505, rs1832196
Marlowe	Age, gender	44/78	174/501	rs3758505, rs1832196
Cellini	Age, gender	142/15	302/164	rs3758505
Nowotny	Age, gender	198/70	552/552	rs3758505, rs1832196
Bian	Age, sex, ethnic	103/36	210/200	rs3758505
Edland	Age, gender	40/26	80/117	rs3758505
Abraham	Age, sex	NA	218/247	rs3758505
Bjork	Age, gender, ethnic	749/284	1269/980	rs1832196
Ozturk	Age, gender	NA	1012/698	rs1832196
Ertekin-Taner	Age	NA	688/688	rs1832196

NINCDS–ADRDA: the National Institute of Neurological and Communicative Disorders and Stroke (NINCDS); Alzheimer's Disease and Related Disorders Association (ADRDA).