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Meta-analysis

The association between the UBQLN1 polymorphism and Alzheimer's disease risk: A systematic review

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Abstract: Recently, some studies suggested that UBQLN1 variant was associated with AD risk. However, the results were inconsistent. This meta-analysis aimed to determine the association between UBQLN1 variant and AD risk. We searched the electronic databases PubMed, Embase, and CNKI databases. Random-effects model was used. All statistical tests were performed using the STATA 11.0 software (StataCorp, College Station, TX, USA). UBQLN1 variant was not associated with the risk of AD (OR=1.05; 95%CI, 0.92–1.19; I^2=35%). The corresponding pooled ORs were not materially altered in sensitivity analysis. The Galbraith plot was used to find the source of the heterogeneity and no study was the outlier. The shape of the funnel plot showed symmetry. Egger's test found no evidence of publication bias (P=0.8). These results suggest that the UBQ-8i polymorphism was not associated with AD risk.

Key words: Alzheimer's disease; UBQLN1; Meta-analysis.

Introduction

Alzheimer's disease (AD) is a neurodegenerative disease with characteristic pathological hallmarks of neuron loss and accumulation of senile plaques and neurofibrillary tangles, resulting in gradual cognitive decline (1). The etiology of the AD is uncertain. The cause for most AD cases is still uncovered except for 1 to 5% of cases which develop as a result of mutations in the presenilin1, presenilin2, or amyloid precursor protein genes (2). Thus, detection of other genetic mutations is important for AD.

Ubiquilin 1 (UBQLN1) is a ubiquitin (Ub)-like (UbL) protein containing an N-terminal UbL domain and a C-terminal Ub associated (UbA) domain (3). UBQLN1 proteins function to facilitate protein disposal through the proteasome and lysosomal degradation pathways. Ubiquilin-1 is involved in the regulation of other quality control pathways such as the ER-associated degradation (ERAD) pathway and autophagy. Recently, some studies suggested that UBQLN1 variant was associated with AD risk (4-7). However, the results were inconsistent. This meta-analysis aimed to determine the association between UBQLN1 variant and AD risk.

Materials and Methods

Identification and Search of Relevant Studies

The PubMed, Embase, and CNKI databases were searched to using the following search terms: (Ubiquilin 1 or UBQLN1) and (Alzheimer's disease or Alzheimer) and (polymorphism or mutation or variant), without restriction on language. The reference list of each relevant publication was also reviewed to ensure that all appropriate studies were included in the meta-analysis.

Study selection

The inclusion criteria were as follows: (1) a case-control study or a cohort study; (2) the study determine the association between UBQLN1 variant and AD risk; (3) sufficient published data about sample size, odds ratio (OR), and their 95% confidence interval (CI).

Data extraction

Information was extracted from all included publications. The following information was extracted from each study: first author, publication year, country, race, age of patients, number of cases and controls, and adjustment. The Newcastle–Ottawa Scale (NOS) was used to evaluate the methodological quality.

Statistical analysis

This meta-analysis used Random-effects model ~~was used~~. Heterogeneity was evaluated by Q statistic and was considered statistically significant when P<0.10. The significance of the pooled OR was determined by the Z-test and was considered statistically when the P value was less than 0.05. Sensitivity analyses were performed to evaluate the effect of individual study on pooled results and assess the stability of results. A single study was deleted each time to reflect the influence of the individual data set to the pooled ORs. Publication bias was analyzed by funnel plots and Egger's test. All statistical tests were performed using the STATA 11.0 software (StataCorp, College Station, TX, USA).

Table 1. Baseline characteristics of the included studies.

First author/year	Country	Ethnicity	Mean age (year)	No. of cases	No. of control	Adjusted	NOS score
Bensemain/2006	France	Caucasian	72.4	613	653	Yes	7
Brouwers a/2006	Belgium	Caucasian	63.7	182	183	Yes	8
Brouwers b/2006	Netherlands	Caucasian	56.1	110	280	Yes	8
Kamboh/2006	USA	Caucasian	77.7	928	797	Yes	8
Arias-Vasquez/2007	Netherlands	Caucasian	69	549	5728	Yes	8

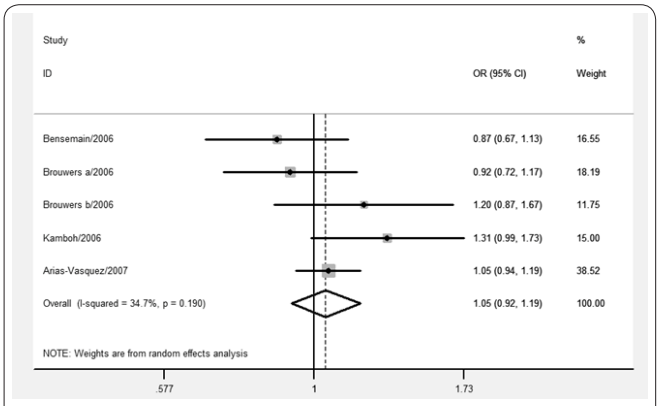

Figure 1. The association between UBQLN1 variant and AD risk.

Results

Study characteristics

A total of 5 studies with 2382 cases and 7641 controls were included for this meta-analysis. All of these studies included Caucasian population. The mean age of the subjects ranged from 56.1 to 77.7 years. All of the studies reported adjusted results and the NOS scores were high. The characteristics of each study are listed in Table 1.

Quantitative data synthesis

UBQLN1 variant was not associated with the risk of AD (OR=1.05; 95%CI, 0.92–1.19; I^2=35%; Figure 1). A single study involved in the meta-analysis was deleted each time to reflect the influence of the individual data set to the pooled ORs, and the corresponding pooled ORs were not materially altered (Figure 2). The Galbraith plot was used to find the source of the heterogeneity. As shown in Figure 3, no study was the outlier. Funnel plot was performed to assess the publication bias of literatures. The shape of the funnel plot showed symmetry (Figure 4). Egger's test found no evidence of publication bias (P=0.8).

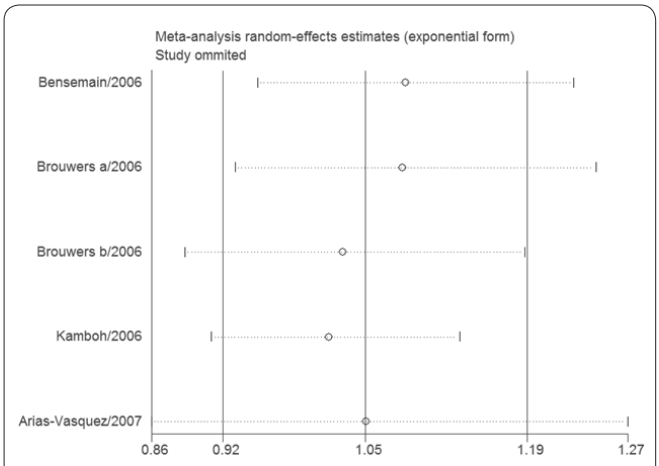

Figure 2. Sensitivity analysis between UBQLN1 variant and AD risk.

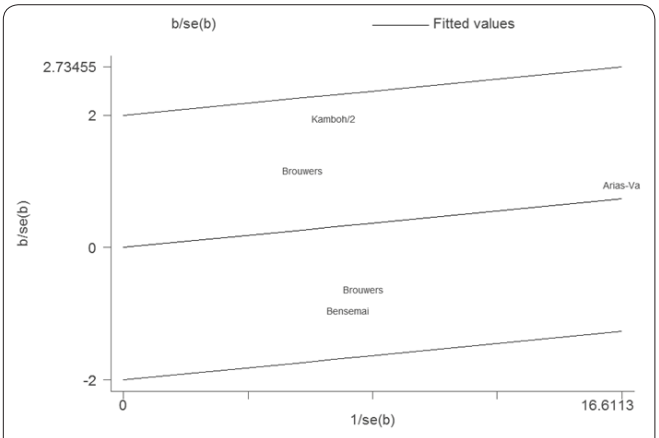

Figure 3. Galbraith plot between UBQLN1 variant and AD risk.

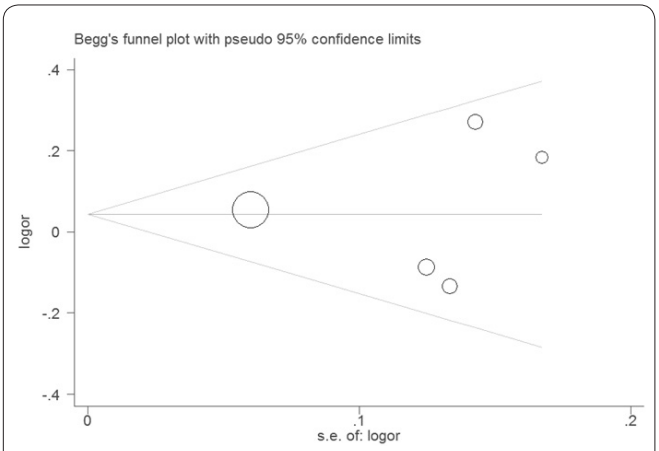

Figure 4. Funnel plot between UBQLN1 variant and AD risk.

Discussion

In the current meta-analysis with 2382 cases and 7641 controls, we found that there was not a significant association between UBQLN1 variant and AD risk. Results from one-way sensitivity analysis suggested high stability and reliability of our results. We used Galbraith plots to explore the sources of heterogeneity and we did not find outliers. Finally, funnel plots and Egger's tests were used to find potential publication bias. The results indicated that there was no significant publication bias.

Natunen et al. suggested that ubiquilin-1 may mechanistically participate in AD molecular pathogenesis by affecting BACE1 and thereby APP processing and Aβ accumulation (8). Zhang et al. found that chloroquine derivative D5 downregulates presenilin expression via the inhibition of ubiquilin 1 expression (9). Mizukami et al. indicated that perseverance of ubiquilin 1changes in CA2/3, CA4 and dentate gyrus, generally considered as more resistant to NFT pathology, but not in the CA1, may mark a compensatory, potentially protective response to increased tau phosphorylation in hippocampal

neurons (10).

Our analysis has several limitations. First, all the included studies were observational studies. Second, the number of the included studies was small. Third, although we performed an extensive review of the main electronic databases, we cannot be sure to have included all relevant studies.

In conclusion, we did not detect a significant association between UBQLN1 variant and AD risk. Further studies with large sample size will be necessary to validate this result.

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