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ORIGINAL ARTICLE

TNF-alpha G308A Polymorphism and the Susceptibility to Alzheimer's Disease: An Updated Meta-analysis

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Background and Aims. Tumor necrosis factor (TNF)-alpha G308A polymorphism has been reported in the association with susceptibility to Alzheimer's disease (AD); however, results have been contradictory. We conducted an updated meta-analysis to evaluate the role of *TNF-alpha* G308A in the occurrence of AD.

Methods. Relevant articles were retrieved from online databases. The combined odds ratio, odds ratio in different genetic models, and the related 95% confidence intervals were calculated. Publication bias and homogeneity among individual studies were estimated. Subgroup analyses and sensitivity analyses were also performed.

Results. In overall analyses, no risk of AD was associated with *TNF-alpha* G308A under different genetic models. However, in the subgroup analyses, a significant association between *TNF-alpha* G308A and AD risk was observed in Chinese. In addition, a significant protective effect of *TNF-alpha* −308A was found in the occurrence of AD among North European populations under a dominant model.

Conclusions. The result of this meta-analysis suggests that *TNF-alpha* G308A polymorphism may be associated with the increased risk of AD in Chinese and decreased risk of AD in northern European populations.

Key Words: Alzheimer's disease, TNF-Alpha, Polymorphism, European geographical difference, Meta-analysis.

Introduction

Alzheimer's disease (AD) is the most common form of dementia in the elderly with clinical features of distinct memory loss and progressive cognitive function decline (1). The neuropathological characteristics of this complex disorder include senile plaques, neurofibrillary tangles and neuronal loss (2). AD is considered as a multifactorial and incurable disease. Approximately 30% of AD is preventable by modifying life style (3). Aging and the apolipoprotein E epsilon 4 allele (APOE4, accounts for ~20% of AD cases) (4) are unpreventable factors but are significantly associated with increased risk of AD (5). Finding other factors involved in AD will help to better understand this disease.

Lines of evidence show that inflammation can exert neuronal loss in AD (6,7). Tumor necrosis factor (TNF)-alpha is a pro-inflammatory cytokine expressed in immune cells, glia and neurons; TNF-alpha (8) and *TNF-alpha* genetic variant are associated with the formation of memory (9). TNF-alpha is important to mediate the inflammatory responses within AD (10). Clinical observations and a pooled analysis have shown that TNF-alpha level is increased in blood (11–13) or cerebrospinal fluid (14) of AD patients compared to the control group.

TNF-alpha gene has been reported to confer risk for AD (15). Multiple polymorphisms in the *TNF-alpha* gene cluster such as *TNF-alpha* G308A (also named rs1800629, located in the promoter region) are documented in AD patients (16). The *TNF-alpha* 308A allele has higher activity than 308G allele in transcription, resulting in higher *TNF-alpha* level (14,17,18). Carrying *TNF-alpha* 308A allele indicates vulnerability to autoimmune diseases and inflammatory disorders (19). Furthermore, *TNF-alpha* G308A showed a marked increased risk with AD in numerous

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studies (20,21). However, contrasting results have also been obtained in several studies (22,23). In the present study we evaluated whether *TNF-alpha* G308A genetic variant has a potential impact on the risk of AD.

Materials and Methods

Literature Search

A computerized search was conducted to retrieve available English or Chinese articles published up to April 2014 from online databases: a) PubMed, b) China National Knowledge Infrastructure (CNKI), c) Wan Fang Med Online, d) AlzGene database. The search strategy used keywords of ''Alzheimer's disease'', ''AD'', ''TNF or TNF-alpha'', ''tumor necrosis factor'', ''polymorphism'' or ''variant''. Articles were selected by abstract reviewing for further evaluation. References of relevant articles were also reviewed to identify additional studies.

We used the following inclusion criteria: a) case-control study design; b) data of *TNF-alpha* G308A genotypic distribution were available in articles or obtained from authors; c) clinical diagnosis of AD. In contrast, animal studies, reviews, case reports, unpublished data and duplicate or overlapped studies were excluded from the current analysis.

Data Extraction

Studies were included based on the inclusion criteria. The data of each study, i.e., first author, year of publication, location of origin or country, genotype distribution or frequency of relevant alleles in cases and controls, were independently extracted by two investigators.

Statistical Analysis

According to the published methods (24,25), pooled odds ratio (OR) with 95% confidence interval (CI) were calculated to estimate the association between *TNF-alpha* G308A and risk of AD in allele model, dominant model, recessive model and homozygote comparison, respectively. The presence of significant heterogeneity is $<10\%$ level of significance (p $<10\%$ in Cochran's Q test) with $I^2 > 50\%$. Ethnicity (i.e., Caucasian, Chinese, and Others) was employed as a stratifying variable in the subgroup analysis. European geographical difference was reported in studies concerning the association between genotypic variants of several genes and the occurrence of AD (25–27). Thus, another subgroup analysis was conducted in the populations from different European geographical regions (i.e., northern or southern European countries). When the publication bias was assessed, p value >0.05 in Egger's and Begg's tests was considered as no publication bias. Hardy–Weinberg equilibrium (HWE) in control group of each study was calculated, with $\chi^2 > 3.84$ (p <0.05) assigned as departure from HWE (28). Influence analysis was further performed by excluding the studies deriving from HWE. Statistical analyses were conducted in the *STATA/SE 11.0* software (Stata Corporation, College Station, TX).

Results

Study Characteristics

We selected 21 articles (14,20–23,29–44) concerning the correlation of *TNF-alpha* G308A with susceptibility to AD based on the inclusion criteria. Studies excluded at each screening stage are shown in Figure S1.

All included studies were of case-controlled design. The total number of AD patients and controls was 4,246 vs. 4,726. *TNF-alpha* G308A genotype distributions and characteristics of the eligible articles are summarized in Table 1.

Results of Overall Analysis and Publication Bias

The combined OR for *TNF-alpha* G308A polymorphism in AD was calculated within the allele model (A allele vs. G allele), dominant model (AA + AG vs. GG), recessive model (AA vs. AG + GG) and homozygote comparison (AA vs. GG). There were evidence of heterogeneity among related studies (A vs. G, $I^2 = 87.2\%$, $p = 0$; AA + AG vs. GG, $I^2 = 87.1\%$, $p = 0$; AA vs. AG + GG, $I^2 = 62\%$, $p = 0$; AA vs. GG, $I^2 = 64.7\%$, $p = 0$, as shown in Table 2). Therefore, the combined OR was estimated by using random effects modeling in Mantel-Haenszel model. In overall, a lack of association between *TNF-alpha* G308A and AD risk was found in the genetic models of interest (A vs. G, OR [95% Cis] = 1.276 [0.982,1.657]; AA + AG vs. GG, OR [95% Cis] = 1.287 [0.957,1.732]; AA vs. AG + GG, OR [95% Cis] = 1.21 [0.705,2.076]; AA vs. GG, OR [95% Cis] = 1.26 [0.716,2.218]).

Publication bias in the combined analysis was estimated using Begg's funnel plot and Egger's test. The results showed that there was no presence of publication bias within each inherited model (Table 2).

Subgroup Analyses in Different Ethnic Subsets

When the subjects were divided into Caucasians, Chinese and other races, a significant association between *TNF-alpha* G308A variants and AD was observed in Chinese group (A vs. G, OR [95% Cis] = 1.734 [1.228,2.449]; AA + AG vs. GG, OR [95% Cis] = 1.527 [1.116,2.089]; AA vs. AG + GG, OR [95% Cis] = 8.366 [1.976,35.421]; AA vs. GG, OR [95% CIs] = 8.938 [2.107,37.906]).

In contrast, there was a null association in either Caucasians or other ethnic population (as shown in Table 2 and