A meta analysis of the relation between TNF-α G308A gene polymorphism and heart disease

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Abstract: Objective: To evaluate the correlation of TNF-α G308A polymorphism and heart disease (HD) using meta-analysis. **Methods:** Databases including PubMed, EMbase, CNKI and WanFang Data were searched (2003 to 2013). **Results:** A total of 5 studies were included, involving 539 heart disease (HD) cases and 624 controls. The results of meta-analysis according to recessive genetic model of TNF-α G308A showed that there were significant differences in RHD risk between the AA genotype carriers and the GA+GG genotype carries (OR=5.06, 95%CI 2.15 to 11.89, P=0.0002). **Conclusion:** Current evidence shows that TNF-α G308A polymorphism is related to RHD, and the AA geno-type carriers tend to face an increasing RHD risk.
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Key words: Heart disease; Tumor necrosis factor α; polymorphism; meta-analysis

1.Introduction

Rheumatic fever, a sequela of group A streptococcal infection, is characterized by inflammation of the joints (arthritis), heart (carditis), central nervous system (chorea), skin (erythema marginatum) and/or subcutaneous nodules. (Stollerman et al., 1988) Any of these five major manifestations may be seen in rheumatic fever and are established as the Jones criteria as revised by the American Heart Association. (Jones 1944;Veasy 1995) It was estimated recently that worldwide 15.6 million people have rheumatic heart disease and that there are 470,000 new cases of rheumatic fever and 233,000 deaths attributable to rheumatic fever or rheumatic heart disease each year (Carapetis et al., 2005).

The identification of modifier genes is an attractive possibility for the improvement of genotype-based risk stratification. Hints for the existence and clinical relevance of genetic modifiers in HD have been brought to light, including TNF-α G308A (Patel et al., 2000). However, it is unclear for the relation between TNF-α G308A gene polymorphism and HD.

In this paper, we will explore the mechanism that TNF-α G308A gene polymorphism influence the HD progress by meta-analysis.

2.Data collection and analysis

2.1 Selection of studies

Two authors will take on the review. The search strategy described will be used to obtain titles and abstracts of studies that may be relevant to the review. They will screen the search results and they will read the full text of eligible studies identified in this way. The two authors will decide on their suitability for inclusion in the review based on whether they meet the prespecified inclusion criteria. We will report disagreement and will resolve disagreement by a consensus procedure, if necessary, with a third review author.

2.2Data extraction and management

Two review authors will extract the data independently to a self-developed data extraction form. Studies reported in non-English language journals will be translated before assessment. Where more than one publication of one trial exists, only the publication with the most complete data will be included. We will write to study authors for further information when necessary. Disagreements will be resolved by majority vote, if necessary, of a third review author. One author will enter data into Review Manager software (RevMan 5.0.20), and a second author will independently check the data entry.

2.3 Measures of treatment effect

For dichotomous data, results will be summarised as risk ratios (RR), with 95% confidence intervals (CI). For continuous out-comes we will use weighted mean difference (WMD) (when measures are in the same unit), or standardisedmean difference (SMD) (when different scales are used to evaluate the same outcome) with 95% CI as well.

2.4 Assessment of heterogeneity

I^2 will be used to assess heterogeneity among studies. $I^2 > 50\%$ will be considered considerable heterogeneity.

2.5 Data synthesis

A ï¬xed-effects model will be used unless significant heterogeneity with $I^2 > 50\%$ among studies. In that case a random-effects model will be used.

2.6 Subgroup analysis and investigation of heterogeneity

Subgroup analysis will be used to explore possible sources of heterogeneity. Heterogeneity among studies will be estimated by the I^2 statistic. Typically, values above 50% are deemed to suggest significant heterogeneity. Values of 25% to 50% are deemed to show modest heterogeneity, and values below 25% are deemed to represent low heterogeneity.

2.7 Sensitivity analysis

We will perform a sensitivity analysis if we find significant heterogeneity (I^2> 50%).

3.Results

3.1 The general data

A total of 45 literatures were retrieved by computer and manual retrieve, and 5 literatures met the inclusion criteria after screening, the publication year was limited from 2003 to 2013,including 539 cases and 624 control. Each study was carried out the baseline comparison of two groups, there was no significant difference.

3.2 The meta results

The Meta-analysis results showed that there was statistically heterogeneity between AA gene type and GA+GG gene type using a fixed effect model (OR=5.06, 95%CI (2.15,11.89), P=0.0002, Figure 1).

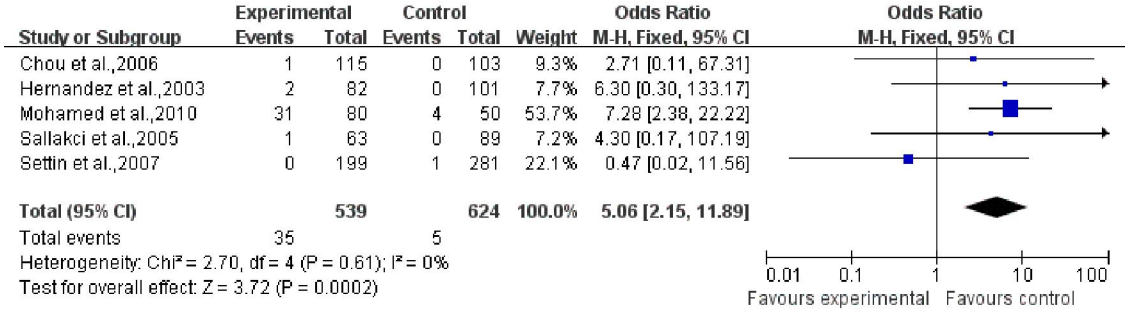

Fig 1. The Meta-analysis results

4.Discussion

Tumor necrosis factor (TNF) is a cytokine with plei-otropic biological activities, including the induction of programmed cell death (apoptosis) and the regulation of immune cell proliferation and di fferentiation (Bazzoni and Beutler 1996), and may influence the transcriptional activity induced by the glucocorticoid of the glucocorticoid receptor gene (Franchimont et al., 1999). Although genetic polymorphisms in the TNF locus have been implicated in the severity of several B-cell lymphopro-liferative diseases(Belhadjjrad et al., 2007), to date, only a few studies have found an association among the rare TNF AA of G308A polymorphism, the increased production of TNF protein, and the non-Hodgkin's lymphomas (NHL) susceptibility.

TNF a induces endothelial cells to secrete vasoactive substances via the autocrine or paracrine pattern, which leads to vasorelaxation or vasoconstriction, and ultimately, to the regulation of blood pressure (BP). The TNF a gene is located in the major histocompatibility complex III region on chromosome 6p21.3. Recent research has revealed that TNF a gene polymorphisms are mostly focused on the probable influence of the promoter district on the expression of the TNF a gene. The TNF a gene polymorphism is also involved in infectious diseases, metabolic syndrome, stroke, hyperuricemia, and so on. (Yee et al., 2000; Sookoian et al., 2005; Liu et al., 2009)

The reported association of G-308 A (rs1800629) polymorphism of the TNF-α gene with myocardial infarction and coronary artery disease has thus generated continuing interest. Considering both the potential effects of the 308 A allele on TNF-α and the putative association between TNF-α and cardiovascular disease, a logical hypothesis would be that the 308 A allele is associated with increased risk of cardiovascular disease. However, analyses of such relations have produced inconsistent results.

The present report demonstrates the potential for large-scale genetic epidemiology to help assess the nature of relationships between putative risk factors and disease (Keavney et al., 2006). It had not previously been possible to determine with certainty whether the observed association between the G-308 A (rs1800629) polymorphism in the TNF gene and heart disease risk was causal, or due to residual biases from incomplete adjustment for all potential risk factors. However, adjustment for the factors measured in this study did not g reatly affect the

negative results. After adjusting for sex, age, BMI, diabetes mellitus, and smoking status, the results indicated that A allele was not associated with an increased risk of heart disease.

In conclusion, we found no evidence to support the theory that the presence of the 308 A allele at the G-308 A (rs1800629) polymorphism of the TNF-α gene variation in heart disease was related to an increased risk of heart disease.

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