Tumor Necrosis Factor-α Gene Polymorphism (G-308A) and Dilated Cardiomyopathy

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Summary

The issue that genetic polymorphism of tumor necrosis factor-α (TNF-α) is associated with dilated cardiomyopathy (DCM) is debatable. We sought to investigate the potential role of TNF-α gene polymorphism (G-308A) in the susceptibility to dilated cardiomyopathy.

We retrieved PubMed, EMBASE, and CNKI to collect all articles which reported on the association between TNF-α G-308A polymorphism and dilated cardiomyopathy. Two authors used the Newcastle-Ottawa Scale (NOS) checklist to assess the quality of the included studies. The odds ratio (OR) with 95% confidence intervals (CI) were pooled in a specific genetic model to assess the association and Stata version 14.0 software was used.

A total of 9 studies with 1338 patients and 1677 controls were included in this study. The results from this meta-analysis indicated that TNF-α G-308A polymorphism significantly increased the risk of dilated cardiomyopathy in heterozygous comparison (GA versus GG: OR = 1.87; 95%CI = 1.03-3.40; P < 0.05). The increased risk of DCM was also found in Asian populations using a dominant model and heterozygous comparison (GA+AA versus GG: OR = 2.00, 95%CI = 1.02-3.92, P < 0.05; GA versus GG: OR = 1.94, 95%CI = 1.23-3.06, P < 0.05).

The current meta-analysis revealed that TNF-α gene polymorphism (G-308A) may be associated with the susceptibility to DCM.

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Key words: Gene variant, Meta-analysis

Dilated cardiomyopathy (DCM), characterized by systolic dysfunction and ventricular chamber dilation, is clinically manifested by heart failure, arrhythmias, and sudden cardiac death.\(^1,2\) In spite of recent advanced medical and surgical conditions, dilated cardiomyopathy remains a leading indication for heart transplantation.\(^2\) DCM, a complex disease, exhibits a wide heterogeneity in phenotype. Previous family studies identified that 30% to 50% of the patients with DCM had a familial origin and mutations in more than 40 genes which mostly encode components of cellular compartments and pathways have been identified as causes in humans.\(^4-10\)

However, only 20% of DCM cases have been found to be inherited,\(^11\) and the candidate gene approach which examines the potential role of a known gene in the pathophysiological process is a strategy widely used.\(^12\) Additional genes, which affect the biochemical or physiological process of the cardiovascular system, are expected to be potential candidates. Some research has indicated that immune dysfunction participates in the pathogenesis of myocytic damage in DCM.\(^13,14\) Thus, genes of common tumor necrosis factor are prospects for playing a major role among those candidates.

TNF-α, a pro-inflammatory cytokine produced by activated monocytes and macrophages, makes a major contribution to the regulation of immune cells which are involved in activating host defense mechanisms and homeostatic tissue repair.\(^15,16\) Whereas, the uncontrolled overexpression of TNF-α may be related to the congestive heart failure and the underlying pathological process of adverse left ventricular remodeling.\(^17\) Various clinical studies have confirmed the role of TNF-α in the pathophysiology of congestive heart failure.\(^18,20\) In patients with DCM, increasing TNF levels have also been found.\(^21\) Accordingly, TNF-α may be related to the pathogenesis of dilated cardiomyopathy.
In the TNF-α gene, numerous polymorphisms are known to exist and the G-308A polymorphism located in the promoter region is the one that could influence the production of TNF-α.23 A French study was the first to evaluate the possible association between TNF-α gene polymorphism (G-308A) and the susceptibility to DCM, although it failed to detect any relationship with the disease.24 Alikasifoglu, et al. also found negative results when they investigated the role of G-308A polymorphism in DCM.25 Nonetheless, the results of recent studies were contradictory. Liaquat, et al. demonstrated a statistically significant association between TNF-α -308GA polymorphism and DCM in a Pakistani population.26 Thus far, there are very few genetic studies on the relationship between G-308A polymorphism and dilated cardiomyopathy and the data is inconsistent.

In the present study, we performed a systematic meta-analysis of all available data from case-control studies to examine the association of known polymorphism of the TNF-α gene with DCM, with the goal of providing more compelling evidence and gaining a better understanding of the relationship between TNF-α G-308A polymorphism and dilated cardiomyopathy.

Methods

We made great efforts to report the present meta-analysis by following the proposed MOOSE (Meta-Analysis of Observational Studies in Epidemiology) 10 guidelines.26

Literature search strategies: Relevant studies published before March 1, 2017 were searched from the following electronic databases: PubMed, Embase, OVID, Cochrane Library, Web of Science, Chinese National Knowledge Infrastructure (CNKI), and Wanfang Databases and were systematically identified case-control studies with the use of a standardized protocol. Various combinations of keywords used in the search strategy included: (“TNF-α” or “G-308A” or “rs1800629”) and (“polymorphism” or “variant” or “mutation”) and (“dilated cardiomyopathy” or “conduction disease”) and the search was limited to English. Two reviewers (M.C. and Y-F.Z.) independently evaluated the identified titles and abstracts. Furthermore, the reference lists of retrieved articles were also checked by hand-search to find other potential sources.

Study selection: The second step of screening was based on full-text review. To be eligible for inclusion in this meta-analysis, a study must have fulfilled the following criteria: 1) The study was a case-control study that focused on the association between TNF-α gene polymorphism (G-308A) and DCM. 2) The control groups were healthy people. 3) Relevant and sufficient data were provided for calculating an odds ratio (OR) with its 95% confidence interval (CI). 4) The publication language was English. 5) The study was published in full text. 6) When duplicate articles were published, the study with the larger sample size and more comprehensive outcome evaluation was included. Any disagreements between reviewers was resolved through discussions until reaching a consensus.

Data extraction: Two reviewers conducted all the data extraction independently with standardized data-collection forms to ensure the accuracy. Any potential inconsistency was resolved by discussion. For each study, the characteristics required to be recorded were: 1) name of first author, 2) year of publication, 3) country of origin, 4) ethnicity, 5) genotype contributions of subjects with and without DCM, 6) mean age in cases and controls, 7) prevalence of female in cases and controls, 8) left ventricular ejection fraction in patients with DCM, 9) source of controls, and 10) the P value of Hardy-Weinberg equilibrium (HWE) in control.

Quality assessment: The 9-point Newcastle-Ottawa Scale (NOS),27 which consists of 3 broad perspectives including selection, comparability and exposure, was used to independently evaluate the quality of studies by two reviewers. The NOS scores range from zero to 9, and a total score of 7 or greater indicated a high-quality study.

Statistical analyses: First, we estimated the relationship between TNF-α gene polymorphism (G-308A) and dilated cardiomyopathy by calculating the pooled odds ratio (OR) and 95% confidence interval (CI) of the allele frequencies. The significance of the pooled OR was determined by the Z-test and \( P < 0.05 \) was considered to indicate a statistically significant result. Then, the genetic models were conducted as follows: dominant model (GA+AA versus GG), recessive model (AA versus GG+GA), homozygous comparison (AA versus GG), and heterozygous comparison (GA versus GG). We choose Chi-square interval to assess the Hardy-Weinberg equilibrium (HWE), and \( P > 0.05 \) was considered to be significant disequilibrium. We also tested heterogeneity between studies using Q-testing and \( P < 0.10 \) and \( I^2 < 50\% \) was observed among studies, a random effect model (DerSimonian-Laird method)28 was used to calculate pooled effect estimates in the presence of heterogeneity; otherwise, a fixed model (Mantel-Haenszel method)29 was used. When significant heterogeneity was tested in the pooled meta-analysis, we performed meta-regression analysis to explore the potential reasons. Several variables were tested such as ethnicity (Asian, Caucasian, African), publication year, genotyping method (PCR-RFLP, non-PCR-RFLP), sample size (total number of cases and controls \( \geq 500, < 500 \)), matching situation between case and control group (Yes, No), and whether deviation from HWE existed (Yes, No). Lastly, visual inspection of the funnel plots was used to detect the potential publication bias by plotting the log ORs against their SEs. We also performed the Begg rank correlation test and Egger linear regression test at the \( P < 0.10 \) level of significance to evaluate the potential publication bias. Sensitivity analysis was conducted by omitting each study in turn to evaluate the stability of the results. All statistical analyses were performed using Stata version 14.0 (Stata Corporation, College Station, TX, USA).

Results

Study characteristics: Initially, a total of 126 potentially
relevant papers published prior to March 2017 were screened through the PubMed, Embase, OVID, Cochrane Library, Web of Science, CNKI, and Wanfang Databases with the search keywords. We initially excluded 84 papers because of obvious irrelevance. After screening the titles and abstracts, 26 papers were disqualified because of duplicated publications and reviews. We then evaluated the eligibility for inclusion for the 16 remaining papers and finally included 9 publications after detailed check. The flow chart of reviews shows the detailed process of selection (Figure 1). Consequently, a total of 1338 DCM cases and 1677 controls were subjected to our meta-analysis.

Results of meta-analysis: The 9 eligible studies provided 1338 patients and 1677 controls for this meta-analysis to assess the association between TNF-α gene polymorphism (G-308A) and susceptibility to DCM. Overall, we found a significant positive relation between G-308A and the risk of dilated cardiomyopathy in heterozygous comparison (OR \( \text{GA versus GG} = 1.87, 95\% \text{CI} = 1.03-3.40, \ P = 0.040, I^2 = 89.1\% \), Figure 2). Unfortunately, no significant evidence was found in the other genetic models (dominant model, allele model, recessive model, homozygous comparison). The results of subgroup analysis according to ethnicity are shown in Table III. When stratified by ethnicity, there was a similar positive association between G-308A polymorphism and susceptibility to DCM in Asian populations under both the dominant model (OR \( \text{GA+AA versus GG} = 2.00, 95\% \text{CI} = 1.02-3.92, P = 0.045, I^2 = 51.2\% \), Figure 3) and heterozygous comparison (OR \( \text{GA versus GG} = 1.94, 95\% \text{CI} = 1.23-3.06, P = 0.004, I^2 = 48.6\% \), Figure 4). No significant result was found in either Caucasian or African populations.

Meta-regression and sensitivity analysis: Given that a significant relationship between TNF-α G-308A polymorphism and increasing risk of DCM was detected under heterozygous comparison and that large heterogeneity was present in the random effect model of combined populations (\( I^2 = 89.1\% \)), 6 variables including ethnicity, publication year, matching situation between case and control...
### Table I. Characteristics of the 10 Studies Included in This Meta-Analysis.

| Author       | Year | Country  | Ethnicity | Mean age in total/range (years) | Gender in total (female%) | LVEF of DCM patients | Other invasive examination | Genotyping method | Source of control | NOS score |
|--------------|------|----------|-----------|-------------------------------|--------------------------|----------------------|--------------------------|------------------|-----------------|----------|
| L.Tiret      | 2000 | France   | Caucasian | 46.8                          | 19.2%                    | 23.3 ± 6.6%          | Coronary angiography     | PCR-SSCP         | Age-matched healthy controls | 8        |
| M.Ito        | 2000 | Japan    | Asian     | 55.4                          | 29.6%                    | 35.5 ± 8.6%          | NA                      | PCR-RFLP         | Age-matched healthy controls | 8        |
| M.Alikasifoglu| 2003 | Turkey   | Asian     | 57.5                          | 30.1%                    | 33.8 ± 5.2%          | NA                      | PCR-RFLP         | Age- and sex- matched, healthy | 8        |
| R.Brooksbank | 2008 | South Africa | African  | 50.3                          | 41.2%                    | 26.3 ± 0.7%          | Radionuclide ventriculography | PCR-RFLP         | Age-, sex- and ethnic-matched, healthy | 8        |
| A.H.Brugink  | 2008 | Netherlands | Caucasian | NA                           | NA                      | NA                   | NA                      | PCR-SS           | Healthy donors | 7        |
| V.Spiroska   | 2009 | Macedonia | Caucasian | NA                           | NA                      | <40%                 | NA                      | PCR-SSP          | Healthy controls | 7        |
| W.B.Liang    | 2010 | China    | Asian     | 18-91                         | 34.1%                    | 33.8 ± 5.2%          | NA                      | PCR-RFLP         | Healthy controls | 7        |
| A.Liaquat    | 2014 | Pakistan | Caucasian | 53.9                          | 29.3%                    | <40%                 | NA                      | PCR              | Healthy controls | 8        |
| B.Mishra     | 2015 | India    | Caucasian | NA                           | NA                      | NA                   | Endomyocardial biopsies  | PCR-RFLP         | Healthy controls | 7        |

NOS indicates Newcastle-Ottawa Scale; NA, not available; and LVEF, left ventricular ejection fraction.

### Table II. Distributions of TNF-α G-308A Polymorphism Genotype and Allele in DCM Patients and Controls

| Author       | Year | Cases/Controls | DCM genotypes | Control genotypes | Allelic frequency (Case/Control) | HWE (Y/N) |
|--------------|------|----------------|----------------|-------------------|-------------------------------|-----------|
| L.Tiret      | 2000 | 428/396        | 322/100/6      | 288/95/13         | 112/121                       | Y (0.145) |
| M.Ito        | 2000 | 48/50          | 35/13/0        | 47/3/0            | 13/3                          | Y (0.827) |
| M.Alikasifoglu| 2003 | 63/93          | 44/1/6/3       | 69/20/4           | 22/28                         | Y (0.125) |
| R.Brooksbank | 2008 | 330/349        | 218/36/1/6     | 265/72/12         | 128/96                        | N (0.015) |
| A.H.Brugink  | 2008 | 40/61          | 23/1/6/1       | 44/15/2           | 18/19                         | Y (0.612) |
| V.Spiroska   | 2009 | 51/301         | 43/8/0         | 231/66/4          | 8/74                          | Y (0.769) |
| W.B.Liang    | 2010 | 110/110        | 73/298/8       | 87/18/5           | 45/28                         | N (0.006) |
| A.Liaquat    | 2014 | 250/300        | 72/149/29      | 223/64/13         | 207/90                        | N (0.005) |
| B.Mishra     | 2015 | 18/17          | 12/6/0         | 13/4/0            | 6/4                           | Y (0.582) |

DCM indicates dilated cardiomyopathy; HWE, Hardy-Weinberg equilibrium; and NA, not available.
groups, whether there was deviation from HWE, genotyping method, and sample size were tested in meta-regression analysis to determine potential reasons. The results indicated that none of the 6 tested variables was the source of heterogeneity (as shown in Table IV). To test the robustness of the combined results, we conducted sensitivity analysis by removing each single study from the total dataset. No notable quantitative alternation in the ORs was seen, whereas the statistical significance would reverse when the 3 studies with controls not in HWE were excluded.

Publication bias: As is well known, publication bias is a common problem when performing a meta-analysis. In the present meta-analysis, Begg’s funnel plot as well as Egger’s test were conducted to evaluate the publication bias of the included studies. As shown in Figure 5, the shape of the Begg funnel plot of the relationship between G-308A polymorphism and susceptibility to DCM did not identify substantial asymmetry under the dominant model. Similarly, there was also no evidence of publication bias from the results of Egger’s test (P_GA versus GG = 0.91).

Discussion

Various studies attempted to estimate the relationship between TNF-α G-308A polymorphism and increasing risk of DCM, but the results have been contradictory because of limited sample sizes and low statistical power. The present meta-analysis of 9 studies demonstrated that there was a significant association between TNF-α G-308A polymorphism and DCM.

As genetic testing for cardiovascular disease becomes more and more common, the causative genes in dilated cardiomyopathy seem to mainly encode cytoskeletal and sarcomeric proteins. However, the yield for vast genes screening is almost 20%. The potential role of known genes in DCM should be explored. It is generally known that inflammation is one of the common pathological mechanisms in dilated cardiomyopathy. Pro-inflammatory cytokines, such as TNF-α, have been found related to progressive left ventricular dysfunction. The TNF-α gene lies in the MHC-III region of the sixth chromosome between HLA-B and HLA-DR, and its concentration controls the effect of TNF-α on cardiac function. The stimulation of TNF-α G-308A polymorphism has been proven to produce high levels of TNF-α and it is considered that the -308A allele is a more powerful transcriptional activator than the common allele. A previous study has demonstrated that the chronic overexpression of TNF-α results in development of DCM in transgenic rats. It was also reported that increasing levels of TNF-α contribute to the pathophysiology of congestive heart failure. Immunoreactivity for TNF-α was observed in the myocardium of idiopathic dilated cardiomyopathy. Both animal model and human studies have concurred to suggest the up-regulation of TNF-α mRNA and protein levels in hearts during DCM, which suggests TNF may play an important role in cardiac inflammation that develops into DCM.

The present meta-analysis, based on 9 eligible studies
Table III. Subgroup Analysis of Different Genetic Models by Ethnicity and Genotyping Method

| Subgroup | Number | A versus G OR (95%CI) | P  | GA+AA versus GG OR (95%CI) | P  | AA versus GG+GA OR (95%CI) | P  | GA versus GG OR (95%CI) | P  | AA versus GG OR (95%CI) | P  |
|----------|--------|-----------------------|----|-----------------------------|----|-----------------------------|----|-------------------------|----|-------------------------|----|
| Overall  | 9      | 1.57 (0.97, 2.54)     | 0.069 | 1.82 (0.99, 3.35)     | 0.053 | 1.43 (0.98, 2.08)     | 0.065 | 1.87 (1.03, 3.40)     | 0.040 | 1.49 (0.61, 3.66)     | 0.386 |
| Caucasian| 5      | 1.38 (0.57, 3.37)     | 0.473 | 1.67 (0.54, 5.17)     | 0.377 | 0.99 (0.27, 3.69)     | 0.994 | 1.74 (0.58, 5.19)     | 0.323 | 1.26 (0.19, 8.23)     | 0.810 |
| Asian    | 3      | 1.79 (0.99, 3.24)     | 0.054 | 2.00 (1.02, 3.92)     | 0.045 | 1.43 (0.58, 3.57)     | 0.439 | 1.94 (1.23, 3.06)     | 0.004 | 1.61 (0.64, 4.03)     | 0.311 |
| African  | 1      | 1.51 (1.13, 2.01)     | 0.005 | 1.62 (1.16, 2.27)     | 0.005 | 1.43 (0.66, 3.07)     | 0.358 | 1.62 (1.14, 2.31)     | 0.008 | 1.62 (0.75, 3.50)     | 0.219 |

Figure 3. Forest plot for the association of TNF-α G-308A polymorphism and susceptibility to DCM in the Asian population under the dominant model.

Figure 4. Forest plot for the association of TNF-α G-308A polymorphism and susceptibility to DCM in the Asian population under the heterozygous comparison.

(1338 DCM patients and 1677 controls), suggested that the -308A allele of TNF-α gene polymorphism could contribute to the development of dilated cardiomyopathy. Compared with the GG genotype, GA genotypes were generally associated with a 1.87-fold increased risk of DCM (95%CI = 1.03-3.40, P = 0.040). Similarly, the result in the further ethnicity-stratified analysis showed that significant association was detected between TNF-α G-308A polymorphism and DCM probably in Asian populations under both the dominant model and heterozygous comparison.

There was strong evidence of heterogeneity in the
pooled studies and then we conducted meta-regression analysis enabling consideration of various covariates to explore the possible source of heterogeneity. All of the 6 considered variants (ethnicity, publication year, genotyping method, sample size, HWE, matching situation between case and control groups) were not the clear source of heterogeneity. Some reasons that might at least partially explain the result include the difference in environmental backgrounds, differences in recruitment procedures of the study population, the severity of DCM, individual characteristics (e.g., mean age, percentage of gender, smoking status) or unknown variables.

It is prudent to acknowledge that several limitations need to be carefully considered. First, this present meta-analysis included 9 studies while 3 of them deviated from HWE. Subsequent sensitivity analysis demonstrates that the statistical significance would become adverse when we excluded the 3 non-HWE studies. The assessment of the quality of the 3 non-HWE studies using the Newcastle-Ottawa Scale indicated that all of them are high quality studies. Furthermore, none of the 3 studies was the main source of heterogeneity due to the results of meta-regression on HWE. Second, the sample sizes of the 9 included studies were small or moderate and may not provide sufficient power to estimate the association. Third, we conducted the search with a language limitation to English which may lead to a language bias, although the Begg funnel plot and Egger test results showed no potential publication bias. Fourth, 3 of 9 studies included ischemic, valvular or virus DCM, while the others did not, for which a potential confounding bias should be considered. Finally, the present study was based on unadjusted estimates and evaluation of potential gene-gene and gene-environment interactions were not addressed due to a lack of original data. Therefore, the findings in our meta-analysis should be interpreted with caution.

In conclusion, despite these limitations, the present meta-analysis suggested a possible association between TNF-α G-308A polymorphism and susceptibility to DCM, indicating that TNF-α G-308A polymorphism may play an important role in the pathogenesis and progression of DCM, especially in Asian populations. Additional studies with larger sample sizes, better designs, and different races are clearly needed to further clarify the association between tumor necrosis factor-α gene polymorphism (G-308A) and dilated cardiomyopathy.

### Disclosures

**Conflicts of interest:** The authors declare no conflict of
interest.

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