ABSTRACT

Objectives: The tumor necrosis factor-alpha (TNF-α) gene may play an important role in coronary heart disease (CHD) and myocardial infarction (MI) risk. Recently, controversial results regarding the association of the G-308 A (rs1800629) polymorphism of the TNF-α gene with CHD/MI have been reported. We herein examine a possible association between the G-308 A (rs1800629) polymorphism of the TNF-α gene and CHD/MI in a sample of the Chinese Han population.

Materials and Methods: We determined the genotypes of TNF-α G-308 A (rs1800629) in 535 unrelated Chinese patients with CHD, 420 patients with MI, and 1020 coronary artery disease-free controls. Additionally, a meta-analysis of all previous studies on the TNF-α G-308 A polymorphism and the risk of CHD and MI was performed.

Results: AA genotypes in the G-308 A (rs1800629) polymorphism of the TNF-α gene did not occur more frequently in CHD/MI patients than in controls; odds ratios (95% confidence intervals) were 1.743 (0.325 to 1.423) for CHD and 1.731 (0.442 to 1.526) for MI, after adjusting for conventional risk factors. Further stratification for age, gender, and other cardiovascular risk factors did not alter the prior negative findings. Pooled meta-analysis of 23 studies also found no statistically significant associations between the TNF-α polymorphism and CHD/MI risk in the genetic additive, dominant, and recessive models. Subgroup analyses showed no association between the TNF-α polymorphism and CHD/MI in Asian and Caucasian populations.

Conclusion: Our study showed no association between the G-308 A (rs1800629) polymorphism of the TNF-α gene (presence of A allele) and CHD/MI in the Chinese Han population. There was no evidence of a difference in risk effects of rs1800629 between Caucasians and Asians.

Key words: Coronary heart disease, meta-analysis, myocardial infarction, polymorphism, tumor necrosis factor-alpha
disease. Furthermore, CHD is a complex disease that is multifactorial and is clearly influenced by environmental factors and genetic predisposition. The reported association of G-308 A (rs1800629) polymorphism of the TNF-α gene with myocardial infarction[4-7] and coronary artery disease[8-10] 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. Elahi et al., for example, conclude from their data on British CHD patients that the 308 A genotype is related to more severe and rapid progression of coronary atherosclerosis.[11,12] However, Georges et al. did not find any relationship between this genotype and CHD in a general Caucasian population.[13] Many researchers have tested the polymorphisms in TNF-α for genetic association with CHD and myocardial infarction (MI) and the results are controversial. To further clarify these inconsistent association findings and to identify the possible pathogenic polymorphisms in the TNF-α gene in relation to CHD and MI, we conducted a detailed association test in the Han Chinese population. To expand the evidence further, we performed a meta-analysis using published data from observational studies.

MATERIALS AND METHODS

Study population

A total of 1975 unrelated subjects, including patients with CHD (n = 535) and MI (n = 420), and non-coronary artery disease (CAD) controls (n = 1020), were enrolled into this study. Patients were consecutively recruited from Tongji Hospital and Union Hospital in Wuhan, Hubei, China, through October 2010. Of the total subjects, 955 had angiographically documented severe coronary atherosclerosis, with a history of previous CHD/MI documented by combining data from clinical history with a thorough review of medical records showing diagnostic electrocardiogram and enzyme changes, and/or the typical sequelae of MI on ventricular angiography.[14] The control subjects, residing in the same communities as the cases, were determined to be free of CHD and peripheral atherosclerotic arterial disease by medical history, clinical examination, and electrocardiography. Both controls and MI cases in this study were genetically unrelated ethnic Han Chinese who provided demographic data by interview. The study protocol was approved by the local institutional review boards on human subject research, and written informed consent was obtained from all participants. The investigation conformed to the principles outlined in the Declaration of Helsinki.

Genotyping of polymorphisms in —Tumor necrosis factor alpha gene

Venous blood (7 ml) was collected from each subject into tubes containing 50 mmol/l Ethylenediaminetetraacetic acid (EDTA) (disodium salt), and genomic deoxynucleic acid (DNA) was isolated with a kit (Tiangen Biotech Co., Ltd., Beijing, China). The novel TNF-α polymorphism was genotyped using the TaqMan 5-nuclease assay on the TaqMan 7900HT Sequence Detection System (Applied Biosystems, Foster City, Calif.) under standard conditions. Polymerase chain reaction (PCR) reactions were carried out in reaction volume of 5 μl containing 5 ng DNA, 2.5 μl 2× Taqman universal PCR Master MixNoAmpErase UNG (Applied Biosystems), 0.125 μl 40× Assay Mix. PCR conditions included 95 °C for 10 minutes, followed by 40 cycles of 15 seconds at 92°C and 1 minute at 60 °C. Two blank controls (DNA hydration solution) and two replicate quality control samples were included in each 384-well format, and two replicate samples were genotyped with 100% concordance. The intensity of each single nucleotide polymorphism (SNP) met the criteria of three clear clusters in two scales generated by Sequence Detection Systems (SDS) software version 2.3 (ABI).[15]

Statistical analysis

Statistical analyses were performed using Statistical Package for the Social Sciences (SPSS) for Windows software version 12.0 (SPSS Inc., Chicago, IL, USA). Descriptive statistics were calculated for all demographic and clinical characteristics of the study subjects. Quantitative clinical data were compared between patients with CHD/MI and control subjects by an unpaired Student's t-test. Qualitative data were compared by the chi-square test. Allele frequencies were estimated by the gene counting method, and the chi-square test was used to identify significant departures from the Hardy-Weinberg equilibrium. The strength of the association between the I/D polymorphism and CHD risk was measured by odds ratios (ORs) and 95% confidence intervals (CIs). In the meta-analysis, for the 308 G/A polymorphism, we first estimated the risk of the variant genotype A/A compared with the wild-type G/G homozygote (additive model) and then evaluated risks of A/A vs. (G/A + G/A) (recessive model) and (A/A + G/A) vs. G/G (dominant
model). Heterogeneity was examined using the standard chi-square test. We considered the presence of significant heterogeneity at the 10% level of significance and values of F exceeding 50% as an indicator of significant heterogeneity. If the chi-square test for heterogeneity was significant, a pooled effect was calculated with a random-effects model, which was used to take into account the within-study and between-study variance. If the chi-square test for heterogeneity was not significant, a pooled effect was calculated with a fixed-effects mode. The meta-analysis was performed using Stata version 10.0 (College Station, TX). All the tests were two-sided and the significant $P$-value was $<0.05$. Power analysis was performed by Power Analysis and Sample Size (PASS) software (PASS version 2008, available at http://www.ncss.com/pass.html).

**Meta-analysis search strategy**

Epidemiological genetic association studies[^4][^7][^11][^13][^16][^32] published before March 2011 on CHD/MI and the 308 G/A polymorphisms were sought by computer-assisted searches, using various combinations of key words (myocardial infarction, coronary heart disease/coronary stenosis/coronary arterial disease, vascular/ischemic heart/isciaemic heart, tumor necrosis factor/TNF, gene/genetics, polymorphism/mutation/variant), supplemented by reviews of reference lists, hand-searching of relevant journals, and correspondence with authors. Studies were included in the meta-analysis if genotype proportions could be obtained for controls and for cases of MI or coronary death. Two investigators independently reviewed study eligibility and extracted data according to a fixed protocol, with any discrepancies resolved by discussion. Twenty-three studies were included in the final analysis. Standard statistical methods were used to obtain inverse-variance-weighted combined estimates of the overall risk ratio for coronary disease/

MI with respect to these genotypes.

### RESULTS AND DISCUSSION

#### Characteristics of patients and control subjects

The baseline characteristics of all participants are summarized in Table 1. The mean age of CHD and MI patients was not significantly different from that of the controls. Compared with the control group, the CHD/MI group had a greater proportion of smokers, a higher average body mass index (BMI), more patients with hypertension and diabetes, and more males. However, the total cholesterol and triglyceride levels were not significantly higher in cases than in controls ($P = 0.044$, $P = 0.035$, respectively), which could be the result of patients taking cholesterol-lowering medication after diagnosis. The proportion of controls, CHD, and MI subjects who reported taking a cholesterol-lowering medication such as a statin was 0.20%, 70.48%, and 71.96%, respectively.

The genotypic and allelic frequencies of the TNF-α G-308 A (rs1800629) polymorphism are shown in Table 2. These data were consistent with the distribution predicted by the Hardy-Weinberg equilibrium. Of the 1975 subjects, 102 heterozygotes and 5 homozygotes for the mutant A allele were detected in CHD subjects, and 87 heterozygotes and 3 homozygotes for the mutant A allele were detected in MI subjects, and the observed A allele frequencies were closely similar among the groups (10.74 % for controls, 10.47 % for patients with CHD, and 10.47% for patients with MI). The prevalence of the G/A and A/A genotypes in controls, patients with CHD, and patients with MI was 20.78%, 20%, and 21.43%, respectively. Further study, stratified by smoking and sex, revealed no significant difference between the control group and each case group. Compared with carriers of the wild-type G/G homozygote, carriers of A allele (GA/AA genotypes) were not at increased risk for

| Table 1: General characteristics of coronary heart disease/myocardial infarction patients and controls who participated in the study |
|-------------------------------------------------------------------------------------------------------------------------|
| **Variables**                                                                                                             | **Controls (n = 1020)** | **(CHD cases)** | **MI cases** |
| Gender, male/female, (%)                                                                                               | 536/484 (52.5/47.5) | 351/184 (65.6/34.4) | 81/141 (66.4/33.6) |
| Age, years                                                                                                               | 53.22 ± 9.15         | 56.62 ± 8.33     | 59.32 ± 10.71 |
| Smoking, no/yes, (%)                                                                                                     | 585/435 (57.35/42.65) | 333/202 (62.24/37.76) | <0.001 |
| HBP, no/yes (%)                                                                                                          | 564/456 (55.29/44.71) | 349/186 (65.23/44.78) | <0.001 |
| Body mass index, kg/m²                                                                                                   | 21.33 ± 1.65         | 25.42 ± 2.10     | 26.31 ± 1.98 |
| Diabetes mellitus, no/yes (%)                                                                                            | 574/446 (56.27/43.73) | 330/205 (61.68/38.32) | 0.028 |
| Total cholesterol, mmol/L                                                                                               | 4.56 ± 0.72          | 5.35 ± 1.23      | 6.02 ± 1.45 |
| Triglyceride, mmol/L                                                                                                     | 1.32 ± 0.44          | 1.99 ± 0.15      | 2.03 ± 0.21 |
| High density lipoproteins                                                                                                                                                         | 2.87 ± 0.41          | 3.45 ± 0.32      | 3.71 ± 0.21 |

Where, CHD = Coronary heart disease; MI = Myocardial infarction; HBP = High blood pressure; BMI = Body mass index.
CHD [Odds Ratio (OR), 0.986; 95% Confidence interval (CI), 0.827 to 1.104; P = 0.625], or for MI (OR, 1.011; 95% CI, 0.965 to 1.043; P = 0.682). Moreover, the lack of association persisted between the AA and GG genotypes, as did an increased risk of CHD (AA vs. GG, OR, 1.652; 95% CI, 0.421 to 1.736) and MI (AA vs. GG, OR, 1.711; 95% CI, 0.432 to 1.255), and of CHD (GA and AA vs. GG, OR, 1.743; 95% CI, 0.325 to 1.423) and MI (GA and AA vs. GG, OR, 1.731; 95% CI, 0.442 to 1.526) even after controlling for other conventional risk factors by multiple logistic regression [Table 2].

As shown in Table 3, there were no significant associations between the rs1800629 and sex, age, BMI, proportions of hypertension, diabetes mellitus, or smoking status in CHD/MI patients or controls. To evaluate the impact of age on the association of the rs1800629 variant and CHD/MI, the samples were divided into two groups based on the median age of controls (≤ 60 and > 60 years). No significant difference of genotype distribution (P = 0.618 and P = 0.633, respectively) between CHD/MI patients and controls was observed in any of the groups [Table 3]. Further study, stratified by smoking and gender, revealed no significant difference between the control group and each case group (data not shown), even after adjusting by multiple logistic regression for other conventional risk factors, such as gender, smoking, BMI, hypertension, and diabetes.

### Meta-analysis results

Table 4 shows the characteristics of studies included in this meta-analysis. The association between the A/A genotype compared with the G/G genotype and CHD/MI risk showed no significance utilizing the random-effects model (OR, 0.90; 95% CI, 0.74–1.09; P = 0.006). Additionally, no

### Table 2: Association of rs1800629 with coronary heart disease/myocardial infarction Cases and Controls in the Chinese Han Population as observed in the study

| TNF-α 308 G/A Genotype | Controls number (%) | CHD cases | MI cases |
|-------------------------|---------------------|-----------|----------|
|                         | Number (%), OR* (95% CI) | P value | Number (%), OR* (95% CI) | P value |
| GG                      | 808 79.22 428 80 1.000 | 330 78.57 | 1.000 |
| GA                      | 205 20.09 102 19.06 1.628 (0.358-1.742) 0.547 | 87 20.71 10.611 (0.472-1.580) 0.631 |
| AA                      | 7 0.69 5 0.94 1.652 (0.421-1.736) 0.718 | 3 0.71 1.711 (0.432-1.255) 0.695 |
| GA and AA               | 212 20.78 107 20 1.743 (0.325-1.423) 0.721 | 90 21.43 1.731 (0.442-1.526) 0.703 |
| Alle                    | 219 10.74 112 10.47 0.986 (0.827-1.104) 0.625 | 93 11.07 1.011 (0.965-1.043) 0.682 |

NC, not calculated, *: Adjusted for sex, age, BMI, DM, and smoking status. Where, CHD = Coronary heart disease; MI = Myocardial infarction; OR = Odds ratio; CI = Confidence interval.

### Table 3: Stratification Analysis for Association between rs1800629 and Risk of coronary heart disease/myocardial infarction

| TNF-α 308 G/A Genotype | GG | CHD cases OR* (95% CI) | P value | MI cases OR* (95% CI) | P value |
|-------------------------|----|-----------------------|---------|-----------------------|---------|
|                         | GA | 1.210 (0.522-3.929) 1.543 (0.214-1.376) 0.858 | 1.507 (0.515-2.564) 0.926 (0.583-1.471) 0.758 |
|                         | AA | 1.133 (0.203-2.414) 0.855 (0.550-3.340) 0.157 | 1.944 (0.584-2.526) 0.543 (0.214-1.376) 0.208 |
| Gender                  | Male | 1.210 (0.522-3.929) 1.543 (0.214-1.376) 0.858 | 1.507 (0.515-2.654) 0.926 (0.583-1.471) 0.758 |
|                         | Female | 1.133 (0.203-2.414) 0.855 (0.550-3.340) 0.157 | 1.944 (0.584-2.526) 0.543 (0.214-1.376) 0.208 |
| Age, years              | ≤ 60 | 1.973 (0.488-2.345) 0.248 (0.218-2.787) 0.618 | 1.353 (0.476-2.604) 0.855 (0.550-1.330) 0.389 |
|                         | > 60 | 1.486 (0.515-2.156) 0.655 (0.199-1.159) 0.633 | 1.617 (0.226-2.680) 1.766 (0.241-2.180) 0.174 |
| Smoke status            | Nonsmokers | 1.596 (0.567-2.228) 0.5419 (0.175-2.004) 0.203 | 1.238 (0.567-2.228) 1.474 (0.150-2.498) 0.294 |
|                         | Smokers | 0.807 (0.168-1.937) 0.401 (0.163-1.992) 0.579 | 0.807 (0.129-1.914) 0.819 (0.519-1.291) 0.262 |
| Hypertension            | No | 1.953 (0.568-2.341) 0.252 (0.065-2.779) 0.485 | 1.473 (0.510-2.695) 1.668 (0.151-2.929) 0.071 |
|                         | Yes | 0.7512 (0.332-1.151) 0.277 (0.112-1.591) 0.294 | 0.891 (0.553-1.434) 0.491 (0.593-1.478) 0.663 |
| Diabetes                | No | 1.025 (0.727-2.756) 0.507 (0.155-1.654) 0.202 | 1.644 (0.116-2.592) 1.584 (0.234-2.465) 0.741 |
|                         | Yes | 0.926 (0.583-1.471) 0.944 (0.584-1.657) 0.708 | 0.493 (0.185-1.312) 0.535 (0.261-1.413) 0.469 |

* ORs were obtained from a logistic regression model with adjustment for age, sex, smoking, BMI, hypertension, and diabetes. Where, CHD = Coronary heart disease; MI = Myocardial infarction; OR = Odds ratio; CI = Confidence interval.
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Table 4: Meta-analysis of rs1800629 and risk of coronary heart disease/myocardial infarction in the patients in the study

| Groups | Number of studies | Statistical methods | Genetics models | OR (95%CI) | I-Square | P value |
|--------|-------------------|---------------------|-----------------|------------|----------|---------|
| All studies | 23 | Fixed | Additive | 0.90 (0.74-1.09) | 49.1% | 0.006 |
| | | Fixed | Dominant | 1.01 (0.95-1.06) | 39% | 0.030 |
| | | Random | Recessive | 1.00 (1.00-1.01) | 61.9% | < 0.001 |
| Caucasian | 16 | Random | Additive | 0.89 (0.72-1.09) | 58% | 0.002 |
| | | Random | Dominant | 1.01 (0.95-1.07) | 51.8% | 0.008 |
| | | Random | Recessive | 1.00 (1.00-1.01) | 68.4% | < 0.001 |
| CHD | 7 | Random | Additive | 0.88 (0.63-1.23) | 77.0% | < 0.001 |
| | | Fixed | Dominant | 1.00 (0.90-1.11) | 31.2% | 0.179 |
| | | Random | Recessive | 1.01 (0.99-1.02) | 83.7% | < 0.001 |
| MI | 8 | Fixed | Additive | 0.86 (0.66-1.13) | 10.3% | 0.350 |
| | | Fixed | Dominant | 1.00 (0.93-1.08) | 49.3% | 0.055 |
| | | Fixed | Recessive | 1.00 (1.00-1.01) | 31.2% | 0.179 |
| CHD and MI | 1 | --- | Additive | 2.86 (0.49-16.78) | --- | --- |
| | | --- | Dominant | 1.39 (0.85-2.26) | --- | --- |
| | | --- | Recessive | 0.98 (0.95-1.02) | --- | --- |
| Asian | 7 | Fixed | Additive | 0.97 (0.61-1.53) | 0 | 0.465 |
| | | Fixed | Dominant | 1.00 (0.83-1.21) | 0 | 0.550 |
| | | Fixed | Recessive | 1.00 (0.99-1.02) | 0 | 0.426 |
| CHD | 5 | Fixed | Additive | 0.93 (0.58-1.49) | 0 | 0.403 |
| | | Fixed | Dominant | 1.02 (0.82-1.27) | 12.3% | 0.335 |
| | | Fixed | Recessive | 1.00 (0.98-1.02) | 18.2% | 0.300 |
| CHD and MI | 2 | --- | Additive | 3.31 (0.14-8.78) | 0 | < 0.001 |
| | | --- | Dominant | 0.96 (0.65-1.40) | 0 | < 0.001 |
| | | --- | Recessive | 1.00 (0.98-1.01) | 0 | < 0.001 |

Where, CHD = Coronary heart disease; MI = Myocardial infarction; OR = Odds ratio; CI = Confidence interval.

Figure 1: Associations between G-308 A (rs1800629) polymorphism of the TNF-α gene and risk of CHD/MI were not observed.
significant association was demonstrated in the dominant model (OR, 1.01; 95% CI, 0.95–1.06; \( P = 0.30 \)). However, this association was significant in the recessive model (OR, 1.00; 95% CI, 1.00–1.01; \( P < 0.001 \)). No significant heterogeneity was present in any of the models (additive model \( I^2 = 49.1\% \), recessive model \( I^2 = 39\% \), and dominant model \( I^2 = 61.9\% \)).

**DISCUSSION**

CHD occurs as a consequence of a pathological process that can be triggered and enhanced by inflammation.\(^{[32-33]}\) Both environmental and genetic risk factors are likely mediators of pathogenesis of this disease. On the basis of the hypothesis that coronary atherosclerosis is a chronic inflammatory disease, we examined the relationship between the G-308 A (rs1800629) polymorphism and the risk of CHD/MI. Our data showed that the G-308 A (rs1800629) polymorphism in the TNF gene was not associated with CHD/MI in the Chinese Han population. The carriers of the A allele were not found to have a higher risk of CHD/MI than the carriers of the G allele,\(^{[18]}\) a finding which agrees with that of the present meta-analysis in Asians and Caucasians. Although a case-control study identified TNF-α SNP (308 G/A (rs1800629)) associated with CHD/MI risk among Italian participants,\(^{[33]}\) confirmation of these results has been mixed. We used twenty-three primary studies for meta-analysis, and the results indicated that there was no association between the TNF G-308 A (rs1800629) polymorphism and risk of CHD and MI as show in Figure 1. A large sample-size study has more statistical power than a small-scale study and can effectively avoid potential bias. Thus, our meta-analysis was based on a large sample size, which greatly enhanced the statistical power compared to that of a single primary study, and ensured the reliability of the results. Our present case-control study and meta-analysis of subsequent studies concluded that common TNF-α polymorphisms are not strongly associated with CHD/MI susceptibility, contributing additional evidence for the lack of association between G-308 A (rs1800629) and CHD/MI risk among our study population.

The present report demonstrates the potential for large-scale genetic epidemiology to help assess the nature of relationships between putative risk factors and disease.\(^{[36]}\) 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 CHD/MI 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 greatly 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 CHD and MI. This result is inconsistent with the results of studies conducted by Dedoussis\(^{[24]}\) and Giacconi\(^{[23]}\) et al. No association was found in the present study between rs3025058 and CHD/MI in a meta-analysis of Asian populations or in a meta-analysis of Caucasian populations.

The inconsistency of these results may have several explanations. First, to study interactions, the present model required large sample sizes to obtain acceptable statistical power, and single interaction effects may be too small to be detected. According to power analysis, our study had greater than 80% and 75% power to detect effects of TNF-α polymorphism (rs1800629) on CHD and MI, respectively, assuming an OR of 1.5. Second, the exclusion of fatal cases in this study is a possible limitation. The exposures under study, especially the genetic exposure, may be strong associated factors with a fatal outcome of MI, although this could not be detected in this study. We genotyped the SNP and did not observe associations with CHD/MI; however, our study was limited to survivors of incident events, and potential stronger associations in CHD were found among the fatal cases. Third, due to the lack of individual patient data, we could not conduct an adjustment estimate by sex, age, BMI, diabetes mellitus, and smoking status information. Finally, genetic variations not only modulate some of these classical cardiovascular risk factors, but also act also in a complex manner.

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 CHD/MI was related to an increased risk of CHD/MI among the Chinese Han population. Furthermore, we found no evidence that the presence of the 308 A allele would interact synergistically with environmental factors, such as hypertension, type 2 diabetes, obesity, and smoking, studied in causing CHD/MI.

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