Tumor necrosis factor-alpha G-308 A polymorphism and risk of coronary heart disease and myocardial infarction: A case-control study and meta-analysis

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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

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INTRODUCTION

Coronary heart disease (CHD), one of the leading causes of mortality, is widely accepted as a chronic inflammatory disease. The immune system contributes to the atherosclerotic process from initiation to plaque rupture.[1-3] Pro-inflammatory TNF-α has repeatedly been found to be involved in the CHD pathological pathway and to be a reliable predictor of cardiovascular

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 deoxyribonucleic 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 I^2 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/ischaemic 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	
		(n = 535)	*P* Value	(n = 420)	*P* Value
Gender, male/female, (%)	536/484 (52.5/47.5)	351/184 (65.6/34.4)	0.041	279/141 (66.4/33.6)	0.032
Age, years	53.22 ± 9.15	56.62 ± 8.33	0.321	59.32 ± 10.71	0.242
Smoking, no/yes, (%)	585/435 (57.35/42.65)	333/202 (62.24/37.76)	<0.001	275/145 (65.48/34.52)	<0.001
HBP, no/yes (%)	564/456 (55.29/44.71)	349/186(65.23/44.78)	<0.001	283/137 (67.38/32.62)	<0.001
Body mass index, kg/m^2	21.33 ± 1.65	25.42 ± 2.10	0.032	26.31 ± 1.98	0.024
Diabetes mellitus, no/yes (%)	574/446 (56.27/43.73)	330/205 (61.68/38.32)	0.028	277/143 (65.95/34.05)	0.022
Total cholesterol, mmol/L	4.56 ± 0.72	5.35 ± 1.23	0.042	6.02 ± 1.45	0.044
Triglyceride, mmol/L	1.32 ± 0.44	1.99 ± 0.15	0.048	2.03 ±.0.21	0.035
High density lipoproteins	2.87 ± 0.41	3.45 ± 0.32	<0.001	3.71 ± 0.21	<0.001

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									
G	1821	89.26	958	89.53	1.000		747 88.93	1.000	
A	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			MI cases		
		GA OR (95% CI)*	AA OR (95% CI)*	*P* value	GA OR (95% CI)*	AA OR (95% CI)*	*P* value
Gender	1.000					1.000	
Male	1.000	1.210 (0.522-3.929)	1.543 (0.214-1.376)	0.858	1.507 (0.515-3.654)	0.926 (0.583-1.471)	0.758
Female	1.000	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	1.000						
≤ 60	1.000	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	1.000	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	1.000						
Nonsmokers	1.000	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	1.000	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	1.000						
No	1.000	1.953 (0.568-2.341)	0.252 (0.065-2.779)	0.485	1.473 (0.510-2.495)	1.668 (0.151-2.292)	0.071
Yes	1.000	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	1.000						
No	1.000	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	1.000	0.926 (0.583-1.471)	0.944 (0.584-1.567)	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 diabetesWhere, CHD = Coronary heart disease; MI = Myocardial infarction; OR = Odds ratio; CI = Confidence interval*

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.

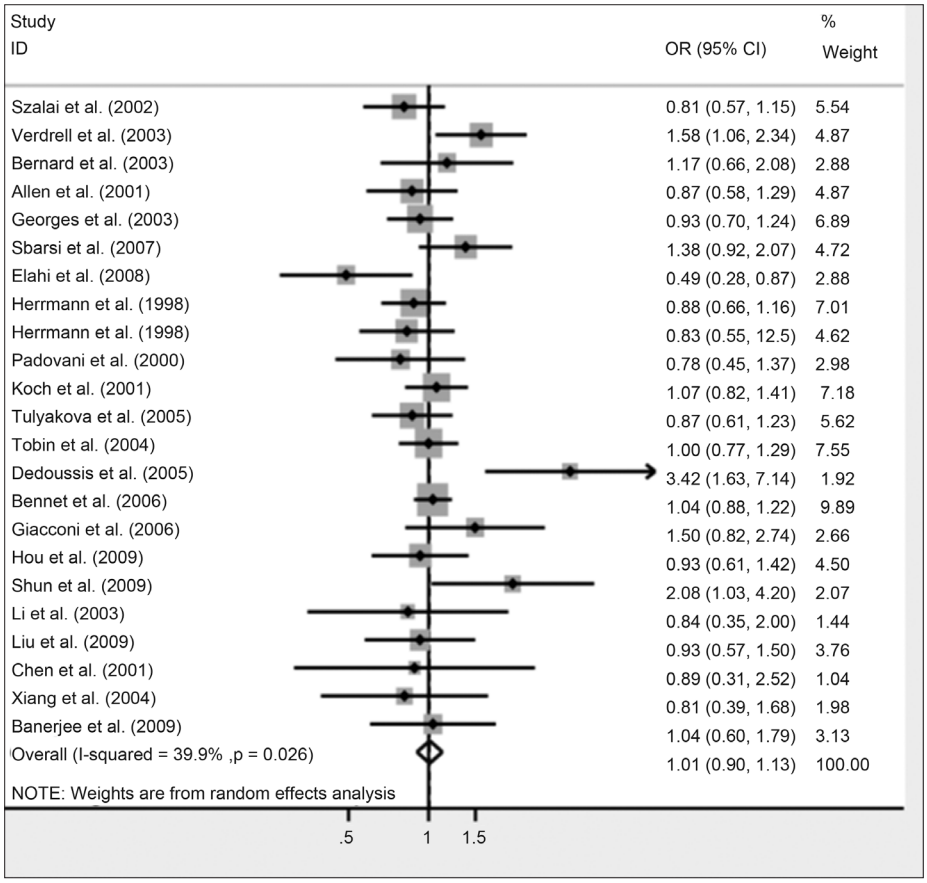

Figure 1: Associations between G-308 A (rs1800629) polymorphism of the TNF-α gene and risk of CHD/MI were not observed

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.[20,33-35] 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,[18] 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[22] 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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REFERENCES

1. Willerson JT, Ridker PM. Inflammation as a cardiovascular risk factor. Circulation 2004;109:II2-10.

2. Ross R. Atherosclerosis--an inflammatory disease. N Engl J Med 1999;340:115-26.
3. Zhao SP, Ye HJ, Zhou HN, Nie S, Li QZ. Gemfibrozil reduces release of tumor necrosis factor-α in peripheral blood mononuclear cells from healthy subjects and patients with coronary heart. Clinica Chimica Acta 2003;332:61-7.
4. Padovani JC, Pazin-Filho A, Simoes MV, Marin-Neto JA, Zago MA, Franco RF. Gene polymorphisms in the TNF locus and the risk of myocardial infarction. Thromb Res 2000;100:263-9.
5. Ranjith N, Pegoraro RJ, Naidoo DP, Shanmugam R, Rom L. Genetic variants associated with insulin resistance and metabolic syndrome in young Asian Indians with myocardial infarction. Metab Syndr Relat Disord 2008;6:209-14.
6. Antonicelli R, Olivieri F, Cavallone L, Spazzafumo L, Bonafe M, Marchegiani F, *et al*. Tumor necrosis factor-alpha gene -308G>A polymorphism is associated with ST-elevation myocardial infarction and with high plasma levels of biochemical ischemia markers. Coron Artery Dis 2005;16:489-93.
7. Bennet AM, van Maarle MC, Hallqvist J, Morgenstern R, Frostegard J, Wiman B, *et al*. Association of TNF-alpha serum levels and TNFA promoter polymorphisms with risk of myocardial infarction. Atherosclerosis 2006;187:408-14.
8. Herrmann SM, Ricard S, Nicaud V, Mallet C, Arveiler D, Evans A, *et al*. Polymorphisms of the tumour necrosis factor-alpha gene, coronary heart disease and obesity. Eur J Clin Invest 1998;28:59-66.
9. Ghazouani L, Khalifa SB, Abboud N, Addad F, Khalfallah AB, Brahim N, *et al*. -308G>A and -1031T>C tumor necrosis factor gene polymorphisms in Tunisian patients with coronary artery disease. Clin Chem Lab Med 2009;47:1247-51.
10. Manginas A, Tsiavou A, Chaidaroglou A, Giamouzis G, Degiannis D, Panagiotakos D, *et al*. Inflammatory cytokine gene variants in coronary artery disease patients in Greece. Coron Artery Dis 2008;19:575-82.
11. Elahi MM, Gilmour A, Matata BM, Mastana SS. A variant of position -308 of the Tumour necrosis factor alpha gene promoter and the risk of coronary heart disease. Heart Lung Circ 2008;17:14-8.
12. Araújo F, Pereira AC, Mota GF, Latorre Mdo R, Krieger JE, Mansur AJ. The influence of tumor necrosis factor −308 and C-reactive protein G1059C gene variants on serum concentration of C-reactive protein: Evidence for an age-dependent association. Clinica Chimica Acta 2004;349:129-34.
13. Georges JL, Rupprecht HJ, Blankenberg S, Poirier O, Bickel C, Hafner G, *et al*. Impact of pathogen burden in patients with coronary artery disease in relation to systemic inflammation and variation in genes encoding cytokines. Am J Cardiol 2003;92:515-21.
14. Apple FS, Smith SW, Pearce LA, Ler R, Murakami MM, Benoit MO, *et al*. Use of the bioMérieux VIDAS® troponin I ultra assay for the diagnosis of myocardial infarction and detection of adverse events in patients presenting with symptoms suggestive of acute coronary syndrome. Clinica Chimica Acta 2008;390:72-5.
15. Shen GQ, Li L, Rao S, Abdullah KG, Ban JM, Lee BS, *et al*. Four SNPs on chromosome 9p21 in a South Korean population implicate a genetic locus that confers high cross-race risk for development of coronary artery disease. Arterioscler Thromb Vasc Biol 2008;28:360-5.
16. Allen RD. Polymorphism of the human TNF-alpha promoter--random variation or functional diversity? Mol Immunol 1999;36:1017-27.
17. Koch W, Kastrati A, Bottiger C, Mehilli J, von Beckerath N, Schomig A. Interleukin-10 and tumor necrosis factor gene polymorphisms and risk of coronary artery disease and myocardial infarction. Atherosclerosis 2001;159:137-44.
18. Szalai C, Fust G, Duba J, Kramer J, Romics L, Prohaszka Z, *et al*. Association of polymorphisms and allelic combinations in the tumour necrosis factor-alpha-complement MHC region with coronary artery disease. J Med Genet 2002;39:46-51.
19. Bernard V, Pillois X, Dubus I, Benchimol D, Labouyrie JP, Couffinhal T, *et al*. The -308 G/A tumor necrosis factor-alpha gene dimorphism: A risk factor for unstable angina. Clin Chem Lab Med 2003;41:511-6.
20. Tatenkulova SN, Mareev V, Zykov KA, Belenkov Iu N. The role of inflammatory factors in pathogenesis of ischemic heart disease. Kardiologiia 2009;49:4-8.
21. Tobin MD, Braund PS, Burton PR, Thompson JR, Steeds R, Channer K, *et al*. Genotypes and haplotypes predisposing to myocardial infarction: A multilocus case-control study. Eur Heart J 2004;25:459-67.
22. Dedoussis GV, Panagiotakos DB, Vidra NV, Louizou E, Chrysohoou C, Germanos A, *et al*. Association between TNF-alpha -308G>A polymorphism and the development of acute coronary syndromes in Greek subjects: The CARDIO2000-GENE Study. Genet Med 2005;7:411-6.
23. Giacconi R, Cipriano C, Muti E, Costarelli L, Malavolta M, Caruso C, *et al*. Involvement of -308 TNF-alpha and 1267 Hsp70-2 polymorphisms and zinc status in the susceptibility of coronary artery disease (CAD) in old patients. Biogerontology 2006;7:347-56.
24. Sbarsi I, Falcone C, Boiocchi C, Campo I, Zorzetto M, De Silvestri A, *et al*. Inflammation and atherosclerosis: The role of TNF and TNF receptors polymorphisms in coronary artery disease. Int J Immunopathol Pharmacol 2007;20:145-54.
25. Hou L, Huang J, Lu X, Wang L, Fan Z, Gu D. Polymorphisms of tumor necrosis factor alpha gene and coronary heart disease in a Chinese Han population: Interaction with cigarette smoking.Thromb Res 2009;123: 822-6.
26. Liu Y, Jin W, Lu L, Chen QJ, Shen WF. Association between single nucleotide polymorphism in the promoter of tumor necrosis factor-α gene and coronary heart disease. J Diagn Concepts Pract 2009;5:506-9.
27. Li Y, Xu P, Chen H, Zhang PA, Huang CX. Association between tumor necrosis factor-α G-308 A gene polymorphism and coronary heart disease: A case-control study. Chin J Geriatr 2003;9:568-9.
28. Shun SY, Zeng XQ, Qi AM, Fan WH, Zhang JC. Association of tumor necrosis factor-alpha gene polymorphisms in the promoter region with chronic periodontitis and coronary heart disease. J Clin Stomatol 2009;5:279-82.
29. Chen ZQ, Ma JF, Qiu FY, Shi SL, Chen H. Plasma levels of TNF-α, but not TNF-α G-308 A gene polymorphism, is associated with coronary heart disease. Chin J Geriatr Cardiovasc Cerebrovasc Dis 2001;06:156-8.
30. Xiang PX, Li Y, Zhang PA, Chen H. Plasma TNF-α level and TNF-α gene polymorphism in patients with coronary heart disease: A case-control study. Lab Med 2004;5:434-7.
31. Banerjee I, Pandey U, Hasan OM, Parihar R, Tripathi V, Ganesh S. Association between inflammatory gene polymorphisms and coronary artery disease in an Indian population. J Thromb Thrombolysis 2009;27: 88-94.
32. Tulyakova G, Nasibullin T, Salmanov A, Avzaletdinova D, Khusnutdinova E, Zakirova A. Association of the -308 (G/A) polymorphism of tumor necrosis factor-γ with myocardial infarction and sudden cardiac death. Balk J Med Genet 2004;8:31-5.
33. Wannamethee SG, Whincup PH, Shaper AG, Rumley A, Lennon L, Lowe GD. Circulating inflammatory and hemostatic biomarkers are associated with risk of myocardial infarction and coronary death, but not angina pectoris, in older men. J Thromb Haemost 2009;7:1605-11.
34. Sarwar N, Thompson AJ, Di Angelantonio E. Markers of inflammation and risk of coronary heart disease. Dis Markers 2009;26:217-25.
35. Kostner KM, Fahti RB, Case C, Hobson P, Tate J, Marwick TH. Inflammation, complement activation and endothelial function in stable and unstable coronary artery disease. Clinica Chimica Acta 2006;365:129-34.
36. Keavney B, Danesh J, Parish S, Palmer A, Clark S, Youngman L, *et al*. Fibrinogen and coronary heart disease: test of causality by 'Mendelian randomization'. Int J Epidemiol 2006 ;35:935-43.

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