

The TNF- α -308G/A polymorphism is associated with migraine risk: A meta-analysis

LIAN GU^{1*}, YAN YAN^{1,4*}, JIANXIONG LONG², LI SU², YANLING HU³,
QING CHEN⁴, JUANJUAN XIE⁴ and GUANGLIANG WU⁴

¹Department of Internal Neurology, First Affiliated Hospital, Guangxi Traditional Chinese Medicine University;

²School of Public Health, Guangxi Medical University; ³Medical Research Center, Guangxi Medical University;

⁴Guangxi Traditional Chinese Medicine University, Nanning, Guangxi, P.R. China

Received January 22, 2012; Accepted March 21, 2012

DOI: 10.3892/etm.2012.533

Abstract. Migraine is a neurasthenia and the genetic etiology has not been determined. Several studies concerning the correlation between the tumor necrosis factor (TNF)- α -308G/A polymorphism and migraine have been published, but their results remain controversial and the small samples in each study do not allow sufficient statistical power. In the present study, odds ratios (ORs) with 95% confidence intervals (CIs) were used to assess the strength of the association between the polymorphism and migraine. An inverse-variance method was applied to estimate the frequency of the putative risk allele in the controls. Heterogeneity was determined using Cochran's Q test and the inconsistency index (I^2). Begg's test and the inverted funnel plot were used to assess the publication bias. Five studies on Asian populations, comprising 985 cases and 958 controls, were included in the meta-analysis. The overall results revealed that the TNF- α -308G/A polymorphism was associated with migraine risk in Asians. The ORs were 1.735 (95% CI, 1.129-2.666) for A vs. G; 1.781 (95% CI, 1.166-2.718) for GA vs. GG; 1.821 (95% CI, 1.153-2.874) for AA+GA vs. GG. The subgroup analysis was based on migraine with aura (MA) and migraine without aura (MO) and there was a statistically significant result for MA [the OR was 1.728 (95% CI, 1.095-2.726) for GA vs. GG and 1.651 (95% CI, 1.049-2.598) for AA+GA vs. GG] but not for MO. In conclusion, the TNF- α -308G/A polymorphism was associated with migraine risk.

Introduction

Migraine is a common, chronic, recurrent and neurovascular disorder which is associated with digestive system and autonomic nervous system symptoms (1). The two main clinical types are MA (migraine with aura) and MO (migraine without aura). In the general population, 10% of males and 24% of females suffer from migraine (2,3). A review (4) reported that the global incidence of adult migraine is over 10%. It has been confirmed that migraine is associated with other diseases. Research has shown that MA may increase the risk of cardiovascular disease (CVD), myocardial infarction and ischemic stroke in female patients (5). The mortality rate of patients with MA who have CVD and stroke is higher than that of those who do not suffer from migraine (6).

However, the pathophysiology of migraine remains unclear. Previously, the vascular hypothesis (7) proposed that migraine was caused by intracranial and extracranial vascular dysfunction. However, this hypothesis did not address neurogenic changes and did not explain the typical migraine (MA) and common migraine (MO) phenomena. Neurogenic inflammation may be a key mechanism in stimulating the trigeminal system and causing the headache.

Tumor necrosis factor (TNF) is a pro-inflammatory molecule and a polypeptide effector of the inflammatory reaction which also appears to play a role in migraine. TNF- α activates the transcription of calcitonin gene-related peptide (CGRP) and plays a key role in migraine pathophysiology (8). A study (9) revealed that levels of CGRP in the external jugular vein are significantly increased during a migraine. The TNF- α gene is located on chromosome 6p21, in the class III area of the major histocompatibility complex (MHC) (10). The -308G/A polymorphism in TNF- α is associated with certain autoimmune, neoplastic and infectious diseases (11). Polymorphisms in the TNF- α gene (-308G/A) have been confirmed to increase the production of TNF- α *in vitro*.

Migraine is correlated with genetic susceptibility. The correlation between the -308G/A polymorphism in the TNF- α gene and migraine has been widely evaluated. Several studies have reported that TNF- α polymorphisms at -308 may be a risk factor for migraine in the Asian population (12-15), but one study did not agree (16) and the results of another were

Correspondence to: Professor Yanling Hu, Medical Research Center, Guangxi Medical University, Shuangyong, Nanning, Guangxi 0771, P.R. China
E-mail: ylhupost@163.com

*Contributed equally

Key words: migraine, tumor necrosis factor -308, polymorphism, meta-analysis

unclear (17). The reason may be the small number of samples and different genetic region between these studies. To further study the correlation between the TNF- α -308G/A polymorphism and migraine risk, we performed a meta-analysis in an Asian population.

Materials and methods

Search strategy. A systematic literature search in HuGENet, Pubmed, EMBASE and Google scholar was carried out to identify original studies concerning the correlation between the TNF- α -308G/A polymorphism and migraine on Sep 10, 2011. The search key words were as follows: 'migraine', 'headache' and 'variant or polymorphism or SNP' and 'tumor necrosis factor or tumor necrosis factor- α or TNF- α ' and 'rs1800629'. We also searched studies selected from the references of the retrieved studies.

The included articles had to meet the following criteria: i) evaluation of the TNF- α -308 G/A polymorphism and migraine risk; ii) case-control study; iii) sufficient data concerning gene frequency.

Data extraction. Two independent investigators (L.G. and Y.Y.) extracted the data and reached a consensus in all cases. The information quoted from each study included: first author, year of publication, country or region in which the study was performed, sample size, diagnostic criteria for migraine, selection method of controls, genotyping method, genotype distribution, gene frequency, clinical type of migraine and migraine risk factor. For the repeated studies, we only used the data from the latest and most comprehensive research.

Statistical analysis. The Hardy-Weinberg equilibrium (HWE) was used to test the genotype distribution in the controls of each study using Pearson's Square ($P \geq 0.05$) (18). Between-study heterogeneity was evaluated using Cochran's Q statistic (19) and the inconsistency index (I^2) (20). We set $P < 0.05$ for the Q-test and $I^2 > 50\%$ as the threshold of heterogeneity (20). Random effects models were used when heterogeneity existed, otherwise fixed effects models were selected. Logistic regression analysis was used to evaluate the association between the TNF- α -308 G/A polymorphism and migraine risk. As the frequency of the AA genotype in the majority of the studies was zero, we could not use common methods to select the genetic model. Therefore, we used three models (AA+GA vs. GG, A vs. G and GA vs. GG) to assess the association between the TNF- α -308G/A polymorphism and migraine risk. Begg's and Egger's tests were used to assess possible publication bias. Sensitivity analysis was performed on all studies, including those that deviated from HWE. All analyses were performed using STATA 11.1 (Stata, College Station, TX, USA).

Results

Study inclusion and characteristics. Eleven studies concerning the association between the TNF- α -308G/A polymorphism and migraine susceptibility were retrieved from HuGENet, Pubmed, EMBASE and Google scholar. However, five studies (21-25) were performed in Caucasian populations and were excluded from our study. Finally, six studies (12-17)

Table I. Characteristics of all eligible studies in this meta-analysis.

Author (ref.)	Year	Country	Sample size		Diagnostic criteria		Genotyping methods	Source of controls	P-value for HWE
			Cases	Controls	Cases	Controls			
Yilmaz <i>et al</i> (12)	2010	Turkey	67	96	ICHD-II	Hospital workers, students of the university, family members of patients	RFLP-PCR	Population, hospital, family members of patients	0.5845
Ates <i>et al</i> (14)	2011	Turkey	203	202	HIS	Healthy hospital workers with no previous or current history of migraine who lived in Tokat, Turkey	ARMS-PCR	Hospital	0.228
Ghosh <i>et al</i> (15)	2010	India	216	216	HIS	Healthy staff members and the general population, age- and gender-matched	RFLP-PCR	Population	0.5507
Mazaheri <i>et al</i> (13)	2006	Iran	221	183	HIS	Medical and non-medical staffs, matched for age and geographic area	SSP-PCR	Hospital and population	0.0006
Herken <i>et al</i> (16)	2005	Turkey	60	62	HIS	Same ethnic origin as patients	RFLP-PCR	Population	1.0000
Lee <i>et al</i> (17)	2007	South Korea	439	382	HIS	Korean females	PCR	Population	0.1608

ICHD-II, International Classification of Headache Disorders-II; HIS, International Headache Society; HWE, Hardy-Weinberg equilibrium; RFLP, restriction fragment length polymorphism; ARMS, amplification refractory mutation system; SSP, single specific primer; PCR, polymerase chain reaction.

Table II. Distribution of TNF- α genotype and alleles between the cases and controls.

Author (ref.)	Year	Disease	Cases					Controls				
			GG	GA	AA	G	A	GG	GA	AA	G	A
Ates <i>et al</i> (14)	2011	Migraine	125	78	0	328	78	162	40	0	364	40
Ghosh <i>et al</i> (15)	2010	Migraine	175	41	0	391	41	191	24	1	406	26
		MA	65	19	0	149	19	191	24	1	406	26
		MO	110	22	0	242	22	191	24	1	406	26
Herken <i>et al</i> (16)	2005	Migraine	54	5	1	113	7	53	9	0	115	9
		MA	36	4	0	76	4	53	9	0	115	9
		MO	18	1	1	37	3	53	9	0	115	9
Lee <i>et al</i> (17)	2007	Migraine	377	61	1	815	63	338	41	3	717	47
		MA	54	11	0	119	11	338	41	3	717	47
		MO	282	44	1	608	46	338	41	3	717	47
Yilmaz <i>et al</i> (12)	2010	MO	37	23	7	97	37	79	16	1	174	18
Mazaheri <i>et al</i> (13)	2006	MA	51	163	7	265	177	94	86	3	274	92

TNF, tumor necrosis factor; MA, migraine with aura; MO, migraine without aura.

Table III. Summary of comparative results.

Variables	N	A vs. G		GA vs. GG		AA+GA vs. GG	
		OR (95% CI)	I ² (%)	OR (95% CI)	I ² (%)	OR (95% CI)	I ² (%)
Total	5	1.735 (1.129-2.666)	69.10	1.781 (1.166-2.718)	60.8	1.821 (1.153-2.874)	67.8
Subgroup analysis							
MA	3	1.516 (0.986-2.331)	20.3	1.728 (1.095-2.726)	35.2	1.651 (1.049-2.598)	31.7
MO	4	1.654 (0.916-2.985)	69.80	1.557 (1.124-2.156)	49.20	1.650 (0.917-2.969)	63.10

MA, migraine with aura; MO, migraine without aura; OR, odds ratio; CI, confidence interval; I², inconsistency index.

were included in our meta-analysis. Of these included studies, three were performed in Turkey (12,14,16) and the others were carried out in India (15), South Korea (17) and Iran (13). All the included studies were case-control designed, comprising 1,206 cases and 1,141 controls.

Of the included studies, five (13-17) selected migraine patients based on International Headache Society (HIS) diagnosis and one (12) based on the International Classification of Headache Disorders-II (ICHD-II). All controls were healthy, however, the sources of controls in the studies varied (Table I).

In addition, among the included studies, one concerned only MO (12) and another only MA (13), three (15-17) clarified the clinical type of migraine and one (14) did not clarify the clinical type.

Meta-analysis database. In the controls, the prevalence rate of AA homozygosity in the -308G/A variant was 0.52% and the GA distribution was 13.5%. For clinical types, the prevalence rates of AA were 0.6% and 0.7% in the control subjects of MA and MO, respectively. The respective prevalence rates of GA were 11.2% and 11.9%. The genotype distribution of the included studies and the P-values for HWE testing are shown in Tables I and II.

Main results, subgroup analyses. Six studies concerning the correlation between the TNF- α -308G/A polymorphism and migraine are shown in Table I. Yilmaz *et al* (12), Mazaheri *et al* (13), Ates *et al* (14) and Ghosh *et al* (15) revealed a significant association between the TNF- α -308G/A polymorphism and migraine risk. However, Hasan *et al* (16) revealed no significant association between the polymorphism and migraine and the results of Lee *et al* (17) were uncertain. Of these six studies, one (13) deviated from HWE (P=0.0006). After excluding this study, the samples contained 985 cases and 958 controls.

The results of the meta-analysis are shown in Table III. The overall ORs and 95% CIs were calculated based on the data of the five included studies. After computing in Stata, random effects models were used and a significant association between the TNF- α -308G/A polymorphism and migraine risk was revealed in the A vs. G, GA vs. GG and dominant (AA+GA vs. GG) models. The ORs were 1.735 (95% CI, 1.129-2.666) for A vs. G, 1.781 (95% CI, 1.166-2.718) for GA vs. GG, 1.821 (95% CI, 1.153-2.874) for AA+GA vs. GG. There was significant between-study heterogeneity (I²=69.1% for A vs. G, 60.8% for GA vs. GG and 67.8% for AA+GA vs. GG).

The meta-analysis consisted of three case-control studies concerning MA (15-17) and four case-control studies concerning MO (12,15-17). The summary result of the subgroup analysis revealed a significant correlation between the TNF- α -308G/A polymorphism and MA risk. The ORs were 1.728 (95% CI, 1.095-2.726) for GA vs. GG and 1.651 (95% CI, 1.049-2.598) for AA+GA vs. GG, and no significant between-study heterogeneity was found. However, the correlation between the TNF- α -308G/A polymorphism and MO risk was not significant; the ORs were 1.654 (95% CI, 0.916-2.985) for A vs. G and 1.650 (95% CI, 0.917-2.969) for AA+GA vs. GG, and there was significant between-study heterogeneity. The results are shown in Table III.

Begg's and Egger's tests were performed to check publication bias, however, the result showed that publication bias was not significant (data not shown).

Discussion

TNF- α is a pro-inflammatory molecule and a polypeptide effector of the inflammatory reaction. It activates the transcription of CGRP and plays a key role in migraine pathophysiology. The TNF- α -308G/A polymorphism has been confirmed to be correlated with certain neuropsychiatric disorders and a number of studies have been performed to confirm the hypothesis that the TNF- α -308G/A polymorphism is associated with migraine risk; however, the results have been conflicting. Therefore, we conducted this meta-analysis.

In this meta-analysis, the results showed that the TNF- α -308G/A polymorphism was significantly correlated with migraine risk in several comparisons. Heterogeneity is an unavoidable problem. In our meta-analysis, heterogeneity may be due to a mixed population, with patients of different ethnicities and from different geographic regions. Other factors, including diagnostic criteria, genotyping methods and selection methods of controls may also lead to heterogeneity.

The subgroup analysis was based on MA and MO and the results revealed that the TNF- α -308G/A polymorphism was associated with MA risk, but not with MO. It is possible that the genetic susceptibility to the two clinical types are different. Russell and colleagues (26,27) have confirmed that the genetic bases of MA and MO are markedly different: MA is more dependent on genetic factors and MO is determined by genetic and environmental effects. In addition, migraine is a complex disease which is also correlated with psychological factors. The small sample size in our study may be another reason for the results of the subgroup analysis.

The limitations of our study should be addressed. First, the diagnostic criteria for migraine in the included studies were not the same; for example, one study based the diagnosis on the International Classification of Headache Disorders-II (ICHD-II), so the use of this article may have led to selection bias. Second, all of the included studies in our meta-analysis were in English, so certain studies in other languages may have been missed and we were unable to provide a more accurately powerful result. Third, we lacked a unified source of controls. The controls were selected from three sources: hospital-based, healthy population and family members of the migraine patients.

In conclusion, our meta-analysis revealed that the -308G/A polymorphism in the TNF gene is associated with migraine

risk in the Asian population. However, we did not further research the gene-to-gene and gene-to-environment interactions of TNF- α -308G/A and migraine. The sample size in the present study was small, therefore, larger studies with thousands of subjects should be performed.

Acknowledgements

This study was supported by the Significant Scientific Research Foundation of the Guangxi Health Department (grant no. 200933), the Science and Technology Project of Traditional Chinese Medicine, Guangxi (grant no. 200911LX203) and the Scientific Research of the Provincial Education Department, Guangxi (grant no. GZKZ1107).

References

1. Haut SR, Bigal ME and Lipton RB: Chronic disorders with episodic manifestations: focus on epilepsy and migraine. *Lancet Neurol* 5: 148-157, 2006.
2. Russell MB and Olesen J: Migrainous disorder and its relation to migraine without aura and migraine with aura. A genetic epidemiological study. *Cephalalgia* 16: 431-435, 1996.
3. Lipton RB and Stewart WF: Prevalence and impact of migraine. *Neurol Clin* 15: 1-13, 1997.
4. Stovner L, Hagen K, Jensen R, *et al*: The global burden of headache: a documentation of headache prevalence and disability worldwide. *Cephalalgia* 27: 193-210, 2007.
5. Schurks M, Buring JE and Kurth T: Migraine, migraine features, and cardiovascular disease. *Headache* 50: 1031-1040, 2010.
6. Gudmundsson LS, Scher AI, Aspelund T, *et al*: Migraine with aura and risk of cardiovascular and all cause mortality in men and women: prospective cohort study. *BMJ* 341: c3966, 2010.
7. Goadsby PJ: Pathophysiology of migraine: A disease of the brain. In: *Headache*. Goadsby PJ and Silberstein SD (eds). Butterworth-Heinemann, Boston, pp5-24, 1997.
8. Durham PL: Calcitonin gene-related peptide (CGRP) and migraine. *Headache* 46 (Suppl 1): S3-S8, 2006.
9. Goadsby PJ, Edvinsson L and Ekman R: Vasoactive peptide release in the extracerebral circulation of humans during migraine headache. *Ann Neurol* 28: 183-187, 1990.
10. Carroll MC, Katzman P, Alicot EM, *et al*: Linkage map of the human major histocompatibility complex including the tumor necrosis factor genes. *Proc Natl Acad Sci USA* 84: 8535-8539, 1987.
11. Wilson AG, Giovine FS and Duff GW: Genetics of tumour necrosis factor-alpha in autoimmune, infectious, and neoplastic diseases. *J Inflamm* 45: 1-12, 1995.
12. Yilmaz IA, Ozge A, Erdal ME, Edgünlü TG, Cakmak SE and Yalin OO: Cytokine polymorphism in patients with migraine: some suggestive clues of migraine and inflammation. *Pain Med* 11: 492-497, 2010.
13. Mazaheri S, Hajilooi M and Rafiei A: The G-308A promoter variant of the tumor necrosis factor-alpha gene is associated with migraine without aura. *J Neurol* 253: 1589-1593, 2006.
14. Ates O, Kurt S, Altinisik J, Karaer H and Sezer S: Genetic variations in tumor necrosis factor alpha, interleukin-10 genes, and migraine susceptibility. *Pain Med* 12: 1464-1469, 2011.
15. Ghosh J, Joshi G, Pradhan S and Mittal B: Investigation of TNFA 308G > A and TNFB 252G > A polymorphisms in genetic susceptibility to migraine. *J Neurol* 257: 898-904, 2010.
16. Herken H, Emin EM, Mustafa Y, Kaan S and Yildirim B: The -308 G/A polymorphism of tumor necrosis factor alpha gene is not associated with migraine. *Pain Clinic* 17: 389-393, 2005.
17. Lee KA, Jang SY, Sohn KM, Won HH, Kim MJ, Kim JW and Chung CS: Association between a polymorphism in the lymphotoxin-a promoter region and migraine. *Headache* 47: 1056-1062, 2007.
18. Egger M, Davey Smith G, Schneider M and Minder C: Bias in meta-analysis detected by a simple, graphical test. *BMJ* 315: 629-634, 1997.
19. Petiti DB (ed): *Meta-Analysis, Decision Analysis and Cost-Effectiveness Analysis: Methods for Quantitative Synthesis in Medicine*. 1st edition. Oxford University Press, New York, 1994.

20. Higgins JP, Thompson SG, Deeks JJ and Altman DG: Measuring inconsistency in meta-analyses. *BMJ* 327: 557-560, 2003.
21. Rainero I, Grimaldi LM, Salani G, Valfrè W, Rivoiro C, Savi L and Pinessi L: Association between the tumor necrosis factor- α -308 G/A gene polymorphism and migraine. *Neurology* 62: 141-143, 2004.
22. Trabace S, Brioli G, Lulli P, Morellini M, Giacobazzo M, Ciciarelli G and Martelletti P: Tumor necrosis factor gene polymorphism in migraine. *Headache* 42: 341-345, 2002.
23. Poscente M, Brioli G, Lulli P, Morellini M, Martelletti P, Trabace S and Giacobazzo M: TNFA gene: the -308 promoter polymorphism in migraine. *J Headache Pain* 1 (Suppl 2): S169-S171, 2000.
24. Asuni C, Stochino ME, Cherchi A, *et al*: Migraine and tumour necrosis factor gene polymorphism. An association study in a Sardinian sample. *J Neurol* 256: 194-197, 2009.
25. Schürks M, Kurth T, Buring JE and Zee RY: A candidate gene association study of 77 polymorphisms in migraine. *J Pain* 10: 759-766, 2009.
26. Russell MB and Olesen J: Increased familial risk and evidence of genetic factor in migraine. *BMJ* 311: 541-544, 1995.
27. Russell MB, Ulrich V, Gervil M and Olesen J: Migraine without aura and migraine with aura are distinct disorders. A population-based twin survey. *Headache* 42: 332-336, 2002.