Int J Clin Exp Med 2016;9(8):15467-15476
www.ijcem.com /ISSN:1940-5901/IJCEM0029756

Original Article

Effects of rs1799983 and rs1800779 polymorphisms in the endothelial nitric oxide synthase gene on migraine susceptibility with and without aura: a meta-analysis

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Received April 3, 2016; Accepted July 3, 2016; Epub August 15, 2016; Published August 30, 2016

Abstract: Polymorphisms (rs1799983 and rs1800779) in the endothelial nitric oxide synthase (eNOS) gene have been reported to be associated with migraine susceptibility; however, published findings have been never reached a consensus. To obtain a more accurate estimate of the effects of eNOS rs1799983 and rs1800779 polymorphisms on migraine susceptibility, we performed this meta-analysis. A comprehensive online search of PubMed, Ovid, EBSCO, the Cochrane Library, the Web of Science, the China National Knowledge Infrastructure, Wanfang, and Chinese Biomedicine databases. All publications published before February 29, 2016, were selected regardless of whether the article was published in Chinese or English. Ten eligible studies comprised 1819 patients with migraine and 3144 controls. Pooled odds ratios (ORs) with corresponding 95% confidence intervals (CIs) were calculated to evaluate associations using fixed or random-effects models. Our results showed that rs1799983 was associated with susceptibility to migraine with aura (MA) in the genetic recessive (TT versus GT+GG: OR=1.41, 95% CI=1.02-1.96) and co-dominant (TT versus GG: OR=1.50, 95% CI=1.04-2.15) models. However, the robustness of the results may be weak. Moreover, no significant associations were found between the rs1799983 polymorphism and migraine susceptibility in cases of migraine without aura (MO) or between the rs1800779 polymorphism and migraine susceptibility in cases of MA and MO. Thus, the current meta-analysis suggested that the rs1799983 polymorphism in *eNOS* is associated with MA susceptibility. Further studies with larger sample sizes are needed to evaluate these associations in patients of different ethnicities.

Keywords: Migraine, endothelial nitric oxide synthase, polymorphisms

Introduction

Migraine is a common neurovascular disorder affecting approximately 12%-16% of the population (primarily women) and is characterized by severe recurrent headache, with or without nausea, vomiting, phonophobia, photophobia, and neurological disturbances [1-3]. The International Headache Society (IHS) classifies migraine into two main subtypes: migraine with aura (MA) and migraine without aura (MO) [4].

Although the complex pathogenic mechanisms of migraine remain unclear, nitricoxide (NO) has been shown to be involved in the pathogenesis of migraine [5, 6]. NO is synthesized from l-arginine and molecular oxygen by enzymes in the NO synthase (NOS) family. There are three isoforms of NOS proteins: inducible nitric oxide synthase (iNOS), neuronal nitric oxide synthase (nNOS), and endothelial nitric oxide synthase (eNOS). eNOS is a Ca2+-dependent enzyme that releases NO from the endothelium into the blood. Once in circulation, NO can cause smooth muscle relaxation and may be in involved in the initial headache response [7]. Additionally, NO levels are increased in platelets during the painful phase, and exogenous administration of NO worsens headache pain [8]. NO has also been shown to increase the activity of the calcitonin gene-related peptide promoter in trigeminal neurons [9].

With recent advancements in genome-wide association studies (GWAS) in the medical field, an increasing number of studies have reported that genetic alterations may be used to predict the risk of various diseases. Moreover, researchers have established a strong link between single nucleotide polymorphisms (SNPs) in eNOS and migraine with and without aura (MA and MO, respectively) [2, 10-15]; however, the results of these studies have been inconclusive. Therefore, in this study, we conducted a meta-analysis to provide better evidence for the association between polymorphisms in *eNOS* and migraine susceptibility.

Materials and methods

Literature and search strategy

Until the February 29, 2016, in order to carry out case-control researches or cohort researches for the assessment of the relations between the polymorphisms of eNOS and the susceptibility of migraine, information had been searched on PubMed, Ovid, EBSCO, the Cochrane Library, the Web of Science, Wanfang, the Chinese Biomedicine Database as well as the China National Knowledge Infrastructure (CNKI). Besides, for purpose of conducting the search of electronic database, the query items adopted were as follows: "migraine"; "eNOS", "endothelial nitric oxide synthase", or "NOS3"; and "polymorphism", "polymorphisms", "SNP", "variant", "genotype", or "mutation". At the same time, in order to determine other researches that might be helpful, the bibliography listing the main textbooks, reviews as well as articles that were included were searched individually and manually. When it came to the researches that were overlapping, the research adopted was the one boasting the largest size of sample only.

Inclusion criteria

Researches in which all of the standards as follows were satisfied were adopted: firstly, case-control researches or cohort researches that investigated the relations between rs1799983 and rs1800779 polymorphisms in eNOS and migraine; secondly, researches including patients who were diagnosed as having MO or MA according to IHS criteria [4]; thirdly, researches choosing the members of a family who were uncorrelated genetically as the control subjects; and fourthly, researches in which adequate data were offered to calculating the odds ratios with 95% confidence intervals.

Exclusion criteria

Researches in which all of the standards as follows were satisfied were not adopted: firstly, researches without control subjects; secondly, researches without the report of genotype frequency or researches in which the genotype frequency was unable to be acquired from the authors; thirdly, researches in which the investigations were carried out on basis of studies that were overlapping; and fourthly, posters, abstracts, seminars, snapshots, case reports, comments, letters, reviews as well as editorials.

Data extraction

From every publication that was adopted, two researchers that were independent of each other extracted the data as follows with the application of a standardized form: the first author, the publication year, the state, the subtypes of migraine, the controls' source, the way of genotyping as well as the frequencies of allele or genotype. With regard to the disagreements, they were dealt with through discussing or consulting with a third researcher so that an agreement could be reached eventually.

Statistical analysis

Due to the fact that the knowledge existing at present is limited, it becomes somewhat difficult to identify the genetic model by which the relations between the rs1799983 and rs1800779 polymorphisms in eNOS and the susceptibility of migraine can be explained in the best way. Therefore, the analysis was carried out on all of the probable genetic models. Meanwhile, for purpose of evaluating the connection strength between the rs1799983 and rs1800779 polymorphisms in eNOS and the susceptibility of migraine, individual or pooled odds ratios with 95% confidence intervals were figured out with the application of the Version 5.3 of Review Manager (kindly provided by The Cochrane Collaboration, Oxford, England; available at: http://www.cochrane.org/software/revman.htm). Besides, through examining the forest plots, the heterogeneity among researches was graphically evaluated; while the existence

Table 1. Summary of characteristics of all included studies in the meta-analysis

First Author	Year	Conu-try	Genotype-case-MA VR Ho/Ht/ WT Ho	Genotype-case-MO VR Ho/Ht/ WT Ho	Genotype-control VR Ho/Ht/ WT Ho	Source of Control	Genotype Method	ENOS Polymor-phism	HWE *P*-Value
Borroni	2006	Italy	13/16/24	10/37/56	16/50/59	population	PCR	rs1799983	0.30
Eroz	2014	Turkey	8/64/20	8/52/24	7/54/62	hospital	PCR-RFLP	rs1799983	0.28
	2014	Turkey	18/59/15	18/41/25	14/51/58	hospital	PCR-RFLP	rs1800779	0.59
Goncalves	2011	Brazil	4/11/29	11/43/80	5/51/61	population	Taqman	rs1799983	0.16
Gruber	2010	Austria	0/12/8	5/16/13	11/34/31	population	Taqman	rs1799983	0.74
	2010	Austria	3/11/6	9/15/10	12/39/25	population	Taqman	rs1800779	0.62
Guler	2014	Turkey	5/20/33	5/46/66	8/58/59	hospital	PCR	rs1799983	0.21
	2014	Turkey	6/28/24	10/61/46	12/67/46	hospital	PCR	rs1800779	0.08
Toriello	2008	Spain	42/94/53	28/71/50	60/177/104	population	rt-PCR	rs1799983	0.30
	2008	Spain	47/100/41	37/75/37	77/176/88	Population	Rt-PCR	rs1800779	0.54

VR, variant; WT, wild-type; Ht, heterozygote; VR Ho, variant homozygote; WT Ho, wild-type homozygote; HWE Hardy-Weinberg equilibrium.

Table 2. Impact of eNOS rs1799983 and rs1800779 Polymorphismas on Migraine susceptibility

eNOS variant	Study group	Simple size (case/control)	Genetic models		I^2 (%)	P_h	Effect-model	OR [95% CI]	*P*
Rs1798993	MA	456/907	Allele contrast	T vs. G	60	0.03	Random	1.13 [0.84, 1.52]	0.41
			Dominant model	TT+GT vs. GG	76	0.001	Random	1.12 [0.66, 1.87]	0.68
			Recessive model	TT vs. GT+GG	0	0.52	Fixed	1.41 [1.02, 1.96]	0.04
			Co-dominant model	TT vs. GG	4	0.39	Fixed	1.50 [1.04, 2.15]	0.03
				GT vs. GG	79	0.003	Random	1.03 [0.57, 1.86]	0.91
			Over-dominant model	TT+GG vs. GT	79	0.0003	Random	1.03 [0.59, 1.80]	0.91
	MO	621/907	Allele contrast	T vs. G	55	0.05	Random	0.99 [0.77, 1.26]	0.91
			Dominant model	TT+GT vs. GG	65	0.01	Random	0.96 [0.66, 1.40]	0.84
			Recessive model	TT vs. GT+GG	0	0.61	Fixed	1.08 [0.77, 1.51]	0.65
			Co-dominant model	TT vs. GG	20	0.28	Fixed	1.03 [0.72, 1.48]	0.86
				GT vs. GG	64	0.02	Random	0.94 [0.64, 1.38]	0.76
			Over-dominant model	TT+GG vs. GT	56	0.04	Random	1.08 [0.78, 1.50]	0.65
Rs1800779	MA	358/665	Allele contrast	C vs. T	73	0.01	Random	1.28 [0.85, 1.91]	0.23
			Dominant model	CC+TC vs. TT	81	0.001	Random	1.54 [0.74, 3.22]	0.25
			Recessive model	CC vs. TC+TT	0	0.67	Fixed	1.24 [0.89, 1.73]	0.20
			Co-dominant model	CC vs. TT	62	0.05	Random	1.68 [0.79, 3.58]	0.18
				TC vs. TT	79	0.002	Random	1.52 [0.72, 3.18]	0.27
			Over-dominant model	CC+TT vs. TC	66	0.03	Random	0.79 [0.48, 1.30]	0.35
	MO	384/665	Allele contrast	C vs. T	53	0.09	Random	1.21 [0.91, 1.60]	0.19
			Dominant model	CC+TC vs. TT	41	0.17	Fixed	1.19 [0.91, 1.57]	0.21
			Recessive model	CC vs. TC+TT	9	0.35	Fixed	1.31 [0.94, 1.82]	0.11
			Co-dominant model	CC vs. TT	41	0.17	Fixed	1.40 [0.95, 2.06]	0.08
				TC vs. TT	12	0.33	Fixed	1.12 [0.82, 1.54]	0.48
			Over-dominant model	CC+TT vs. TC	0	0.64	Fixed	1.00 [0.78, 1.29]	0.98

of significant heterogeneity was evaluated in the statistical aspect by adopting the chi-square-based Q-statistic test of heterogeneity and the heterogeneity degree within the researches that were adopted was evaluated by employing the inconsistency index (I^2). In addition, it was considered that a high degree of heterogeneity could be suggested if the AX^2-test *P*-value (P_h) was below 0.1 or the value of I^2 was above 50% [16, 17]. The Z-test was applied to determining the pooled statistical data significance and the data would be significant if

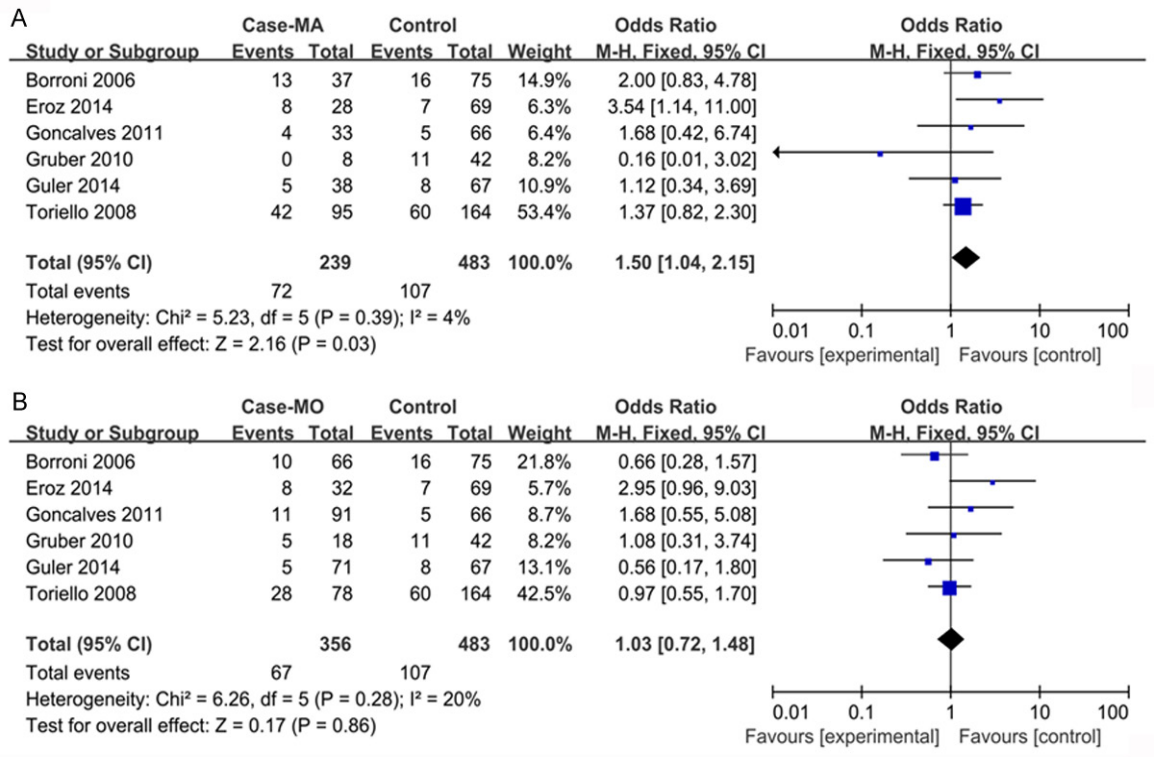

Figure 1. Forest plots of meta-analysis of association the rs1799983 polymorphism in eNOS and migraine susceptibility (TT vs. GG, A: rs1799983 polymorphism and MA susceptibility, B: rs1799983 polymorphism and MO susceptibility).

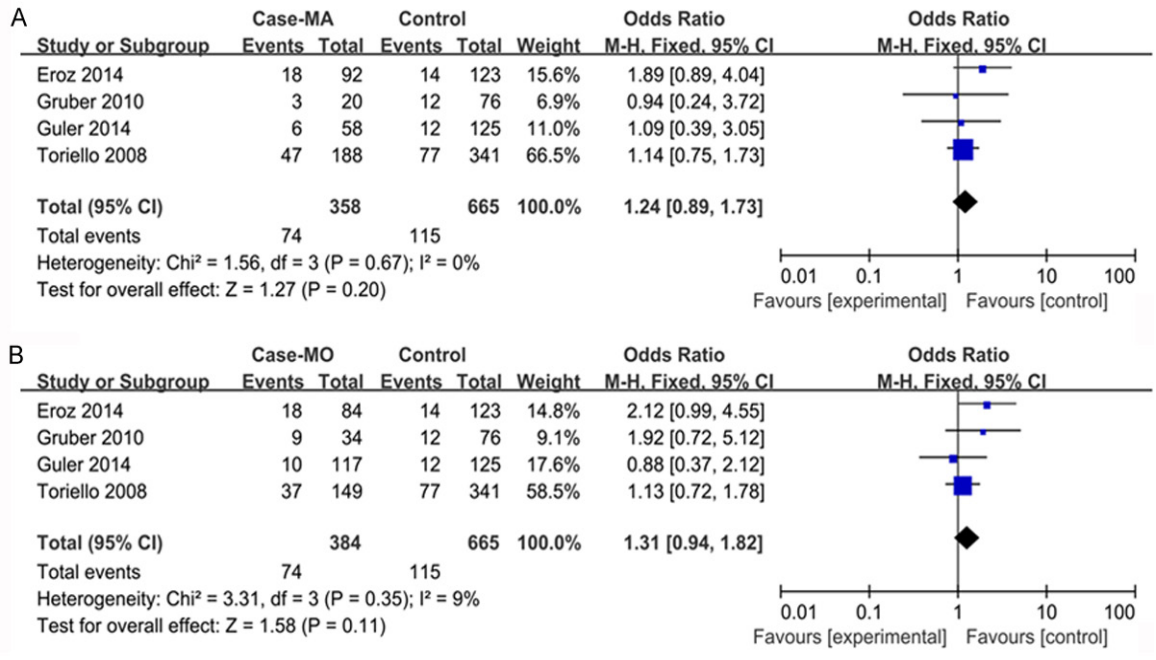

Figure 2. Forest plots of meta-analysis of association the rs1800779 polymorphism in eNOS and migraine susceptibility (CC vs. TC+TT, A: rs1800779 polymorphism and MA susceptibility, B: rs1800779 polymorphism and MO susceptibility).

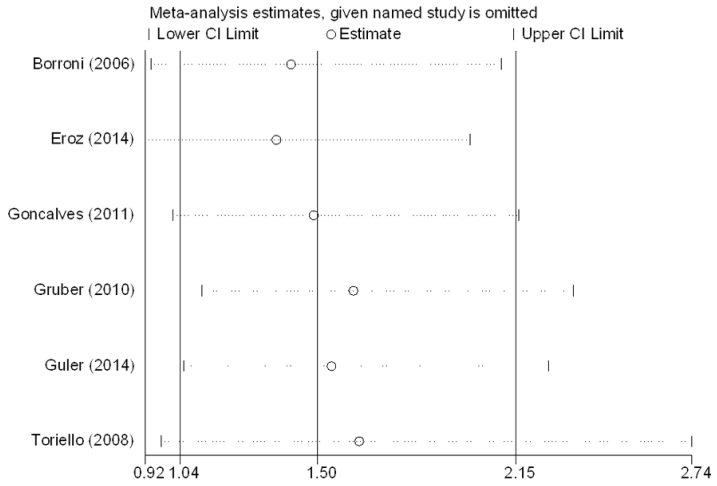

Figure 3. Sensitivity analysis of meta-analysis of association the rs1799983 polymorphism in eNOS and migraine with aura susceptibility using the recessive model.

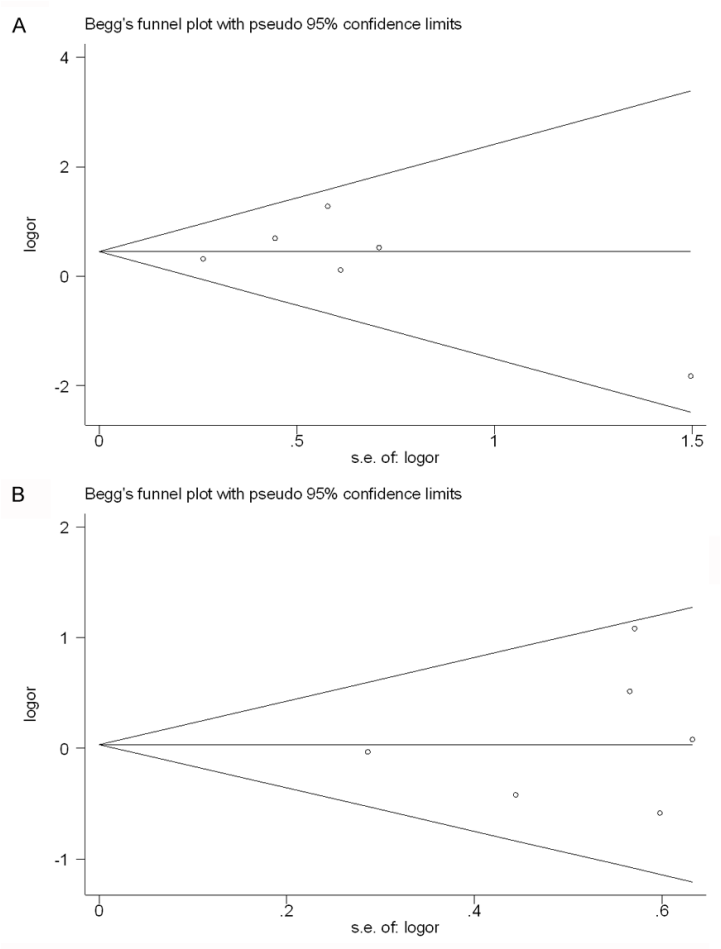

Figure 4. Begg's funnel plots for publication bias test on the associations of the rs1799983 polymorphism in eNOS and migraine susceptibility (TT vs. GG, A: rs1799983 polymorphism and MA susceptibility, B: rs1799983 polymorphism and MO susceptibility).

the *P* values were below 0.05, while the absence of heterogeneity (with P_h above 0.1 or I^2 below 50%) and the presence of heterogeneity (with P_h below 0.1 or I^2 above 50%) were determined by adopting the fixed-effects or random-effects model [18, 19]. Furthermore, the Begg's funnel plot was employed to measure the possibility of bias in publication and every research's standard deviation of logOR was plotted against its logOR: if the plot was asymmetric, then the probability of bias in publication might exist [20]. At the same time, Egger's linear regression test was also used to further evaluate the asymmetry of funnel plot, in which the significance would be indicated if the *P*-value was below [21]. The tests of both Begg and Egger were carried out with the application of the software of Stata 12.0 (Stata Corporation, College Station, TX, USA). Moreover, when various contrasts were analyzed, the analysis of sensitivity was conducted through omitting the individual researches sequentially so that the reliability of the results could be strengthened. At last, the X^2 goodness-of-fit test was applied in the software of Stata 12.0 to examining the deviation of genotype frequencies in control subjects from Hardy-Weinberg equilibrium, with the level of significance being set at $P<0.05$.

Results

Study characteristics

Initially, 22 potentially relevant publications met the requirements of the search strategy. The titles, abstracts, and full texts of all retrieved publications were carefully reviewed and screened using the defined criteria. Seven studies met the defined inclusion criteria and were included in the

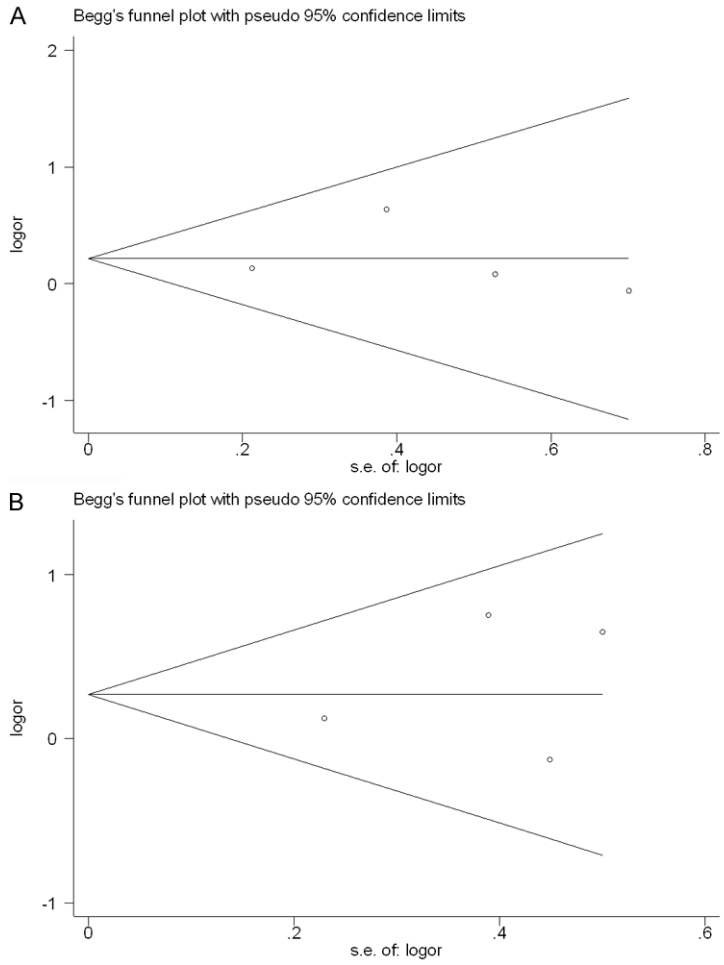

Figure 5. Begg's funnel plots for publication bias test on the associations of the rs1800779 polymorphism in eNOS and migraine susceptibility (CC vs. TC+TT, A: rs1800779 polymorphism and MA susceptibility, B: rs1800779 polymorphism and MO susceptibility).

current meta-analysis [2, 10-15]; however, because the two papers written by Goncalves [13, 14] contained overlapping data, we included the research subjects only from the study with the larger sample size [13]. Therefore, 10 case-control studies from six publications (all in English) were used in this study, comprising 1819 patients with migraine (814 with MA and 1005 with MO) and 3144 controls. All control subjects from the included studies showed deviation from the Hardy-Weinberg equilibrium (all $P>0.05$). The detailed characteristics of the included studies are summarized in **Table 1**.

Analysis of the association between the rs1799983 polymorphism in eNOS and migraine susceptibility

The detailed results of our analysis of the rs1799983 polymorphism in*eNOS* and migraine susceptibility are shown in **Table 2** and **Figure 1**. In total, six studies, including 1077 migraine cases (456 cases of MA and 621 cases of MO) and 907 controls and examining the association between the rs1799983 polymorphism in *eNOS* and migraine susceptibility, were included in our meta-analysis. We found a significant association between the rs1799983 polymorphism and migraine susceptibility in cases of MA by using the following two genetic models: recessive (TT versus GT+GG: OR=1.41, 95% CI=1.02-1.96) and co-dominant (TT versus GG: OR=1.50, 95% CI=1.04-2.15); however, this association was not identified using the following other genetic models: allele contrast (T versus G: OR=1.13, 95% CI=0.84-1.52), dominant (TT+TG versus GG: OR=1.12, 95% CI=0.66-1.87), co-dominant (TG versus GG: OR=1.03, 95% CI=0.57-1.86), and over-dominant (TT+GG versus TG: OR=1.03, 95% CI=0.59-1.80). Moreover, no significant associations were found using the above allele and genotype contrasts to test the association between the rs1799983 polymorphism and migraine susceptibility in cases of MO for the following genetic models: allele contrast (T versus G: OR=0.99; 95% CI=0.77-1.26), dominant (TT+TG versus GG: OR=0.96, 95% CI=0.66-1.40), recessive (TT versus GT+GG: OR=1.08, 95% CI=0.77-1.51), co-dominant (TT versus GG: OR=1.03, 95% CI=0.72-1.48; TG versus GG: OR=0.94, 95% CI=0.64-1.38), and over-dominant (TT+GG versus TG: OR=1.08, 95% CI: 0.78-1.50).

Analysis of the association between the rs1800779 polymorphism in eNOS and migraine susceptibility

The detailed results of our analysis of the association between the rs1800779 polymorphism in eNOS and migraine susceptibility are shown in **Table 2** and **Figure 2**. Four studies of 742cases (358 cases of MA and 384 cases of

MO) and 665 controls were analyzed. No significant associations (all P>0.05) were found using the above genetic models for both MA and MO. In patients with MA, data from the various genetic models were as follows: allele contrast (C versus T: OR=1.28, 95% CI =0.85-1.91), dominant (CC+TC versus TT: OR=1.54, 95% CI=0.74-3.22), recessive (CC versus TC+TT: OR=1.24, 95% CI=0.89-1.73), co-dominant (CC versus TT: OR=1.68, 95% CI=0.79-3.58; TC versus TT: OR=1.52, 95% CI=0.72-3.18), and over-dominant (CC+CT versus TT: OR=0.79, 95% CI=0.48-1.30). In patients with MO, data from the various genetic models were as follows: allele contrast (C versus T: OR=1.21, 95% CI = 0.91-1.60), dominant (CC+TC versus TT: OR=1.19, 95% CI=0.91-1.57), recessive (CC versus TC+TT: OR=1.31, 95% CI = 0.94-1.82), co-dominant (CC versus TT: OR=1.40, 95% CI = 0.95-2.06; TC versus TT: OR=1.12, 95% CI = 0.82-1.54), and over-dominant (CC+CT versus TT: OR=1.00, 95% CI = 0.78-1.29).

Sensitivity analysis and publication bias

Sensitivity analysis was performed by sequential omission of individual studies to investigate the influence of each study on the overall OR. The significance of the pooled OR in the analysis of both rs1799983 and rs1800779 was not excessively affected in any of the contrasts analyzed. However, when eliminating any study published by Borroni [10], Eroz [15], or Torielo [11] in the recessive model (**Figure 3**) and co-dominant model of the rs1799983 polymorphism ,the new confidence interval contained 1, indicating that the robustness of the meta-analysisresultsmaybeweak.Noevidenceofpublication bias was found in the symmetrical graphics obtained using Begg's funnel plot for both rs-1799983 (**Figure 4**) and rs1800779 (**Figure 5**) polymorphisms for either MA or MO; this finding was supported by the results of Egger's tests (each genetic model *P*>0.05).

Discussion

Migraine has a multi factorial background. However, the importance of genetic factors in the pathogenesis of migraine has become increasingly apparent [22, 23]. eNOS has been implicated in the formation of prostaglandins, which may contribute to the initiation and progression of several types of nervous system diseases, including cerebrovascular disease, cerebral stroke [24, 25], and migraine. In 2006, Borroni [10] first assessed the relationship between the rs1799983 polymorphism in *eNOS* and migraine susceptibility in 156 patients with migraine and 125 healthy volunteers, concluding that homozygous Asp298 is an independent risk factor for MA. Subsequently, many additional studies have described the relationship between *eNOS* polymorphisms and MA or MO. However, the results have been inconsistent, possibly owing to limited sample sizes. In order to address the inconsistencies and limitations of previously published studies and to draw a more robust conclusion, we performed the current meta-analysis. The key findings of this study were as follows: (1) the rs1799983 polymorphism in *eNOS* was associated with MA susceptibility, but not with MO susceptibility; and (2) the rs1800779 polymorphism in *eNOS* was not associated with MA susceptibility or MO susceptibility.

The effects of polymorphisms in eNOS on migraine susceptibility have been examined in a previous meta-analysis reported by Chen [26]. The results suggested that the "T" allele of the rs1799983 variant in eNOS increases the risk of MA among non-Caucasians (co-dominant model: pooled OR=2.10; 95% CI=1.14-3.88). Our first meta-analysis included six case-control studies involving 1077 migraine cases (456 cases of MA and 621 cases of MO) and 907 controls and investigated the association between the rs1799983 polymorphism in eNOS and migraine susceptibility. We also found a notable increase in risk of MA in patients with the rs1799983 T variant by using both recessive and co-dominant models. However, we did not categorize patients according to ethnicity owing to lack of sufficient information. For example, the primary articles used in the meta-analysis did not describe patient ethnicity; we could have only predicted ethnicity according to the information provided in the articles, which would not have been sufficiently rigorous. Second, if we are correctly interpreting the text, the included study published by Gruber [12], in which the study subjects were Australians, did not analyze only Caucasians. Third, and most importantly, overlapped data were included [13, 14], and recently published information [2] was omitted, which may have biased the results. Therefore, for these reasons, the estimations for both the MA and MO groups may not be completely accurate.

Moreover, the positive estimations observed in the current study contrast with some previous individual studies by Eroz [15] and Borroni [10], who showed that individuals with the TT genotype had a higher risk of MA occurrence individuals with the GG genotype. Unfortunately, this positive estimation was not observed when eliminating any of the three studies by Borroni, Eroz, and Torielo [10, 11, 15], mostly due to sample sizes and ethnic factors. Therefore, further studies in different ethnic groups using large sample sizes and well-matched controls are greatly needed to clarify these associations.

Interestingly, no significant association was observed in patients with MO, in contrast to the results of the study by Eroz [15], mostly due to the ethnicity factors. Moreover, five other previous studies [2, 10-13] found no association between the *eNOS* polymorphism and migraine susceptibility, in line with the results of our meta-analysis. Generally, small sample sizes likely account for the discrepancies between studies. An assessment of the association between the rs1799983 polymorphism in *eNOS* and migraine susceptibility found that more precise estimates were obtained using large sample numbers than when using individual analyses with smaller sample sizes. Moreover, smaller sample sizes serve to amplify the effects of variations in genetic background, which may contribute to variations in the association of SNPs with migraine.

To the best of our knowledge, this meta-analysis based on four case-control studies, including 358 cases of MA, 384 cases of MO, and 665 controls, is the first meta-analysis carried out to investigate the association between the rs1800779 polymorphism in *eNOS* and migraine susceptibility using all eligible published studies. We found no significant association between migraine susceptibility and the rs1800779 polymorphism in *eNOS*, consistent with the findings of previous studies [2, 11, 12], suggesting that the rs1800779 polymorphism was not associated with migraine susceptibility in patients with MA or MO.

Additionally, to date, this is the first comprehensive meta-analysis carried out to investigate the association between the rs1799983 and rs1800779 polymorphisms in *eNOS* and migraine susceptibility using all eligible published studies. No single-center study is comparable to the current work in terms of the number of included cases. However, several limitations must be acknowledged. First, heterogeneity can interfere with the interpretation of results of a meta-analysis. Although the likelihood was minimized by using a rigorous search strategy, explicit inclusion criteria, and strict data extraction and analysis, significant inter-study heterogeneity was found in nearly every comparison studied, particularly for the rs1800779 polymorphism and MA susceptibility. Second, there was some selection bias in the primary studies. In particular, the study published by Goncalves [13] included only women, and the distribution of genotypes for each polymorphism was assessed for deviation from the Hardy-Weinberg equilibrium. Third, we could not perform subgroup analysis by ethnicity because of the lack of complete data from many studies. Additionally, the results obtained in the present study are based on unadjusted estimations, and some major confounding variables, including gender, obesity [27], and environmental factors, should be taken into consideration for a more accurate analysis.

In conclusion, based on data from molecular and epidemiological studies, our meta-analysis combining all currently available data suggested that the rs1799983 polymorphism in *eNOS* was associated with MA susceptibility but not with MO susceptibility and that the rs1800779 polymorphism in *eNOS* was not associated with MA or MO susceptibility. However, migraine morbidity can be attributed various genes [28, 29] environmental stimuli [30], and even gene-gene and gene-environmental exposure interactions. Therefore, future studies considering gene-gene and gene-environment interactions are needed to provide a more comprehensive understanding of the potential role of *eNOS* polymorphisms in the pathogenesis of migraine.

Acknowledgements

This work was supported by grants from the Humanities and social sciences research project of Hubei Provincial Department of Education (No. 16Y124) and Science and technology research project of Hubei Provincial Department of Education (No. B2016500).

Disclosure of conflict of interest

None.

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