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Tumor Necrosis Factor Gene Polymorphisms and Migraine: A Systematic Review and Meta-Analysis

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Abstract

Background—Data on the association between *TNF-alpha* and *TNF-beta* gene polymorphisms and migraine are conflicting.

Methods—We performed a systematic review and meta-analysis of studies published until January 2011. We used data from published papers and as provided after contact with the authors. We calculated study specific odds ratios (OR) and 95% confidence intervals (CI) assuming additive, dominant, and recessive genetic models as well as pooled effect estimates.

Results—Among the ten studies identified the best evidence is available for the *TNF-alpha* -308G>A and *TNF-beta* 252A>G polymorphisms indicating no overall association with migraine. Subgroup analyses suggested that the A allele of the *TNF-alpha* -308G>A variant more than doubles the risk for migraine among populations with a heterogeneous ethnic background, which was driven by associations for MO (additive model: pooled OR=2.87; 95% CI 1.86–4.43). Further, the risk for MA was increased among Asian populations (additive model: pooled OR=1.71; 95% CI 1.07–2.71). Both observed effects were stronger among females than males.

Conclusions—Our results indicate no overall association between *TNF-alpha* and *TNF-beta* gene variants. However, associations differed among specific populations. Our findings need to be treated with caution and further targeted research is warranted to evaluate population-specific effects including population stratification.

Keywords

migraine; tumor necrosis factor; lymphotoxin; polymorphism; meta-analysis

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Introduction

Migraine is a common neurological disorder affecting 10–20% of the population and women 3–4 times more often than men (1). Clinically migraine presents with recurrent headache attacks, associated symptoms of vegetative disturbance, and hypersensitivity of various functional systems of the nervous system (1, 2). Further, about one-third of migraineurs experience transient neurological symptoms mostly involving the visual system prior to or during a migraine attack, which are known as migraine aura (2).

Migraine pathophysiology is incompletely understood. Current concepts view migraine as an inherited brain disorder intermittently leading to neuronal dysfunctions of various parts of the nervous system (1, 3). A “neurogenic inflammation” appears to be a key mechanism in activating the trigeminal system and causing the headache (4).

Tumor necrosis factor-alpha (TNF-alpha) is an important inflammatory cytokine and modulator of immune responses, which also appears to play a role in migraine. For example, studies have reported changes in serum (5–7) and urine concentrations (8) of TNF-alpha as well as altered serum concentrations of the soluble TNF-alpha receptor (9) among migraineurs. A link between TNF-alpha and migraine is further plausible, since TNF-alpha can stimulate transcription of calcitonin gene-related peptide (CGRP), which plays a pivotal role in migraine pathophysiology (10).

The genes coding for TNF-alpha and the closely related TNF-beta (lymphotoxin-alpha, LT-alpha) are located in the class III gene cluster of the major histocompatibility complex on chromosome 6 (11). Variants in these genes have been shown to modulate cytokine levels of TNF-alpha and TNF-beta (12, 13); hence, various polymorphisms in the *TNF-alpha* and *TNF-beta* genes have been investigated among migraineurs. The most frequently studied variants are the -308G>A polymorphism in the promoter region of the *TNF-alpha* gene (rs1800629) and the 252A>G polymorphism in intron 1 of the *TNF-beta* gene (rs909253). However, results are conflicting with some studies suggesting associations with migraine for the *TNF-alpha* -308G>A (14–18) and the *TNF-beta 252A>G* polymorphism (19, 20), while others do not (14, 17, 19–23).

We sought to summarize the current evidence on the association between polymorphisms in the *TNF-alpha/TNF-beta* gene cluster and migraine including migraine with aura (MA) and migraine without aura (MO) by systematically reviewing the literature and performing a meta-analysis.

Methods

Selection of studies

We followed the guidelines for systematic reviews of genetic association studies (24). Two investigators (M.S., P.M.R.) independently searched MEDLINE, EMBASE, and Science Citation Index from inception to January 2011 combining text words and MESH terms, where appropriate, for tumor necrosis factor and lymphotoxin (“tumor necrosis factor” or “tumor necrosis factor-alpha” or “tumor necrosis factor-beta” or lymphotoxin or “lymphotoxin-alpha” or “lymphotoxin-beta” or TNF or LTA) with terms for genetic variations (“gene” or “polymorphism” or “genetic variation”) and terms for headache and migraine (“headache” or “headache disorders” or “migraine” or “migraine disorders”). The search terms were combined with the “explode” feature where applicable. We considered all publications without language restrictions. In addition, we manually searched the reference list of all primary articles and review articles.

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A priori, we defined the following criteria for inclusion:

1. Studies must have a cross-sectional, case-control or cohort design.
2. Authors must investigate patients with migraine, diagnosed according to the criteria of the International Headache Society (IHS) (25, 26) or according to modified IHS criteria and healthy control subjects.
3. Authors must investigate genetic variants located in the *TNF-alpha* and/or *TNF-beta* gene.
4. Information on genotype frequencies for the polymorphisms investigated among migraineurs and non-migraineneurs must be presented in the publication or be obtainable from the authors upon request.
5. In publications with overlapping cases and/or controls the largest study with usable genetic data was included.

In a first step, two investigators (M.S., P.M.R.) by consensus identified all studies not meeting any of the pre-specified criteria by screening the title and abstracts. These studies were excluded. In a second step, the same investigators evaluated the full-paper publications of the remaining studies. Studies were excluded if they did not meet all criteria.

Data extraction and contact with authors

Two investigators (M.S., P.M.R.) independently extracted data from the published studies and entered them in a customized database. Disagreements were resolved by consensus. The extracted data included authors' names and title of study, year of publication, country of origin, setting (clinic vs. population), study design, genotyping method, migraine status (migraine, MA, MO), age range and gender of study individuals, study size, allele and genotype frequencies, and additional potentially relevant information. We sought to collect genetic information for all migraineurs and migraineurs with and without aura separately as well as for the whole study population and females and males separately. If not presented in the paper, allele and genotype frequencies were calculated where possible. For studies, which did not allow extraction of all relevant information including genotype and allele frequencies, we contacted the authors to obtain the missing information. We wrote e-mails to the corresponding authors explaining our project and asking them to provide the additional data. Authors not responding within two weeks were sent up to four reminder e-mails.

Statistical analysis

We first used logistic regression to calculate odds ratios (ORs) and 95% confidence intervals (CIs) for the association between genetic polymorphisms and migraine assuming additive, dominant, and recessive genetic models for each study. The additive model assumes that the risk for migraine among carriers of the heterozygous genotype is half way between carriers of the homozygous genotypes. While the dominant model assumes that carriers of the heterozygous and homozygous variant genotypes have the same risk of developing migraine compared with carriers of the homozygous wild-type genotype, a recessive model assumes that carrying the homozygous variant genotype is necessary to alter the risk for migraine compared to carriers of the heterozygous and homozygous wild-type genotype. We also determined Hardy-Weinberg Equilibrium (HWE) for each study. We investigated (overall) migraine, MA, and MO. We further performed analyses stratified by gender and country of origin (countries with European populations vs. countries with Asian populations vs. countries with populations of heterogeneous ethnic background [Turkey and Iran]), where applicable.

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We weighted the log of the ORs by the inverse of their variance to obtain pooled estimates. We ran random-effects models, which include assumptions about the variability between studies. We performed the DerSimonian and Laird Q test for heterogeneity and also calculated the I^2 statistic for each analysis (27). We used Galbraith plots to visually examine the impact of individual studies on the overall homogeneity test statistic. We further used meta-regression to investigate whether gender, country of study origin, or clinical phenotype (migraine with aura, migraine without aura) significantly impact the pooled results. We evaluated potential small study effects such as publication bias statistically with the methods described by Begg and Mazumdar (28) and Egger (29).

All analyses were performed using SAS version 9.1 (SAS Institute Inc, Cary, NC) and STATA 10.1 (Stata, College Station, Texas, USA).

Since we only utilized data from previously published studies, we did not obtain approval of an ethics committee or written informed consent.

Results

Figure 1 summarizes the process of identifying eligible studies. After title and abstract evaluation we were left with 11 records (14–23, 30). We identified one additional publication by manually searching the reference lists of the records (31). Of the twelve records, we excluded two: one abstract (30), because detailed results were later published in full (19) and one paper (31), because the study population overlapped with that of a record already included for our analysis (20). We were finally left with ten studies (14–23).

Contact with authors

In eight papers genotype and allele frequencies were only reported for all participants and/or for overall migraine, but not stratified by gender and/or aura (16–23). After contacting the authors we could obtain complete data for five studies (18–22); however, not for two studies (16, 23). We also included genotype and allele frequencies from our previous study (17).

Study characteristics

Table 1a summarizes the characteristics of the studies included according to the polymorphisms investigated. Ten studies have investigated the *TNF-alpha* -308G>A (rs1800629) (14–23), six the *TNF-beta* 252A>G (rs909253) (14, 17, 19–22), and two the *TNF-alpha* -238G>A (rs361525) and *TNF-alpha* -376G>A (rs1800750) polymorphisms (17, 22). Additional polymorphisms in the *TNF-alpha* and *TNF-beta* genes have been investigated in single studies (Table 1b). All studies used standard polymerase chain reaction genotyping methods.

Eight studies investigated mixed female and male populations (14–16, 18–20, 22, 23), while two study populations consisted only of females (17, 21). Migraineurs in six studies consisted of migraineurs with aura and without aura (14, 16, 17, 20, 21, 23), while four studies only investigated MO (15, 18, 19, 22). One study had a cohort design (17), the remainder were case-control studies (14–16, 18–23). One study was performed among children/adolescents (22), the other studies among adults (14–21, 23). Five studies were performed in European populations (16, 17, 19, 20, 22), two in Turkish populations (18, 23), two in Asian populations (14, 21), and one in a Iranian population (15).

The allele and genotype frequencies for the investigated polymorphisms among migraineurs and controls as well as the p-value for the Hardy-Weinberg Equilibrium (HWE) are listed in Table 2.

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Table 3 summarizes for each of the studies the ORs (95% CI) for the association between the polymorphisms and migraine.

Tables 4 and 5 summarize the pooled effect estimates, measures of heterogeneity, and tests for small study effects for the *TNF-alpha* -308G>A and *TNF-beta* 252A>G polymorphisms.

Association between the TNF-alpha -308G>A (rs1800629) polymorphism and migraine

Genotype distributions in control and migraine populations were in HWE in all but one study (Table 2). Five studies suggested an increased risk of migraine assuming additive and dominant models (14, 15, 17, 18, 20) (Table 3). In contrast, one study suggested a reduced risk (16). The effects were stronger among females than males. The remaining four studies did not suggest an association between any of the genotypes and migraine (19, 21–23). Effect estimates for some of the associations assuming a recessive model could not be calculated, due to missing observations for the AA genotype in some studies.

Our overall pooled analyses do not suggest an association between the *TNF-alpha* -308G>A polymorphism and migraine (Figure 2, Table 4). The pooled OR (95% CI) from an additive model for migraine was 1.16 (0.80–1.68). Effect estimates were similar when assuming a dominant model and lower in recessive models. There was high heterogeneity among all participants (additive model: I^2=88.5%). Since meta-regression indicated that country of study origin had a significant modifying effect on the overall pooled OR (European populations: reference; Asian populations: p=0.18; populations of heterogeneous ethnic background: p=0.02) we performed pooled analyses among studies in these populations separately. The effect estimates were lower among Europeans than among Asians, a pattern most pronounced among males. Analyses among populations of heterogeneous descent suggested a significantly increased risk for migraine assuming an additive model (pooled OR=2.32; 95% CI 1.18–4.56), which was driven by a four-fold increased risk among females (pooled OR=4.02; 95% CI 2.71–5.94).

Analyses stratified by clinical phenotype also do not suggest an association between the *TNF-alpha* -308G>A polymorphism and MA (all participants, additive model: pooled OR=1.20; 95% CI 0.92–1.55) or MO (all participants, additive model: pooled OR=1.11; 95% CI 0.74–1.67) (Table 4). This agrees with results from meta-regression indicating that clinical phenotype is not a significant source of heterogeneity (all p>0.23). While heterogeneity among studies investigating MO was high (all participants, additive model: I^2=88.6%), it was low among those investigating MA (all participants, additive model: I^2=28.3%). Pooled results of the two studies among Asian populations suggested an increased risk assuming additive and dominant models, specifically for MA and were most pronounced among females assuming a dominant model (pooled OR=2.06; 95% CI 1.19–3.58).

For migraine analyses among males suggested potential small study effects (additive model: Begg's test: p=0.04; Egger's test: p=0.002). When considering gender stratified results meta-regression did not indicate that gender significantly impacts pooled results for migraine, MA or MO in additive or dominant models (all p-values ≥0.34). Meta-regression among effect estimates from recessive models could not be performed.

Association between the *TNF-beta* 252A>G (rs909253) polymorphism and migraine

Genotype distributions in all control and migraine populations were in HWE (Table 2). One study suggested a decreased risk of migraine assuming additive and dominant models for MO (20) (Table 3). In contrast, effect estimates suggested an increased risk for MA among females. Effect estimates for some of the associations could not be calculated due to missing observations for some of the genotypes. Two studies suggested an increased risk for

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migraine (19, 21). Three studies did not suggest an altered risk for migraine for any of the genotypes (14, 17, 22).

Our overall pooled analyses do not suggest an association between the *TNF-beta* 252A>G polymorphism and migraine (Figure 3, Table 5). The pooled OR (95% CI) from an additive model for migraine was 1.02 (0.87–1.21). The effect estimates were similar for females and males and results did not change in dominant or recessive models. There was moderate heterogeneity among all participants (additive model: I^2=66.0%), which only appeared among males (additive model: I^2=60.8%), but not females (additive model: I^2=0.0%).

Study results stratified by clinical phenotype also do not suggest an association between the *TNF-beta* 252A>G polymorphism and MA (all participants, additive model: pooled OR=1.03; 95% CI 0.95–1.12) or MO (all participants, additive model: pooled OR=1.00; 95% CI 0.83–1.22) (Table 5). The results were similar in dominant and recessive models as well as for females and males. This agrees with results from meta-regression on clinical phenotype (all p>0.39). Studies among participants with MA did not suggest heterogeneity (all participants, additive model: I^2=0.0%). In contrast, for MO there was moderate heterogeneity (all participants, additive model: I^2=69.3%), which only appeared for males (additive model: I^2=56.8%), but not females (additive model: I^2=0.0%).

For MA there was indication for a small study effect among females assuming a recessive model (Begg's test: p=0.04; Egger's test: p=0.005). Meta-regression did not indicate that country of study origin significantly impacts the pooled results for migraine, MA, or MO (all p-values>0.10). In addition, when considering gender stratified study results meta-regression did not indicate that gender significantly impacts the pooled results for migraine or MO (all p-values≥0.68). Meta-regression among effect estimates from gender stratified analyses could not be performed.

Association between the *TNF-alpha* -238G>A (rs361525) polymorphism and migraine

The genotype distribution among controls deviated from HWE in one study (p=0.006) (17) (Table 2). In the second study, the Hardy-Weinberg principle was given among migraineurs and controls (22). The minor allele frequency (MAF) in both studies was low (≤5.1%).

Results from both studies do not suggest a statistically significant association between the *TNF-alpha* -238G>A polymorphism and migraine (Table 3).

Pooled results did not suggest an association for migraine (all participants, additive model: pooled OR=0.97; 95% CI 0.88–1.08) or MO (all participants, additive model: pooled OR=0.91; 95% CI 0.66–1.26). There was no indication for heterogeneity among the studies (additive model, migraine: I^2=0.0%; MO: I^2=14.0%). Only one study investigated associations in MA (17), suggesting no association (Table 3).

Association between the *TNF-alpha* -376G>A (rs1800750) polymorphism and migraine

In one study HWE and effect estimates could not be calculated (22) (Tables 2 and 3). In the second study the genotype distribution among controls was not in HWE (p=0.002) and the MAF was <2% (17). Results suggested an increased risk for all three models. Pooled analyses could not be performed.

Sensitivity analyses

Galbraith plots—For some of our analyses, Galbraith plots identified individual studies as important sources of heterogeneity. Hence, we performed sensitivity analyses by excluding studies that fell outside the margin set by the z score ±2 standard deviations.

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With regard to the *TNF-alpha* -308G>A polymorphism Galbraith plots identified studies introducing heterogeneity for migraine, MO, and among females only for MA. After excluding these studies, associations remained statistically insignificant. For example, among all participants and assuming an additive model the pooled OR (95% CI) was 1.04 (0.94–1.15) for migraine and 0.98 (0.90–1.06) for MO after excluding three studies (15, 16, 18) and 1.15 (1.04–1.27) for females with MA after excluding one study (14).

With regard to the *TNF-beta* 252A>G polymorphism Galbraith plots identified studies introducing heterogeneity for migraine and MO. Excluding these studies did not change the associations. For example, among all participants and assuming an additive model the pooled OR (95% CI) for migraine was 1.02 (0.96–1.08) and for MO 1.02 (0.94–1.10) after excluding two studies (19, 20).

Excluding other studies—We further investigated if study design and age of the study population impacts the pooled results by excluding the cohort study (17) and the study among children/adolescents (22), respectively. For the *TNF-alpha* -308G>A and the *TNF-beta* 252A>G polymorphisms this did not change the associations with migraine, MA, or MO for any of the models assumed (data not shown). Further, excluding the study where genotype distribution of the *TNF-alpha* -308G>A polymorphism deviated from HWE (15) did not change the results (e.g. additive model, all participants: OR=1.02, 95% CI 0.72–1.44).

Discussion

The overall results from this meta-analysis do not indicate an association between any of the investigated polymorphisms and migraine, which did not change in sensitivity analyses. However, among studies investigating the *TNF-alpha* -308G>A polymorphism the association differs by country of origin and clinical phenotype has a modifying effect. Compared to studies among European and Asian populations those among populations of heterogeneous ethnic background (Turkey and Iran) suggested an increased risk for migraine and MO. The effect was stronger among females than males translating into a four-fold increased risk. In addition, results for MA suggested a two-fold increased risk among Asian populations which may be stronger in females than males. The results from these subgroup analyses, however, need to be treated with caution due to potential population stratification and small study numbers.

An inflammatory process is important in the pathophysiology of migraine and has been named “neurogenic inflammation” (4). TNF-alpha is an inflammatory cytokine with a plausible link to migraine. First, an increased release of TNF-alpha has been reported in MO (5, 6) and TNF-alpha plasma levels are higher during than between migraine attacks (7). Further, lower serum concentrations of the soluble receptor for TNF-alpha have been reported in migraineurs compared to controls, while the serum concentrations of TNF-alpha did not differ (9). In contrast, among women with menstrual migraine urine secretion of TNF-alpha appears to be markedly decreased (8). Second, TNF-alpha was shown to stimulate CGRP gene transcription and CGRP plays a key role in the pathophysiology of migraine (10). Third, TNF-alpha is crucial in the development of inflammatory hyperalgesia (32), a phenomenon related to allodynia experienced by some migraine patients.

Levels of TNF-alpha and the closely related TNF-beta are under genetic control. The *TNF-alpha* -308G>A polymorphism modulates transcriptional activity of the TNF gene (12) and *TNF-alpha* and *TNF-beta* polymorphisms have been shown to determine secretion of TNF-alpha and TNF-beta (13). Hence, studies have investigated the role of gene polymorphisms in the *TNF-alpha* and the *TNF-beta* gene in migraine (Table 1). However, despite biological

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plausibility, study results were conflicting and our meta-analysis does not support an overall association between any of the investigated gene variants and migraine including its subtypes.

There are two possible explanations for the observed overall lack of associations. Either, there may be truly no association and in some studies positive results may have occurred due to chance or certain study characteristics or the pattern of association may be more complex involving additional factors. In this context the following considerations need to be discussed.

First, pooling study results on the *TNF-alpha* -308G>A and *TNF-beta* 252A>G polymorphisms indicated remaining moderate to high heterogeneity for migraine and MO which may be due to differences between subgroups. This is plausible given that migraine susceptibility differs for example by gender (33) and ethnicity (34). For the *TNF-alpha* -308G>A variant analyses stratified by country of study origin eliminate part of that heterogeneity. We observed that Asian populations are at increased risk for MA, the effects being stronger among females than males. We also found that populations with a heterogeneous ethnic background have an increased risk for migraine and MO compared to European and Asian populations. We cannot exclude that this is a spurious finding due to population stratification. Population stratification denotes a systematic difference in allele frequencies between subpopulations in a population for example due to different ancestry, nonrandom mating, and physical separation. If cases and controls stem from different subpopulations and a marker under investigation has different allele frequencies in these subpopulations, an association (or lack of association) may occur reflecting the ancestral difference rather than the disease susceptibility.

Second, these differential associations were based on small numbers of studies. While we made the effort to gather the maximum amount of information including data stratified by gender and clinical phenotype, additional information was unavailable from two studies for the *TNF-alpha* -308G>A polymorphism (16, 23). This information would have been valuable in sketching more clearly associations with migraine among populations of different descent.

Third, although all studies used strict or modified IHS classification criteria (25, 26), there is the potential for migraine as well as MA and MO to be misclassified given its biologically heterogeneity and wide clinical spectrum (35).

Fourth, the investigated gene variants may be associated with certain migraine traits or measures of migraine severity like attack frequency rather than IHS defined migraine status.

Fifth, we have included all available genetic association studies and not prematurely excluded any study based on HWE. This approach increases the total sample size and thus the power to detect a potential association and also allows for greater flexibility at the analysis level by performing sensitivity analyses. This is in keeping with recommendations for performing meta-analyses (36). Our analyses indicate that excluding studies where HWE among controls is deviated does not change the results.

Sixth, the available studies varied in sample size. In particular one cohort study (17) was much larger than the other case-control studies. While a very large study may dominate the overall pooled results in a meta-analysis, there was no such indication from our analyses. Results from sensitivity analyses excluding the cohort study were very similar to the overall results for the *TNF-alpha* -308G>A and *TNF-beta* 252A>G polymorphisms.

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Seventh, almost 200 known single nucleotide polymorphisms (SNPs) have been reported in the *TNF-alpha* and *TNF-beta* genes (37, 38), which may affect gene transcription and TNF level. Some SNPs may have a low MAF as seen in some of the included studies (Table 2), obviating reliable analyses; however, such variants are unlikely to strongly influence a common and complex disorder like migraine. While there are single reports suggesting an association between other SNPs with migraine, no follow-up studies are available yet (Table 1b). Many of the gene variants, however, including gene interactions, have not been investigated yet.

Eighth, TNF-alpha's and TNF-beta's role in migraine is likely not just determined by their levels, but also by their functional effect at the receptor level, which is likewise under genetic control and unaccounted for in all studies.

Finally, many neurotransmitters like CGRP, serotonin, dopamine, orexin, and glutamate are important for migraine pathophysiology (39). While a functional interaction between TNF-alpha and CGRP has been shown (10), many more interactions between inflammatory markers and neurotransmitters are likely involved in migraine.

Additional targeted research is warranted to further clarify a potential role of *TNF-alpha* and *TNF-beta* gene variants in migraine. An important next step is performing genome-wide association studies (GWAS) in large populations. The first one has recently been published implicating the glutamate pathway in a population primarily suffering from MA (40). While other GWAS are under way, these are unlikely to answer questions raised by our meta-analysis namely a possible genetic effect among non-European populations, since all are performed in populations of European descent. Hence, additional large studies such as GWAS need to be performed in other populations that also account for potential population stratification, in order to discern potential genetic differences in migraine susceptibility.

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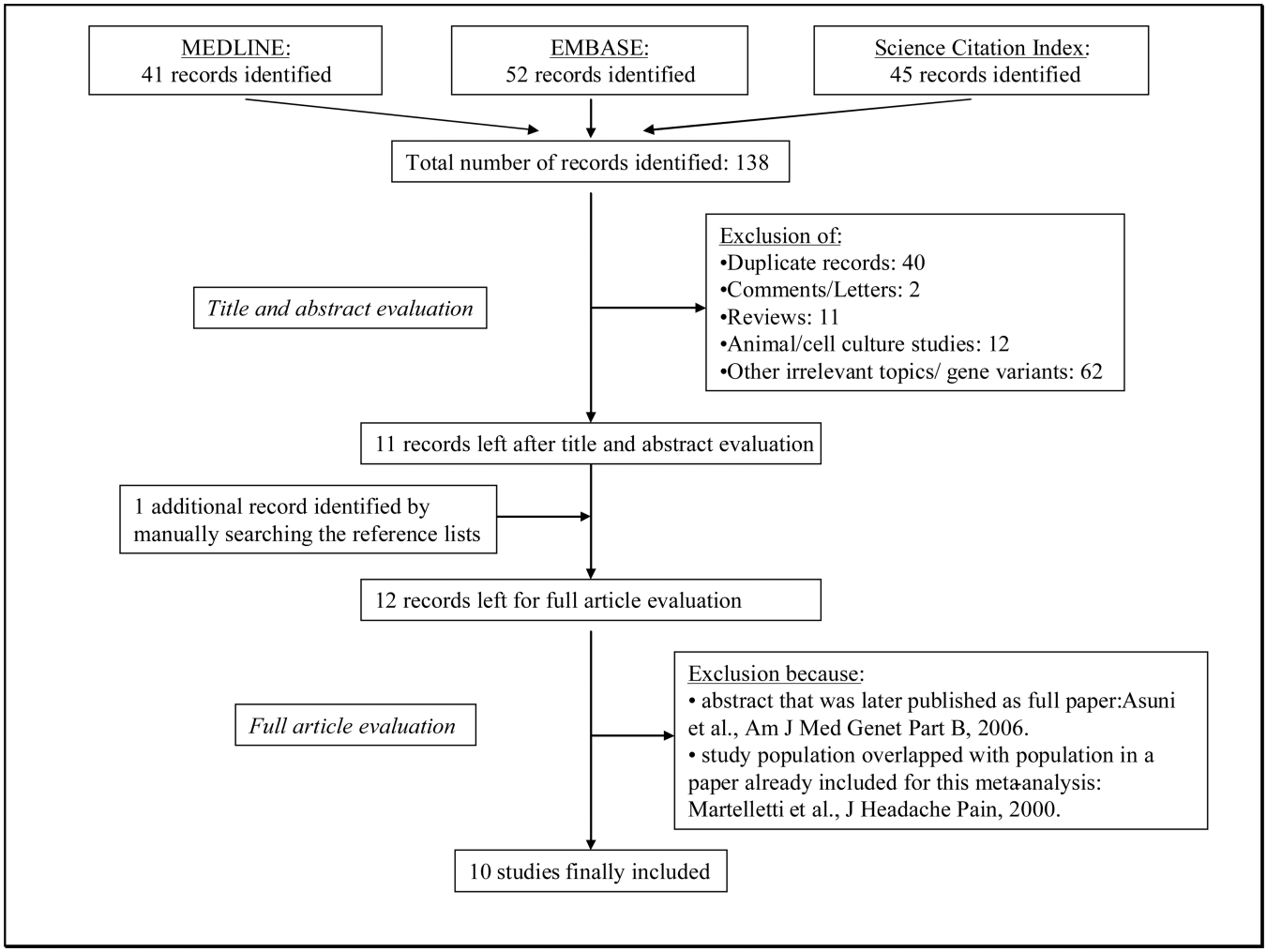

Figure 1.
Process of identifying studies

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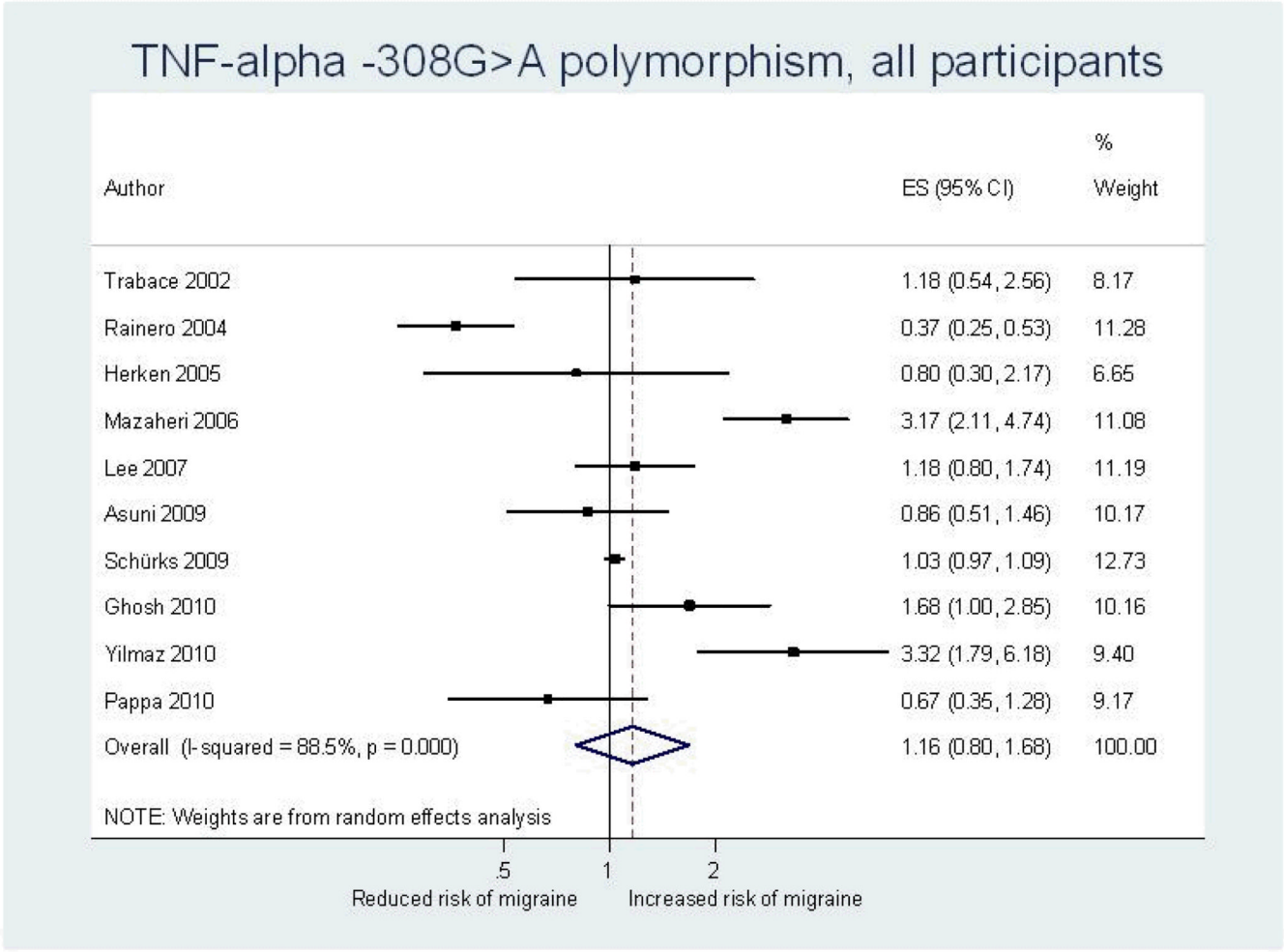

Figure 2.
Odds ratios for the association between the *TNF-alpha* -308G>A polymorphism and migraine assuming an additive model from individual studies and from the pooled analysis. ES=estimate (indicates odds ratio). CI=confidence interval.

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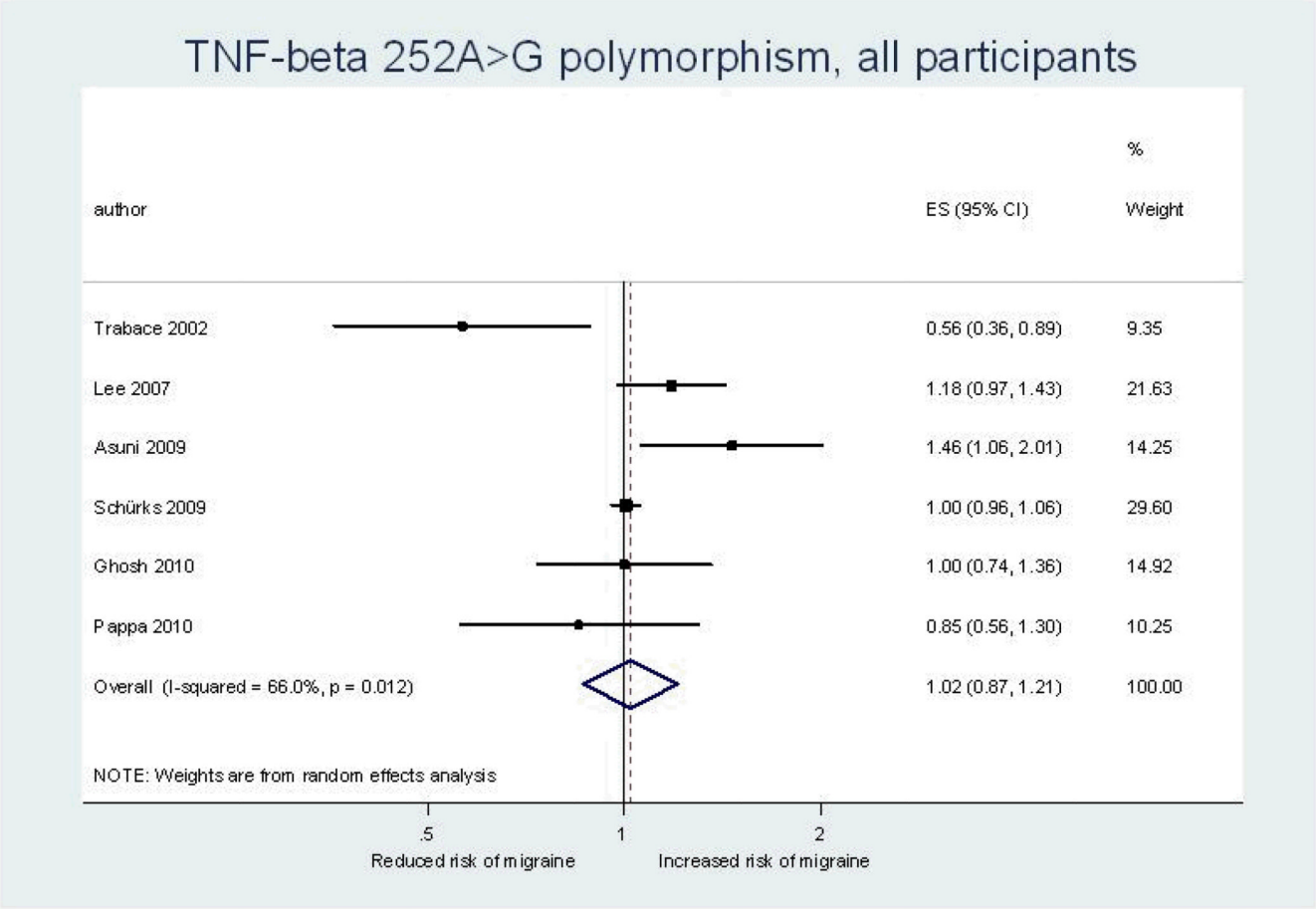

Figure 3.
Odds ratios for the association between the *TNF- beta* 252A>G polymorphism and migraine assuming an additive model from individual studies and from the pooled analysis. ES=estimate (indicates odds ratio). CI=confidence interval.

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Table 1

Characteristics of the included studies according to the polymorphisms investigated

a) Polymorphisms that were investigated in at least 2 studies

***TNF-alpha* -308G>A (rs1800629) polymorphism**								
				Study size with genotype information				
Author	**Country**	**Setting**	**Participants**	**Controls**	**Migraine**	**MA**	**MO**	**Comment**
Trabace 2002 (20)	Italy	clinic	all	**101**	**79**	**32**	**47**	Other gene variants investigated: *TNF-beta* 252A>G (rs909253).
			females	45	62	27	35	
			males	56	17	5	12	
Rainero 2004 (16)	Italy	clinic	all	**306**	**299**	**38**	**261**	
			females	231	215	NA	NA	
			males	75	84	NA	NA	
Herken 2005 (23)	Turkey	clinic	all	**60**	**60**	**40**	**20**	Cases and controls are predominantly male.
			females	8	11	NA	NA	
			males	52	49	NA	NA	
Mazaheri 2006 (15)	Iran	clinic	all	**183**	**221**	----	**221**	
			females	123	196	----	196	
			males	60	25	----	25	
Lee 2007 (21)	Korea	clinic	all/females	**382**	**439**	**65**	**327**	Other gene variants investigated: total of 15 SNPs in the *TNF-alpha/TNF-beta* region.
Asuni 2009 (19)	Italy (Sardinia)	clinic	all	**278**	**299**	----	**299**	Other gene variants investigated: *TNF-beta* 252A>G (rs909253).
			females	144	261	----	261	
			males	134	38	----	38	
Schürks 2009 (17)	US	population	all/females	**20,425**	**4577**	**1275**	**1951**	Other gene variants investigated: *TNF-beta* 252A>G (rs909253), rs1041981; *TNF-alpha* -238G>A (rs361525), -376G>A (rs1800750), 244G>A (rs673).
Ghosh 2010 (14)	India	clinic	all	**216**	**216**	**84**	**132**	Other gene variants investigated: *TNF-beta* 252A>G (rs909253).
			females	152	152	63	89	

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a) Polymorphisms that were investigated in at least 2 studies

TNF-alpha -308G>A (rs1800629) polymorphism								
				Study size with genotype information				
Author	**Country**	**Setting**	**Participants**	**Controls**	**Migraine**	**MA**	**MO**	**Comment**
			males	64	64	21	43	
Yilmaz 2010 (18)	Turkey	clinic	all	**96**	**67**	----	**67**	Other gene variants investigated: *IL-1RA* VNTR, *IL-1beta* 3953C>T (rs1143634), *IL-1alpha* 4845G>T (rs17561).
			females	83	57	----	57	
			males	13	10	----	10	
Pappa 2010 (22)	Northern Greece	clinic	all	**178**	**103**	----	**103**	Other gene variants investigated: *TNF-alpha* -238G>A (rs361525), *TNF-alpha* -376A>G (rs1800750), *TNF-alpha* -857C>T (rs1799724), *TNF-alpha* -1031T>C (rs1799964), *TNF-beta* 252A>G (rs909253).
			females	60	57	----	57	
			males	118	46	----	46	
Total number of subjects				**22,227**	**6360**	**1534**	**3428**	
TNF-beta 252A>G (rs909253) polymorphism								
				Study size with genotype information				
Author	**Country**	**Setting**	**Participants**	**Controls**	**Migraine**	**MA**	**MO**	**Comment**
Trabace 2002 (20)	Italy	clinic	all	**101**	**77**	**30**	**47**	Other gene variants investigated: *TNF-alpha* -308G>A (rs1800629).
			females	43	60	25	35	
			males	58	17	5	12	
Lee 2007 (21)	Korea	clinic	all/females	**382**	**439**	**65**	**327**	Other gene variants investigated: total of 15 SNPs in the *TNF-alpha/TNF-beta* region.
Asuni 2009 (19)	Italy (Sardinia)	clinic	all	**278**	**299**	----	**299**	Other gene variants investigated: *TNF-alpha* -308G>A (rs1800629).
			females	144	261	----	261	
			males	134	38	----	38	
Schürks 2009 (17)	US	population	all/females	**19,269**	**4332**	**1213**	**1824**	Other gene variants investigated: *TNF-beta* rs1041981; *TNF-alpha* -238G>A (rs361525), -308G>A (rs1800629), -376G>A (rs1800750), 244G>A (rs673).

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a) Polymorphisms that were investigated in at least 2 studies

***TNF-alpha* -308G>A (rs1800629) polymorphism**								
				Study size with genotype information				
Author	**Country**	**Setting**	**Participants**	**Controls**	**Migraine**	**MA**	**MO**	**Comment**
Ghosh 2010 (14)	India	clinic	all	**216**	**216**	**84**	**132**	Other gene variants investigated: *TNF-beta* 252A>G (rs909253).
			females	152	152	63	89	
			males	64	64	21	43	
Pappa 2010 (22)	Northern Greece	clinic	all	**178**	**103**	----	**103**	Other gene variants investigated: *TNF-alpha* -238G>A (rs361525), *TNF-alpha* -376A>G (rs1800750), *TNF-alpha* -857C>T (rs1799724), *TNF-alpha* -1031T>C (rs1799964), *TNF-beta* 252A>G (rs909253).
			females	60	57	----	57	
			males	118	46	----	46	
Total number of subjects				**20,424**	**5466**	**1392**	**2732**	
***TNF-alpha* -238G>A (rs361525) and *TNF-alpha* -376G>A (rs1800750) polymorphisms**								
				Study size with genotype information				
Author	**Country**	**Setting**	**Participants**	**Controls**	**Migraine**	**MA**	**MO**	**Comment**
Schürks 2009 (17)	US	population	all/females	**20,425**	**4577**	**1275**	**1951**	Other gene variants investigated: *TNF-beta* rs1041981; *TNF-alpha* -238G>A (rs361525), -376G>A (rs1800750), 244G>A (rs673)
Pappa 2010 (22)	Northern Greece	clinic	all	**178**	**103**	----	**103**	Other gene variants investigated: *TNF-alpha* -308G>A (rs1800629), *TNF-alpha* -857C>T (rs1799724), *TNF alpha* -1031T>C (rs1799964), *TNF-beta* 252A>G (rs909253).
			females	60	57	----	57	
			males	118	46	----	46	
Total number of subjects				**20,603**	**4680**	**1275**	**2054**	

b) Polymorphisms that were investigated in single studies

Author	**Country**	**Setting**	**Gene**	**Polymorphism**	**Association**
Lee 2007 (21)	Korea	clinic	*TNF-alpha/ TNF-beta*	rs13192469; rs2516390; rs928815; rs2844483; rs2009658; rs915654; rs2071590; rs2239704; rs3889157; rs1800630; rs3093664; rs769177	**No**
			TNF-beta	rs2844482	**Yes**

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b) Polymorphisms that were investigated in single studies

Author	Country	Setting	Gene	Polymorphism	Association
Schürks 2009 (17)	US	population	*TNF-alpha*	rs673	**Yes**
			TNF-beta	rs1041981	**No**
Pappa 2010 (22)	Northern Greece	clinic	*TNF-alpha*	rs1799724; rs1799964	**No**

TNF: tumor necrosis factor; *IL-1*: Interleukin 1; MA: migraine with aura; MO: migraine without aura; NA: not available.

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Table 2

Allele and genotype frequencies as well as Hardy-Weinberg Equilibrium according to the investigated polymorphisms

***TNF-alpha* -308G>A (rs1800629) polymorphism**									
					Allele frequencies, n (%)		**Genotype frequencies, n (%)**		
Author	**Participants**	**Disease status**	**Study size**	**HWE**	**G**	**A**	**GG**	**GA**	**AA**
Trabace 2002 (20)	all	controls	101	0.052	189 (93.6)	13 (6.4)	90 (89.1)	9 (8.9)	2 (2.0)
		migraine	79	1.000	146 (92.4)	12 (7.6)	67 (84.8)	12 (15.2)	0 (0.0)
		MA	32	1.000	57 (89.1)	7 (10.9)	25 (78.1)	7 (21.9)	0 (0.0)
		MO	47	1.000	89 (94.7)	5 (5.3)	42 (89.4)	5 (10.6)	0 (0.0)
	females	controls	45	0.116	85 (94.4)	5 (5.6)	41 (91.1)	3 (6.7)	1 (2.2)
		migraine	62	1.000	114 (91.9)	10 (8.1)	52 (83.9)	10 (16.1)	0 (0.0)
		MA	27	1.000	48 (88.9)	6 (11.1)	21 (77.8)	6 (22.2)	0 (0.0)
		MO	35	1.000	66 (94.3)	4 (5.7)	31 (88.6)	4 (11.4)	0 (0.0)
	males	controls	56	0.234	104 (92.9)	8 (7.1)	49 (87.5)	6 (10.7)	1 (1.8)
		migraine	17	1.000	32 (94.1)	2 (5.9)	15 (88.2)	2 (11.8)	0 (0.0)
		MA	5	1.000	9 (90.0)	1 (10.0)	4 (80.0)	1 (20.0)	0 (0.0)
		MO	12	1.000	23 (95.8)	1 (4.2)	11 (91.7)	1 (8.3)	0 (0.0)
Rainero 2004 (16)	all	controls	306	0.693	502 (82.0)	110 (18.0)	207 (67.6)	88 (28.8)	11 (3.6)
		migraine	299	1.000	554 (92.6)	44 (7.4)	256 (85.6)	42 (14.0)	1 (0.3)
		MA	38	1.000	66 (86.8)	10 (13.2)	28 (73.7)	10 (26.3)	0 (0.0)
		MO	261	1.000	488 (93.5)	34 (6.5)	228 (87.4)	32 (12.3)	1 (0.4)
	females	controls	231	1.000	382 (82.7)	80 (17.3)	158 (68.4)	66 (28.6)	7 (3.0)
		migraine	215	0.611	401 (93.3)	29 (6.7)	186 (86.5)	29 (13.5)	0 (0.0)
	males	controls	75	0.475	120 (80.0)	30 (20.0)	49 (65.3)	22 (29.3)	4 (5.3)
		migraine	84	0.504	153 (91.1)	15 (8.9)	70 (83.3)	13 (15.5)	1 (1.2)
Herken 2005 (23)	all	controls	62	1.000	115 (92.7)	9 (7.3)	53 (85.5)	9 (14.5)	0 (0.0)
		migraine	60	0.170	113 (94.2)	7 (5.8)	54 (90.0)	5 (8.3)	1 (1.7)

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TNF-alpha -308G>A (rs1800629) polymorphism									
					Allele frequencies, n (%)		Genotype frequencies, n (%)		
Author	**Participants**	**Disease status**	**Study size**	**HWE**	**G**	**A**	**GG**	**GA**	**AA**
		MA	40	1.000	76 (95.0)	4 (5.0)	36 (90.0)	4 (10.0)	0 (0.0)
		MO	20	0.079	37 (92.5)	3 (7.5)	18 (90.0)	1 (5.0)	1 (5.0)
Mazaheri 2006 (15)	all	controls	183	0.0004	274 (74.9)	92 (25.1)	94 (51.4)	86 (47)	3 (1.6)
		MO	221	<0.0001	265 (60)	177 (40)	51 (23.1)	163 (73.8)	7 (3.2)
	females	controls	123	0.001	191 (77.6)	55 (22.4)	68 (55.3)	55 (44.7)	0 (0.0)
		MO	196	<0.0001	233 (59.4)	159 (40.6)	44 (22.4)	145 (74)	7 (3.6)
	males	controls	60	0.141	83 (69.2)	37 (30.8)	26 (43.3)	31 (51.7)	3 (5.0)
		MO	25	0.007	32 (64.0)	18 (36.0)	7 (28.0)	18 (72.0)	0 (0.0)
Lee 2007 (21)	all/females	controls	382	0.158	717 (93.8)	47 (6.2)	338 (88.5)	41 (10.7)	3 (0.8)
		migraine	439	0.716	815 (92.8)	63 (7.2)	377 (85.9)	61 (13.9)	1 (0.2)
		MA	65	1.000	119 (91.5)	11 (8.5)	54 (83.1)	11 (16.9)	0 (0.0)
		MO	327	1.000	608 (93.0)	46 (7.0)	282 (86.2)	44 (13.5)	1 (0.3)
Asuni 2009 (19)	all	controls	278	0.560	526 (94.6)	30 (5.4)	249 (89.6)	28 (10.1)	1 (0.4)
		MO	299	0.476	570 (95.3)	28 (4.7)	272 (91.0)	26 (8.7)	1 (0.3)
	females	controls	144	1.000	273 (94.8)	15 (5.2)	129 (89.6)	15 (10.4)	0 (0.0)
		MO	261	0.452	497 (95.2)	25 (4.8)	237 (90.8)	23 (8.8)	1 (0.4)
	males	controls	134	0.333	253 (94.4)	15 (5.6)	120 (89.6)	13 (9.7)	1 (0.7)
		MO	38	1.000	73 (96.1)	3 (3.9)	35 (92.1)	3 (7.9)	0 (0.0)
Schürks 2009 (17)	all/females	controls	20,425	0.559	33,771 (82.7)	7079 (17.3)	13947 (68.3)	5877 (28.8)	601 (2.9)
		migraine	4577	0.094	7531 (82.3)	1623 (17.7)	3081 (67.3)	1369 (29.9)	127 (2.8)
		MA	1275	0.420	2060 (80.8)	490 (19.2)	827 (64.9)	406 (31.8)	42 (3.3)
		MO	1951	0.868	3240 (83.0)	662 (17.0)	1346 (69.0)	548 (28.1)	57 (2.9)
Ghosh 2010 (14)	all	controls	216	0.557	406 (94.0)	26 (6.0)	191 (88.4)	24 (11.1)	1 (0.5)
		migraine	216	0.235	391 (90.5)	41 (9.5)	175 (81.0)	41 (19.0)	0 (0.0)

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TNF-alpha -308G>A (rs1800629) polymorphism									
					Allele frequencies, n (%)		Genotype frequencies, n (%)		
Author	**Participants**	**Disease status**	**Study size**	**HWE**	**G**	**A**	**GG**	**GA**	**AA**
		MA	84	0.595	149 (88.7)	19 (11.3)	65 (77.4)	19 (22.6)	0 (0.0)
		MO	132	0.604	242 (91.7)	22 (8.3)	110 (83.3)	22 (16.7)	0 (0.0)
	females	controls	152	0.446	285 (93.8)	19 (6.3)	134 (88.2)	17 (11.2)	1 (0.7)
		migraine	152	0.363	273 (89.8)	31 (10.2)	121 (79.6)	31 (20.4)	0 (0.0)
		MA	63	0.594	109 (86.5)	17 (13.5)	46 (73.0)	17 (27.0)	0 (0.0)
		MO	89	1.000	164 (92.1)	14 (7.9)	75 (84.3)	14 (15.7)	0 (0.0)
	males	controls	64	1.000	121 (94.5)	7 (5.5)	57 (89.1)	7 (10.9)	0 (0.0)
		migraine	64	1.000	118 (92.2)	10 (7.8)	54 (84.4)	10 (15.6)	0 (0.0)
		MA	21	1.000	40 (95.2)	2 (4.8)	19 (90.5)	2 (9.5)	0 (0.0)
		MO	43	1.000	78 (90.7)	8 (9.3)	35 (81.4)	8 (18.6)	0 (0.0)
Yilmaz 2010 (18)	all	controls	96	0.590	174 (90.6)	18 (9.4)	79 (82.3)	16 (16.7)	1 (1.0)
		MO	67	0.233	97 (72.4)	37 (27.6)	37 (55.2)	23 (34.3)	7 (10.4)
	females	controls	83	0.455	152 (91.6)	14 (8.4)	70 (84.3)	12 (14.5)	1 (1.2)
		MO	57	0.308	83 (72.8)	31 (27.2)	32 (56.1)	19 (33.3)	6 (10.5)
	males	controls	13	1.000	22 (84.6)	4 (15.4)	9 (69.2)	4 (30.8)	0 (0.0)
		MO	10	1.000	14 (70.0)	6 (30.0)	5 (50.0)	4 (40.0)	1 (10.0)
Pappa 2010 (22)	all	controls	178	0.680	321 (90.2)	35 (9.8)	145 (81.5)	31 (17.4)	2 (1.1)
		MO	103	1.000	192 (93.2)	14 (6.8)	89 (86.4)	14 (13.6)	0 (0)
	females	controls	60	0.516	107 (89.2)	13 (10.8)	48 (80.0)	11 (18.3)	1 (1.7)
		MO	57	1.000	105 (92.1)	9 (7.9)	48 (84.2)	9 (15.8)	0 (0.0)
	males	controls	118	1.000	214 (90.7)	22 (9.3)	97 (82.2)	20 (16.9)	1 (0.8)
		MO	46	1.000	87 (94.6)	5 (5.4)	41 (89.1)	5 (10.9)	0 (0.0)
TNF-beta 252A>G (rs909253) polymorphism									

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TNF-alpha -308G>A (rs1800629) polymorphism									
					Allele frequencies, n (%)		Genotype frequencies, n (%)		
Author	**Participants**	**Disease status**	**Study size**	**HWE**	**G**	**A**	**GG**	**GA**	**AA**
					Allele frequencies, n (%)		**Genotype frequencies, n (%)**		
Author	**Participants**	**Disease status**	**Study size**	**HWE**	**A**	**G**	**AA**	**AG**	**GG**
Trabace 2002 (20)	all	controls	101	0.404	124 (61.4)	78 (38.6)	40 (39.6)	44 (43.6)	17 (16.8)
		migraine	77	0.546	115 (74.7)	39 (25.3)	44 (57.1)	27 (35.1)	6 (7.8)
		MA	30	0.106	41 (68.3)	19 (31.7)	16 (53.3)	9 (30.0)	5 (16.7)
		MO	47	0.656	74 (78.72)	20 (21.28)	28 (59.57)	18 (38.30)	1 (2.13)
	females	controls	43	0.391	67 (77.9)	19 (22.1)	27 (62.8)	13 (30.2)	3 (7.0)
		migraine	60	0.345	87 (72.5)	33 (27.5)	33 (55.0)	21 (35.0)	6 (10.0)
		MA	25	0.230	31 (62.0)	19 (38.0)	11 (44.0)	9 (36.0)	5 (20.0)
		MO	35	1.000	56 (80.0)	14 (20.0)	22 (62.9)	12 (34.3)	1 (2.9)
	males	controls	58	0.328	84 (72.4)	32 (27.6)	32 (55.2)	20 (34.5)	6 (10.3)
		migraine	17	1.000	28 (82.4)	6 (17.6)	11 (64.7)	6 (35.3)	0 (0.0)
		MA	5	---	10 (100.0)	0 (0.0)	5 (100.0)	0 (0.0)	0 (0.0)
		MO	12	0.536	18 (75.0)	6 (25.0)	6 (50.0)	6 (50.0)	0 (0.0)
Lee 2007 (21)	all/females	controls	382	0.915	439 (57.5)	325 (42.5)	125 (32.7)	189 (49.5)	68 (17.8)
		migraine	439	0.070	467 (53.2)	411 (46.8)	134 (30.5)	199 (45.3)	106 (24.1)
		MA	65	0.803	69 (53.1)	61 (46.9)	19 (29.2)	31 (47.7)	15 (23.1)
		MO	327	0.118	347 (53.1)	307 (46.9)	99 (30.3)	149 (45.6)	79 (24.2)
Asuni 2009 (19)	all	controls	278	0.597	482 (86.7)	74 (13.3)	210 (75.5)	62 (22.3)	6 (2.2)
		MO	299	1.000	488 (81.6)	110 (18.4)	199 (66.6)	90 (30.1)	10 (3.3)
	females	controls	144	1.000	244 (84.7)	44 (15.3)	103 (71.5)	38 (26.4)	3 (2.1)
		MO	261	1.000	429 (82.2)	93 (17.8)	176 (67.4)	77 (29.5)	8 (3.1)
	males	controls	134	0.207	238 (88.8)	30 (11.2)	107 (79.9)	24 (17.9)	3 (2.2)
		MO	38	1.000	59 (77.6)	17 (22.4)	23 (60.5)	13 (34.2)	2 (5.3)

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TNF-alpha -308G>A (rs1800629) polymorphism									
					Allele frequencies, n (%)		Genotype frequencies, n (%)		
Author	**Participants**	**Disease status**	**Study size**	**HWE**	**G**	**A**	**GG**	**GA**	**AA**
Schürks 2009 (17)	all/females	controls	19,269	0.557	25,570 (66.4)	12,968 (33.6)	8501 (44.1)	8568 (44.5)	2200 (11.4)
		migraine	4332	0.564	5738 (66.2)	2926 (33.8)	1891 (43.7)	1956 (45.2)	485 (11.2)
		MA	1213	0.315	1597 (65.8)	829 (34.2)	517 (42.6)	563 (46.4)	133 (11.0)
		MO	1824	0.528	2420 (66.3)	1228 (33.7)	809 (44.4)	802 (44.0)	213 (11.7)
Ghosh 2010 (14)	all	controls	216	0.858	328 (75.9)	104 (24.1)	125 (57.9)	78 (36.1)	13 (6.0)
		migraine	216	0.354	328 (75.9)	104 (24.1)	127 (58.8)	74 (34.3)	15 (6.9)
		MA	84	0.162	125 (74.4)	43 (25.6)	49 (58.3)	27 (32.1)	8 (9.5)
		MO	132	1.000	203 (76.9)	61 (23.1)	78 (59.1)	47 (35.6)	7 (5.3)
	females	controls	152	0.467	241 (79.3)	63 (20.7)	97 (63.8)	47 (30.9)	8 (5.3)
		migraine	152	0.359	234 (77.0)	70 (23.0)	92 (60.5)	50 (32.9)	10 (6.6)
		MA	63	0.092	96 (76.2)	30 (23.8)	39 (61.9)	18 (28.6)	6 (9.5)
		MO	89	1.000	138 (77.5)	40 (22.5)	53 (59.6)	32 (36.0)	4 (4.5)
	males	controls	64	0.563	87 (68.0)	41 (32.0)	28 (43.8)	31 (48.4)	5 (7.8)
		migraine	64	0.753	94 (73.4)	34 (26.6)	35 (54.7)	24 (37.5)	5 (7.8)
		MA	21	1.000	29 (69.0)	13 (31.0)	10 (47.6)	9 (42.9)	2 (9.5)
		MO	43	0.681	65 (75.6)	21 (24.4)	25 (58.1)	15 (34.9)	3 (7.0)
Pappa 2010 (22)	all	controls	178	0.503	279 (78.4)	77 (21.6)	111 (62.4)	57 (32.0)	10 (5.6)
		MO	103	0.747	167 (81.1)	39 (18.9)	68 (66.0)	31 (30.1)	4 (3.9)
	females	controls	60	0.709	95 (79.2)	25 (20.8)	38 (63.3)	19 (31.7)	3 (5.0)
		MO	57	1.000	94 (82.5)	20 (17.5)	38 (66.6)	18 (31.6)	1 (1.8)
	males	controls	118	0.590	184 (78.0)	52 (22.0)	73 (61.9)	38 (32.2)	7 (5.9)
		MO	46	0.366	73 (79.3)	19 (20.7)	30 (65.2)	13 (28.3)	3 (6.5)
TNF-alpha -238G>A (rs361525) polymorphism									
-					Allele frequencies, n (%)		Genotype frequencies, n (%)		

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TNF-alpha -308G>A (rs1800629) polymorphism									
					Allele frequencies, n (%)		Genotype frequencies, n (%)		
Author	**Participants**	**Disease status**	**Study size**	**HWE**	**G**	**A**	**GG**	**GA**	**AA**
Schürks 2009 (17)	all/females	controls	20,425	0.006	38,780 (94.9)	2070 (5.1)	18,427 (90.2)	1926 (9.4)	72 (0.4)
		migraine	4577	0.431	8705 (95.1)	449 (4.9)	4136 (90.4)	433 (9.5)	8 (0.2)
		MA	1275	0.763	2422 (95.0)	128 (5.0)	1149 (90.1)	124 (9.7)	2 (0.2)
		MO	1951	0.784	3730 (95.6)	172 (4.4)	1783 (91.4)	164 (8.4)	4 (0.2)
Pappa 2010 (22)	all	controls	178	1.000	348 (97.8)	8 (2.2)	170 (95.5)	8 (4.5)	0 (0.0)
		MO	103	1.000	199 (96.6)	7 (3.4)	96 (93.2)	7 (6.8)	0 (0.0)
	females	controls	60	1.000	119 (99.2)	1 (0.8)	59 (98.3)	1 (1.7)	0 (0.0)
		MO	57	1.000	111 (97.4)	3 (2.6)	54 (94.7)	3 (5.3)	0 (0.0)
	males	controls	118	1.000	229 (97.0)	7 (3.0)	111 (94.1)	7 (5.9)	0 (0.0)
		MO	46	1.000	88 (95.7)	4 (4.3)	42 (91.3)	4 (8.7)	0 (0.0)
TNF-alpha -376G>A (rs1800750) polymorphism									
					Allele frequencies, n (%)		Genotype frequencies, n (%)		
Author	**Gender**	**Disease status**	**Study size**	**HWE**	**G**	**A**	**GG**	**GA**	**AA**
Schürks 2009 (17)	all/females	controls	20,425	0.002	40,283 (98.6)	567 (1.4)	19,869 (97.3)	545 (2.7)	11 (0.1)
		migraine	4578	0.307	9012 (98.4)	144 (1.6)	4436 (96.9)	140 (3.1)	2 (0.04)
		MA	1276	0.374	2504 (98.1)	48 (1.9)	1229 (96.3)	46 (3.6)	1 (0.1)
		MO	1951	1.000	3851 (98.7)	51 (1.3)	1900 (97.4)	51 (2.6)	0 (0.0)
Pappa 2010 (22)	all	controls	178	---	356 (100.0)	0 (0.0)	178 (100.0)	0 (0.0)	0 (0.0)
		MO	103	1.000	205 (99.5)	1 (0.5)	102 (99.0)	1 (1.0)	0 (0.0)
	females	controls	60	---	120 (100)	0 (0.0)	60 (100)	0 (0.0)	0 (0.0)
		MO	57	1.000	113 (99.1)	1 (0.9)	56 (98.2)	1 (1.8)	0 (0.0)
	males	controls	118	---	236 (100)	0 (0.0)	118 (100)	0 (0.0)	0 (0.0)

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TNF-alpha -308G>A (rs1800629) polymorphism									
					Allele frequencies, n (%)		Genotype frequencies, n (%)		
Author	**Participants**	**Disease status**	**Study size**	**HWE**	**G**	**A**	**GG**	**GA**	**AA**
		MO	46	---	92 (100)	0 (0.0)	46 (100)	0 (0.0)	0 (0.0)

TNF: tumor necrosis factor; HWE: p value from exact test for the Hardy-Weinberg Equilibrium; MA: migraine with aura; MO: migraine without aura.

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Table 3

Odds ratios (95% confidence intervals) for the association between the investigated polymorphisms and migraine

***TNF-alpha* -308G>A (rs1800629) polymorphism**									
				additive		**dominant**		**recessive**	
Author	**Participants**	**Disease status**	**Study size**	**OR (95% CI)**	**p-value**	**OR (95% CI)**	**p-value**	**OR (95% CI)**	**p-value**
Trabace 2002 (20)	all	controls	101	Referent		Referent		Referent	
		migraine	79	1.176 (0.541–2.559)	0.682	1.465 (0.610–3.523)	0.393	---	---
		MA	32	1.665 (0.671–4.131)	0.272	2.291 (0.805–6.521)	0.120	---	---
		MO	47	0.841 (0.314–2.253)	0.730	0.974 (0.318–2.982)	0.963	---	---
	females	controls	45	Referent		Referent		Referent	
		migraine	62	1.457 (0.494–4.294)	0.495	1.970 (0.576–6.738)	0.280	---	---
		MA	27	1.982 (0.599–6.554)	0.262	2.928 (0.744–11.524)	0.124	---	---
		MO	35	1.026 (0.294–3.573)	0.968	1.323 (0.306–5.708)	0.708	---	---
	males	controls	56	Referent		Referent		Referent	
		migraine	17	0.833 (0.185–3.754)	0.812	0.933 (0.175–4.980)	0.936	---	---
		MA	5	1.368 (0.183–10.201)	0.760	1.750 (0.170–17.987)	0.638	---	---
		MO	12	0.607 (0.081–4.543)	0.627	0.636 (0.071–5.714)	0.687	---	---
Rainero 2004 (16)	all	controls	306	Referent		Referent		Referent	
		migraine	299	0.365 (0.250–0.531)	<0.0001	0.351 (0.235–0.525)	<0.0001	0.090 (0.012–0.701)	0.022
		MA	38	0.694 (0.346–1.389)	0.302	0.747 (0.349–1.598)	0.452	---	---
		MO	261	0.323 (0.214–0.487)	<0.0001	0.303 (0.196–0.468)	<0.0001	0.103 (0.013–0.804)	0.030
	females	controls	231	Referent		Referent		Referent	
		migraine	215	0.339 (0.215–0.537)	<0.0001	0.337 (0.209–0.545)	<0.0001	---	---
	males	controls	75	Referent		Referent		Referent	
		migraine	84	0.415 (0.215–0.803)	0.009	0.377 (0.179–0.794)	0.010	0.214 (0.023–1.957)	0.172
Herken 2005 (23)	all	controls	62	Referent		Referent		Referent	
		migraine	60	0.802 (0.297–2.165)	0.664	0.654 (0.218–1.966)	0.450	---	---
		MA	40	0.654 (0.187–2.287)	0.507	0.654 (0.187–2.287)	0.507	---	---

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TNF-alpha -308G>A (rs1800629) polymorphism									
				additive		dominant		recessive	
Author	**Participants**	**Disease status**	**Study size**	**OR (95% CI)**	**p-value**	**OR (95% CI)**	**p-value**	**OR (95% CI)**	**p-value**
		MO	20	1.033 (0.283–3.766)	0.961	0.655 (0.129–3.316)	0.609	---	---
Mazaheri 2006 (15)	all	controls	183	Referent		Referent		Referent	
		MO	221	3.166 (2.113–4.745)	<0.0001	3.520 (2.298–5.393)	<0.0001	1.962 (0.500–7.697)	0.334
	females	controls	123	Referent		Referent		Referent	
		MO	196	4.278 (2.655–6.895)	<0.0001	4.271 (2.620–6.963)	<0.0001	---	---
	males	controls	60	Referent		Referent		Referent	
		MO	25	1.415 (0.599–3.346)	0.429	1.966 (0.715–5.406)	0.190	---	---
Lee 2007 (21)	all/females	controls	382	Referent		Referent		Referent	
		migraine	439	1.178 (0.798–1.740)	0.410	1.263 (0.836–1.910)	0.268	0.289 (0.030–2.787)	0.283
		MA	65	1.390 (0.711–2.716)	0.335	1.565 (0.761–3.216)	0.223	---	---
		MO	327	1.151 (0.759–1.745)	0.509	1.226 (0.786–1.912)	0.369	0.388 (0.040–3.747)	0.413
Asuni 2009 (19)	all	controls	278	Referent		Referent		Referent	
		MO	299	0.864 (0.512–1.458)	0.583	0.852 (0.491–1.479)	0.570	0.929 (0.058–14.932)	0.959
	females	controls	144	Referent		Referent		Referent	
		MO	261	0.916 (0.475–1.766)	0.792	0.871 (0.441–1.719)	0.690	---	---
	males	controls	134	Referent		Referent		Referent	
		MO	38	0.707 (0.205–2.436)	0.583	0.735 (0.200–2.703)	0.643	---	---
Schürks 2009 (17)	all/females	controls	20,425	Referent		Referent		Referent	
		migraine	4577	1.029 (0.969–1.092)	0.356	1.046 (0.976–1.120)	0.201	0.941 (0.775–1.143)	0.542
		MA	1275	1.136 (1.025–1.258)	0.015	1.166 (1.036–1.313)	0.011	1.124 (0.817–1.544)	0.473
		MO	1951	0.975 (0.893–1.064)	0.568	0.968 (0.875–1.070)	0.524	0.993 (0.754–1.308)	0.959
Ghosh 2010 (14)	all	controls	216	Referent		Referent		Referent	
		migraine	216	1.683 (0.995–2.846)	0.052	1.790 (1.045–3.065)	0.034	---	---
		MA	84	2.054 (1.084–3.893)	0.027	2.234 (1.155–4.321)	0.017	---	---

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TNF-alpha -308G>A (rs1800629) polymorphism									
				additive		dominant		recessive	
Author	**Participants**	**Disease status**	**Study size**	**OR (95% CI)**	**p-value**	**OR (95% CI)**	**p-value**	**OR (95% CI)**	**p-value**
		MO	132	1.436 (0.788–2.617)	0.238	1.528 (0.823–2.838)	0.180	---	---
	females	controls	152	Referent		Referent		Referent	
		migraine	152	1.750 (0.950–3.222)	0.073	1.907 (1.015–3.583)	0.045	---	---
		MA	63	2.436 (1.191–4.983)	0.015	2.751 (1.309–5.781)	0.008	---	---
		MO	89	1.284 (0.624–2.639)	0.497	1.390 (0.654–2.952)	0.392	---	---
	males	controls	64	Referent		Referent		Referent	
		migraine	64	1.508 (0.536–4.245)	0.437	1.508 (0.536–4.245)	0.437	---	---
		MA	21	0.857 (0.164–4.486)	0.855	0.857 (0.164–4.486)	0.855	---	---
		MO	43	1.861 (0.621–5.581)	0.268	1.861 (0.621–5.581)	0.268	---	---
Yilmaz 2010 (18)	all	controls	96	Referent		Referent		Referent	
		MO	67	3.321 (1.785–6.178)	0.000	3.768 (1.849–7.676)	0.0003	11.074 (1.330–92.207)	0.026
	females	controls	83	Referent		Referent		Referent	
		MO	57	3.521 (1.772–6.996)	0.000	4.206 (1.909–9.268)	0.0004	9.644 (1.129–82.419)	0.038
	males	controls	13	Referent		Referent		Referent	
		MO	10	2.473 (0.543–11.264)	0.242	2.250 (0.407–12.439)	0.353	---	---
Pappa 2010 (22)	all	controls	178	Referent		Referent		Referent	
		MO	103	0.667 (0.348–1.276)	0.221	0.691 (0.351–1.362)	0.286	---	---
	females	controls	60	Referent		Referent		Referent	
		MO	57	0.704 (0.287–1.725)	0.443	0.750 (0.289–1.944)	0.554	---	---
	males	controls	118	Referent		Referent		Referent	
		MO	46	0.555 (0.202–1.525)	0.254	0.563 (0.199–1.596)	0.280	---	---
TNF-beta 252A>G (rs909253) polymorphism									
				additive		dominant		recessive	

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TNF-alpha -308G>A (rs1800629) polymorphism									
				additive		dominant		recessive	
Author	**Participants**	**Disease status**	**Study size**	**OR (95% CI)**	**p-value**	**OR (95% CI)**	**p-value**	**OR (95% CI)**	**p-value**
Author	**Participants**	**Disease status**	**Study size**	**OR (95% CI)**	**p-value**	**OR (95% CI)**	**p-value**	**OR (95% CI)**	**p-value**
Trabace 2002 (20)	all	controls	101	Referent		Referent		Referent	
		migraine	77	0.564 (0.359–0.885)	0.013	0.492 (0.269–0.898)	0.021	0.418 (0.156–1.116)	0.082
		MA	30	0.763 (0.427–1.362)	0.360	0.574 (0.253–1.304)	0.185	0.988 (0.331–2.947)	0.983
		MO	47	0.438 (0.246–0.780)	0.005	0.445 (0.220–0.901)	0.025	0.107 (0.014–0.833)	0.033
	females	controls	43	Referent		Referent		Referent	
		migraine	60	1.296 (0.701–2.397)	0.408	1.381 (0.620–3.075)	0.430	1.481 (0.349–6.284)	0.594
		MA	25	1.925 (0.937–3.954)	0.074	2.148 (0.788–5.855)	0.135	3.332 (0.722–15.367)	0.123
		MO	35	0.886 (0.413–1.898)	0.755	0.997 (0.396–2.510)	0.995	0.392 (0.039–3.946)	0.427
	males	controls	58	Referent		Referent		Referent	
		migraine	17	0.584 (0.226–1.507)	0.266	0.671 (0.219–2.060)	0.486	---	---
		MA	5	---	---	---	---	---	---
		MO	12	0.882 (0.330–2.353)	0.801	1.231 (0.355–4.271)	0.744	---	---
Lee 2007 (21)	all/females	controls	382	Referent		Referent		Referent	
		migraine	439	1.180 (0.975–1.430)	0.090	1.107 (0.824–1.487)	0.499	1.470 (1.045–2.068)	0.027
		MA	65	1.195 (0.822–1.737)	0.351	1.178 (0.662–2.094)	0.578	1.386 (0.735–2.611)	0.313
		MO	327	1.188 (0.966–1.462)	0.103	1.120 (0.815–1.540)	0.486	1.471 (1.022–2.118)	0.038
Asuni 2009 (19)	all	controls	278	Referent		Referent		Referent	
		MO	299	1.461 (1.061–2.013)	0.020	1.552 (1.078–2.233)	0.018	1.569 (0.562–4.374)	0.390
	females	controls	144	Referent		Referent		Referent	
		MO	261	1.205 (0.812–1.787)	0.355	1.213 (0.778–1.893)	0.395	1.486 (0.388–5.691)	0.563
	males	controls	134	Referent		Referent		Referent	
		MO	38	2.155 (1.128–4.116)	0.020	2.585 (1.190–5.612)	0.016	2.426 (0.390–15.075)	0.342
Schürks 2009 (17)	all/females	controls	19,269	Referent		Referent		Referent	

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TNF-alpha -308G>A (rs1800629) polymorphism									
				additive		dominant		recessive	
Author	**Participants**	**Disease status**	**Study size**	**OR (95% CI)**	**p-value**	**OR (95% CI)**	**p-value**	**OR (95% CI)**	**p-value**
		migraine	4332	1.005 (0.957–1.056)	0.828	1.019 (0.954–1.089)	0.577	0.978 (0.881–1.086)	0.680
		MA	1213	1.024 (0.939–1.116)	0.597	1.063 (0.945–1.195)	0.309	0.955 (0.794–1.150)	0.630
		MO	1824	1.001 (0.931–1.075)	0.988	0.990 (0.899–1.091)	0.846	1.026 (0.883–1.192)	0.736
Ghosh 2010 (14)	all	controls	216	Referent		Referent		Referent	
		migraine	216	1.000 (0.736–1.358)	1.000	0.963 (0.657–1.411)	0.845	1.165 (0.541–2.511)	0.697
		MA	84	1.080 (0.724–1.612)	0.705	0.981 (0.589–1.636)	0.942	1.644 (0.656–4.123)	0.289
		MO	132	0.948 (0.661–1.359)	0.772	0.951 (0.613–1.476)	0.823	0.874 (0.340–2.251)	0.781
	females	controls	152	Referent		Referent		Referent	
		migraine	152	1.135 (0.781–1.648)	0.507	1.150 (0.723–1.829)	0.555	1.268 (0.486–3.304)	0.628
		MA	63	1.175 (0.734–1.880)	0.502	1.085 (0.592–1.991)	0.791	1.895 (0.630–5.705)	0.256
		MO	89	1.106 (0.710–1.722)	0.655	1.198 (0.700–2.050)	0.510	0.847 (0.248–2.897)	0.791
	males	controls	64	Referent		Referent		Referent	
		migraine	64	0.759 (0.436–1.320)	0.329	0.644 (0.321–1.294)	0.217	1.000 (0.275–3.637)	1.000
		MA	21	0.947 (0.431–2.079)	0.892	0.856 (0.318–2.299)	0.757	1.242 (0.223–6.932)	0.805
		MO	43	0.672 (0.356–1.270)	0.221	0.560 (0.256–1.224)	0.146	0.885 (0.200–3.913)	0.872
Pappa 2010 (22)	all	controls	178	Referent		Referent		Referent	
		MO	103	0.852 (0.559–1.299)	0.457	0.853 (0.513–1.417)	0.539	0.679 (0.207–2.222)	0.522
	females	controls	60	Referent		Referent		Referent	
		MO	57	0.805 (0.416–1.559)	0.520	0.864 (0.404–1.849)	0.706	0.339 (0.034–3.361)	0.356
	males	controls	118	Referent		Referent		Referent	
		MO	46	0.927 (0.525–1.636)	0.793	0.865 (0.425–1.762)	0.690	1.106 (0.273–4.475)	0.887

TNF-alpha -238G>A (rs361525) polymorphism									
				additive		dominant		recessive	
Author	**Participants**	**Disease status**	**Study size**	**OR (95% CI)**	**p-value**	**OR (95% CI)**	**p-value**	**OR (95% CI)**	**p-value**

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TNF-alpha -308G>A (rs1800629) polymorphism									
				additive		dominant		recessive	
Author	**Participants**	**Disease status**	**Study size**	**OR (95% CI)**	**p-value**	**OR (95% CI)**	**p-value**	**OR (95% CI)**	**p-value**
Schürks 2009 (17)	all/females	controls	20,425	Referent		Referent		Referent	
		migraine	4577	0.967 (0.872–1.073)	0.528	0.983 (0.882–1.096)	0.763	0.495 (0.238–1.028)	0.059
		MA	1275	0.990 (0.826–1.187)	0.916	1.011 (0.837–1.223)	0.907	0.444 (0.109–1.812)	0.258
		MO	1951	0.866 (0.740–1.014)	0.074	0.869 (0.737–1.025)	0.095	0.581 (0.212–1.591)	0.291
Pappa 2010 (22)	all	controls	178	Referent		Referent		Referent	
		MO	103	1.549 (0.545–4.405)	0.411	1.549 (0.545–4.405)	0.411	---	---
	females	controls	60	Referent		Referent		Referent	
		MO	57	3.278 (0.331–32.467)	0.310	3.278 (0.331–32.467)	0.310	---	---
	males	controls	118	Referent		Referent		Referent	
		MO	46	1.510 (0.420–5.425)	0.527	1.510 (0.420–5.425)	0.527	---	---
TNF-alpha -376G>A (rs1800750) polymorphism									
				additive		dominant		recessive	
Author	**Participants**	**Disease status**	**Study size**	**OR (95% CI)**	**p-value**	**OR (95% CI)**	**p-value**	**OR (95% CI)**	**p-value**
Schürks 2009 (17)	all/females	controls	20,425	Referent		Referent		Referent	
		migraine	4578	1.132 (0.943–1.358)	0.182	1.144 (0.949–1.379)	0.159	0.811 (0.180–3.661)	0.786
		MA	1276	1.352 (1.009–1.811)	0.044	1.368 (1.010–1.852)	0.043	1.458 (0.188–11.286)	0.718
		MO	1951	0.942 (0.708–1.253)	0.682	0.960 (0.718–1.283)	0.782	---	---
Pappa 2010 (22)	all	controls	178	Referent		Referent		Referent	
		MO	103	---	---	---	---	---	---
	females	controls	60	Referent		Referent		Referent	
		MO	57	---	---	---	---	---	---
	males	controls	118	Referent		Referent		Referent	
		MO	46	---	---	---	---	---	---

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TNF: tumor necrosis factor; OR: odds ratio; MA: migraine with aura; MO: migraine without aura.

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Table 4

Association between the *TNF-alpha* -308G>A (rs1800629) polymorphisms and migraine from random effects model, heterogeneity, and small study effects

Migraine									
						Heterogeneity		Small study effects p-value	
Genetic model	**Participants**	**No of studies**	**Pooled OR (95% CI)**	**Q**	**df**	**p-value**	**I^2 in %**	**Begg test**	**Egger's test**
additive	All (14–23)	10	1.16 (0.80–1.68)	78.6	9	<0.0001	88.5	0.66	0.68
	European descent (16, 17, 19, 20, 22)	5	0.75 (0.46–1.22)	30.3	4	<0.0001	86.8	1.00	0.30
	Asian descent (14, 21)	2	1.35 (0.96–1.89)	1.1	1	0.29	12.5	0.32	----
	Heterogeneous descent (15, 18, 23)	3	2.32 (1.18–4.56)	6.7	2	0.04	70.3	0.12	0.37
	Females	9	1.29 (0.83–2.00)	73.4	8	<0.0001	89.1	0.53	0.51
	European descent (16, 17, 19, 20, 22)	5	0.77 (0.44–1.32)	23.4	4	<0.0001	82.9	1.00	0.38
	Asian descent (14, 21)	2	1.34 (0.93–1.92)	1.2	1	0.28	12.8	0.32	----
	Heterogeneous descent (15, 18)	2	4.02 (2.71–5.94)	0.2	1	0.65	0.0	0.32	----
	Males (14–16, 18–20, 22)	7	0.86 (0.52–1.42)	9.6	6	0.14	37.6	0.18	0.18
	European descent (16, 19, 20, 22)	4	0.51 (0.32–0.83)	1.1	3	0.78	0.0	0.04	0.002
	Asian descent (14)	1	1.51 (0.54–4.25)	----	----	----	----	----	----
	Heterogeneous descent (15, 18)	2	1.62 (0.77–3.43)	0.4	1	0.53	0.0	0.32	----
dominant	All (14–23)	10	1.21 (0.81–1.80)	79.5	9	<0.0001	88.7	0.66	0.65
	European descent (16, 17, 19, 20, 22)	5	0.77 (0.46–1.29)	29.8	4	<0.0001	86.6	1.00	0.35
	Asian descent (14, 21)	2	1.44 (1.03–2.00)	1.0	1	0.31	1.5	0.32	----
	Heterogeneous descent (15, 18, 23)	3	2.35 (1.02–5.42)	8.3	2	0.02	75.9	0.12	0.41
	Females (14–22)	9	1.36 (0.86–2.15)	70.8	8	<0.0001	88.7	0.53	0.46
	European descent (16, 17, 19, 20, 22)	5	0.79 (0.45–1.40)	22.7	4	<0.0001	82.4	1.00	0.44
	Asian descent (14, 21)	2	1.45 (0.99–2.11)	1.2	1	0.28	12.9	0.32	----
	Heterogeneous descent (15, 18)	2	4.25 (2.81–6.44)	0.0	1	0.97	0.0	0.32	----
	Males (14–16, 18–20, 22)	7	0.90 (0.51–1.58)	10.3	6	0.11	41.6	0.65	0.20
	European descent (16, 19, 20, 22)	4	0.51 (0.30–0.85)	1.5	3	0.69	0.0	0.04	0.01

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Migraine

Genetic model	Participants	No of studies	Pooled OR (95% CI)	Heterogeneity Q	df	p-value	I^2 in %	Small study effects p-value Begg test	Egger's test
	Asian descent (14)	1	1.51 (0.54–4.25)	----	----	----	----	----	----
	Heterogeneous descent (15, 18)	2	2.04 (0.85–4.86)	0.0	1	0.89	0.0	----	----
recessive	All (15–19, 21)	6*	0.95 (0.36–2.52)	12.5	5	0.03	59.9	0.85	0.99
	European descent (16, 17, 19)	3*	0.50 (0.11–2.23)	5.1	2	0.08	60.6	0.60	0.51
	Asian descent (21)	1*	0.29 (0.03–2.79)	----	----	----	----	----	----
	Heterogeneous descent (15, 18)	2*	3.83 (0.73–19.95)	1.8	1	0.18	44.7	0.32	----
	Females (17, 18, 21)	3*	1.28 (0.29–5.72)	5.6	2	0.06	64.0	0.60	0.79
	European descent (17)	1*	0.94 (0.78–1.14)	----	----	----	----	----	----
	Asian descent (21)	1*	0.29 (0.03–2.79)	----	----	----	----	----	----
	Heterogeneous descent (18)	1*	9.64 (1.13–82.42)	----	----	----	----	----	----
	Males (16)	1*	0.21 (0.02–1.96)	----	----	----	----	----	----

Migraine with aura

Genetic model	Participants	No of studies	Pooled OR (95% CI)	Heterogeneity Q	df	p-value	I^2 in %	Small study effects p-value Begg test	Egger's test
additive	All (14, 16, 17, 20, 21, 23)	6	1.20 (0.92–1.55)	7.0	5	0.22	28.3	0.57	0.80
	European descent (16, 17, 20)	3	1.10 (0.83–1.46)	2.6	2	0.27	23.1	0.60	0.86
	Asian descent (14, 21)	2	1.71 (1.07–2.71)	0.7	1	0.41	0.0	0.32	----
	Heterogeneous descent (23)	1	0.65 (0.19–2.29)	----	----	----	----	----	----
	Females (14, 17, 20, 21)	4	1.42 (0.98–2.07)	5.3	3	0.15	43.8	0.17	0.13
	European descent (17, 20)	2	1.14 (1.03–1.26)	0.8	1	0.36	0.0	0.32	----
	Asian descent (14, 21)	2	1.81 (1.05–3.14)	1.3	1	0.26	20.5	0.32	----

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Migraine									
						Heterogeneity		Small study effects p-value	
Genetic model	**Participants**	**No of studies**	**Pooled OR (95% CI)**	**Q**	**df**	**p-value**	**I^2 in %**	**Begg test**	**Egger's test**
	Males (14, 20)	2	1.04 (0.29–3.71)	0.1	1	0.73	0.0	0.32	----
	European descent (20)	1	1.37 (0.18–10.20)	----	----	----	----	----	----
	Asian descent (14)	1	0.86 (0.16–4.87)	----	----	----	----	----	----
dominant	All (14, 16, 17, 20, 21, 23)	6	1.29 (0.94–1.78)	8.0	5	0.16	37.5	0.85	0.61
	European descent (16, 17, 20)	3	1.16 (0.80–1.68)	2.9	2	0.23	31.4	0.60	0.95
	Asian descent (14, 21)	2	1.90 (1.17–3.09)	0.5	1	0.48	0.0	0.32	----
	Heterogeneous descent (23)	1	0.65 (0.19–2.29)	----	----	----	----	----	----
	Females (14, 17, 20, 21)	4	1.65 (1.02–2.68)	7.2	3	0.07	58.1	0.17	0.08
	European descent (17, 20)	2	1.42 (0.68–2.98)	1.7	1	0.19	41.9	0.32	----
	Asian descent (14, 21)	2	2.06 (1.19–3.58)	1.1	1	0.29	12.4	0.32	----
	Males (14, 20)	2	1.09 (0.28–4.20)	0.2	1	0.62	0.0	0.32	----
	European descent (20)	1	1.75 (0.17–17.99)	----	----	----	----	----	----
	Asian descent (14)	1	0.86 (0.16–4.87)	----	----	----	----	----	----
recessive	All (17)	1*	1.12 (0.82–1.54)	----	----	----	----	----	----

Migraine without aura									
						Heterogeneity		Small study effects p-value	
Genetic model	Participants	No of studies	Pooled OR (95% CI)	Q	df	p-value	I^2 in %	Begg test	Egger's test
additive	All (14–23)	10	1.11 (0.74–1.67)	78.6	9	<0.0001	88.6	0.66	0.68
	European descent (16, 17, 19, 20, 22)	5	0.68 (0.41–1.13)	27.6	4	<0.0001	85.5	1.00	0.28
	Asian descent (14, 21)	2	1.24 (0.88–1.74)	0.4	1	0.55	0.0	0.32	----
	Heterogeneous descent (15, 18, 23)	3	2.87 (1.86–4.43)	2.8	2	0.25	28.0	0.12	0.33
	Females (14, 15, 17–22)	8	1.44 (0.91–2.27)	49.4	7	<0.0001	85.8	1.00	0.22

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Migraine									
						Heterogeneity		Small study effects p-value	
Genetic model	**Participants**	**No of studies**	**Pooled OR (95% CI)**	**Q**	**df**	**p-value**	**I^2 in %**	**Begg test**	**Egger's test**
	European descent (17, 19, 20, 22)	4	0.97 (0.89–1.06)	0.5	3	0.91	0.0	0.50	0.37
	Asian descent (14, 21)	2	1.18 (0.83–1.70)	0.1	1	0.80	0.0	0.32	----
	Heterogeneous descent (15, 18)	2	4.02 (2.71–5.94)	0.2	1	0.65	0.0	0.32	----
	Males (14, 15, 18–20, 22)	6	1.11 (0.69–1.77)	4.9	5	0.43	0.0	0.57	0.89
	European descent (19, 20, 22)	3	0.61 (0.29–1.27)	0.1	2	0.96	0.0	0.60	0.81
	Asian descent (14)	1	1.86 (0.62–5.58)	----	----	----	----	----	----
	Heterogeneous descent (15, 18)	2	1.62 (0.77–3.43)	0.4	1	0.53	0.0	0.32	----
dominant	All (14–23)	10	1.13 (0.73–1.76)	80.4	9	<0.0001	88.8	0.66	0.66
	European descent (16, 17, 19, 20, 22)	5	0.68 (0.40–1.16)	26.7	4	<0.0001	85.0	1.00	0.34
	Asian descent (14, 21)	2	1.32 (0.92–1.90)	0.3	1	0.57	0.0	0.32	----
	Heterogeneous descent (15, 18, 23)	3	2.94 (1.57–5.50)	4.0	2	0.13	50.4	0.12	0.35
	Females (14, 15, 17–22)	8	1.52 (0.94–2.46)	47.9	7	<0.0001	85.4	0.81	0.18
	European descent (17, 19, 20, 22)	4	0.97 (0.87–1.07)	0.5	3	0.91	0.0	1.00	0.71
	Asian descent (14, 21)	2	1.27 (0.86–1.86)	0.1	1	0.78	0.0	0.32	----
	Heterogeneous descent (15, 18)	2	4.25 (2.81–6.44)	0.0	1	0.97	0.0	0.32	----
	Males (14, 15, 18–20, 22)	6	1.18 (0.71–1.97)	4.9	5	0.42	0.0	0.57	0.85
	European descent (19, 20, 22)	3	0.63 (0.29–1.34)	0.1	2	0.95	0.0	0.60	0.76
	Asian descent (14)	1	1.86 (0.62–5.58)	----	----	----	----	----	----
	Heterogeneous descent (15, 18)	2	2.04 (0.85–4.86)	0.0	1	0.89	0.0	0.32	----
recessive	All (15–19, 21)	6*	1.03 (0.40–2.62)	11.2	5	0.047	55.4	0.85	0.99
	European descent (16, 17, 19)	3*	0.54 (0.13–2.27)	4.6	2	0.10	56.1	0.60	0.50
	Asian descent (21)	1*	0.39 (0.04–3.75)	----	----	----	----	----	----
	Heterogeneous descent (15, 18)	2*	3.83 (0.73–19.95)	1.8	1	0.18	44.7	0.32	----
	Females (17, 18, 21)	3*	1.39 (0.34–5.70)	5.0	2	0.08	59.6	0.60	0.74

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Migraine									
						Heterogeneity		Small study effects p-value	
Genetic model	**Participants**	**No of studies**	**Pooled OR (95% CI)**	**Q**	**df**	**p-value**	**I^2 in %**	**Begg test**	**Egger's test**
	European descent (17)	1*	0.99 (0.75–1.31)	----	----	----	----	----	----
	Asian descent (21)	1*	0.39 (0.04–3.75)	----	----	----	----	----	----

OR: odds ratio.

*effect estimates for some studies could not be calculated due to small numbers

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Table 5

Association between the *TNF-beta* 252A>G (rs909253) polymorphisms and migraine from random effects model, heterogeneity, and small study effects

Migraine									
						Heterogeneity		Small study effects p-value	
Genetic model	**Participants**	**No of studies**	**Pooled OR 95% CI)**	**Q**	**df**	**p-value**	**I^2 in %**	**Begg test**	**Egger's test**
additive	All (14, 17, 19–22)	6	1.02 (0.87–1.21)	14.7	5	0.01	66.0	0.57	1.00
	Females (14, 17, 19–22)	6	1.02 (0.97–1.07)	4.7	5	0.46	0.0	0.85	0.22
	Males (14, 19, 20, 22)	4	1.00 (0.59–1.69)	7.7	3	0.05	60.8	0.50	0.86
dominant	All (14, 17, 19–22)	6	1.02 (0.84–1.23)	11.6	5	0.04	56.8	0.19	0.82
	Females (14, 17, 19–22)	6	1.03 (0.97–1.10)	1.8	5	0.88	0.0	0.57	0.15
	Males (14, 19, 20, 22)	4	1.01 (0.53–1.94)	7.9	3	0.047	62.2	0.50	0.96
recessive	All (14, 17, 19–22)	6	1.06 (0.80–1.42)	9.4	5	0.10	46.6	0.85	0.89
	Females (14, 17, 19–22)	6	1.13 (0.89–1.43)	6.7	5	0.25	24.9	0.85	0.44
	Males (14, 19, 22)	3*	1.25 (0.54–2.91)	0.7	2	0.72	0.0	0.12	0.07
Migraine with aura									
						Heterogeneity		Small study effects p-value	
Genetic model	Participants	No of studies	Pooled OR (95% CI)	Q	df	p-value	I^2 in %	Begg test	Egger's test
additive	All (14, 17, 20, 21)	4	1.03 (0.95–1.12)	1.7	3	0.64	0.0	0.50	0.97
	Females (14, 17, 20, 21)	4	1.09 (0.93–1.28)	3.7	3	0.29	19.2	0.17	0.08
	Males (14)	1*	0.95 (0.43–2.08)	---	---	---	---	---	---
dominant	All (14, 17, 20, 21)	4	1.05 (0.94–1.18)	2.4	3	0.50	0.0	0.17	0.44
	Females (14, 17, 20, 21)	4	1.08 (0.96–1.21)	2.0	3	0.58	0.0	0.17	0.25
	Males (14)	1*	0.86 (0.32–2.30)	---	---	---	---	---	---
recessive	All (14, 17, 20, 21)	4	1.00 (0.84–1.19)	2.4	3	0.50	0.0	0.50	0.21
	Females (14, 17, 20, 21)	4	1.24 (0.82–1.88)	4.9	3	0.18	38.8	0.04	0.005

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Migraine									
						Heterogeneity		Small study effects p-value	
Genetic model	**Participants**	**No of studies**	**Pooled OR 95% CI)**	**Q**	**df**	**p-value**	**I^2 in %**	**Begg test**	**Egger's test**
	Males (14)	1*	1.24 (0.22–6.93)	---	---	---	---	---	---

Migraine without aura									
						Heterogeneity		Small study effects p-value	
Genetic model	Participants	No of studies	Pooled OR (95% CI)	Q	df	p-value	I^2 in %	Begg test	Egger's test
additive	All (14, 17, 19–22)	6	1.00 (0.83–1.22)	16.3	5	0.006	69.3	0.35	0.81
	Females (14, 17, 19–22)	6	1.02 (0.96–1.09)	3.8	5	0.58	0.0	0.57	0.60
	Males (14, 19, 20, 22)	4	1.05 (0.63–1.78)	6.9	3	0.07	56.8	0.50	0.96
dominant	All (14, 17, 19–22)	6	1.01 (0.82–1.25)	11.6	5	0.04	56.9	0.35	0.86
	Females (14, 17, 19–22)	6	1.01 (0.93–1.10)	1.8	5	0.88	0.0	0.85	0.28
	Males (14, 19, 20, 22)	4	1.10 (0.55–2.20)	8.0	3	0.046	62.5	1.0	0.89
recessive	All (14, 17, 19–22)	6	1.07 (0.77–1.50)	9.4	5	0.10	46.7	0.35	0.62
	Females (14, 17, 19–22)	6	1.09 (0.92–1.30)	5.3	5	0.38	5.5	0.85	0.78
	Males (14, 19, 22)	3*	1.23 (0.51–3.00)	0.7	2	0.69	0.0	0.60	0.31

*effect estimates for some studies could not be calculated due to small numbers