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Sex Hormone Receptor Gene Polymorphisms and Migraine: A Systematic Review and Meta-Analysis

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Abstract

Data on the association between sex hormone receptor polymorphisms and migraine are conflicting. We performed a systematic review and meta-analysis on this topic searching for studies published until August 2009. For each study we calculated odds ratios (ORs) and 95% confidence intervals (CIs) assuming additive, dominant, and recessive genetic models. We then calculated pooled ORs and 95% CIs. Among the 7 genes targeted 4 variants were investigated in multiple studies. Effect estimates from an additive model suggest that the *ESR-1* 594 G>A (pooled OR 1.37; 95% CI 1.02–1.83) and *ESR-1* 325 C>G (pooled OR 1.16; 95% CI 1.03–1.32) variants are associated with any migraine. This pattern does not differ between migraine with and without aura. In contrast the *ESR-1* Pvu II C>T and *PGR* PROGINS insert polymorphism do not appear to be associated with migraine. Results were driven by studies among Caucasians and may differ in other ethnic groups.

Keywords

migraine; sex hormone receptors; polymorphisms; meta-analysis

Introduction

Migraine is a common, chronic disorder characterized by recurrent headache attacks and combinations of gastrointestinal and autonomic nervous system symptoms (1), affecting 10–20% of the population. Up to one third of migraine patients experience an aura prior to or during the migraine headache.

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Population-based, clinical, and physiological studies support an important role for sex hormones in the pathogenesis of migraine. For example migraine prevalence is 3- to 4-fold higher among women than men, a subgroup of women suffer from menstrual migraine or menstruation related migraine, migraine prevalence often changes during pregnancy or after menopause, and both estrogen withdrawal and changes in estrogen levels can trigger migraine attacks (2–4). These findings have prompted studies investigating the association of variants in genes coding for proteins in sex hormone receptor pathways and metabolism with migraine.

Gene variants located in the estrogen receptor 1 gene (*ESR-1*) (5–11), estrogen receptor 2 gene (*ESR-2*) (11), progesterone receptor gene (*PGR*) (7,8,12), androgen receptor gene (*AR*) (12), follicle stimulating hormone receptor gene (*FSHR*) (11), nuclear receptor interacting protein 1 (*NRIP1*) (11), and cytochrome P450, family 19, subfamily A, polypeptide 1 gene (*CYP19A1*) (11) have been targeted. However, many results were either contradictory, which may be due to differences in ethnicity, sample sizes, and the proportion of MA and MO among the study populations, or have not been replicated in independent populations.

We sought to summarize the current evidence on the association between variants in genes coding for proteins in sex hormone receptor pathways and metabolism 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 (13). Two investigators (M.S., P.M.R.) independently searched MEDLINE, EMBASE, and Science Citation Index from inception to August 2009 combining text words and MESH terms, were appropriate, for sex hormones (“hormones” or “sex hormones” or “estrogen” or “progesterone”) 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 did not use any language restrictions. In addition, we manually searched the reference list of all primary articles and review articles.

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 and healthy control subjects.
3. Authors must provide information on genotype frequencies of the investigated polymorphisms or sufficient data to calculate these.
4. In studies with overlapping cases and/or controls the largest study with extractable data was included.
5. Studies must be published as full articles.

In a first step, two investigators (M.S., T.K.) 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 remaining studies in their entirety. Studies were excluded if they did not meet all criteria.

Data extraction

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 and title of study, year of publication, country of origin, ethnicity of population investigated, setting (clinic vs. population), study design, genotyping method, migraine status (any migraine, MA, MO), age and gender of study individuals, study size, allele and genotype frequencies, and information on additional genetic variants as well as gene-gene and gene-environment interactions, if investigated. If not given, genotype frequencies were calculated where possible. We did not contact the authors to collect further information.

Statistical analysis

We first used logistic regression to calculate odds ratios (ORs) and 95% confidence intervals (CIs) for the association between sex hormone receptor polymorphisms and migraine assuming additive, dominant, and recessive genetic models. We calculated these for polymorphisms which were investigated in at least two independent study populations. 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 with carriers of the heterozygous and homozygous wild-type genotype. We also determined Hardy-Weinberg Equilibrium (HWE) for the control group in each study. We investigated any migraine, MA, and MO.

We then pooled results from all studies and subsequently stratified analyses by ethnicity and gender where applicable.

We weighted the log of the ORs by the inverse of their variance to obtain pooled relative risk estimates. We ran random-effects models which include assumptions on potential variability across studies. We performed the DerSimonian and Laird Q test for heterogeneity and also calculated the I^2 statistic for each analysis (14). This statistic describes the percentage of total variation across studies that is due to heterogeneity rather than chance (25%: low, 50%: medium, 75%: high heterogeneity). We used Galbraith plots to visually examine the impact of individual studies on the overall homogeneity test statistic. We evaluated potential publication bias visually by examining for possible skewness in funnel plots (15) and statistically with the methods described by Begg and Mazumdar (15) and Egger (16). The latter method uses a weighted regression approach to investigate the association between outcome effects (log odds ratio) and its standard error in each study.

We considered a p-value<0.05 as statistically significant.

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 previously published data, 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 had identified 9 studies (5–12,17). We excluded one more study (17) after evaluating the remaining articles in its entirety and were left with 8 studies for this analysis.

Study characteristics

Seven genes involved in sex hormone receptor pathways and metabolism have been investigated in the identified studies: estrogen receptor 1 gene (*ESR-1*) (5–11), estrogen receptor 2 gene (*ESR-2*) (11), progesterone receptor gene (*PGR*) (7,8,12), androgen receptor gene (*AR*) (12), follicle stimulating hormone receptor gene (*FSHR*) (11), nuclear receptor interacting protein 1 (*NRIP1*) (11), cytochrome P450, family 19, subfamily A, polypeptide 1 gene (*CYP19A1*) (11). One study further investigated the methylenetetrahydrofolate reductase gene (*MTHFR*) (9). This gene will not be considered for the present analysis.

Table 1a summarizes the characteristics of the 8 studies included according to the polymorphisms investigated. Four studies (5 study populations: 2 populations from 1 study (6)) have investigated the *ESR-1* 594 G>A (rs2228480) (6,7,9,10), 6 the *ESR-1* 325 C>G (rs1801132) (5,7–11), 2 the *ESR-1* Pvu II C>T (rs2234693) (5,8), 2 the *ESR-1* 30 T>C (rs2077647) (7,9), and 3 (4 study populations: 2 populations from 1 study (12)) the *PGR* PROGINS insert (*Alu* insert) polymorphism (7,8,12).

Additional polymorphisms have only been looked at in single studies (Table 1b): various *ESR-1* polymorphisms (7,9), *AR* CAG repeat (12), *FSHR* rs6166 (11), *ESR-2* rs4986938 (11), *CYP19A1* rs10046 (11), *NRIP1* rs2229741 (11).

For the meta-analysis we will only consider polymorphisms that have been investigated in at least two independent study populations. The data given in 1 (9) of the 2 (7,9) studies investigating the *ESR-1* 30 T>C polymorphism did not allow calculating genotype frequencies. Hence, we could not determine pooled relative risk estimates and we did not include this polymorphism in our meta-analysis.

Almost all studies were performed in Caucasian populations. One study was in an Indian population (8). Further, most (5,6,8,10–12), but not all studies (7,9), presented results stratified by gender in addition to results for the overall study population.

The allele and genotype frequencies for the investigated polymorphisms for migraineurs and controls in each of the studies are summarized in Table 2.

Table 3 summarizes for each of the studies the p-value for the Hardy-Weinberg Equilibrium (HWE) in the controls as well as ORs (95% CI) for the association between the polymorphisms and migraine assuming additive, dominant, and recessive genetic models.

Table 4 summarizes the pooled effect estimates, measures for heterogeneity, and tests for publication bias for each of the polymorphisms.

Association between the *ESR-1* 594 G>A polymorphism and migraine

Among the 5 study populations from 4 studies investigating the association between the *ESR-1* 594 G>A polymorphism and migraine, there was a statistically significant positive association in two study populations (6) suggesting an increased risk for migraine among carriers of the A allele, which did not appear in the other studies (7,9,10) (Table 3).

The pooled effect estimates among all studies suggest that the A allele is associated with an increased risk for any migraine (additive mode: pooled OR 1.37; 95% CI 1.02–1.83) (Table 4). The association appeared most pronounced for carriers of the GA/AA genotype (dominant mode: pooled OR 1.50; 95% CI 1.10–2.06). However, there was medium heterogeneity across all studies (dominant mode: $I^2=64.5\%$). Further, the increased risk for the GA/AA genotype appeared to be slightly higher among men (dominant mode: pooled OR 1.80; 95% CI 1.16–2.80) than among women (dominant mode: pooled OR 1.56; 95% CI

0.98–2.48), where it did not reach statistical significance. In addition, heterogeneity was medium among studies investigating women (dominant mode: $I^2=73.5\%$) and absent among studies investigating men. The results for MA and MO were very similar. Neither Begg's test nor Egger's test indicated publication bias for the dominant model.

Association between the *ESR-1* 325 C>G polymorphism and migraine

Among the 6 studies investigating the *ESR-1* 325 C>G polymorphism, 2 suggested an increased risk for migraine among carriers of the GG genotype (recessive mode), which appeared to be strongest among women (10,11), while the others did not find an altered risk (5,7–9) (Table 3).

The pooled effect estimates suggest that the G allele is associated with a slightly increased risk for having any migraine (additive mode: pooled OR 1.16; 95% CI 1.03–1.32) (Table 4). The association was most pronounced for carriers of the GG genotype (recessive mode: pooled OR 1.40; 95% CI 0.93–2.11); however, this result did not reach statistical significance. Further, the effect estimates among studies in Caucasian populations were very similar to the overall result, which included a study in the Indian population. The association between the GG genotype and any migraine was stronger among women than men. Heterogeneity among the studies was low (recessive mode: $I^2=38.9\%$). The overall association was the same for MA (recessive mode: pooled OR 1.60; 95% CI 1.19–2.17) and MO (recessive mode: pooled OR 1.44; 95% CI 0.97–2.13). In addition, the pattern of a stronger association among women than men also occurred for MA and MO. Neither Begg's test nor Egger's test indicated publication bias when assuming a recessive model.

Association between the *ESR-1* Pvu II C>T polymorphism and migraine

Among the 2 studies investigating the *ESR-1* Pvu II C>T polymorphism, 1 found an increased risk for migraine among carriers of the T allele (8), while the other did not (5) (Table 3).

The pooled effect estimates between the 2 studies neither suggest an association for any of the genotypes with any migraine, MA or MO nor a difference between women and men when looking at any migraine. One study provided gender specific effect estimates for MA and MO, which suggested a higher risk among women than men (8). Heterogeneity between the 2 studies was high. This is most likely due to the low number of studies and remaining uncertainties which may include genotypic ethnic differences. Formal investigation using Begg's test did not indicate publication bias.

Association between the *PGR* PROGINS insert polymorphism and migraine

Among the 4 study populations investigating the *PGR* PROGINS insert polymorphism, 2 found an increased risk among carriers of the “2” allele (=Alu insert) (12), 1 found a protective association (8), and 1 did not find an association (7) (Table 3).

The pooled effect estimates among all studies do not suggest an association between any of the genotypes and any migraine (additive mode: pooled OR 1.02; 95% CI 0.55–1.87) (Table 4). This finding did not differ between MA (additive mode: pooled OR 1.11; 95% CI 0.68–1.81) and MO (additive mode: pooled OR 1.01; 95% CI 0.48–2.13). However, further analyses suggested that there may be a moderately increased association for having any migraine among Caucasians, which appeared strongest in a dominant model (pooled OR 1.49; 95% CI 0.98–2.26). While the direction and association of the effect estimates among Caucasians were similar for both migraine subgroups, they only reached statistical significance in MA (dominant mode: pooled OR 1.49; 95% CI 1.10–2.01), but not MO (dominant mode: pooled OR 1.56; 95% CI 0.79–3.09). Heterogeneity across all studies was

medium to high for any migraine, MA, and MO, it was low among the studies investigating MA among Caucasians (dominant mode: $I^2=4.3\%$). This may support the significant results for Caucasians among MA.

Sensitivity analyses

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

For the association between the *ESR-1* 594 G>A polymorphism and migraine Galbraith plots did not identify individual studies as significant sources of heterogeneity for any migraine and MO (dominant model). One study (6) was excluded when looking at MA, which lowered the effect estimates, however, the association remained statistically significant (dominant mode: pooled OR 1.18; 95% CI 1.01–1.38).

For the association between *ESR-1* 325 C>G polymorphism and any migraine, MA, and MO, Galbraith plots did not identify individual studies as important sources of heterogeneity in any of the models.

For the association between the *ESR-1* Pvu II C>T polymorphism and migraine we did not perform a formal sensitivity analysis, because 1) only 2 studies were pooled and 2) the heterogeneity index was high, already suggesting that pooled results need to be interpreted with caution.

Effect estimates from the sensitivity analysis did not change the association between the *PGR* PROGINS insert polymorphism and migraine. They were all slightly higher for any migraine, MA, and MO assuming additive or dominant models. For example, after excluding 2 studies (8,12) the pooled OR for the association with any migraine assuming a dominant model was 1.34 (95% CI 0.74–2.41).

Discussion

The results of this meta-analysis suggest an association between the *ESR-1* 594 G>A and 325 C>G polymorphisms and migraine. The risk for MA and MO appears to increase by 40–60% for each of the variants and follows a dominant model in case of the *ESR-1* 594 G>A and a recessive model in case of the *ESR-1* 325 C>G polymorphism. In contrast, pooled results for the *ESR-1* Pvu II C>T and the *PGR* PROGINS insert polymorphisms did not suggest an association with migraine. This pattern of association may differ by ethnicity. However, while most studies were conducted in Caucasian populations, only 1 was done in an Indian population (8), which does not allow an evaluation among non-Caucasian populations. Further, given a lack of replication studies, we cannot conclusively assess an association of additional polymorphisms in *ESR-1* (7,9), *AR* (12), *FSHR* (11), *ESR-2* (11), *CYP19A1* (11), and *NR1P1* (11) with migraine or migraine subgroups.

Evidence from population-based, clinical, and physiological studies suggests a pivotal role for sex hormones in the pathogenesis of migraine (2–4). In addition, association studies have investigated multiple variants in genes coding for sex hormone receptors or proteins involved in their pathways and metabolism. Among those, multiple studies looked at the *ESR-1* 594 G>A (6,7,9,10), *ESR-1* 325 C>G (5,7–11), *ESR-1* Pvu II C>T (5,8), *ESR-1* 30 T>C (7,9), and *PGR* PROGINS insert polymorphisms (7,8,12). Apart from the 2 studies, that did not find an association between the *ESR-1* 30 T>C polymorphism and migraine, results from studies in the other polymorphisms were contradictory.

ESR-1 is located on chromosome 6q25.1 and has eight exons (18). The receptor is expressed, for example, in the hypothalamus, limbic system, hippocampus, and the brainstem of the human brain (19), regions which are implicated in many pain syndromes including migraine. The *ESR-1* 594 G>A (exon 8) and 325 C>G (exon 4) polymorphisms are synonymous, hence, their functional implication is unknown (20). While our results support that the variant alleles are associated with an increased risk for migraine, they are likely not causative, since they do not alter the amino acid sequence of the receptor. They may be in linkage disequilibrium with another causative variant or set of variants (haplotype) within *ESR-1*. The Pvu II C>T polymorphism is intronic, thus located in a non-coding region. It does not alter the protein sequence, but may affect splicing and thus modify protein production (21). While our overall pooled results do not support a role for this variant in migraine, the individual results from the 2 available studies may suggest a difference between Caucasians (5) and Indians (8) (also reflected by the large heterogeneity for the pooled effect estimates). We may speculate that post-transcriptional modification such as splicing differs between ethnic groups. *PGR* is located on chromosome 11q22 (22). Progesterone receptors are located in various human brain regions (23) and their expression is regulated by estrogen and progesterone levels (24). The PROGINS polymorphism is a 306bp long *Alu* insertion in intron 7 and may negatively affect progesterone receptor expression (25). Our pooled analysis suggests that this *Alu* insert increases the risk for migraine only among Caucasians.

Some limitations need to be considered. Firstly, migraine is biologically heterogeneous. Although in all studies patients were classified according to the criteria established by the International Headache Society (26,27), the clinical spectrum among patients is wide, which may be a source of misclassification. Secondly, while sample sizes for migraineurs and controls in the studies are about 200 or more (Table 1), power to detect overall and more so gender- or aura-specific associations in subgroups may not be adequate. In addition, not all studies looking at one polymorphism investigated any migraine and also presented stratified analyses according to aura subtype and gender. Further, the total number of studies identified was eight, which is limited. These studies looked at many different gene variants and not all studies investigated the same ones. For example, there were only two studies investigating the *ESR-1* Pvu II C>T polymorphism with conflicting results (5,8). The non-significant results from the pooled analysis may be due to insufficient pooled sample size. Thirdly, power also depends on the minor allele frequencies of the polymorphisms investigated. For example, the minor allele frequency for the *PGR* PROGINS insert polymorphism is less than 10% in some of the studies leaving few or no observations among the homozygous ‘22’ carriers. Although pooling available study results increases precision and power, there may still be remaining uncertainties. Fourthly, initial publications of genetic association studies oftentimes report positive associations, while successive ones do not find an association. We have performed this meta-analysis at an early stage; however, we still consider it valuable. While the systematic review part allows an overview of the available studies including individual results, the meta-analytic part also enables evaluation of magnitude and direction of combined results from pooled effect estimates including sources of heterogeneity. Fifthly, ethnicity may be a source of heterogeneity in the association between polymorphisms in genes coding for proteins in sex hormone receptor pathways and metabolism and migraine. The available data suggest this for the *ESR-1* Pvu II C>T and *PGR* PROGINS insert polymorphisms. However, only one study was performed in a non-Caucasian population. Sixthly, residual heterogeneity among Caucasians for the *ESR-1* 594 G>A, *ESR-1* Pvu II C>T, and *PGR* PROGINS insert polymorphisms were medium to high, indicating that the effect estimates carry further unidentified sources of uncertainties. In addition, the results from the single study among Indians (8), suggesting an increased risk for migraine among carriers of the *ESR-1* Pvu II T allele and a reduced risk among carriers of the *PGR* PROGINS *Alu* insertion await replication. Seventhly, in one

study (10) genotype distribution of *ESR-1* 594 G>A and 325 C>G and in another (8) of *ESR-1* Pvu II C>T was in Hardy-Weinberg Disequilibrium. Eighthly, we only used extractable data from the papers. One (9) of 2 (7,9) studies investigating the *ESR-1* 30 T>C polymorphism did not allow us to extract genotype frequencies, hence, we could not calculate pooled effect estimates. However, both studies did not find an association with migraine, which would likely not change in a pooled analysis. Finally, since we did not have primary data among the studies investigating multiple polymorphisms, we were not able to perform haplotype analyses or investigate potential gene-gene interactions. Such interactions were suggested by individual studies (8,11).

Additional research is warranted to further delineate the association between gene variants coding for proteins in sex hormone receptor pathways and metabolism and migraine, among Caucasian and more so among non-Caucasian populations. We suggest the following criteria to be applied in future studies: Firstly, studies need to be adequately powered. Power in genetic association studies is determined by both sample size and allele frequencies. Samples sizes of at least several hundred migraineurs and non-migraineurs are needed to detect at least moderate associations. If the minor allele frequency of a polymorphism investigated is low the sample size must be further increased to have adequate power. Secondly, results should not just be presented overall, but also stratified by gender and migraine aura status. This must also be considered with regard to power. Thirdly, investigators should use standardized migraine classification including aura status. Finally, analyses should focus on main gene effects first, since power to detect gene-gene interactions is often limited.

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Figure 1.
Process of study selection

Table 1

Characteristics of the included studies according to the polymorphisms investigated

a) Polymorphisms that have been investigated in at least 2 papers with extractable data									
<i>ESR-I 594 G>A polymorphism (rs2228480)</i>									
Study size with genotypic information									
Author and year	Country	Ethnicity	Setting	Gender	Controls	Any migraine	MA	MO	Comment
Colson, 2004(6)	Australia	Caucasian	population	women+men women men	224 167 57	224 167 57	139 103 36	85 64 21	Study population 1 from paper Colson, 2004(6)
Colson, 2004(6)	Australia	Caucasian	population	women+men women men	260 224 36	260 224 36	221 191 30	39 33 6	Study population 2 from paper Colson, 2004(6)
Oterino, 2006(10)	Spain	Caucasian	clinic	women+men women men	232 142 90	367 286 81	197 155 42	170 131 39	Other polymorphisms investigated: rs1801132 (<i>ESR-I</i> 325 C>G).
Kaunisto, 2006(9)	Finland	Caucasian	mixed population and clinic	women+men	900	-----	898	-----	Other polymorphisms investigated: 6 <i>MTHFR</i> and 26 <i>ESR-I</i> polymorphisms.
Corominas, 2009(7)	Spain	Caucasian	NS	women+men	210	210	86	102	'Any migraine' also contains 22 patients with hemiplegic migraine. Other polymorphisms investigated: rs1801132 (<i>ESR-I</i> 325 C>G), rs2077647 (<i>ESR-I</i>), and <i>PGR</i> PROGENS insert.
Total number of subjects					1,826	1,061	1,541	396	
<i>ESR-I 325 C>G polymorphism (rs1801132)</i>									
Study size with genotypic information									
Author and year	Country	Ethnicity	Setting	Gender	Controls	Any migraine	MA	MO	Comment
Colson, 2006(5)	Australia	Caucasian	clinic	women+men women	249 189	231 167	141 -----	75 -----	'Any migraine' also contains 15 patients with 'MA+MO'.

a) Polymorphisms that have been investigated in at least 2 papers with extractable data										
ESR-I 594 G>A polymorphism (rs2228480)										
Study size with genotypic information										
Author and year	Country	Ethnicity	Setting	Gender	Controls	Any migraine	MA	MO	Comment	
				men	60	64	-----	-----	Other polymorphisms investigated: rs2234693 (ESR-I Pvu II C>T).	
Oterino, 2006(10)	Spain	Caucasian	clinic	women+men women men	232 142 90	367 286 81	197 155 42	170 131 39	Compared to dbSNP and other studies the allele and genotype frequencies in the paper appear flipped because the minus strand instead of the plus strand appears to be used to determine the mutation. Other polymorphisms investigated: rs2228480 (ESR-I 594 G>A).	
Kaunisto, 2006(9)	Finland	Caucasian	mixed population and clinic	women+men	888	-----	896	-----	Other polymorphisms investigated: 6 MTHFR and 26 ESR-I polymorphisms.	
Oterino, 2008(11)	Spain	Caucasian	clinic	women+men women men	372 263 109	356 269 87	198 152 46	158 117 41	Compared to dbSNP and other studies the allele and genotype frequencies in the paper appear flipped because the minus strand instead of the plus strand appears o be used to determine the mutation. Other polymorphisms investigated: rs6166 (FSHR), rs4986938 (ESR-2), rs10046 (CYP19A1), and rs2229741 (NR1P1).	
Corominas, 2009(7)	Spain	Caucasian	NS	women+men	210	210	86	102	'Any migraine' also contains 22 patients with hemiplegic migraine. Other polymorphisms investigated: rs2228480 (ESR-I 594 G>A), rs2077647 (ESR-I), and PGR PROGINS insert.	
Joshi, 2009(8)	India	Indian	clinic	women+men women men	217 150 67	217 150 67	84 63 21	133 87 46	Other polymorphisms investigated: rs2234693 (ESR-I Pvu II C>T) and PGR PROGINS insert.	
Total number of subjects					2,168	1,381	1,602	638		
ESR-I Pvu II C>T polymorphism (rs2234693)										
Study size with genotypic information										
Author and year	Country	Ethnicity	Setting	Gender	Controls	Any migraine	MA	MO	Comment	
Colson, 2006(5)	Australia	Caucasian	clinic	women+men	202	231	145	73	'Any migraine' also contains 13 patients with 'MA+MO'. Other polymorphisms investigated: rs1801132 (ESR-I 325 C>G).	

a) Polymorphisms that have been investigated in at least 2 papers with extractable data											
ESR-I 594 G>A polymorphism (rs2228480)											
					Study size with genotypic information						
Author and year	Country	Ethnicity	Setting	Gender	Controls	Any migraine	MA	MO	Comment		
				women	140	167	----	----			
				men	62	64	----	----			
Joshi, 2009(8)	India	Indian	clinic	women+men	217	217	84	133	Other polymorphisms investigated: rs1801132 (ESR-I 325 C>G) and PGR PROGINS insert.		
				women	150	150	63	87			
				men	67	67	21	46			
Total number of subjects					419	448	229	206			
PGR PROGINS insert											
					Study size with genotypic information						
Author and year	Country	Ethnicity	Setting	Gender	Controls	Any migraine	MA	MO	Comment		
Colson, 2005(12)	Australia	Caucasian	clinic	women+men	216	232	144	88	Study population 1 from paper Colson, 2005(12)		
				women	151	165	----	----	Other polymorphisms investigated: CAG repeat in exon 1 of the AR.		
				men	65	67	----	----			
Colson, 2005(12)	Australia	Caucasian	clinic	women+men	263	277	227	50	Study population 2 from paper Colson, 2005(12)		
				women	222	238	----	----	Other polymorphisms investigated: CAG repeat in exon 1 of the AR.		
				men	41	39	----	----			
Corominas, 2009(7)	Spain	Caucasian	NS	women+men	210	210	86	102	'Any migraine' also contains 22 patients with hemiplegic migraine.		
									Other polymorphisms investigated: rs2228480 (ESR-I 594 G>A), rs2077647 (ESR-I), and rs1801132 (ESR-I 325 C>G).		
Joshi, 2009(8)	India	Indian	clinic	women+men	217	217	84	133	Other polymorphisms investigated: rs1801132 (ESR-I 325 C>G) and rs2234693 (ESR-I Pvu II C>T).		
				women	150	150	63	87			
				men	67	67	21	46			
Total number of subjects					906	936	541	373			

b) Polymorphisms that have been investigated in single studies						
Polymorphism(s)	Author and year	Country	Ethnicity	Setting	Association	
AR CAG repeat in exon 1	Colson, 2005(12)	Australia	Caucasian	clinic	NO	
26 <i>ESR-1</i> polymorphisms (including rs1801132 and rs2228480)	Kaunisto, 2006(9)	Finland	Caucasian	mixed population and clinic	rs6557170, rs2347867, rs6557171, rs4870062, rs1801132 were nominally associated with MA, but did not remain significant after correction for multiple testing.	
<i>FSHR</i> rs6166	Oterino, 2008(11)	Spain	Caucasian	clinic	YES	
<i>ESR-2</i> rs4986938	Oterino, 2008(11)	Spain	Caucasian	clinic	YES	
<i>CYP19A1</i> rs10046	Oterino, 2008(11)	Spain	Caucasian	clinic	YES	
<i>NR1P</i> rs2229741	Oterino, 2008(11)	Spain	Caucasian	clinic	YES	
<i>ESR-1</i> rs2077647	Corominas, 2009(7)	Spain	Caucasian	NS	NO	

Table 2
Allele and genotype frequencies of the included studies according to the investigated polymorphisms

ESR-1 594 G>A polymorphism (rs2228480)									
		Allele frequencies, n (%)			Genotype frequencies, n (%)				
Author	Population	Disease status	Study size	G	A	GG	GA	AA	
Colson, 2004 ^{*,(6)}	women+men	controls	224	323 (72.0)	125 (28.0)	112 (50.0)	99 (44.0)	13 (6.0)	
		any migraine	224	282 (63.0)	166 (37.0)	81 (36.0)	120 (54.0)	23 (10.0)	
		MA	139	176 (63.0)	102 (37.0)	55 (40.0)	66 (47.0)	18 (13.0)	
		MO	85	106 (62.0)	64 (38.0)	26 (31)	54 (64)	5 (6.0)	
	women	controls	167	239 (72.0)	95 (28.0)	84 (50.0)	71 (43.0)	12 (7.0)	
		any migraine	167	213 (64.0)	121 (36.0)	63 (38.0)	87 (52.0)	17 (10.0)	
		MA	103	135 (66.0)	71 (34.0)	44 (43.0)	47 (46.0)	12 (11.0)	
		MO	64	78 (61.0)	50 (39.0)	19 (30.0)	40 (62.0)	5 (8.0)	
	men	controls	57	84 (74.0)	30 (26.0)	28 (49.0)	28 (49.0)	1 (2.0)	
		any migraine	57	69 (61.0)	45 (39.0)	18 (32.0)	33 (58.0)	6 (10.0)	
		MA	36	41 (57.0)	31 (43.0)	11 (31.0)	19 (53.0)	6 (16.0)	
		MO	21	28 (68.0)	14 (32.0)	7 (33.0)	14 (67.0)	0 (0.0)	
Colson, 2004 ^{*,(6)}	women+men	controls	260	397 (76.0)	123 (24.0)	152 (58.0)	93 (36.0)	15 (6.0)	
		any migraine	260	331 (64.0)	189 (36.0)	103 (40.0)	125 (48.0)	32 (12.0)	
		MA	221	274 (62.0)	168 (38.0)	82 (37.0)	110 (50.0)	29 (13.0)	
		MO	39	57 (73.0)	21 (27.0)	21 (54.0)	15 (38.0)	3 (8.0)	
	women	controls	224	346 (77.0)	102 (23.0)	132 (59.0)	82 (37.0)	10 (4.0)	
		any migraine	224	282 (63.0)	166 (37.0)	88 (39.0)	106 (47.0)	30 (14.0)	
		MA	191	235 (62.0)	147 (38.0)	71 (37.0)	93 (49.0)	27 (14.0)	
		MO	33	47 (71.0)	19 (29.0)	17 (52.0)	13 (39.0)	3 (9.0)	
	men	controls	36	51 (71.0)	21 (29.0)	20 (55.0)	11 (31.0)	5 (14.0)	
		any migraine	36	49 (68.0)	23 (32.0)	15 (42.0)	19 (53.0)	2 (5.0)	
		MA	30	39 (65.0)	21 (35.0)	11 (37.0)	17 (56.0)	2 (7.0)	

ESR-I 594 G>A polymorphism (rs2228480)									
				Allele frequencies, n (%)			Genotype frequencies, n (%)		
Author	Population	Disease status	Study size	G	A		GG	GA	AA
		MO	6	10 (83.0)	2 (17.0)		4 (67.0)	2 (33.0)	0 (0.0)
Oterino, 2006(10)	women+men	controls	232	380 (81.9)	84 (18.1)		161 (69.4)	58 (25.0)	13 (5.6)
		any migraine	367	591 (80.5)	143 (19.5)		240 (65.4)	111 (30.2)	16 (4.4)
		MA	197	317 (80.5)	77 (19.5)		128 (64.9)	61 (31.0)	8 (4.1)
		MO	170	274 (80.6)	66 (19.4)		112 (65.9)	50 (29.4)	8 (4.7)
	women	controls	142	232 (81.8)	52 (18.2)		93 (65.5)	38 (26.8)	11 (7.7)
		any migraine	286	461 (80.6)	111 (19.4)		187 (65.5)	87 (30.3)	12 (4.2)
		MA	155	248 (80.0)	62 (20.0)		99 (63.8)	50 (32.3)	6 (3.9)
		MO	131	213 (81.3)	49 (18.7)		88 (67.2)	37 (28.2)	6 (4.6)
	men	controls	90	156 (86.7)	24 (13.3)		68 (75.6)	20 (20.2)	2 (2.2)
		any migraine	81	130 (80.2)	32 (19.8)		53 (65.4)	24 (29.7)	4 (4.9)
MA		42	69 (82.1)	15 (17.9)		29 (69.0)	11 (26.2)	2 (4.8)	
MO		39	61 (78.2)	17 (21.8)		24 (61.5)	13 (33.4)	2 (5.1)	
Kaunisto, 2006(9)	women+men	controls	900	1458 (81.0)	342 (19.0)		594 (66.0)	270 (30.0)	36 (4.0)
		MA	898	1428 (80.0)	368 (20.0)		566 (63.0)	296 (33.0)	36 (4.0)
Corominas, 2009(7)	women+men	controls	210	361 (86.0)	59 (14.0)		157 (74.8)	47 (22.4)	6 (2.9)
		any migraine	210	360 (85.7)	60 (14.3)		154 (73.3)	52 (24.8)	4 (1.9)
		MA	86	150 (87.2)	22 (12.8)		65 (75.6)	20 (23.3)	1 (1.2)
		MO	102	171 (83.8)	33 (16.2)		72 (70.6)	27 (26.5)	3 (2.9)
ESR-I 325 C>G polymorphism (rs1801132)									
				Allele frequencies, n (%)			Genotype frequencies, n (%)		
Author	Gender	Disease status	Study size	C	G		CC	CG	GG
Colson, 2006(5)	women+men	controls	249	396 (79.0)	102 (21.0)		160 (64.0)	76 (31.0)	13 (5.0)

<i>ESR-1 594 G>A polymorphism (rs2228480)</i>									
			Allele frequencies, n (%)			Genotype frequencies, n (%)			
Author	Population	Disease status	Study size	G	A	GG	GA	AA	
Oterino, 2006(10)		any migraine	231	356 (77.0)	106 (23.0)	133 (58.0)	90 (39.0)	8 (3.0)	
		MA	141	213 (76.0)	69 (24.0)	77 (55.0)	59 (42.0)	5 (3.0)	
		MO	75	120 (80.0)	30 (20.0)	47 (62.0)	26 (35.0)	2 (3.0)	
	women	controls	189	302 (80.0)	76 (20.0)	122 (64.0)	58 (31.0)	9 (5.0)	
		any migraine	167	254 (76.0)	80 (24.0)	94 (56.0)	66 (40.0)	7 (4.0)	
	men	controls	60	94 (78.0)	26 (22.0)	38 (63.0)	18 (30.0)	4 (7.0)	
		any migraine	64	102 (80.0)	26 (20.0)	39 (61.0)	24 (37.0)	1 (2.0)	
	women+men	controls	232	377 (81.3)	87 (18.8)	159 (68.5)	59 (25.5)	14 (6.0)	
		any migraine	367	568 (77.4)	166 (22.6)	238 (64.9)	92 (25.0)	37 (10.1)	
		MA	197	304 (77.2)	90 (22.8)	127 (64.5)	50 (25.4)	20 (10.1)	
		MO	170	264 (77.6)	76 (22.4)	111 (65.3)	42 (24.7)	17 (10.0)	
	women	controls	142	237 (83.5)	47 (16.5)	101 (71.1)	35 (24.7)	6 (4.2)	
		any migraine	286	432 (75.5)	140 (24.5)	179 (62.6)	74 (25.9)	33 (11.5)	
		MA	155	233 (75.2)	77 (24.8)	96 (61.9)	41 (26.5)	18 (11.6)	
		MO	131	199 (76.0)	63 (24.0)	83 (63.4)	33 (25.2)	15 (11.4)	
	men	controls	90	140 (77.8)	40 (22.2)	58 (64.4)	24 (26.7)	8 (8.9)	
		any migraine	81	136 (84.0)	26 (16.0)	59 (72.9)	18 (22.2)	4 (4.9)	
		MA	42	71 (84.5)	13 (15.5)	31 (73.8)	9 (21.4)	2 (4.8)	
		MO	39	65 (83.3)	13 (16.7)	28 (71.8)	9 (23.1)	2 (5.1)	
	women+men	controls	888	1363 (77.0)	413 (23.0)	513 (58.0)	337 (38.0)	38 (4.0)	
Kaunisto, 2006(9)		MA	896	1328 (74.0)	464 (26.0)	499 (57.0)	330 (37.0)	67 (7.0)	
Oterino, 2008(11)	women+men	controls	372	615 (82.7)	129 (17.3)	257 (69.1)	101 (27.2)	14 (3.8)	
		any migraine	356	557 (78.2)	155 (21.8)	230 (64.6)	97 (27.2)	29 (8.1)	
		MA	198	308 (77.8)	88 (22.2)	126 (63.6)	56 (28.3)	16 (8.1)	

ESR-1 594 G>A polymorphism (rs2228480)									
				Allele frequencies, n (%)			Genotype frequencies, n (%)		
Author	Population	Disease status	Study size	G	A	GG	GA	AA	
Corominas, 2009(7)	women	MO	158	249 (78.8)	67 (21.2)	104 (65.8)	41 (25.9)		13 (8.2)
		controls	263	438 (83.3)	88 (16.7)	185 (70.3)	68 (25.9)		10 (3.8)
		any migraine	269	411 (76.4)	127 (23.6)	167 (62.1)	77 (28.6)		25 (9.3)
		MA	152	230 (75.7)	74 (24.3)	92 (60.5)	46 (30.3)		14 (9.2)
	MO	117	181 (77.4)	53 (22.6)	75 (64.1)	31 (26.5)		11 (9.4)	
	men	controls	109	177 (81.2)	41 (18.8)	72 (66.0)	33 (30.3)		4 (3.7)
		any migraine	87	146 (83.9)	28 (16.1)	63 (72.4)	20 (23.0)		4 (4.6)
		MA	46	78 (84.8)	14 (15.2)	34 (73.9)	10 (21.7)		2 (4.3)
		MO	41	68 (82.9)	14 (17.1)	29 (70.7)	10 (24.4)		2 (4.9)
	women+men	controls	210	339 (80.7)	81 (19.3)	136 (64.8)	67 (31.9)		7 (3.3)
any migraine		210	338 (80.5)	82 (19.5)	140 (66.7)	58 (27.6)		12 (5.7)	
MA		86	135 (78.5)	37 (21.5)	55 (64.0)	25 (29.1)		6 (7.0)	
MO		102	169 (82.8)	35 (17.2)	72 (70.6)	25 (24.5)		5 (4.9)	
Joshi, 2009(8)	women+men	controls	217	272 (62.7)	162 (37.3)	81 (37.3)	110 (50.7)		26 (12.0)
		any migraine	217	265 (61.1)	169 (38.9)	75 (34.6)	115 (53.0)		27 (12.4)
		MA	84	106 (63.1)	62 (36.9)	32 (38.1)	42 (50.0)		10 (11.9)
		MO	133	159 (59.8)	107 (40.8)	43 (32.3)	73 (54.9)		17 (12.8)
	women	controls	150	185 (61.7)	115 (38.3)	53 (35.3)	79 (52.7)		18 (12.0)
		any migraine	150	185 (61.7)	115 (38.3)	55 (36.7)	75 (50.0)		20 (13.3)
		MA	63	82 (65.1)	44 (34.9)	26 (41.3)	30 (47.6)		7 (11.6)
		MO	87	103 (59.2)	71 (40.8)	29 (33.3)	45 (51.7)		13 (14.9)
	men	controls	67	87 (64.9)	47 (35.1)	28 (41.8)	31 (46.3)		8 (11.9)
		any migraine	67	80 (59.7)	54 (40.3)	20 (29.9)	40 (59.7)		7 (10.4)
MA		21	24 (57.1)	18 (42.9)	6 (28.6)	12 (57.1)		3 (14.3)	
MO		46	56 (60.9)	36 (39.1)	14 (30.4)	28 (60.9)		4 (8.7)	

<i>ESR-I 594 G>A polymorphism (rs2228480)</i>									
				Allele frequencies, n (%)		Genotype frequencies, n (%)			
Author	Population	Disease status	Study size	G	A	GG	GA	AA	
<i>ESR-I Pvu II C>T (rs2234693)</i>									
				Allele frequencies, n (%)		Genotype frequencies, n (%)			
Author	Gender	Disease status	Study size	C	T	CC	CT	TT	
Colson, 2006(5)	women+men	controls	202	189 (47.0)	215 (53.0)	46 (23.0)	97 (48.0)	59 (29.0)	
		any migraine	231	232 (50.0)	230 (50.0)	55 (24.0)	122 (53.0)	54 (23.0)	
		MA	145	142 (49.0)	148 (51.0)	29 (20.0)	84 (58.0)	32 (22.0)	
		MO	73	77 (53.0)	69 (47.0)	22 (30.0)	33 (45.0)	18 (25.0)	
	women	controls	140	138 (49.0)	142 (51.0)	34 (24.0)	70 (50.0)	36 (26.0)	
Joshi, 2009(8)		any migraine	167	167 (50.0)	167 (50.0)	38 (23.0)	91 (54.0)	38 (23.0)	
	men	controls	62	51 (41.0)	73 (59.0)	12 (19.0)	27 (44.0)	23 (37.0)	
		any migraine	64	65 (51.0)	63 (49.0)	17 (27.0)	31 (48.0)	16 (25.0)	
	women+men	controls	217	287 (66.1)	147 (33.9)	88 (40.6)	111 (51.2)	18 (8.3)	
		any migraine	217	230 (53.0)	204 (47.0)	47 (21.7)	136 (62.7)	34 (15.7)	
		MA	84	86 (51.2)	82 (48.8)	14 (16.7)	58 (69.0)	12 (14.3)	
		MO	133	144 (54.1)	122 (45.9)	33 (24.8)	78 (58.6)	22 (16.5)	
	women	controls	150	201 (67.0)	99 (33.0)	61 (40.7)	79 (52.7)	10 (6.7)	
		any migraine	150	161 (53.7)	139 (46.3)	34 (36.7)	93 (50.0)	23 (13.3)	
		MA	63	65 (51.6)	61 (58.4)	10 (15.9)	45 (71.4)	8 (12.7)	
		MO	87	96 (55.2)	78 (44.8)	24 (27.6)	48 (55.2)	15 (17.2)	
	men	controls	67	86 (64.2)	48 (35.8)	27 (40.3)	32 (47.8)	8 (11.9)	
		any migraine	67	69 (51.5)	65 (48.5)	13 (19.4)	43 (64.2)	11 (16.4)	
		MA	21	21 (50.0)	21 (50.0)	4 (19.0)	13 (61.9)	4 (19.0)	
		MO	46	48 (52.2)	44 (47.8)	9 (19.6)	30 (65.2)	7 (15.2)	

<i>ESR-1 594 G>A polymorphism (rs2228480)</i>											
Author	Population	Disease status	Study size	G	A	Allele frequencies, n (%)	Genotype frequencies, n (%)				
							GA	GG	GA	AA	
<i>PGR PROGINS insert</i>											
Author	Gender	Disease status	Study size	1	2	Allele frequencies, n (%)	Genotype frequencies, n (%)				
							11	12	11	12	22
Colson, 2005 ⁷ (12)	women+men	controls	216	395 (91.0)	37 (9.0)		182 (84.0)	31 (15.0)			3 (1.0)
		any migraine	232	401 (86.0)	63 (14.0)		173 (75.0)	55 (23.0)			4 (2.0)
		MA	144	253 (88.0)	35 (12.0)		113 (78.0)	27 (19.0)			4 (3.0)
		MO	88	148 (84.0)	28 (16.0)		60 (68.0)	28 (32.0)			0 (0.0)
	women	controls	151	287 (95.0)	15 (5.0)		138 (91.0)	11 (7.0)			2 (2.0)
		any migraine	165	293 (89.0)	37 (11.0)		130 (79.0)	33 (20.0)			2 (1.0)
Colson, 2005 ⁷ (12)	men	controls	65	108 (83.0)	22 (17.0)		44 (68.0)	20 (31.0)			1 (1.0)
		any migraine	67	108 (81.0)	26 (19.0)		43 (64.0)	22 (33.0)			2 (3.0)
	women+men	controls	263	488 (93.0)	38 (7.0)		228 (87.0)	32 (12.0)			3 (1.0)
		any migraine	277	484 (87.0)	70 (13.0)		215 (78.0)	54 (19.0)			8 (3.0)
		MA	227	397 (87.0)	57 (13.0)		176 (77.0)	45 (20.0)			6 (3.0)
		MO	50	87 (87.0)	13 (13.0)		39 (78.0)	9 (18.0)			2 (4.0)
Corominas, 2009(7)	women	controls	222	412 (93.0)	32 (7.0)		193 (87.0)	26 (12.0)			3 (1.0)
		any migraine	238	422 (89.0)	54 (11.0)		188 (79.0)	46 (19.0)			4 (2.0)
	men	controls	41	76 (93.0)	6 (7.0)		35 (85.0)	6 (15.0)			0 (0.0)
		any migraine	39	62 (79.0)	16 (21.0)		27 (69.0)	8 (20.0)			4 (11.0)
	women+men	controls	210	344 (81.9)	76 (18.1)		142 (67.6)	60 (28.6)			8 (3.8)
		any migraine	210	346 (82.4)	74 (17.6)		142 (67.6)	62 (29.5)			6 (2.9)
		MA	86	139 (80.8)	33 (19.2)		56 (65.1)	27 (31.4)			3 (3.5)
		MO	102	172 (84.3)	32 (15.7)		72 (70.6)	28 (27.5)			2 (2.0)

ESR-1 594 G>A polymorphism (rs2228480)									
		Allele frequencies, n (%)			Genotype frequencies, n (%)				
Author	Population	Disease status	Study size	G	A	GG	GA	AA	
Joshi, 2009(8)	women+men	controls	217	392 (90.3)	42 (9.7)	175 (80.6)	42 (19.4)	0 (0.0)	
		any migraine	217	418 (96.3)	16 (3.7)	201 (92.6)	16 (7.4)	0 (0.0)	
		MA	84	161 (95.8)	7 (4.2)	77 (91.8)	7 (8.2)	0 (0.0)	
		MO	133	257 (96.6)	9 (3.4)	124 (93.2)	9 (6.8)	0 (0.0)	
	women	controls	150	267 (89.0)	33 (11.0)	117 (78.0)	33 (22.0)	0 (0.0)	
		any migraine	150	285 (95.0)	15 (5.0)	135 (90.0)	15 (10.0)	0 (0.0)	
		MA	63	119 (94.4)	7 (5.6)	56 (88.9)	7 (11.1)	0 (0.0)	
		MO	87	166 (95.4)	8 (4.6)	79 (90.8)	8 (9.2)	0 (0.0)	
	men	controls	67	125 (93.3)	9 (6.7)	58 (86.6)	9 (13.4)	0 (0.0)	
		any migraine	67	133 (99.3)	1 (0.7)	66 (98.5)	1 (1.5)	0 (0.0)	
		MA	21	42 (100.0)	0 (0.0)	21 (100.0)	0 (0.0)	0 (0.0)	
		MO	46	91 (98.9)	1 (1.1)	45 (97.8)	1 (2.2)	0 (0.0)	

* Two study populations from paper Colson, 2004(6)

† Two study populations from paper Colson, 2005(12)

MA: migraine with aura; MO: migraine without aura; ESR-1 estrogen receptor 1 gene; PGR progesterone receptor gene.

Table 3

Hardy-Weinberg Equilibrium and odds ratios (95% confidence intervals) for additive, dominant, and recessive genetic models according to the investigated polymorphisms

<i>ESR-1 594 G>A (rs2228480)</i>										
Author	Population	Disease status	Study size	HWE	additive	p value	OR (95% CI)	dominant	p value	recessive
Colson, 2004 ^{*(6)}	women+men	controls	224	0.18	Referent		Referent	Referent		Referent
		any migraine	224	----	1.62 (1.19–2.19)	0.002	1.77 (1.21–2.58)	0.003		1.86 (0.92–3.77)
		MA	139	----	1.54 (1.10–2.16)	0.01	1.53 (0.99–2.35)	0.05		2.41 (1.14–5.10)
		MO	85	----	1.73 (1.13–2.63)	0.01	2.27 (1.34–3.86)	0.003		1.01 (0.35–2.94)
	women	controls	167	0.71	Referent		Referent	Referent		Referent
		any migraine	167	----	1.48 (1.05–2.09)	0.03	1.67 (1.08–2.58)	0.02		1.46 (0.68–3.17)
		MA	103	----	1.34 (0.91–1.95)	0.14	1.36 (0.83–2.23)	0.23		1.70 (0.74–3.95)
		MO	64	----	1.74 (1.09–2.77)	0.02	2.40 (1.29–4.44)	0.005		1.10 (0.37–3.24)
	men	controls	57	0.08	Referent		Referent	Referent		Referent
		any migraine	57	----	2.20 (1.14–4.25)	0.02	2.09 (0.98–4.49)	0.06		6.59 (0.77–56.55)
Colson, 2004 ^{*(6)}		MA	36	----	2.52 (1.22–5.24)	0.01	2.19 (0.91–5.28)	0.08		11.20 (1.29–97.37)
		MO	21	----	1.69 (0.64–4.48)	0.29	1.93 (0.68–5.49)	0.21		----
	women+men	controls	260	0.87	Referent		Referent	Referent		Referent
		any migraine	260	----	1.86 (1.41–2.46)	<0.0001	2.15 (1.51–3.05)	<0.0001		2.29 (1.21–4.34)
		MA	221	----	2.01 (1.51–2.69)	<0.0001	2.39 (1.65–3.45)	<0.0001		2.47 (1.29–4.73)
		MO	39	----	1.19 (0.69–2.03)	0.53	1.21 (0.61–2.37)	0.59		1.36 (0.38–4.94)
	women	controls	224	0.70	Referent		Referent	Referent		Referent
		any migraine	224	----	2.03 (1.50–2.75)	<0.0001	2.22 (1.52–3.24)	<0.0001		3.31 (1.58–6.95)
		MA	191	----	2.18 (1.59–2.99)	<0.0001	2.43 (1.63–3.60)	<0.0001		3.52 (1.66–7.49)
		MO	33	----	1.39 (0.77–2.49)	0.28	1.35 (0.65–2.81)	0.42		2.14 (0.56–8.22)
	men	controls	36	0.12	Referent		Referent	Referent		Referent

ESR-I 594 G>A (rs2228480)											
					additive	dominant					
Author	Population	Disease status	Study size	HWE	OR (95% CI)	p value	OR (95% CI)	p value	OR (95% CI)	p value	
Oterino, 2006(10)	women+men	any migraine	36	----	1.14 (0.56–2.30)	0.72	1.75 (0.69–4.45)	0.24	0.37 (0.07–2.02)	0.25	
		MA	30	----	1.30 (0.63–2.70)	0.48	2.16 (0.80–5.82)	0.13	0.44 (0.08–2.47)	0.35	
		MO	6	----	0.55 (0.12–2.42)	0.43	0.63 (0.10–3.86)	0.61	----	----	
	women	controls	232	0.03	Referent			Referent		Referent	
		any migraine	367	----	1.09 (0.82–1.45)	0.57	1.20 (0.84–1.71)	0.31	0.77 (0.36–1.63)	0.49	
		MA	197	----	1.09 (0.79–1.52)	0.61	1.22 (0.82–1.84)	0.33	0.71 (0.29–1.76)	0.46	
		MO	170	----	1.08 (0.77–1.52)	0.66	1.17 (0.77–1.79)	0.46	0.83 (0.34–2.05)	0.69	
	men	controls	142	0.02	Referent			Referent		Referent	
		any migraine	286	----	0.91 (0.65–1.27)	0.57	1.01 (0.66–1.53)	0.98	0.52 (0.22–1.21)	0.13	
		MA	155	----	0.94 (0.64–1.37)	0.75	1.07 (0.67–1.73)	0.77	0.48 (0.17–1.33)	0.16	
MO		131	----	0.88 (0.59–1.30)	0.51	0.93 (0.56–1.53)	0.77	0.57 (0.21–1.59)	0.28		
Kaunisto, 2006(9)	men	controls	90	0.64	Referent		Referent		Referent		
		any migraine	81	----	1.56 (0.89–2.76)	0.12	1.63 (0.84–3.17)	0.15	2.29 (0.41–12.82)	0.35	
		MA	42	----	1.38 (0.70–2.74)	0.35	1.39 (0.62–3.12)	0.43	2.20 (0.23–16.18)	0.44	
		MO	39	----	1.78 (0.90–3.53)	0.10	1.93 (0.86–4.32)	0.11	2.38 (0.32–17.52)	0.40	
	women+men	controls	900	0.45	Referent		Referent		Referent		
		MA	898	----	1.10 (0.93–1.30)	0.26	1.14 (0.94–1.38)	0.19	1.00 (0.63–1.61)	0.99	
	Corominas, 2009(7)	women+men	controls	210	0.26	Referent		Referent		Referent	
			any migraine	210	----	1.02 (0.70–1.49)	0.92	1.08 (0.70–1.70)	0.74	0.66 (0.18–2.37)	0.52
			MA	86	----	0.90 (0.54–1.51)	0.69	0.96 (0.54–1.71)	0.88	0.40 (0.05–3.37)	0.34
			MO	102	----	1.17 (0.75–1.84)	0.49	1.23 (0.73–2.09)	0.43	1.03 (0.25–4.21)	0.97
ESR-I 325 C>G (rs1801132)											
					additive	dominant					
										recessive	

<i>ESR-I 594 G>A (rs2228480)</i>											
Author	Population	Disease status	Study size	HWE	additive	dominant	recessive				
Author	Gender	Disease status	Study size	HWE	OR (95% CI)	p value	OR (95% CI)	p value	OR (95% CI)	p value	p value
Colson, 2006(5)	women+men	controls	249	0.34	Referent		Referent		Referent		
		any migraine	231	----	1.16 (0.85–1.58)	0.35	1.33 (0.92–1.91)	0.13	0.65 (0.27–1.60)	0.35	
		MA	141	----	1.26 (0.89–1.79)	0.19	1.49 (0.98–2.28)	0.06	0.67 (0.23–1.91)	0.45	
		MO	75	----	0.97 (0.62–1.52)	0.90	1.07 (0.63–1.83)	0.80	0.50 (0.11–2.26)	0.37	
	women	controls	189	0.50	Referent		Referent		Referent		
		any migraine	167	----	1.26 (0.88–1.80)	0.21	1.41 (0.92–2.17)	0.11	0.88 (0.32–2.41)	0.80	
	men	controls	60	0.45	Referent		Referent		Referent		
		any migraine	64	----	0.92 (0.50–1.71)	0.79	1.11 (0.54–2.29)	0.78	0.22 (0.02–2.05)	0.18	
Oterino, 2006(10)	women+men	controls	232	0.02	Referent		Referent		Referent		
		any migraine	367	----	1.21 (0.93–1.57)	0.15	1.18 (0.83–1.68)	0.35	1.75 (0.92–3.30)	0.09	
		MA	197	----	1.23 (0.91–1.66)	0.18	1.20 (0.80–1.80)	0.37	1.76 (0.86–3.58)	0.12	
		MO	170	----	1.20 (0.88–1.64)	0.26	1.16 (0.76–1.76)	0.49	1.73 (0.83–3.62)	0.14	
	women	controls	142	0.22	Referent		Referent		Referent		
		any migraine	286	----	1.45 (1.07–2.07)	0.019	1.47 (0.95–2.28)	0.08	2.96 (1.21–7.23)	0.02	
		MA	155	----	1.52 (1.05–2.21)	0.026	1.51 (0.93–2.46)	0.09	2.98 (1.15–7.73)	0.02	
		MO	131	----	1.47 (1.00–2.16)	0.05	1.43 (0.86–2.37)	0.17	2.93 (1.10–7.80)	0.03	
	men	controls	90	0.04	Referent		Referent		Referent		
		any migraine	81	----	0.72 (0.43–1.18)	0.19	0.68 (0.35–1.30)	0.24	0.53 (0.15–1.84)	0.32	
		MA	42	----	0.69 (0.37–1.30)	0.25	0.64 (0.29–1.45)	0.29	0.51 (0.10–2.53)	0.41	
		MO	39	----	0.74 (0.40–1.40)	0.36	0.71 (0.31–1.62)	0.42	0.55 (0.11–2.74)	0.47	
Kaunisto, 2006(9)	women+men	controls	888	0.07	Referent		Referent		Referent		
		MA	896	----	1.16 (0.99–1.35)	0.07	1.09 (0.90–1.31)	0.38	1.81 (1.20–2.72)	0.005	

<i>ESR-I 594 G>A (rs2228480)</i>										
Author	Population	Disease status	Study size	HWE	additive	p value	dominant	p value	recessive	p value
Oterino, 2008(11)	women+men	controls	372	0.27	Referent	0.05	Referent	0.20	Referent	0.01
	any migraine		356	----	1.28 (1.01–1.64)		1.22 (0.90–1.67)	0.20	2.27 (1.18–4.37)	0.01
	MA		198	----	1.32 (0.99–1.77)	0.06	1.28 (0.89–1.84)	0.19	2.25 (1.07–4.71)	0.03
	MO		158	----	1.25 (0.92–1.71)	0.16	1.16 (0.78–1.72)	0.46	2.29 (1.05–5.00)	0.04
women	controls		263	0.27	Referent		Referent		Referent	
	any migraine		269	----	1.46 (1.09–1.94)	0.01	1.45 (1.01–2.08)	0.04	2.59 (1.22–5.51)	0.01
	MA		152	----	1.52 (1.09–2.12)	0.01	1.55 (1.02–2.35)	0.04	2.57 (1.11–5.93)	0.03
	MO		117	----	1.39 (0.97–2.00)	0.07	1.33 (0.84–2.11)	0.23	2.62 (1.08–6.36)	0.03
men	controls		109	1	Referent		Referent		Referent	
	any migraine		87	----	0.84 (0.50–1.40)	0.50	0.74 (0.40–1.37)	0.34	1.27 (0.31–5.21)	0.74
	MA		46	----	0.78 (0.41–1.50)	0.46	0.69 (0.32–1.48)	0.34	1.19 (0.21–6.75)	0.84
	MO		41	----	0.89 (0.46–1.72)	0.73	0.81 (0.37–1.76)	0.59	1.35 (0.24–7.65)	0.74
Corominas, 2009(7)	women+men	controls	210	0.83	Referent		Referent		Referent	
	any migraine		210	----	1.02 (0.73–1.42)	0.93	0.92 (0.61–1.38)	0.68	1.76 (0.68–4.56)	0.25
	MA		86	----	1.14 (0.74–1.76)	0.54	1.04 (0.61–1.75)	0.89	2.18 (0.71–6.67)	0.17
	MO		102	----	0.87 (0.56–1.34)	0.53	0.77 (0.46–1.28)	0.31	1.50 (0.46–4.83)	0.50
Joshi, 2009(8)	women+men	controls	217	0.25	Referent		Referent		Referent	
	any migraine		217	----	1.08 (0.81–1.44)	0.61	1.13 (0.76–1.67)	0.55	1.04 (0.59–1.86)	0.88
	MA		84	----	0.98 (0.67–1.44)	0.92	0.97 (0.58–1.63)	0.90	0.99 (0.46–2.16)	0.99
	MO		133	----	1.15 (0.82–1.60)	0.42	1.25 (0.79–1.97)	0.34	1.08 (0.56–2.07)	0.82
women	controls		150	0.23	Referent		Referent		Referent	
	any migraine		150	----	1.00 (0.71–1.41)	1	0.94 (0.59–1.51)	0.81	1.13 (0.57–2.23)	0.73
	MA		63	----	0.85 (0.54–1.34)	0.49	0.78 (0.43–1.42)	0.41	0.92 (0.36–2.32)	0.85
	MO		87	----	1.12 (0.75–1.68)	0.58	1.09 (0.63–1.91)	0.76	1.29 (0.60–2.78)	0.52

<i>ESR-I 594 G>A (rs2228480)</i>										
Author	Population	Disease status	Study size	HWE	additive	dominant	recessive	p value	OR (95% CI)	p value
	men	controls	67	1	Referent	Referent	Referent	0.15	Referent	0.78
		any migraine	67	----	1.29 (0.76–2.20)	1.69 (0.83–3.45)	0.86 (0.29–2.52)	0.28	1.23 (0.30–5.13)	0.78
		MA	21	----	1.42 (0.68–2.94)	1.80 (0.62–5.20)	0.70 (0.20–2.49)	0.22		0.58
		MO	46	----	1.22 (0.68–2.20)	1.64 (0.74–3.63)				
<i>ESR-I Pvu II C>T (rs2234693)</i>										
Author	Gender	Disease status	Study size	HWE	additive	dominant	recessive	p value	OR (95% CI)	p value
Colson, 2006(5)	women+men	controls	202	0.67	Referent	Referent	Referent	0.80	Referent	0.17
		any migraine	231	----	0.87 (0.66–1.14)	0.94 (0.60–1.48)	0.74 (0.48–1.14)	0.54	0.69 (0.42–1.13)	0.14
		MA	145	----	0.91 (0.67–1.24)	1.18 (0.70–1.99)	0.79 (0.43–1.46)	0.21		0.46
		MO	73	----	0.80 (0.55–1.16)	0.68 (0.38–1.24)				
	women	controls	140	1	Referent	Referent	Referent	0.75	Referent	0.55
		any migraine	167	----	0.97 (0.70–1.34)	1.09 (0.64–1.85)	0.85 (0.50–1.44)			
	men	controls	62	0.44	Referent	Referent	Referent	0.34	Referent	0.14
		any migraine	64	----	0.69 (0.43–1.13)	0.66 (0.29–1.54)	0.57 (0.26–1.22)			
Joshi, 2009(8)	women+men	controls	217	0.049	Referent	Referent	Referent	<0.0001	Referent	0.02
		any migraine	217	----	2.00 (1.45–2.74)	2.47 (1.62–3.76)	2.05 (1.12–3.76)	0.0002	1.84 (0.85–4.02)	0.12
		MA	84	----	2.23 (1.45–3.43)	3.41 (1.81–6.43)	2.19 (1.13–4.26)	0.0029		0.02
		MO	133	----	1.82 (1.29–2.59)	2.07 (1.28–3.33)				
	women	controls	150	0.03	Referent	Referent	Referent	0.0003	Referent	0.02
		any migraine	150	----	2.06 (1.40–3.03)	2.34 (1.42–3.86)	2.53 (1.16–5.53)	0.0008	2.04 (0.76–5.43)	0.16
		MA	63	----	2.47 (1.45–4.19)	3.63 (1.72–7.69)	2.92 (1.25–6.82)	0.04		0.01
		MO	87	----	1.82 (1.19–2.80)	1.80 (1.02–3.19)				

<i>ESR-1 594 G>A (rs2228480)</i>										
Author	Population	Disease status	Study size	HWE	additive	p value	dominant	p value	recessive	p value
	men	controls	67	1	Referent		Referent		Referent	
		any migraine	67	----	1.88 (1.08–3.26)	0.03	2.80 (1.29–6.10)	0.009	1.45 (0.54–3.87)	0.46
		MA	21	----	1.90 (0.90–4.03)	0.09	2.87 (0.87–9.46)	0.08	1.74 (0.47–6.47)	0.41
		MO	46	----	1.80 (0.99–3.29)	0.06	2.78 (1.16–6.67)	0.02	1.32 (0.44–3.95)	0.61
<i>PGR PROGINS insert</i>										
Author	Gender	Disease status	Study size	HWE	additive	p value	dominant	p value	recessive	p value
Colson, 2005 ⁷ (12)	women+men	controls	216	0.2	Referent		Referent		Referent	
		any migraine	232	----	1.66 (1.08–2.54)	0.02	1.83 (1.14–2.92)	0.01	1.25 (0.28–5.63)	0.78
		MA	144	----	1.42 (0.89–2.27)	0.14	1.47 (0.86–2.52)	0.16	2.03 (0.45–9.20)	0.36
		MO	88	----	2.06 (1.20–3.54)	0.009	2.50 (1.40–4.46)	0.002	----	----
	women	controls	151	0.04	Referent		Referent		Referent	
		any migraine	165	----	2.30 (1.25–4.26)	0.008	2.86 (1.45–5.64)	0.003	0.91 (0.13–6.57)	0.93
	men	controls	65	0.67	Referent		Referent		Referent	
		any migraine	67	----	1.20 (0.62–2.30)	0.59	1.17 (0.57–2.40)	0.67	1.97 (0.17–22.26)	0.58
Colson, 2005 ⁷ (12)	women+men	controls	263	0.14	Referent		Referent		Referent	
		any migraine	277	----	1.75 (1.18–2.62)	0.006	1.88 (1.19–2.96)	0.007	2.58 (0.68–9.81)	0.17
		MA	227	----	1.75 (1.15–2.66)	0.008	1.89 (1.18–3.03)	0.009	2.35 (0.58–9.52)	0.23
		MO	50	----	1.78 (0.95–3.34)	0.07	1.84 (0.86–3.92)	0.12	3.61 (0.59–22.19)	0.17
	women	controls	222	0.09	Referent		Referent		Referent	
		any migraine	238	----	1.60 (1.02–2.49)	0.04	1.77 (1.07–2.92)	0.03	1.25 (0.28–5.64)	0.77
men	controls		41	1	Referent		Referent		Referent	

<i>ESR-1 594 G>A (rs2228480)</i>										
Author	Population	Disease status	Study size	HWE	additive	dominant	recessive	p value	OR (95% CI)	p value
Corominas, 2009(7)		any migraine	39	----	2.66 (1.04–6.82)	2.59 (0.86–7.80)	----	0.09	----	----
	women+men	controls	210	0.64	Referent	Referent	Referent	1	0.74 (0.25–2.18)	0.59
		any migraine	210	----	0.97 (0.68–1.38)	1.00 (0.66–1.51)	----	0.68	0.91 (0.24–3.53)	0.89
		MA	86	----	1.07 (0.69–1.68)	1.12 (0.66–1.90)	----	0.60	0.51 (0.11–2.42)	0.39
Joshi, 2009(8)		MO	102	----	0.84 (0.54–1.32)	0.87 (0.52–1.46)	----	0.04	----	----
	women+men	controls	217	0.23	Referent	Referent	Referent	0.0004	0.33 (0.18–0.61)	0.0004
		any migraine	217	----	0.33 (0.18–0.61)	0.33 (0.18–0.61)	----	0.02	0.38 (0.16–0.88)	0.02
		MA	84	----	0.38 (0.16–0.88)	0.38 (0.16–0.88)	----	0.002	0.30 (0.14–0.64)	0.002
		MO	133	----	0.30 (0.14–0.64)	0.30 (0.14–0.64)	----	0.006	0.39 (0.20–0.76)	0.006
	women	controls	150	0.22	Referent	Referent	Referent	0.07	0.44 (0.19–1.06)	0.07
		any migraine	150	----	0.39 (0.20–0.76)	0.39 (0.20–0.76)	----	0.01	0.36 (0.16–0.82)	0.01
		MA	63	----	0.44 (0.19–1.06)	0.44 (0.19–1.06)	----	0.03	0.10 (0.01–0.79)	0.03
		MO	87	----	0.36 (0.16–0.82)	0.36 (0.16–0.82)	----	0.07	0.14 (0.02–1.17)	0.07
	men	controls	67	1	Referent	Referent	Referent	0.03	0.10 (0.01–0.79)	0.03
		any migraine	67	----	0.10 (0.01–0.79)	0.10 (0.01–0.79)	----	0.07	0.14 (0.02–1.17)	0.07
		MA	21	----	----	----	----	0.07	0.14 (0.02–1.17)	0.07
		MO	46	----	0.14 (0.02–1.17)	0.14 (0.02–1.17)	----	0.07	0.14 (0.02–1.17)	0.07

* Two study populations from paper Colson, 2004(6)

† Two study populations from paper Colson, 2005(12)

HWE: p value from exact test for the Hardy–Weinberg Equilibrium; MA: migraine with aura; MO: migraine without aura; *ESR-1* estrogen receptor 1 gene; *PGR* progesterone receptor gene.

Table 4
Association between sex hormone receptor polymorphisms and migraine, heterogeneity, and publication bias

<i>ESR-1 594 G>A (rs2228480)*</i>										
Any migraine										
Genetic model	Population	No of studies	Relative Risk (95% CI)	Q	df	p-value	I ² in %	p-value Begg	p-value Egger	
additive	all(6,7,10)	4*	1.37 (1.02–1.83)	10.6	3	0.01	71.6	0.50	0.44	
	Women(6,10)	3*	1.40 (0.88–2.24)	12.2	2	0.002	83.6	0.60	0.48	
	Men(6,10)	3*	1.59 (1.10–2.30)	1.8	2	0.41	0	0.60	0.85	
dominant	all(6,7,10)	4*	1.50 (1.10–2.06)	8.4	3	0.04	64.5	0.17	0.47	
	Women(6,10)	3*	1.56 (0.98–2.48)	7.5	2	0.02	73.5	0.60	0.53	
	Men(6,10)	3*	1.80 (1.16–2.80)	0.2	2	0.89	0	0.60	0.82	
recessive	all(6,7,10)	4*	1.34 (0.74–2.43)	6.6	3	0.08	54.8	0.17	0.33	
	Women(6,10)	3*	1.38 (0.49–3.89)	10.4	2	0.006	80.7	0.12	0.11	
	Men(6,10)	3*	1.62 (0.32–8.28)	4.7	2	0.10	57.2	0.12	0.46	
Migraine with aura										
Genetic model	Population	No of studies	Relative Risk (95% CI)	Q	df	p-value	I ² in %	p-value Begg	p-value Egger	
additive	all(6,7,9,10)	5*	1.30 (0.99–1.70)	16.5	4	0.002	75.8	1	0.72	
	Women(6,10)	3*	1.41 (0.86–2.32)	11.5	2	0.003	82.6	0.12	0.24	
	Men(6,10)	3*	1.64 (1.09–2.48)	2.0	2	0.38	0	0.60	0.71	
dominant	all(6,7,9,10)	5*	1.39 (1.02–1.89)	13.9	4	0.01	71.3	1	0.61	

ESR-1 594 G>A (rs2228480)*										
Any migraine										
				Heterogeneity			Publication Bias			
Genetic model	Population	No of studies	Relative Risk (95% CI)	Q	df	p-value	I ² in %	p-value Begg	p-value Egger	
	Women(6,10)	3*	1.55 (0.94–2.56)	7.3	2	0.03	72.7	0.60	0.26	
	Men(6,10)	3*	1.82 (1.09–3.04)	0.7	2	0.70	0	0.60	0.43	
recessive	all(6,7,9,10)	5*	1.35 (0.76–2.38)	10.3	4	0.04	61.2	1	0.77	
	Women(6,10)	3*	1.49 (0.50–4.42)	9.5	2	0.01	78.9	0.12	0.03	
	Men(6,10)	3*	2.02 (0.32–12.75)	5.3	2	0.07	62.5	0.12	0.09	
Migraine without aura										
				Heterogeneity			Publication Bias			
Genetic model	Population	No of studies	Relative Risk (95% CI)	Q	df	p-value	I ² in %	p-value Begg	p-value Egger	
additive	all(6,7,10)	4*	1.25 (1.01–1.55)	3.1	3	0.38	3.2	0.50	0.75	
	Women(6,10)	3*	1.26 (0.81–1.95)	5.1	2	0.08	60.6	0.60	0.57	
	Men(6,10)	3*	1.50 (0.88–2.57)	2.1	2	0.36	3.4	0.12	0.28	
dominant	all(6,7,10)	4*	1.41 (1.03–1.92)	4.3	3	0.24	29.5	0.17	0.83	
	Women(6,10)	3*	1.42 (0.79–2.54)	5.5	2	0.06	63.5	0.60	0.64	
	Men(6,10)	3*	1.71 (0.94–3.12)	1.3	2	0.52	0	0.12	0.23	
recessive	all(6,7,10)	4*	1.00 (0.57–1.74)	0.4	3	0.94	0	0.17	0.23	
	Women(6,10)	3*	1.00 (0.49–2.05)	2.4	2	0.3	16.5	0.12	0.24	
	Men(10)	1	2.38 (0.32–17.52)	---	---	---	---	---	---	

<i>ESR-I 325 C>G (rs1801132)</i>									
Any migraine									
Genetic model	Population	No of studies	Relative Risk (95% CI)	Q	df	p-value	I ² in %	p-value Begg	p-value Egger
additive	all(5,7,8,10,11)	5	1.16 (1.03–1.32)	1.6	4	0.81	0	0.05	0.04
	Caucasians(5,7,10,11)	4	1.19 (1.03–1.36)	1.3	3	0.73	0	0.04	0.06
	Women(5,8,10,11)	4	1.30 (1.09–1.55)	3.5	3	0.32	14.3	0.17	0.43
	Men(5,8,10,11)	4	0.91 (0.70–1.19)	2.6	3	0.45	0	0.17	0.70
dominant	all(5,7,8,10,11)	5	1.16 (0.99–1.37)	1.9	4	0.75	0	0.14	0.30
	Caucasians(5,7,10,11)	4	1.17 (0.98–1.40)	1.9	3	0.59	0	0.50	0.40
	Women(5,8,10,11)	4	1.33 (1.08–1.64)	2.5	3	0.47	0	0.17	0.33
	Men(5,8,10,11)	4	0.96 (0.64–1.44)	4.3	3	0.23	30.7	0.50	0.20
recessive	all(5,7,8,10,11)	5	1.40 (0.93–2.11)	6.5	4	0.16	38.9	1	0.80
	Caucasians(5,7,10,11)	4	1.54 (0.94–2.54)	5.0	3	0.17	40.4	0.50	0.40
	Women(5,8,10,11)	4	1.68 (0.95–2.96)	5.7	3	0.13	47.5	0.50	1.00
	Men(5,8,10,11)	4	0.72 (0.37–1.41)	2.0	3	0.57	0	0.50	0.40
Migraine with aura									
Genetic model	Population	No of studies	Relative Risk (95% CI)	Q	df	p-value	I ² in %	p-value Begg	p-value Egger
additive	all(5,7–11)	6	1.18 (1.06–1.32)	1.8	5	0.88	0	0.57	0.95
	Caucasians(5,7,9–11)	5	1.20 (1.07–1.34)	0.8	4	0.94	0	1	0.35
	Women(8,10,11)	3	1.29 (0.91–1.82)	4.9	2	0.09	58.8	0.12	0.24
	Men(8,10,11)	3	0.89 (0.59–1.34)	2.3	2	0.32	13.0	0.12	0.01
dominant	all(5,7–11)	6	1.15 (1.00–1.31)	2.8	5	0.74	0	0.85	0.62
	Caucasians(5,7,9–11)	5	1.16 (1.01–1.34)	2.3	4	0.68	0	0.62	0.35
	Women(8,10,11)	3	1.28 (0.86–1.90)	3.8	2	0.15	47.4	0.12	0.25
	Men(8,10,11)	3	0.84 (0.48–1.50)	2.6	2	0.27	24.0	0.60	0.15

<i>ESR-I 325 C>G (rs1801132)</i>										
Any migraine										
Genetic model	Population	No of studies	Relative Risk (95% CI)	Q	df	p-value	I ² in %	p-value Begg	p-value Egger	Publication Bias
recessive	all(5,7-11)	6	1.60 (1.19-2.17)	5.6	5	0.35	10.6	0.35	0.35	0.43
	Caucasians(5,7,9-11)	5	1.75 (1.30-2.34)	3.8	4	0.43	0	1	0.58	0.58
	Women(8,10,11)	3	1.93 (0.95-3.92)	3.7	2	0.16	46.1	0.60	0.85	0.85
	Men(8,10,11)	3	0.92 (0.37-2.28)	0.8	2	0.68	0	0.60	0.88	0.88
Migraine without aura										
Genetic model	Population	No of studies	Relative Risk (95% CI)	Q	df	p-value	I ² in %	p-value Begg	p-value Egger	Publication Bias
additive	all(5,7,8,10,11)	5	1.12 (0.96-1.31)	2.4	4	0.67	0	0.05	0.02	0.02
	Caucasians(5,7,10,11)	4	1.11 (0.93-1.33)	2.3	3	0.50	0	0.17	0.06	0.06
	Women(8,10,11)	3	1.33 (1.07-1.66)	1.0	2	0.60	0	0.60	0.54	0.54
	Men(8,10,11)	3	0.95 (0.66-1.36)	1.3	2	0.52	0	0.60	0.42	0.42
dominant	all(5,7,8,10,11)	5	1.09 (0.89-1.34)	2.3	4	0.67	0	0.33	0.30	0.30
	Caucasians(5,7,10,11)	4	1.05 (0.84-1.32)	1.9	3	0.59	0	0.17	0.33	0.33
	Women(8,10,11)	3	1.29 (0.96-1.72)	0.5	2	0.78	0	0.60	0.53	0.53
	Men(8,10,11)	3	0.98 (0.59-1.64)	2.4	2	0.29	18.3	0.60	0.8	0.8
recessive	all(5,7,8,10,11)	5	1.44 (0.97-2.13)	4.3	4	0.37	6.5	0.62	0.51	0.51
	Caucasians(5,7,10,11)	4	1.65 (1.02-2.66)	3.2	3	0.37	4.9	0.17	0.14	0.14
	Women(8,10,11)	3	2.01 (1.19-3.41)	2.2	2	0.33	9.5	0.12	0.20	0.20
	Men(8,10,11)	3	0.77 (0.33-1.82)	0.6	2	0.75	0	0.60	0.68	0.68

<i>ESR-I Pvu II C>T (rs2234693)</i>										
Any migraine										
Genetic model	Population	No of studies	Relative Risk (95% CI)	Q	df	p-value	<i>I</i> ² in %	p-value Begg	p-value Egger	
additive	all(5,8)	2	1.31 (0.58–2.96)	15.3	1	<0.0001	93.5	0.32	---	---
	Women(5,8)	2	1.40 (0.67–2.93)	8.5	1	0.004	88.2	0.32	---	---
	Men(5,8)	2	1.13 (0.43–3.00)	7.1	1	0.01	85.8	0.32	---	---
dominant	all(5,8)	2	1.53 (0.60–3.92)	9.4	1	0.002	89.4	0.32	---	---
	Women(5,8)	2	1.60 (0.76–3.39)	4.2	1	0.04	76.3	0.32	---	---
	Men(5,8)	2	1.38 (0.34–5.65)	6.1	1	0.01	83.6	0.32	---	---
recessive	all(5,8)	2	1.20 (0.44–3.28)	7.3	1	0.01	86.3	0.32	---	---
	Women(5,8)	2	1.41 (0.49–4.10)	5.2	1	0.02	80.7	0.32	---	---
	Men(5,8)	2	0.86 (0.34–2.15)	2.2	1	0.14	54.6	0.32	---	---
Migraine with aura										
Heterogeneity										
Genetic model	Population	No of studies	Relative Risk (95% CI)	Q	df	p-value	<i>I</i> ² in %	p-value Begg	p-value Egger	
additive	all(5,8)	2	1.41 (0.59–3.39)	11.0	1	0.001	90.9	0.32	---	---
	Women(8)	1	2.47 (1.45–4.19)	---	---	---	---	---	---	---
	Men(8)	1	1.90 (0.90–4.03)	---	---	---	---	---	---	---
dominant	all(5,8)	2	1.97 (0.70–5.59)	6.4	1	0.01	84.4	0.32	---	---
	Women(8)	1	3.63 (1.72–7.69)	---	---	---	---	---	---	---
	Men(8)	1	2.87 (0.87–9.46)	---	---	---	---	---	---	---
recessive	all(5,8)	2	1.07 (0.41–2.81)	4.4	1	0.04	77.3	0.32	---	---
	Women(8)	1	2.04 (0.76–5.43)	---	---	---	---	---	---	---
	Men(8)	1	1.74 (0.47–6.47)	---	---	---	---	---	---	---
Migraine without aura										

ESR-1 Pvu II C>T (rs2234693)										
Any migraine										
Genetic model	Population	No of studies	Relative Risk (95% CI)	Q	Heterogeneity		I ² in %	Publication Bias		
					df	p-value		p-value Begg	p-value Egger	
Heterogeneity										
Genetic model	Population	No of studies	Relative Risk (95% CI)	Q	df	p-value	I ² in %	p-value Begg	p-value Egger	
additive	all(5,8)	2	1.21 (0.54–2.72)	10.1	1	0.001	90.1	0.32	---	---
	Women(8)	1	1.82 (1.19–2.80)	---	---	---	---	---	---	---
	Men(8)	1	1.80 (0.99–3.29)	---	---	---	---	---	---	---
dominant	all(5,8)	2	1.21 (0.41–3.57)	8.0	1	0.01	87.5	0.32	---	---
	Women(8)	1	1.80 (1.02–3.19)	---	---	---	---	---	---	---
	Men(8)	1	2.78 (1.16–6.67)	---	---	---	---	---	---	---
recessive	all(5,8)	2	1.31 (0.48–3.54)	4.9	1	0.03	79.4	0.32	---	---
	Women(8)	1	2.92 (1.25–6.82)	---	---	---	---	---	---	---
	Men(8)	1	1.32 (0.44–3.95)	---	---	---	---	---	---	---
PGR PROGINS insert										
Any migraine										
Genetic model	Population	No of studies	Relative Risk (95% CI)	Q	df	p-value	I ² in %	Publication Bias		
								p-value Begg	p-value Egger	
additive	all(7,8,12)	4 [*]	1.02 (0.55–1.87)	23.9	3	<0.0001	87.5	0.50	0.37	
	Caucasians(7,12)	3 [*]	1.39 (0.94–2.06)	6.0	2	0.05	66.5	0.60	0.27	
	Women(8,12)	3 [*]	1.15 (0.44–2.97)	16.8	2	<0.0001	88.1	0.60	0.67	
	Men(8,12)	3 [*]	0.97 (0.28–3.39)	8.1	2	0.02	75.4	0.60	0.56	
dominant	all(7,8,12)	4 [*]	1.06 (0.53–2.09)	24.5	3	<0.0001	87.8	0.50	0.35	

<i>PGR</i> PROGINS insert									
Any migraine									
Genetic model	Population	No of studies	Relative Risk (95% CI)	Q	df	p-value	I ² in %	p-value Begg	p-value Egger
recessive	Caucasians(7,12)	3*	1.49 (0.98–2.26)	5.3	2	0.07	62.5	0.60	0.18
	Women(8,12)	3*	1.26 (0.42–3.76)	19.2	2	<0.0001	89.6	0.60	0.83
	Men(8,12)	3*	0.91 (0.24–3.40)	7.4	2	0.03	72.9	0.60	0.58
	all(7,12)	3*	1.22 (0.59–2.55)	2.0	2	0.37	0.7	0.60	0.56
Migraine with aura	Caucasians(7,12)	3*	1.22 (0.59–2.55)	2.0	2	0.37	0.7	0.60	0.56
	Women(12)	2*	1.11 (0.34–3.69)	0.1	1	0.81	0	0.32	---
	Men(12)	1	1.97 (0.17–22.26)	---	---	---	---	---	---
Genetic model	Population	No of studies	Relative Risk (95% CI)	Q	df	p-value	I ² in %	p-value Begg	p-value Egger
additive	all(7,8,12)	4*	1.11 (0.68–1.81)	10.9	3	0.01	72.6	0.17	0.08
	Caucasians(7,12)	3*	1.40 (1.05–1.86)	2.5	2	0.29	18.8	0.60	0.59
	Women(8)	1	0.44 (0.19–1.06)	---	---	---	---	---	---
	men	0	---	---	---	---	---	---	---
dominant	all(7,8,12)	4*	1.13 (0.65–1.96)	11.1	3	0.01	72.9	0.17	0.04
	Caucasians(7,12)	3*	1.49 (1.10–2.01)	2.1	2	0.35	4.3	0.60	0.42
	Women(8)	1	0.44 (0.19–1.06)	---	---	---	---	---	---
	men	0	---	---	---	---	---	---	---
recessive	all(7,12)	3*	1.59 (0.70–3.61)	1.0	2	0.59	0	0.60	0.58
	Caucasians(7,12)	3*	1.59 (0.70–3.61)	1.0	2	0.59	0	0.60	0.58
	women	0	---	---	---	---	---	---	---

PGR PROGENS insert											
Any migraine											
Genetic model			Population	No of studies	Relative Risk (95% CI)	Q	df	p-value	I ² in %	p-value Begg	p-value Egger
		men		0	---	---	---	---	---	---	---
Migraine without aura											
Genetic model			Population	No of studies	Relative Risk (95% CI)	Q	df	p-value	I ² in %	p-value Begg	p-value Egger
additive		all(7,8,12)	4 [*]		1.01 (0.48–2.13)	20.0	3	<0.0001	85.0	0.50	0.70
		Caucasians(7,12)	3 [*]		1.42 (0.79–2.57)	7.3	2	0.03	72.5	0.60	0.38
		Women(8)	1		0.36 (0.16–0.82)	---	---	---	---	---	---
		Men(8)	1		0.14 (0.02–1.17)	---	---	---	---	---	---
dominant		all(7,8,12)	4 [*]		1.06 (0.45–2.50)	21.5	3	<0.0001	86.0	1	0.76
		Caucasians(7,12)	3 [*]		1.56 (0.79–3.09)	7.5	2	0.02	73.5	0.60	0.65
		Women(8)	1		0.36 (0.16–0.82)	---	---	---	---	---	---
		Men(8)	1		0.14 (0.02–1.17)	---	---	---	---	---	---
recessive		all(7,12)	2		1.28 (0.19–8.76)	2.6	1	0.11	61.3	0.32	---
		Caucasians(7,12)	2		1.28 (0.19–8.76)	2.6	1	0.11	61.3	0.32	---
		women	0		---	---	---	---	---	---	---
		men	0		---	---	---	---	---	---	---

* 2 studies from the paper Colson, 2004

* 2 studies from the paper Colson, 2005(12)