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5-HTTLPR Polymorphism in the Serotonin Transporter Gene and Migraine: A Systematic Review and Meta-Analysis

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Abstract

Data on the association between the *SLC6A4* 5-HTTLPR polymorphism and migraine are conflicting. We performed a systematic review and meta-analysis among studies published until September 2009. For each study with genotype information we calculated odds ratios (OR) and 95% confidence intervals (CI) assuming additive, dominant, and recessive genetic models. We then calculated pooled ORs and 95% CIs. Among the ten studies identified there was no overall association between the polymorphism and any migraine for Europeans or Asians. However, European women carrying the S allele had an increased risk for any migraine (dominant model: pooled OR=2.02; 95% CI 1.24–3.28). Results among Europeans further suggested an increased risk for migraine with aura among carriers of the S/S genotype (recessive model: pooled OR=1.41; 95% CI 0.83–2.40). While our results indicate no overall association between the *SLC6A4* 5-HTTLPR polymorphism and migraine among Europeans and Asians, gender and migraine aura status may have modifying roles among Europeans.

Keywords

migraine; serotonin transporter gene; *SLC6A4*; 5-HTTLPR; meta-analysis

Introduction

Migraine is a common, chronic disorder affecting 10–20% of the population; women 3–4 times more often than men (1). Up to one third of migraine patients experience an aura prior to or during the migraine headache.

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Despite many advances in migraine research over the last decades, migraine pathophysiology is still incompletely understood. Current concepts view migraine as an inherited brain disorder, characterized by neurotransmitter imbalances that lead to neuronal dysfunctions in the form of recurrent headache attacks and combinations of gastrointestinal and autonomic nervous system symptoms (1,2). The serotonergic system appears to play a pivotal role and alterations in serotonin metabolism and in the processing of central serotonin-mediated responses have been described as typical for migraineurs (3).

Following axonal release serotonin (5-hydroxytryptamine; 5-HT) action is rapidly terminated by presynaptic reuptake (4). This is performed by the serotonin transporter SLC6A4 (5-HTT) (5), which is mostly expressed in the brainstem and midbrain (6), areas implicated in migraine pathophysiology. A 44-bp insertion/deletion polymorphism in the promoter region of the SLC6A4 gene, termed 5-HTTLPR (5-HTT Linked Polymorphic Region), has been described (7,8). This 5-HTTLPR polymorphism translates into a long (L) and short (S) allele, which show functional differences. The S allele is associated with half the number of serotonin transporters compared with carriers of the L/L genotype (9). This results in a slower synaptic clearing of serotonin in carriers of the S allele. Subsequently it was speculated that the SLC6A4 5-HTTLPR polymorphism accounts for altered serotonin levels in migraineurs and may thus be associated with migraine.

However, results from studies looking at the association between the SLC6A4 5-HTTLPR polymorphism and migraine are conflicting. Some have reported an association with any migraine (10,11), some only with migraine with aura (12,13), and others did not find an association (14–20). This may in part be due to differences in genotype and allele frequencies between ethnic groups (21,22), sample size, and study characteristics.

We sought to summarize the current evidence on the association between the SLC6A4 5-HTTLPR polymorphism 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 (23). Two investigators (M.S., P.M.R.) independently searched MEDLINE, EMBASE, and Science Citation Index from inception to September 2009 combining text words and MESH terms, where appropriate, for serotonin and serotonin transporter (“Serotonin Plasma Membrane Transport Proteins” or “serotonin transporter” or “serotonin” or “SLC6A4”) 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 full articles without 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 and must be published as full papers.
2. Authors must investigate patients with migraine, diagnosed according to the criteria of the International Headache Society (IHS) (24,25) and healthy control subjects.
3. Authors must provide information on genotype frequencies of the SLC6A4 5-HTTLPR polymorphism or sufficient data to calculate these.

4. In studies with overlapping cases and/or controls the largest study with extractable data was included.

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 range 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. If allele or genotype frequencies given did not match with the number of patients reported, the respective subgroup was excluded. 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 the *SLC6A4* 5-HTTLPR polymorphism and migraine assuming additive, dominant, and recessive genetic models. The additive model assumes that the risk for migraine among carriers of the heterozygous genotype (L/S) is half way between carriers of the homozygous genotypes (L/L, S/S). While the dominant model assumes that carriers of the heterozygous (L/S) and homozygous mutant genotypes (S/S) have the same risk of developing migraine compared with carriers of the homozygous wild-type genotype (L/L), a recessive model assumes that carrying the homozygous mutant genotype (S/S) is necessary to alter the risk for migraine compared to carriers of the heterozygous (L/S) and homozygous wild-type genotype (L/L). We also determined Hardy-Weinberg Equilibrium (HWE) for each study. The Hardy-Weinberg principle states that allele and genotype frequencies in a population remain constant (are in equilibrium) from generation to generation. Deviations from HWE might for example indicate genotyping error, limited population size, population substructure, or newly occurred mutations. A *p*-value ≥ 0.05 from a chi-square test used to test for HWE in the control population makes such errors/conditions unlikely (no deviation from HWE) and is considered a quality measure of a study. We investigated any migraine, MA, and MO.

We *a priori* decided to perform separate analyses among European and Asian populations since the genotype and allele frequencies differ between ethnic groups (21,22). We then pooled results from studies stratified by country of origin. We grouped the Turkish study (20) with the other studies in European populations based on the similarity of allele and genotype frequencies in the controls (Table 2).

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 and provide more conservative estimates. We performed the DerSimonian and Laird *Q* test for heterogeneity and also calculated the I^2 statistic for each analysis (26). 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 (27) and statistically with the methods described by Begg and Mazumdar (27) and Egger (28). The former method uses adjusted rank correlations, the latter method a weighted regression approach to investigate the association between outcome effects (log odds ratio) and its standard error in each study. P-values <0.05 may be regarded as an indication for publication bias.

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 were left with 18 studies (10–20,29–35). We excluded eight more studies (19,29–35) after evaluating the full paper versions of the remaining articles and were left with ten studies for this analysis (10,12–18,20,30).

Study characteristics

Table 1 summarizes the characteristics of the ten included studies. Six studies were performed in European populations (10–13,17,18), one in a Turkish population (20), and three in Asian populations (14–16). Seven studies investigated only mixed female and male populations (12–15,17,18,20) and three only women (10,11,16). Eight studies presented results for any migraine (10–15,17,20), five for MA (11–13,17,18), and five for MO (11–13,16,17). All studies had a case-control design and used standard polymerase chain reaction genotyping methods.

The allele and genotype frequencies for the *SLC6A4* 5-HTTLPR polymorphism 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 HWE in the controls as well as ORs (95% CI) for the association between the *SLC6A4* 5-HTTLPR polymorphism and migraine assuming additive, dominant, and recessive genetic models. Genotype distributions in all control populations were in HWE. Table 4 summarizes the pooled ORs (95% CI), measures of heterogeneity, and publication bias.

Association between the *SLC6A4* 5-HTTLPR polymorphism and migraine

Four of the ten studies suggested an increased risk for migraine among carriers of the S allele (Table 3) (10–13). In two studies among European women this occurred for any migraine and appeared most pronounced under a dominant model (10,11), while in the other two among mixed populations this appeared only for MA and seemed to follow a recessive model (12,13).

Our overall pooled analyses do not suggest an association between the *SLC6A4* 5-HTTLPR polymorphism and any migraine (Table 4). The pooled OR (95% CI) from an additive model for any migraine was 1.16 (0.93–1.43) among Europeans (10–13,17,20) and 1.14 (0.85–1.55) among Asians (14,15). This did not change when assuming dominant or recessive models of inheritance. When we analyzed the subgroup of European women, however, the risk for any migraine appeared to be significantly increased, which was most pronounced assuming a dominant model (dominant model: pooled OR=2.02; 95% CI 1.24–3.28).

The studies looking at MA were all performed among European populations (11–13,17,18). The pooled effect estimates suggested an increased risk for carriers of the S/S genotype, however, this did not become statistically significant (recessive model: pooled OR=1.41; 95% CI 0.83–2.40). There was medium heterogeneity among these studies (recessive model: $I^2=63.9\%$).

For MO neither the studies among Europeans (11–13,17) nor the study in an Asian population (16) suggested an association with the *SLC6A4* 5-HTTLPR polymorphism. Formal investigation using Begg's test suggested some publication bias when assuming a recessive model among Europeans for MO ($p=0.04$), however, Egger's test did not. Neither test suggested publication bias for any of the outcomes or for any of the other models.

Sensitivity analyses

When we repeated the analysis on the association between the *SLC6A4* 5-HTTLPR polymorphism and any migraine, excluding the study in the Turkish population (20), the results among the European populations were very similar to the overall results (additive model: pooled OR=1.19; 95% CI 0.92–1.53).

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.

For all analyses the effect estimates were lower and none indicated a statistically significant association. For example, for the association with any migraine the pooled OR (95% CI) from the additive model was 1.08 (0.91–1.27) after excluding one study (10). Likewise, for the association with MA among Europeans the pooled OR (95% CI) from the recessive model was 1.20 (0.70–2.07) after excluding one study (13).

Discussion

The overall results from this meta-analysis do not indicate an association between the *SLC6A4* 5-HTTLPR polymorphism and migraine among European and Asian populations. Studies among European women, however, indicate a twofold increased risk for any migraine for carriers of the S allele. The association with MA has only been investigated in European populations. While the pooled results suggested a 40% increased risk for MA among carriers of the S/S genotype compared to the other genotypes, these results were not statistically significant and there was remaining heterogeneity among studies.

Family and twin studies have clearly established a genetic component in migraine with a heritability of up to 50% (36). While mutations in individual genes have clearly been implicated in rare migraine forms such as familial hemiplegic migraine, it has been notoriously difficult to identify genetic markers for common forms of migraine (37).

The importance of serotonin in migraine has been acknowledged for some decades (3) and a dysfunction in the serotonergic system agrees with both pathophysiological models of a cortical dysbalance (38) as well as treatment success of triptans, which are serotonin receptor agonists (39). Among the main features in migraineurs are alterations in serotonin metabolism and in the processing of central serotonin-mediated responses compared to non-migraineurs (3). Since the *SLC6A4* 5-HTTLPR polymorphism determines serotonin levels with carriers of the S allele having impaired transporter activities (9), it was hypothesized that this variant may also be a marker for migraine. Despite biological plausibility, however, individual studies on the association between the *SLC6A4* 5-HTTLPR polymorphism and migraine came to conflicting results and our meta-analysis does not support an association.

Results from our overall analysis are in agreement with two family-based studies. One used linkage analysis and did not find significant linkage of markers in the *SLC6A4* gene region with migraine (33). The other employed the transmission disequilibrium test and did not find association of any of the 5-HTTLPR genotypes with overall migraine, MA, or MO (31). There are two possible explanations for the negative results. Either there may be truly no association and the positive studies may have occurred by chance or the pattern of association may be more complex and may depend on additional factors. Our results support the latter notion.

In this respect the following limitations of our meta-analysis need to be considered. First, migraine is a complex, heterogeneous disorder with a wide clinical spectrum (37). Hence, patients with different clinical phenotypes are summarized as having migraine and even strict classification according to IHS criteria (24,25) may not sufficiently capture this variability and may be a source of misclassification in all studies. For example, the *SLC6A4* 5-HTTLPR polymorphism may not simply be associated with any migraine, but with attack frequency, as suggested by one study (15). Further, the association may be different for MA and MO. There is some indication for this from our pooled analyses, since the risk for MA may be increased by 40% for carriers of the S/S genotype. However, this was not statistically significant, possibly due to low sample size, and there was medium heterogeneity ($I^2=63.9\%$) leaving residual uncertainties. Moreover, the *SLC6A4* 5-HTTLPR polymorphism may be associated with early age of migraine onset. In one of the studies migraineurs were children and adolescents (17), however, this study did not find an association. Second, in addition to the 5-HTTLPR polymorphism another common polymorphism in the *SLC6A4* gene, a variable number tandem repeat in intron 2 (termed STin2 VNTR), has been investigated with regard to its association with migraine, the results being likewise controversial (32,34). The structural organization of the STin2 VNTR polymorphism is more complex than that of the 5-HTTLPR polymorphism, since it consists of three alleles and five genotypes. This does not easily allow employing genetic models (additive, dominant, recessive) based on one degree of freedom tests; hence, we did not include it in our present analysis. Third, *SLC6A4* is a large polymorphic gene comprising 37,810 bp organized in 15 exons and 14 introns with 380 single nucleotide polymorphisms (SNPs) reported (40,41), which in addition to the *SLC6A4* 5-HTTLPR and STin2 VNTR polymorphisms may affect function of the transporter. Fourth, the traditional concept of the *SLC6A4* 5-HTTLPR polymorphism as being biallelic, with the S allele being associated with a lower number of serotonin transporters compared with carriers of the L/L genotype (9) has been challenged. Recent data suggest the existence of a low-frequency L_G-allele variant, harboring an A>G SNP in its sequence, whose functional properties may be similar to the A allele (42,43). However, this additional genotypic information was not available for any of the studies included in our analyses; hence, we could not investigate an association with migraine. Fifth, serotonin's role in migraine is not just determined by transporter activity, but also by serotonin's functional effect at the receptor level, which is likewise under genetic control and unaccounted for in all the studies. Sixth, although serotonin appears to be pivotal, other neurotransmitters like dopamine, orexin, and glutamate are also important in migraine pathophysiology (44). Hence, migraine susceptibility is likely a function of the interaction between various neurotransmitters, which again is determined by the interaction of various genetic variants. Seventh, migraine susceptibility is different between women and men, as indicated by the higher prevalence among women (45). Our results suggest that this may also be the case with regard to the *SLC6A4* 5-HTTLPR polymorphism, as European women carrying the S allele have a twofold increased risk for any migraine. Unfortunately, only three studies (10,11,16) were conducted in women and all other studies only reported results for mixed gender populations. Eighth, associations with migraine may differ by ethnicity, especially since the genotype distribution of the *SLC6A4* 5-HTTLPR polymorphism shows ethnic differences (21,22). We have acknowledged this in our analysis

by stratifying studies according to country of origin. However, studies are scarce among Asians and unavailable from other populations of non-European descent. Hence, in particular with regard to MA, a potential link with the *SLC6A4* 5-HTTLPR polymorphism remains unclear. Finally, we only used extractable data from the papers. However, only one paper did not provide genotypic information (19). The authors reported no association of the *SLC6A4* 5-HTTLPR polymorphism and migraine; hence, this would likely not have changed our results.

Additional research appears warranted to further delineate the association between the *SLC6A4* 5-HTTLPR polymorphism and migraine, in particular among women and in MA. Further, studies in non-European populations are scarce and may yield different results. Future studies need to be adequately powered, should use standardized migraine classification including aura status, and should also present results stratified by gender and migraine aura status. Further, gene-gene interactions should be investigated, even if individual gene variants do not suggest an association with migraine. Finally, other than migraine status, age at onset or markers of migraine severity including attack frequency and aura frequency may be better outcomes.

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Figure 1.
Process of identifying studies

Table 1
 Characteristics of included studies investigating the association between the *SLC6A4* 5-HTTLPR polymorphism and migraine

Author and year	Country	Setting	Population	Study size with genotypic information		Comment
				Controls	Any migraine	
Yilmaz, 2001 (20)	Turkey	NS	mixed	80	52	Other polymorphisms investigated: <i>SLC6A4</i> VNTR in intron 2.
Kotani, 2002 (15)	Japan	NS	mixed	190	151	Migraine attacks were more frequent for carriers of S/S genotype compared with L/S+L/L genotypes.
Juhasz, 2003 (11)	Hungary	clinic	women	101	126	Other polymorphisms investigated: <i>5HTT2A</i> 102 T>C (rs6313)
Marziniak, 2005 (13)	Germany	clinic	mixed	115	197	
Borroni, 2005 (12)	Italy	clinic	mixed	105	144	
Kim, 2005 (14)	Korea	clinic	mixed	170	52	No association of any genotype with intensity or frequency of migraine or aura.
Park, 2006 (16)	Korea	clinic	women	100	---	Other polymorphisms investigated: <i>SLC6A4</i> VNTR in intron 2.
Todt, 2006 (18)	Germany	NS	mixed	506	---	
Szilagyi, 2006 (17)	Hungary	clinic	mixed	464	87	Other polymorphisms investigated: <i>SLC6A4</i> VNTR in intron 2.
Gonda, 2007 (10)	Hungary	clinic	women	52	45	Cases were children and adolescents, controls high school and university students.
Total number of subjects				1,883	854	
						668
						455

MA: migraine with aura; MO: migraine without aura; NS: not specified

Table 2

Allele and genotype frequencies for the *SLC6A4* 5-HTTLPR polymorphism

Author	Disease status	Study size	Allele frequencies, n (%)			Genotype frequencies, n (%)		
			L	S	L/L	L/S	S/S	
Yilmaz, 2001 (20)	controls	80	83 (51.9)	77 (48.1)	25 (31.3)	33 (41.3)	22 (27.5)	
	any migraine	52	53 (51.0)	51 (49.0)	16 (30.8)	21 (40.4)	15 (28.8)	
Kotani, 2002 (15)	controls	190	87 (22.9)	293 (77.1)	11 (6.0)	65 (34.0)	114 (60.0)	
	any migraine	151	66 (21.9)	236 (78.1)	7 (5.0)	52 (34.0)	92 (61.0)	
Juhász, 2003 (11)	controls	101	122 (60.4)	80 (39.6)	38 (37.6)	46 (45.5)	17 (16.9)	
	any migraine	126	129 (51.2)	123 (48.8)	32 (25.4)	65 (51.6)	29 (23.0)	
	MA	10	10 (50.0)	10 (50.0)	3 (30.0)	4 (40.0)	3 (30.0)	
	MO	116	119 (51.3)	113 (48.7)	29 (25.0)	61 (52.6)	26 (22.4)	
Marziniak, 2005 (13)	controls	115	132 (57.4)	98 (42.6)	38 (33.0)	56 (48.7)	21 (18.3)	
	any migraine	197	211 (53.6)	183 (46.4)	61 (31.0)	89 (45.2)	47 (23.8)	
	MA	96	84 (43.7)	108 (56.3)	20 (20.8)	44 (45.8)	32 (33.4)	
Borroni, 2005 (12)	controls	105	118 (56.2)	92 (43.8)	32 (30.7)	54 (51.3)	19 (18.0)	
	any migraine	144	162 (56.2)	126 (43.8)	52 (36.1)	58 (40.3)	34 (23.6)	
	MA	52	48 (46.2)	56 (53.8)	13 (25.0)	22 (42.3)	17 (32.7)	
Kim, 2005 (14)	controls	170	83 (24.4)	257 (75.6)	9 (5.3)	65 (38.2)	96 (56.5)	
	any migraine	52	20 (19.2)	84 (80.8)	2 (3.8)	16 (30.8)	34 (65.4)	
Park, 2006 (16)	controls	100	43 (22.0)	157 (78.0)	2 (2.0)	39 (39.0)	59 (59.0)	
	MO	97	43 (22.0)	151 (78.0)	4 (4.0)	35 (36.0)	58 (60.0)	
Todd, 2006 (18)	controls	506	617 (61.0)	395 (39.0)	188 (37.2)	241 (47.6)	77 (15.2)	
	MA	472	599 (63.5)	345 (36.5)	188 (39.8)	223 (47.2)	61 (12.9)	
Szilagyi, 2006 (17)	controls	464	540 (58.2)	388 (41.8)	167 (36.0)	206 (44.4)	91 (19.6)	
	any migraine	87	107 (61.5)	67 (38.5)	34 (39.1)	39 (44.8)	14 (16.1)	

Author	Disease status	Study size	Allele frequencies, n (%)			Genotype frequencies, n (%)		
			L	S	L/L	L/S	S/S	
MA	MA	38	47 (61.8)	29 (38.2)	16 (42.1)	15 (39.5)	7 (18.4)	
	MO	49	60 (61.2)	38 (38.8)	18 (36.7)	24 (49.0)	7 (14.3)	
Gonda, 2007 (10)	controls	52	66 (63.46)	38 (36.54)	20 (38.46)	26 (50.0)	6 (11.54)	
	any migraine	45	41 (45.56)	49 (54.44)	8 (17.77)	25 (55.56)	12 (26.67)	

MA: migraine with aura; MO: migraine without aura

Table 3

Hardy-Weinberg Equilibrium and odds ratios (95% confidence intervals) for the association between the *SLC6A4* 5-HTTLPR polymorphism and migraine

Author	Disease status	Study size	HWE*	Additive Model OR (95% CI)	p value	Dominant Model OR (95% CI)	p value	Recessive Model OR (95% CI)	p value
Yilmaz, 2001 (20)	controls	80	0.12	Referent		Referent		Referent	
	any migraine	52	----	1.03 (0.66–1.63)	0.89	1.02 (0.48–2.18)	0.95	1.07 (0.49–2.32)	0.87
Kotani, 2002 (15)	controls	190	0.68	Referent		Referent		Referent	
	any migraine	151	----	1.06 (0.74–1.52)	0.75	1.26 (0.48–3.34)	0.64	1.04 (0.67–1.61)	0.86
Juhász, 2003 (11)	controls	101	0.67	Referent		Referent		Referent	
	any migraine	126	----	1.45 (1.00–2.12)	0.05	1.77 (1.00–3.13)	0.05	1.48 (0.76–2.88)	0.25
	MA	10	----	1.49 (0.61–3.64)	0.39	1.41 (0.34–5.77)	0.64	2.12 (0.50–9.02)	0.31
	MO	116	----	1.45 (1.00–2.14)	0.06	1.81 (1.01–3.24)	0.05	1.43 (0.72–2.82)	0.30
Marziniak, 2005 (13)	controls	115	1	Referent		Referent		Referent	
	any migraine	197	----	1.16 (0.84–1.60)	0.37	1.10 (0.67–1.80)	0.70	1.40 (0.79–2.49)	0.25
	MA	96	----	1.70 (1.16–2.50)	0.01	1.88 (1.00–3.51)	0.05	2.24 (1.19–4.23)	0.01
	MO	101	----	0.80 (0.55–1.17)	0.25	0.72 (0.41–1.26)	0.25	0.78 (0.38–1.61)	0.50
Borroni, 2005 (12)	controls	105	0.70	Referent		Referent		Referent	
	any migraine	144	----	1.00 (0.71–1.41)	0.99	0.78 (0.45–1.33)	0.35	1.40 (0.75–2.62)	0.29
	MA	52	----	1.49 (0.93–2.38)	0.10	1.32 (0.62–2.79)	0.48	2.20 (1.03–4.72)	0.04
	MO	92	----	0.80 (0.54–1.18)	0.26	0.60 (0.33–1.07)	0.08	1.03 (0.50–2.12)	0.94
Kim, 2005 (14)	controls	170	0.83	Referent		Referent		Referent	
	any migraine	52	----	1.37 (0.79–2.38)	0.27	1.40 (0.29–6.68)	0.68	1.46 (0.76–2.78)	0.26
Park, 2006 (16)	controls	100	0.23	Referent		Referent		Referent	
	MO	97	----	0.96 (0.58–1.59)	0.87	0.48 (0.09–2.65)	0.40	1.03 (0.59–1.83)	0.91
Todd, 2006 (18)	controls	506	1	Referent		Referent		Referent	
	MA	472	----	0.90 (0.75–1.08)	0.26	0.89 (0.69–1.16)	0.39	0.83 (0.58–1.19)	0.30
Szilágyi, 2006 (17)	controls	464	0.06	Referent		Referent		Referent	

Author	Disease status	Study size	HWE*	Additive Model OR (95% CI)	p value	Dominant Model OR (95% CI)	p value	Recessive Model OR (95% CI)	p value
Gonda, 2007 (10)	any migraine	87	---	0.88 (0.64–1.21)	0.44	0.88 (0.55–1.40)	0.58	0.79 (0.43–1.46)	0.44
	MA	38	---	0.87 (0.55–1.38)	0.55	0.77 (0.40–1.51)	0.45	0.93 (0.40–2.17)	0.86
	MO	49	---	0.90 (0.59–1.34)	0.58	0.97 (0.53–1.78)	0.92	0.68 (0.30–1.57)	0.37
Gonda, 2007 (10)	controls	52	0.77	Referent		Referent		Referent	
	any migraine	45	----	2.25 (1.20–4.25)	0.01	2.89 (1.12–7.45)	0.03	2.79 (0.95–8.19)	0.06

MA: migraine with aura; MO: migraine without aura

* p-value for Hardy-Weinberg Equilibrium.

Table 4

Association between the *SLC6A4* 5-HTTLPR polymorphisms and migraine, heterogeneity, and publication bias

Any migraine											
Genetic model	Population	No of studies	Odds ratio (95% CI)	Q	Heterogeneity			Publication Bias			
					df	p-value	I ² in %	p-value Begg	p-value Egger		
additive	Europeans (10-13,17,20)	6	1.16 (0.93-1.43)	9.3	5	0.10	46.1	0.19	0.11		
	European women (10,11)	2	1.68 (1.12-2.51)	1.4	1	0.24	26.5	0.32	---		
	Asians (14,15)	2	1.14 (0.85-1.55)	0.6	1	0.45	0	0.32	---		
dominant	Europeans (10-13,17,20)	6	1.16 (0.83-1.61)	9.2	5	0.10	45.9	0.19	0.18		
	European women (10,11)	2	2.02 (1.24-3.28)	0.8	1	0.39	0	0.32	---		
	Asians (14,15)	2	1.30 (0.57-2.97)	0.01	1	0.92	0	0.32	---		
recessive	Europeans (10-13,17,20)	6	1.27 (0.96-1.68)	5.0	5	0.42	0	0.35	0.27		
	European women (10,11)	2	1.76 (1.00-3.10)	1.0	1	0.33	0	0.32	---		
	Asians (14,15)	2	1.16 (0.81-1.66)	0.7	1	0.40	0	0.32	---		
Migraine with aura*											
Genetic model	Population	No of studies	Odds ratio (95% CI)	Q	Heterogeneity			Publication Bias			
					df	p-value	I ² in %	p-value Begg	p-value Egger		
additive	Europeans (11-13,17,18)	5	1.19 (0.86-1.63)	12.0	4	0.02	66.6	0.62	0.25		
	Europeans (11-13,17,18)	5	1.08 (0.78-1.50)	5.9	4	0.21	32.1	0.62	0.33		
	Europeans (11-13,17,18)	5	1.41 (0.83-2.40)	11.1	4	0.03	63.9	1.00	0.24		
Migraine without aura*											
Genetic model	Population	No of studies	Odds ratio (95% CI)	Q	Heterogeneity			Publication Bias			
					df	p-value	I ² in %	p-value Begg	p-value Egger		
additive	Europeans (11-13,17)	4	0.95 (0.72-1.27)	6.3	3	0.10	52.1	0.50	0.74		
	Asians (16)	1	0.96 (0.58-1.59)	---	---	---	---	---	---		
dominant	Europeans (11-13,17)	4	0.93 (0.58-1.50)	8.0	3	0.05	62.7	1.00	0.82		
	Asians (16)	1	0.48 (0.09-2.65)	---	---	---	---	---	---		

Migraine without aura*										
Genetic model	Population	No of studies	Odds ratio (95% CI)	Q	Heterogeneity			Publication Bias		
					df	p-value	I ² in %	p-value Begg	p-value Egger	
recessive	Europeans (11-13,17)	4	0.97 (0.67-1.41)	2.3	3	0.52	0	0.04	0.17	
	Asians (16)	1	1.03 (0.59-1.83)	---	---	---	---	---	---	

* There is no study available looking at the association between the *SLC6A4* 5-HTTLPR polymorphism and migraine with aura among Asian populations.