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IP Indian Journal of Neurosciences

Journal homepage: https://www.ijnonline.org/

Original Research Article

No association between rs6295 of *5-HT1A* and risk of migraine: Evidence from meta-analysis

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ARTICLE INFO

Article history:
Received 02-10-2024
Accepted 19-10-2024
Available online 20-11-2024

Keywords:
Migraine
rs6295
5-HT1A
-1019C/G

ABSTRACT

Background: Migraine is considered a complex disorder with polygenic inheritance and *5-HT1A* is associated with a variant i.e., rs6295 has been hypothesized to be involved in determining the disease susceptibility.
Aim: Therefore, in the present study we aimed to find the risk between the rs6295 and migraine susceptibility using a meta-analysis approach.
Materials and Methods: The present study utilizes the PRISMA guideline to review existing literature to perform pooled analysis, and also includes quality assessment, association analysis, publication, and heterogeneity analysis using the NOS tool, OR with 95% CI, tests of Begg's with Egger's test, and $\chi 2$ based on Cochran's Q Test with I^2 tests respectively.
Results: In the present study we didn't observe any statistical association between the rs6295 and risk of migraine (allele: 1.01 [0.83-1.22], p-value=0.92). Further sub-grouping based on the clinical sub-type, no association was observed in either group i.e., MA (allele: 1.02 [0.73-1.40], p-value=0.90) and MWA (allele: 1.03 [0.75-1.41], p-value0.83).
Conclusions: In the present analysis after critical analysis, it was observed that rs6295 didn't pose any significant risk to the disease susceptibility.

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1. Introduction

Migraine is a disabling neurovascular disorder that is more commonly found in women than in males and can have various cause.[1] Serotonin (5-HT/ 5-hydroxytryptamine) has long been recognized as a key molecule in the development of migraine headaches.[2] There are a lot of serotonin receptors in the central nervous system, and they're engaged in mediating a lot of different processes. One of these serotonin receptors is encoded by *5-HT1A* (5q11.2-q13), which is responsible for encoding a protein that is 422 amino acids long.A common SNP controls the expression of the *5-HT1A* gene called -1019C/G, also known as rs6295, in the promoter region of the gene.[3] Thus, it was hypothesized that the variable in question could potentially determine susceptibility to the disease. Therefore, the objective of the current study was to determine the association between migraine susceptibility and rs6295 risk through the utilization of a meta-analysis methodology.

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https://doi.org/10.18231/j.ijn.2024.044
2581-8236/© 2024 Author(s), Published by Innovative Publication.

2. Materials and Methods

Following the PRISMA (prisma-statement.org) recommendations, we searched electronic databases including PubMed-NCBI, Google Scholar, and Semantic Scholars for relevant articles after utilizinga combination of keywords, including "*5-HT1A* and risk of migraine," "-1019C/G and risks of migraine," and "rs6295 and risk of migraine," to search literature. After the following inclusion/exclusion criteria have been met (Figure 1B), several features can be extracted from each study (Table 1). The quality of all research was evaluated after data extraction using the criteria specified in the Newcastle-Ottawa scale (NOS) (Ottawa Hospital Research Institute (ohri.ca).

Genotypic and allelic frequencies were calculated followed by HWE (Hardy Weinberg Equilibrium) assessment. Association between the variant under study and migraine was done by using the Odds Ratio with a 95% Confidence Interval under different genetic models where a selection of the genetic models was based on the Dersimonian and Laird method (P < 0.10 or I2 > 50%: Random model) and the Mantel-Haenszel method (P ≥ 0.10 and I2 ≤ 50%). The heterogeneity and the publication bias were assessed using the $\chi 2$ based on Cochran's Q Test with I-square (I^2) tests (<0.10) and Begg's and Egger's tests. We also performed a sensitivity analysis to determine how individual studies affected pooled ORs and 95% confidence intervals using the condition "exclusion of each study" (Training.cochrane.org/handbook/current) (Figure 1C). The statistical analysis was carried out by Meta-Genyo(MetaGenyo: Meta-Analysis of Genetic Association Studies)**.** In addition, we also observed the power of study using post-hoc power calculator (Post-hoc Power Calculator (clincalc.com).

3. Results

After searching the available online database and systematically excluding studies (Figure 1A), a total of four studies were found that were conducted in different populations (Table 1) and discussed the association between rs6295 and migraine susceptibility. These studies were conducted in Turkey.[4,5] Germany. and China.[6] After combining data from the four studies, the final group size was 1189 individuals, with 637 migraine sufferers and 552 healthy controls. It was found that the frequency of the variant allele (*G*-rs6295) was higher in the case group (q=51.88%) in comparison to the control group (q=50.72%). Furthermore, it was found that one study failed to appear in HWE; as a result, it was removed from further analysis.[7] (Yucel et al., 2016); finally, three studies were further examined for association.[4,6]

Concerning the association, the polled analysis showed that there is no significant association between the rs6295

Table 1: Features of studies

Study	Region	Ethnicity	Diagnostic Criteria	Source of Controls	Case/ Controls	Tech	Type	Case			Control			HWE	NOS
								HR	HT	HW	HR	HT	HW		
Ates et al., 2013	Turkey	Caucasian	IHS	HB	203/202	PCR-RFLP	Migraine	43	92	68	46	87	69	0.14	6
Yucel et al., 2016	Turkey	Caucasian	ICHD	HB	135/139	Array	Migraine	28	64	43	32	53	54	0.04	6
Marziniak et al., 2007	Germany	Caucasian	IHS	HB	197/117	PCR-RFLP	Migraine	50	103	44					
							MA	26	53	19	32	57	29	0.71	6
							MWA	24	50	25					
Yang et al., 2005	China	Asian	IHS	HB	102/93	PCR-RFLP	Migraine	63	34	5					
							MA	20	16	2	54	35	4	0.71	6
							MWA	43	18	3					

IHS: International Headache Society, **ICHD:** International Classification ofHeadache Disorders, **HB:** HospitalBased, **MA:** Migraine with Aura, **MWA:** Migraine without Aura, **HR:** Homozygote Recessive, **HT:** Heterozygote, **HW:** Homozygous Wild, **HWE:** HardyWeinberg Equilibrium,NOS:Newcastle-OttawaScale

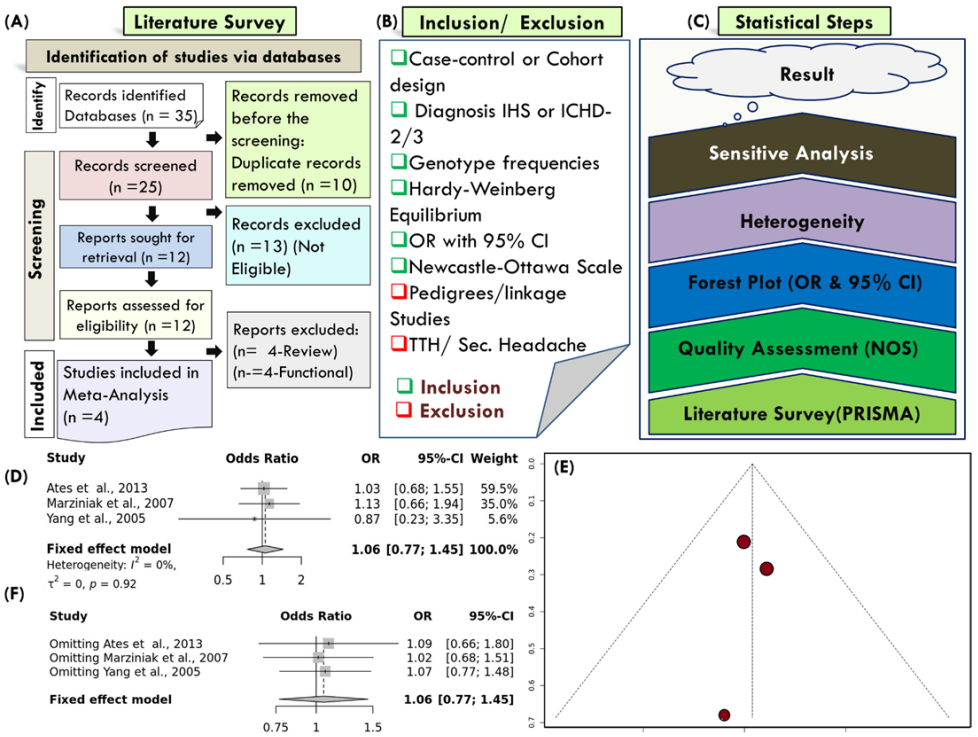

Figure 1: (**A**):Schematicrepresentation of literature survey according to PRISMA guidelines; (**B**): Inclusion and exclusion criteria; (**C**): Flow diagram depicts thestatistical test performed in the present analysis; (**D**): Forest plot represents the non-significant association between rs6295 and risk of migraine under the dominant model; (**E**): Symmetrical funnel plot depicts nopublication bias under the dominant model; (**F**): Sensitivity analysis for dominant model.

Table 2: Overall association

Type	Model	Number of studies	Test of association			Test of heterogeneity			Publication bias
			OR	95% CI	p-val	Model	p-val	I^2	p-val (Egger's test)
Migraine	Allele	3	1.01	0.8324-1.2233	0.927	F	0.9288	0	0.035
	Recessive	3	0.98	0.7240-1.3130	0.868	F	0.7732	0	0.3117
	Dominant	3	1.06	0.7681-1.4493	0.741	F	0.924	0	0.668
	OD	3	1.06	0.8120-1.3809	0.672	F	0.6409	0	0.4032
	HR vs HW	3	0.98	0.6587-1.4482	0.907	F	0.9794	0	0.9343
	HR vs HT	3	0.96	0.6973-1.3126	0.784	F	0.6761	0	0.3647
	HT vs HW	3	1.09	0.7776-1.5352	0.610	F	0.8509	0	0.5021
MA	Allele	2	1.02	0.7382-1.4077	0.907	F	0.4729	0	NA
	Recessive	2	0.90	0.5617-1.4463	0.667	F	0.7009	0	NA
	Dominant	2	1.27	0.6898-2.3431	0.442	F	0.5868	0	NA
	OD	2	1.24	0.7998-1.9288	0.334	F	0.9254	0	NA
	HR vs HW	2	1.14	0.5606-2.3242	0.715	F	0.6018	0	NA
	HR vs HT	2	0.85	0.5169-1.3906	0.513	F	0.8834	0	NA
	HT vs HW	2	1.34	0.7051-2.5524	0.371	F	0.6544	0	NA
MWA	Allele	2	1.03	0.7565-1.4151	0.831	F	0.3298	0	NA
	Recessive	2	1.10	0.7030-1.7317	0.669	F	0.2401	0.275	NA
	Dominant	2	0.96	0.5399-1.6972	0.881	F	0.949	0	NA
	OD	2	0.90	0.5885-1.3686	0.615	F	0.2408	0.273	NA
	HR vs HW	2	0.90	0.4593-1.7783	0.769	F	0.8207	0	NA
	HR vs HT	2	1.13	0.7015-1.8154	0.618	F	0.2219	0.33	NA
	HT vs HW	2	0.96	0.5239-1.7642	0.899	F	0.6548	0	NA

and migraine under different genetic models such as allele (1.01 [0.83-1.22], p-value=0.927), dominant (1.06 [0.76-1.44], p-value=0.741) (Figure 1D), and recessive (0.98 [0.72-1.31], p-value=0.868) (Table 2). Further sub-grouping into two clinical subtypes no association was observed (Table 2). In addition to statistical association, no significant heterogeneity was observed therefore, fixed models were chosen for estimating the risk of association. Population-specific risk attribution was also observed but we failed to observe any statistically significant association. All genetic models demonstrated p-values more than the chosen value (Table 2), as indicated by the results of Egger's test, hence providing evidence that publication bias was absent (Figure 1E). Furthermore, a comprehensive analysis was also conducted on all genetic models by excluding individual trials, and the results indicated that the combined odds ratios did not exhibit significant alterations. This observation highlights the remarkable consistency and robustness of the meta-analysis (Figure 1F).

Furthermore, after evaluating the power of the study using the Post-hoc Power Calculator (Post-hoc Power Calculator (clincalc.com), it was discovered that the current sample size was insufficient to identify actual differences, which immediately reflects the requirement for additional samples.

4. Discussion

Migraine is considered a severe, disabling neurovascular disorder that is found to be more common in women than in men and can have different causes.[7] and has been classified into two clinical subtypes i.e., migraine with aura (MA) and migraine without aura (MWA) (International Classification of Headache Disorders - ICHD-3). Serotonin (5-HT), a neurotransmitter, is thought to be one of the numerous elements that could lead to the development of migraine headaches. Serotonin is known to exert its effects on the brain via certain serotonin receptors, such as *5-HT1A*. Pieces of evidence from different studies have shown thatthe receptors are present in the nuclei of the pontine raphe during the initial phase of migraine attacks.[8] Additionally, it has been observed that during the interictal period, receptor density increases in the posterior cortical and limbic regions of migraine patients with MWA.[9–14] Since the expression of the protein can be altered by a polymorphic site in the promoter region (-1019C/G), researchers have suggested that this polymorphic site plays a role in determining disease susceptibility. After this, several separate studies were conducted to find the statistical association between the variant of interest and the risk of migraine.[4–6,15] However, the findings of all of these studies pointed to the same conclusion, which was "that there was no substantial connection between the two variables". The other side of the coin is that drawing conclusions based on such small research samples doesn't tell us anything much. As a result, we aimed to conduct a meta-analysis to review the studies and determine the real risk involved.

After polling studies, we didn't find any significant risk of overall migraine due to rs6295 under different genetic models (Table 2). Further subgrouping based on the criteria of presence or absence of aura i.e., migraine with aura and migraine without aura, no significant association was observed in both groups after assuming different genetic models (Table 2). Therefore, it can be concluded that the variant (rs6295) is not statistically associated with the risk susceptibility to migraine which has been previously found by multiple independent studies.[4–6] But it is also important to note that this non-significant association might be due to a low sample size which we observed using post-hoc calculation. However, there have been multiple pieces of evidence that showed that individuals who are homozygous carriers of the rs6295 gene show significant relief in their symptoms of nausea and headache. Therefore, it is also possible to propose that the variant may not be responsible for determining the risk of disease, but that it may be related to the alteration of clinical characteristics of migraine instead.[15]

Enclosing the section, the variant rs6295 is not associated with the risk of migraine or its clinical subtypes but, with a specific future perspective, more studies must be conducted in order to find a significant association.

5. Conclusion

Migraine is a complex disorder with polygenic inheritance and *5-HT1A* was hypothesized to be involved in determining the disease susceptibility however the current study found that rs6295 did not represent a statistically significant risk to disease susceptibility.

6. Ethics Approval and Consent to Participate

Not applicable

7. Consent for Publication

Not applicable

8. Conflict of Interest

The authors declare that they have no conflict of interest.

9. Sources of Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

10. Data Availability Statement

All data generated or analyzed during this study are included in this article. Further inquiries can be directed to the corresponding author.

11. Acknowledgments

Authors are highly thankful to the Institute of Human Genetics, University of Jammu, and Department of Human Genetics (Sri Pratap College, Srinagar, Cluster University Srinagar) for support in the present study.

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Cite this article: Sudershan A, Sheikh BA, Malik SA, Kumar H, Kumar P. No association between rs6295 of *5-HT1A* and risk of migraine: Evidence from meta-analysis. *IP Indian J Neurosci* 2024;10(4):211-215.