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Review

Pituitary Adenylate Cyclase-Activating Peptide-38 in migraine: A systematic review and meta-analysis

Sreevani Namani[1], Ramesh Bangaraiahgari[2], Maheshkumar Kuppusamy[3], Laxmi Narayana Sripuram[2], Thanalakshmi Jagadeesan[4]

[1]Department of Research and Development, Saveetha Institute of Medical and Technical Sciences, Chennai, India
[2]Department of Biochemistry, TRR Institute of Medical Sciences, Telangana, India
[3]Department of Physiology, Government Yoga and Naturopathy Medical College and Hospital, Chennai, India
[4]Department of Physiology, Chettinad Hospital and Research Institute, Chettinad Academy of Research and Education, Chennai, India

Abstract

Migraine is a complex neurological disorder characterized by recurrent headaches accompanied by sensory disturbances. It involves a combination of genetic, environmental, and neurovascular factors. The objective of this systematic review and meta-analysis was to investigate the correlation between migraine and specific mutant genes by examining the association of Pituitary Adenylate Cyclase-Activating Peptide-38 genes with migraine. A comprehensive search was conducted in major scientific databases, such as PubMed, Scopus, and Embase, to identify relevant studies published up until September 2023. The inclusion criteria encompassed studies that examined the genes (PACAP-38) and various aspects of migraine. Two independent reviewers performed data extraction and quality assessment to ensure the accuracy and reliability of the collected information. Seven studies, comprising 737 patients, were included in the final analysis. The random effects model yielded a standardized mean difference (SMD) of 0.55 (95% CI:-0.15 to 1.25, t=1.45, p=0.19). Heterogeneity among the studies was substantial, with I^2 indicating 93% variability (95% CI: 84.6% to 96.5%). The heterogeneity was statistically significant (Q= 87.2, df=6, p<0.001). The prediction interval ranged from -1.40 to 2.51. This systematic review and meta-analysis establish a strong link between PACAP-38 and susceptibility to migraine. These findings highlight the significance of genetic factors in migraine development, emphasizing the need for further investigation to elucidate underlying mechanisms and explore the clinical implications of these genetic associations.

Keywords: Meta-analysis, migraine, mutant gene, review

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Migraine is a complex neurological disorder that impacts a significant portion of the global population [1]. It is a condition marked by repeated occurrences of headaches ranging from moderate to severe intensity. These headache episodes frequently co-occur with other symptoms, such as nausea, vomiting, heightened sensitivity to light and sound, and, in certain cases, visual disturbances called auras preceding the headache itself [2]. While the precise underlying reason for migraine is still unclear, it is believed to arise from an interplay of genetic influences, environmental triggers, and neurovascular mechanisms in the brain. It is important that the occurrence rates and degree of effects caused by migraine demonstrate variation across different geographic regions and nations [3]. Italy, for instance, has been identified as having the highest rate of migraine-related disability, followed closely by Thailand, Norway, Spain, Brazil, and Ethiopia [4, 5]. These variations in prevalence rates highlight the influence of geographic and cultural factors on the occurrence and management of migraine. In Asia, the estimated average prevalence of migraine is 12.7%, emphasizing the significant impact of the condition on the continent [6]. The World Health Organization (WHO) recognizes migraine as the sixth most debilitating disorder

Address for correspondence: Thanalakshmi Jagadeesan, MD. Department of Physiology, Chettinad Hospital and Research Institute, Chettinad Academy of Research and Education, Chennai, India
Phone: 99400 49086 **E-mail:** dhana.ibms@gmail.com **ORCID:** 0000-0002-0905-617X

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worldwide, causing significant disability and a reduced quality of life for affected individuals [7]. The consequences of migraine reach further than just the individual level, as it places a substantial strain on healthcare infrastructures and economic productivity due to the utilization of medical resources and missed workdays or inability to work effectively [8].

Genetic factors play a significant role in the development and susceptibility to migraine. Various studies have identified several mutant genes that may contribute to the pathophysiology of the condition [9]. PACAP-38, a neuropeptide involved in various physiological processes, has been suggested to play a role in the regulation of neuroinflammation and pain modulation in migraine [10]. Understanding the genetic basis of migraine can provide valuable insights into its underlying mechanisms and potential targets for therapeutic interventions [11, 12]. By undertaking a systematic review and meta-analysis that synthesizes studies examining the connection between these mutated genes and migraine, we can assess the collective strength of the evidence and determine the degree to which these genetic variants contribute to the development of the condition. This comprehensive analysis can help identify genetic markers or pathways that may be useful in diagnosing, managing, and developing targeted treatments for individuals with migraine. The findings from this systematic review and meta-analysis have the potential to contribute to the field of migraine research by shedding light on the genetic mechanisms involved in the development and manifestation of the condition.

Methods

Search strategy

Multiple electronic databases, including PubMed, Embase, Scopus, and Web of Science, were systematically searched to identify relevant studies published up until the literature search cutoff date of November 1, 2023. The search terms were carefully selected to capture articles related to migraine and specific mutant genes (PACAP-38). The search was limited to human studies and articles published in English.

Study selection

Two reviewers independently screened the titles and abstracts of the retrieved articles based on predefined inclusion and exclusion criteria. Full-text articles were obtained for potentially relevant studies and further assessed for eligibility. Inclusion criteria included studies investigating the association between the PACAP-38 gene and migraine susceptibility using cross-sectional, cohort, or case-control study designs. Animal studies, case reports, reviews, and conference abstracts were excluded.

Data extraction

Data from eligible studies were independently extracted by two reviewers using a standardized form. The extracted information included study characteristics, participant demographics, genotype frequencies, and relevant outcomes. Any discrepancies or disagreements were resolved through discussion and consensus.

Risk of bias assessment

Two separate authors conducted a risk of bias assessment according to the ROBINS-I tool guidelines, ensuring independent evaluation. This evaluation covered six areas: choice of comparison groups, confounding bias, determination of exposure, assessment of outcomes, handling missing data, and presentation of findings. Bias risk was categorized as low, moderate, serious, or critical based on domain assessment [13].

Data synthesis and statistical analysis

We utilized either random-effects or fixed-effects models based on the heterogeneity observed among the studies included in our analysis. Effect sizes (Mean Standardized Difference, SMD) and their corresponding 95% confidence intervals were calculated. The I^2 statistic was used to assess heterogeneity between studies. We conducted subgroup and sensitivity analyses to investigate potential sources of heterogeneity and assess the robustness of our results. The analysis was carried out using R statistical software version 4.0.2.

Results

Study characteristics

Following a systematic search, we initially identified 172 studies. Through screening of titles, abstracts, and full texts, seven case-control studies were deemed eligible and met the inclusion criteria (Fig. 1) [14–20]. In total, 737 patients were included in the qualitative analysis, consisting of 427 individuals with migraine and 310 control participants. The included studies spanned diverse geographic regions and age groups to investigate the role of PACAP levels in migraine pathophysiology (Table 1). Across the studies, participants' ages varied widely, ranging from pediatric (8 years) to middle-aged and older adults (42 years). The research was conducted in countries including the United Kingdom [18], Hungary [15], Iran [19], China [14, 17], and Spain [16, 20], reflecting a global perspective on migraine research. The minimum sample size was 9, and the maximum sample size was 106 among the experimental group. Various study designs, including experimental, exploratory, and case-control approaches, were employed, each providing unique insights into PACAP's involvement in migraine. All studies included in our analysis measured PACAP levels utilizing enzyme-linked immunosorbent assay (ELISA) methodology.

Meta-analysis

The random-effects model showed an SMD of 0.55 (95% CI:-0.15 to 1.5), indicative of a potential positive effect, though lacking statistical significance (p=0.12). Interestingly, the inclusion of PACAP-38 mutation status did not substantially alter the observed effect size. Nevertheless, considerable heterogeneity persisted among studies, with an I^2 value of 93%, suggesting notable variability in effect sizes even after accounting for PACAP-38 mutations. The wide prediction interval, spanning from -1.40 to 2.51, underscores the uncertainty surrounding the true effect size (Fig. 2). We attempted a sensitivity and specificity analysis to overcome the heterogeneity.

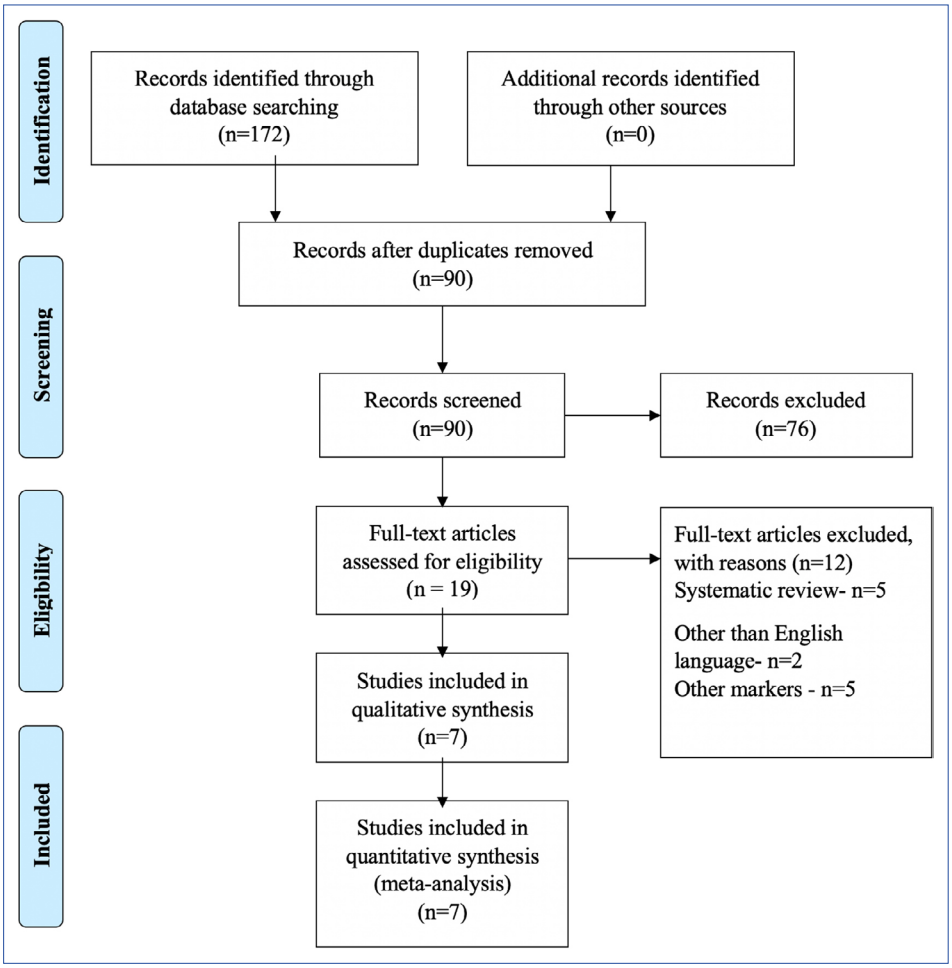

Figure 1. A PRISMA diagram illustrating the search strategy.

The updated meta-analysis (Fig. 3), conducted after removing Liu et al. [14] and Perez-Pereda et al. [20], includes 5 studies with a total of 386 observations (250 experimental, 136 control). The random-effects model reveals a standardized mean difference (SMD) of 0.07 (95% CI: [-0.0006, 0.15]), suggesting a small positive effect that is borderline significant (p = 0.05). Notably, the analysis demonstrates very low heterogeneity among the included studies, with I^2=0.0% [0.0%; 79.2%], Tau^2=0.0003, and a Q statistic of 0.27 (p=0.99). The prediction interval [-0.27, 0.42] indicates the range within which true effect sizes in similar studies are likely to fall.

Risk of bias

Within the included studies (Table 2), two were identified to possess an overall moderate risk of bias, whereas the remaining studies were classified as having a low risk. Specifically, two studies exhibited moderate risks of bias related to confounding and selection of participants [14, 19]. None of the studies were identified as having serious or critical risks of bias.

Discussion

The present meta-analysis synthesized findings from seven studies investigating the impact of PACAP levels in migraine pathophysiology. Our analysis indicated an SMD of 0.55, implying a potential positive effect of PACAP on migraine. However, it is important to note that this effect did not reach statistical significance (p=0.12). Notably, the inclusion of PACAP-38 mutation status did not significantly alter the observed effect size, indicating that other factors may contribute to the variability in PACAP levels observed across studies. Despite the intriguing trend toward a positive effect, considerable heterogeneity was evident among the included studies, with an I^2 value of 93%. The significant heterogeneity observed suggests notable variability in effect sizes, likely stemming from differences in study populations, methodologies, and clinical characteristics among migraine patients. The wide prediction interval, spanning from -1.40 to 2.51, underscores the uncertainty surrounding the true effect size of PACAP on migraine. This uncertainty may be attributed to the limited number of studies included in the analysis, as well as the complex and multifactorial nature of migraine pathophysiology.

PACAP is believed to have multiple roles in the development of migraines, including the activation of TVS and intracranial vasodilation [17]. Previous studies propose that reduced interictal PACAP-38 concentrations in individuals with migraines may originate from various factors, such as suboptimal brain energy

Table 1. Characteristics of the included studies

Author	Country	Age	Type of the participants	Study design	Sample size	Marker	Result
Zagami et al. [18] 2014	United Kingdom	37±8 years	Migraine with or without aura	Experimental study	T=15	PACAP	PACAP levels are elevated migraineurs during spontaneous migraines
Tuka et al. [15] 2016	Hungary	40.1±12	Migraine	Exploratory study	T=18 EHC=9 C=9	PACAP	PACAP-38 levels were found higher during CH attacks compared to the inter-bout phase
Han et al. [17] 2015	China	40.86±11.97	Migraine & Tension-type headache	Case control	M=133 TTH=106 C=50	PACAP	Migraine patients had lower interictal plasma PACAP levels than patients with TTH and healthy controls
Cernuda-Morollό et al. [16] 2016	Spain	42.8±13.4	Women with Chronic Migraine	Case control study	T=86 M=35 C=32	PACAP and vasoactive intestinal peptide (VIP)	No difference found in PACAP levels
Pérez-Pereda et al. [20] 2020	Spain	41±10 years	Chronic migraine patients	Case control study	CM=101 EM=98 C=97	PACAP-38, Calcitonin gene-related peptide (CGRP),	PACAP serum levels were higher in CM than in EM or HC
Liu et al. [14] 2022	China	4–18 years	Children with Migraine	Case control study	T=143 M=76 C=77	PACAP-38 and calcitonin gene-related peptide (CGRP),	PACAP-38 and CGRP levels in migraine patients during the ictal and interictal periods were higher than those in controls
Togha et al. [19] 2021	Iran	39 years	Migraine patients	Case control	T=89 CM=36 EM=23 C=30	TRPV1, PACAP, and VIP	Serum level TRPV1, PACAP, and VIP were higher among the migraine patients

PACAP: Pituitary Adenylate Cyclase-Activating Peptide; CM: Chronic migraine; EM: Episodic migraine.

levels, mitochondrial abnormalities, imbalances in neuronal Mg^{2+}, and the degradation of PACAP-releasing circuits [17]. Administering PACAP might result in an expansion of the superficial temporal artery diameter and a reduction in mean blood flow velocity in the middle cerebral artery [21]. Numerous studies have examined the relationship between plasma PACAP levels and various phases of migraines, yielding mixed results. Specifically, two studies have focused on interictal peripheral levels of PACAP in migraine patients, revealing decreased levels in individuals experiencing migraines [14, 15]. Another study observed decreased interictal serum PACAP levels in patients with EM, but no significant difference was detected between CM patients and controls [22]. The findings from Han et al.'s [17] study indicate a noteworthy decrease in PACAP levels in plasma among individuals with both episodic migraine (EM) and chronic migraine (CM) when compared to those in the healthy control group. Some evidence suggests that sumatriptan treatment may cause decreased PACAP levels [18]. Additionally, interictal PACAP levels have been observed to show a negative correlation with the duration of migraine disease [15, 17]. In contrast to our findings, elevated serum PACAP levels in patients with CM were identified by Pérez-Pereda et al. [20], distinction that more effectively differentiated them from cases of EM and control subjects.

Overall, while our analysis suggests a potential association between PACAP levels and migraine, the findings should be interpreted with caution due to the high heterogeneity and wide prediction interval. Future research should aim to elucidate the underlying mechanisms driving the observed variability in PACAP levels and explore potential therapeutic implications for targeting the PACAP pathway in migraine management. Furthermore, larger-scale studies employing standardized methodologies are necessary to provide deeper insights into the role of PACAP in migraine and its potential as a therapeutic target.

Limitations

A limitation of our meta-analysis is the intrinsic heterogeneity among the studies included, potentially contributing to the observed variability in effect sizes. The diverse study populations, methodologies, and clinical characteristics of migraine patients across different geographic regions and age groups could have influenced

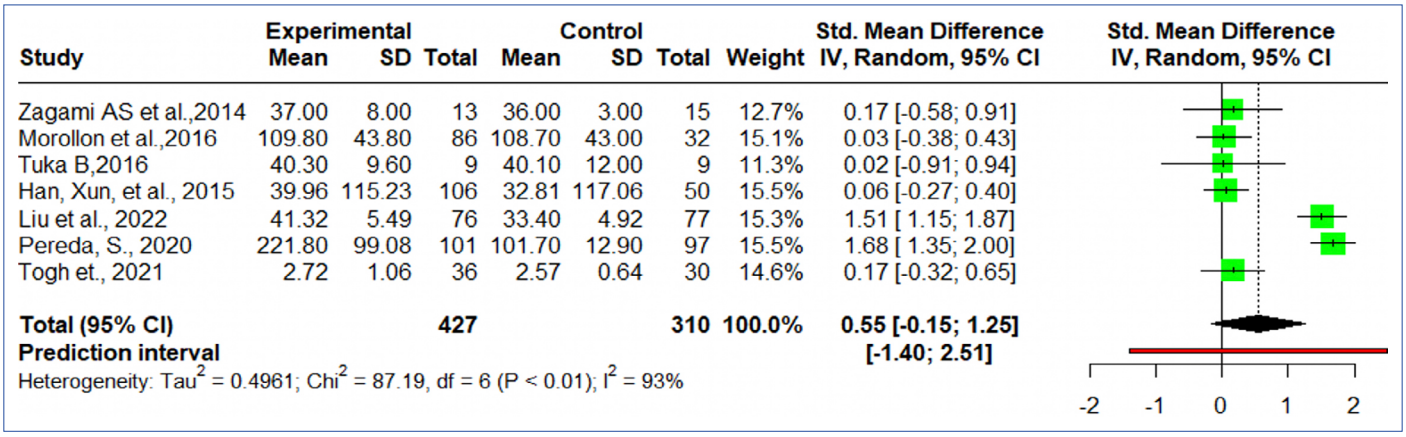

Figure 2. Forest plot for the PACAP-38 mutation gene in Migraine.

SD: Standard deviation; CI: Confidence interval; I^2: I-squared (measure of heterogeneity); PACAP-38: Pituitary Adenylate Cyclase-Activating Peptide-38.

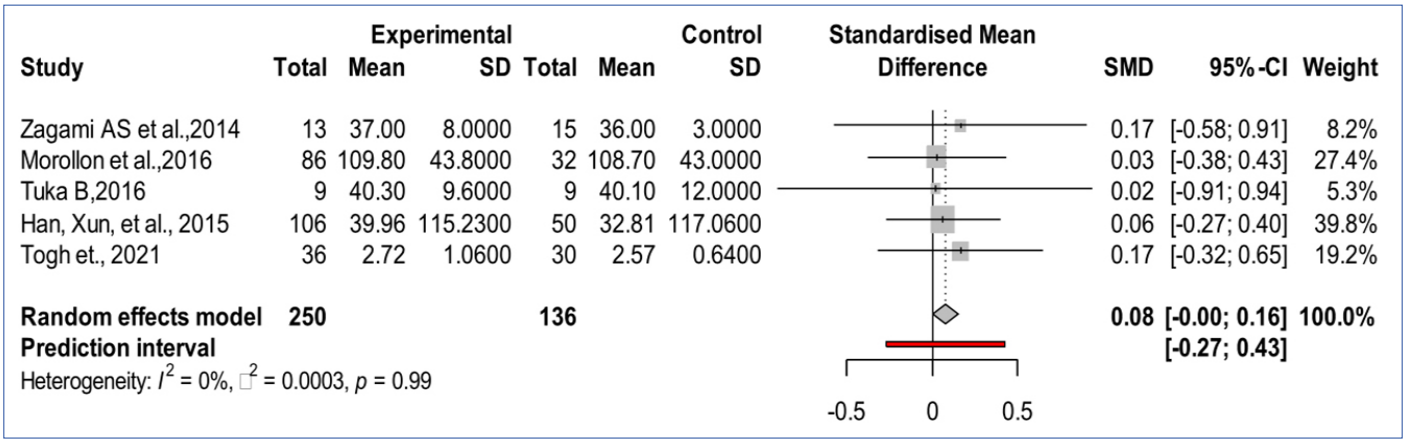

Figure 3. Forest plot after sensitivity analysis of the included studies.

SD: Standard deviation; SMD: Standardized mean difference; CI: Confidence interval; I^2: I-squared (measure of heterogeneity).

the results. Additionally, the limited number of studies available for inclusion may have restricted the generalizability of our findings and increased the risk of publication bias.

Strengths

Despite these limitations, our meta-analysis offers several strengths. By synthesizing data from multiple studies, we provided a comprehensive overview of the current literature regarding PACAP levels in migraine pathophysiology. The inclusion of studies from diverse geographic regions and age groups enhances the external validity of our findings, providing insights into PACAP's role in migraine across different populations. Additionally, our analysis utilized rigorous statistical methods, including a random-effects model, to account for heterogeneity among studies and provide robust estimates of effect sizes. Overall, our study contributes to the growing body of evidence on PACAP and migraine, highlighting the need for further research in this area.

Table 2. Risk of bias

Author	Selection of comparison groups	Bias due to confounding	Ascertainment of exposure	Measurement of outcome	Missing data	Reporting of results	Overall risk of bias
Zagami et al. [18] 2014	Low	Low	Low	Low	Low	Low	Low
Tuka et al. [15] 2016	Low	Low	Low	Low	Low	Low	Low
Han et al. [17] 2015	Low	Low	Low	Low	Low	Low	Low
Cernuda-Morollón et al. [16] 2016	Low	Low	Low	Low	Low	Low	Low
Pérez-Pereda et al. [20] 2020	Low	Low	Low	Low	Low	Low	Low
Liu et al. [14] 2022	Moderate	Low	Low	Low	Low	Low	Moderate
Togha et al. [19] 2021	Low	Moderate	Low	Low	Low	Low	Moderate

Conclusion

In conclusion, the results of this systematic review and meta-analysis suggest a potential involvement of PACAP-38 genes in migraine development. However, it is imperative to conduct further research to validate these findings and comprehensively grasp the intricate interplay between genetics and migraine. Future research should focus on investigating the potential mechanisms underlying the association between PACAP-38 genes and migraine, as well as examining other genetic and environmental factors that may contribute to the development of this disorder. Moreover, longitudinal studies are necessary to determine the temporal relationship between PACAP-38 genes and the onset of migraine.

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