



Research Article

Genetic Variations of Dao with Migraine in the Mexican Population

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Summary

Migraine is a neurological disorder characterized by high prevalence and significant disability. Approximately 16% of the population suffers from migraine; it predominantly affects women aged 35–45 years, and in 60–80% of cases, there is a genetic predisposition to migraine. The enzyme Diaminooxidase (DAO), encoded by the AOC1 gene, is primarily responsible for degrading exogenous histamine present in food. Single-nucleotide polymorphisms (SNPs) in the AOC1 gene have been associated with reduced DAO enzymatic activity, which facilitates the accumulation of histamine and is considered a pathophysiological factor linked to the occurrence of migraine. There are reports indicating that up to 87% of migraine cases are associated with DAO deficiency. The primary SNPs associated with this condition are rs10156191, rs2052129, rs1049793, and rs1049742. This study aims to determine the prevalence of these most common SNPs in Mexican patients with migraine who also have DAO deficiency. As a result, only four SNPs from the AOC1 gene were considered in adults with migraine in the Mexican Republic; these included 349 Mexican patients with migraine aged 18 years or older. The prevalence of one or more SNPs associated with DAO deficiency among migraine patients was 81.66%; among these, rs1049793—the most frequently identified SNP—had a prevalence of 68.5%. Additionally, 26 distinct SNP combinations were identified; notably, genotype 1 (rs2052129, rs10156191, rs1049742 without mutation, and rs1049793 as heterozygous) was present in 121 patients (34.7%). We conclude that the detection of SNPs associated with DAO deficiency in 82% of migraine patients highlights its importance as a predisposing factor for the development of this disorder, enabling more effective diagnosis and treatment approaches.

Introduction

Migraine is a complex, multifactorial neurological disorder that involves disruptions in the functioning of multiple neural and vascular networks, and is associated with genetic, hormonal, environmental, dietary, sleep-related, and psychological factors. During each migraine attack, four phases are identified, each corresponding to known clinical manifestations [1].

A) Prodromic or premonitory phase: This phase appears at the onset of headache and can occur anywhere from

several days to just hours before the migraine. The most frequently observed symptoms include changes in mood (anxiety, depression, irritability, or euphoria), sonophobia, constipation, increased thirst and urinary frequency, food cravings, neck pain, difficulty concentrating, and frequent yawning [2,3].

B) Aura phase: This phase appears immediately prior to the onset of headache (in the case of migraine) or develops gradually over a period of minutes to one hour.

C) Headache or migraine phase. This phase typically lasts

between 4 and 72 hours, depending on the individual and the frequency of the attacks.

- D) Prodromic phase: After the onset of pain, symptoms similar to those of the prodromic phase may emerge within hours or days.

From a pathophysiological perspective, the mechanisms underlying migraine pain suggest an important role in peripheral neuronal inflammation. Certain external and internal factors—such as stress, hormonal changes, or widespread cortical depression—induce the inflammatory phase by releasing neuropeptides that, upon interacting with blood vessels, trigger vasodilation, plasma extravasation, activation of satellite glial cells, and mast cell degranulation. Consequently, migraine has been considered to result from inflammation caused by the local release of neuropeptides, such as calcitonin gene-related peptide (CGRP). Once released, these neuropeptides stimulate the release of histamine from adjacent mast cells; in turn, this systemic histamine induces the release of CGRP, thereby establishing a bidirectional relationship between histamine and neuropeptides in neurogenic inflammation [4].

Histamine, discovered in 1907 by Windaus and Vogt, is an indazolic monoamine synthesized through the decarboxylation of the amino acid L-histidine, a process catalyzed by the enzyme L-histidine carboxylase. It participates in various immunological and physiological mechanisms, such as the stimulation of gastric secretion, muscle contraction, vasodilation, cell proliferation/differentiation, embryonic development, wound healing processes, permeability, and immunomodulation. As a result, the nervous system functions as a neurotransmitter and thereby regulates various physiological processes, including temperature regulation, memory, wakefulness/sleep, and pain sensation. Histamine is also found in various tissues of the body, such as the skin, connective tissue, lungs, and the gastrointestinal tract. This also applies to various cell types: mast cells, basophils, endothelial cells, ependymal cells, neurons, glial cells, dendritic cells, T cells, platelets, adrenal chromaffin cells, and cells resembling gastric enterochromaffin cells [5,6]. In the central nervous system (CNS), histamine is produced by histaminergic neurons located in the tuberomammillary nucleus—situated in the posterior portion of the hypothalamus—and these neurons extend their axons throughout the brain.

Material and methods

Methods: This research project aims to include 394 patients diagnosed with migraine based on clinical criteria. The sample size was calculated using the following formula for finite populations.

Where: n = sample size; N = study population;

$Z_{\alpha} (0.05) = 1.96$ (95% confidence level);

p = frequency of the wild-type allele;

q = frequency of the "mutated" allele;

d = maximum allowable error: 0.05.

Fifty-six (56) adult patients will be recruited from each of the seven cities located across the three geographical regions of Mexico of 394 patients is reached. This regional distribution of participants will enable the collection of valuable information regarding the country's genetic background and its association with migraine attributable to DAO deficiency.

Inclusion Criteria:

1. Men and women aged ≥ 18 years with a clinical diagnosis of migraine.
2. Patients born and residing in the following cities: Chihuahua, Monterrey, Guadalajara, Mexico City, San Luis Potosí, Veracruz, and Mérida. The place of birth must be verified using a CURP or birth certificate.
3. Patients who have read and signed the informed consent form, understand the study requirements, and are willing to follow the study procedures and investigator's instructions.

Exclusion criteria:

The following patients will not be included in this research study:

1. Patients under the age of 18;
2. Patients aged 18 or older who have not provided written informed consent;
3. Patients who do not meet the necessary criteria for proper sample collection;
4. Patients residing in the cities specified in this protocol but who were not born there;
5. Patients with acute inflammatory diseases;
6. Patients with a history of any disorder characterized by headache other than migraine.

This procedure was performed for the genotyping of variants in the AOC1 gene; genomic DNA was extracted using the TaqMan® Sample-to-SNP™ DNA Extraction Kit (Applied Bio systems, Thermo Fisher Scientific, Germany), which involves adding a cell lysis buffer to lyse the cell membranes and incubating the sample under controlled temperature conditions before adding the DNA stabilizing solution to the sample.

The protocol was approved by the Ethics and Research Committee of La Misión S.A. de C.V. Hospital, located in Monterrey, Nuevo León, Mexico; the approval number is LC.DAO.2024.01. An informed consent form was obtained from all patients who agreed to participate in the study, and the form was signed by each patient, two witnesses, and the associated researcher.

Results

A total of 394 patient samples from both genders were collected across six regions, distributed as follows: two samples

from the northern region, three from the central region, and three from the southern region; these samples were then used for the analysis of the four polymorphisms in the AOC1 gene (Deaminase Oxidase, DAO) (Tables 1,2).

The DAO variants were identified using the described technique; the four most significant polymorphisms reported in the literature were analyzed, and significant variability as well as reference values (functional DAO) were identified (including rs2052129, rs10156191 [G/G], rs1049742, and rs1049793). The following results were obtained according to age group, gender, and predominant genotype in patients with chronic migraine; treatment modalities were not analyzed, as they were not the focus of this study. The mean age of the study cohort was 39.3 ± 13.8 years (range: 18–83 years); among the participants, 289 (82.8%) were women and 60 (17.2%) were men. The minimum prevalence of a SNP associated with DAO genetic deficiency was 81.66%, with rs1049793 being the most frequent SNP (68.5%). A history of allergic disorders was reported in 35% of the participants, and a history of ADHD in 11% (Table 3).

As shown in Table 1, the predominant symptom identified in this study was anxiety; furthermore, the region where the rs1049793 polymorphism was detected was located in the central part of the areas within the Mexican Republic (Table 2).

Among the participants, 29% had a family history of allergies; however, the prevalence of migraine among this group was particularly high (Tables 4,5).

In pursuit of determining the frequency of the genetic polymorphisms rs2052129, rs10156191, rs1049742, and rs1049793 associated with DAO deficiency in the population, we successfully identified a clear predominance of a particular polymorphism—specifically rs1049793—in all regions of the country; this predominance was observed in the central region.

Table 1: Polymorphisms and predominant symptoms in the study cohort.

CARACTERISTIC	TOTAL n= 349	%
4 Polimorfism	13	3.72%
3 Polimorfism	34	9.74%
2 Polimorfism	54	15.47%
1 Polimorfism	184	52.72%
0 Polimorfism	64	18.34%

Table 2: Number of polymorphisms in samples and by region in the Mexican Republic.

NORTH/ rs1049793	58	64.44%	CENTER/ rs1049793	114	67.86%
NORTH/ rs10156191	23	25.55%	CENTER/ rs10156191	54	32.14%
NORTH/ rs2052129	21	23.33%	CENTER/ rs2052129	48	28.57%
NORTH/ rs1049742	4	4.44%	CENTER/ rs1049742	10	5.95%

SOUTH/rs1049793	58	31%
SOUTH/rs10156191	23	25.5 %
SOUTH/rs2052129	21	23
SOUTH/ rs1049742	4	4.44%

Table 3: Family history of inflammatory disorders and polymorphism findings. Antecedent Familiar Hereditary.

FIBROMIALGY	26	7%
DAH	34	10%
MIGRAÍNE	189	54%
ALERGY	102	29%

Table 4: Personal Medical History.

DAH	37	11%
ALERGY	122	35%
CHRONIC DEGENERATIVE	111	32%

Table 5: Polymorphism Forms.

Rs1049793	239	68.50%
North	58	24%
Center	114	48%
South	67	28%
Rs10156191	99	28%
North	23	23%
Center	54	55%
south	22	22%
Rs2052129	93	27%
North	21	23%
Center	48	52%
South	24	26%
Rs109742	15	4%
North	4	27%
Center	10	67%
South	1	6%

However, this finding cannot be considered absolute, as the sample selected was predominantly from that Mexican region where migraine was diagnosed.

Conclusion

The most commonly identified variant in our study corresponds to that reported in the literature – the rs1049793 polymorphism – with a prevalence of 68.5% and a migraine-to-non-migraine ratio of 4:1. In this study, we observed a predominance of a single gene accounting for more than 85% of cases; in smaller proportions, we identified more than two polymorphisms, but no direct association was found between these polymorphisms and other inflammatory manifestations.

Based on the results obtained, we can clarify the following points:

1. The predominant gender distribution of migraine is female-to-male ratio of 4.8:1, which is consistent with reported literature;
2. The rs1049793 polymorphism variant is predominant (68.5%) among the Mexican population with migraine;
3. In 52.72% of cases, only one of the examined polymorphisms was detected; it is noteworthy that the number of cases exhibiting two, three, or four polymorphisms in the sampled individuals corresponded to 15.47, 9.74, and 3.72, respectively. No polymorphisms were reported in the remaining 18.74%

of cases; nevertheless, migraine symptoms were present in these individuals, suggesting that there is, on average, a weaker direct association between migraine and potential migraine-causing factors related to DAO, as observed in this study within our population (14–5).

4. Comorbid conditions associated with migraine included unspecified allergies, ADHD (in these two comorbidities, the DAO-related condition was not specified), and chronic degenerative diseases such as arthritis, diabetes, and hypertension not associated with DAO16–7.
5. It is feasible to adopt an approach in treatment that involves the use of complementary dietary therapies to space out migraine episodes among the Mexican population.

Discussion

From a pathophysiological perspective, the presence of the Rs1049793 polymorphism is highly consistent with findings reported in studies conducted in Spain among migraine patients [7–18]. However, in none of the reported studies has the type of migraine been classified according to the ICH classification system for headaches;

This would be particularly interesting in the group of histaminergic disorders, where a higher prevalence of this polymorphism is likely, and thus warranting preventive measures regarding dietary management in individuals with histaminergic conditions that may exacerbate the recurrence of headache episodes – thereby potentially improving quality of life and enabling patients to resume their usual activities.

While it is true that this study involved only age groups aged 18 years and older, we should also consider the pediatric age group, which was not included in the study but is not exempt from experiencing migraine; however, based on the preliminary data obtained from this study, it is feasible to extend these findings to other age groups affected by migraine and implement preventive measures through dietary recommendations that avoid stimulating histaminergic pathways, thereby reducing the potential risk of recurrent, disabling migraine episodes and improving quality of life. Nevertheless, there are no definitive reports that can fully validate our hypothesis; thus, this is a preliminary study that opens the door to a better understanding of the pathophysiology of migraine in our population [19,20].

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