Predictability of migraine by identifying novel biomarkers in PAM rs73189054 at chromosome 5q21 Position

Hsiao-Ling Huang
Yuanpei University of Medical Technology

Chun Hsiang Lin
Yuanlin Christian Hospital

Wen-Hsiu Liu
Chung Shan Medical University

Ying-Shiung Lee
Chung Shan Medical University

Chi-Ling Wu (aling10570@gmail.com)
Chung Shan Medical University

Research Article

Keywords: Migraine, Genetics, Causal inference, Gene set enrichment analysis, Epidemiology, Complex traits

Posted Date: January 3rd, 2023

DOI: https://doi.org/10.21203/rs.3.rs-2403801/v1

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Abstract

Background

Some genes influenced by these variants are highly expressed in vascular tissues and dysfunction can play a role in migraine. The richest tissues are part of blood vessels. In this study, a novel biomarker to predict prevalent migraine by association and mechanisms was presented.

Methods

Using Microarray data collection and processing and migraine summary GWAS database. Then using gene set enrichment analysis (GSEA), heuristic fine mapping by FUMA GWAS, and identification of PAM in the position of chromosome 5q21 by Pheweb of the biobank and MR-based platform.

Results

GSEA identified positions that were significantly increased by PAM overexpression, and gene expression was assessed in migraine patients (GSE76242). On position chromosome 5q21, modules were enriched in migraine patients with an enrichment score - 0.50, the nominal enrichment score was 1.15, and the nominal p-value (0.30142567) migraine.

In FUMAGWAS, we added an analyzer for gene set analysis by enrichment. One of the GeneSets was chromosome 5q21, N was 15, n was 2, the value of P was 2.14e-4, the adjusted P was 1.60e-2, and the genes were the PAM gene and were assigned by the SNP coding area rs73189054 (lead SNP).

Conclusions

In conclusion, this study provides a novel migraine rs73189054 from PAM rs73189054, in the position of chromosome 5q21. In particular, it could be determined to predict the susceptibility and vulnerability of migraine.

Introduction

Migraine is a chronic disease in all regions, cultures, and socioeconomic statuses. It has a direct impact on more than one billion humans throughout their lives [1–3]. Furthermore, migraine is the second main cause of disability and more than all other combined neurological diseases in the 2016 Global Disease burden study [4]. Migraines are the second most common disorder in neurology after tension headaches, and in the general population they occur approximately 15% per year, with a prevalence of approximately 15% per year [1, 3].

Migraine is a multicomponent neurological disorder with a severe and weak headache. Often, nausea, vomiting, paralysis, light, and sound sensitivity are accompanied. Furthermore, migraine is the most common brain disorder and affects 14% of the population [4–7].

The inception mechanisms of the migraine attack were uncertain. Furthermore, evidence favors peripheral-age perivascular trigeminal afferents of peripheral origin [3, 8, 9]. Furthermore, other data indicate that the genesis of the central nervous system, including the brain stem and the neuronal dysfunction of the diencephalon and brain stem, is more likely [3, 8, 9].

Migraine is affected by changes in the neuronal and vascular systems, including dispersed depression of the nervous system (CSD), nervous excitation, and the trigeminal vascular system [10]. In general, this study revealed possible vascular components of migraine and highlighted the character of platelet accumulation and vascular contraction. Furthermore, the life that occurs, especially one of importance and stress, can affect the risk of migraine [11]. In this
study, the identified loci showed improved gene expression in smooth muscle tissue and vascular, consistent with the main theory of migraine, which emphasizes the vascular etiology [12]. Moskowitz recommends that migraine be determined by the activation and sensitivity of trigeminovascular neurons. These receptors enter the meninges and their vessels, a prognostic for the structure of the central nervous system. When these neurons are activated, vasoactive peptides are released, and local inflammation reactions are produced. [3, 13–15].

Migraine is a type of inheritance with an estimated inheritance rate of 30 to 60%. Consequently, genetic studies have led to significant advances in understanding genetic ecology [11, 16–18].

Genetic migraine is complex and it is unknown which loci and genes are involved in the pathogenesis. Moreover, it could be based on more than one source of genetics and different loci. And it may act in conjunction to provide susceptibility and disease characteristics in such individuals to environmental factors [7].

Materials And Methods

2.1. The Gathering and Processing of Microarray Data

The migraine genetic expression profile data was obtained from the Gene Expression Omnibus Database (GEO) [19] https://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=GSE72642

Comparison of human peripheral blood genome profiles T, B, natural killer, monocyte, and polymorphonuclear with ischemic stroke, migraine, and Tourette syndrome. The ID of the migraine profile probe matches the genetic sign and genetic explanation provided in the consistent platform file. The managed profile data is used to build the network. (Supplementary data)

2.2 Download the GWAS database at https://pheweb.org/UKB-SAIGE/pheno/340

There were 340: Migraine includes 2870 cases and 398780 controls. Category: neurological. The results of this PheWeb show a genome-wide association of ICD codes with white British code as the data used was publicly available.

2.3 Gene Set Enrichment Analysis (Gsea) Of Migraine

In addition to the positional gene set, the migraine gene set was investigated using the gene set enrichment analysis tool (GSEA) [20, 21]. The expression of enriched genetics was screened between non- migraine and migraine samples in GSE72642. The genetic sets examined confirmed that the C1 modules: A set of positional genes, a set of genes corresponding to each human chromosome, and a set of genes corresponding to each cytogenetic band were enriched in migraine samples. On the 5q21 chromosome, the enrichment score (ES) of 0.5037546, the normalization score (NES) of 1.1619002, the nominal p-value of 0.3195021, the FDR p value1.0, FWER p value1.0 (Figure). The combined results of enriching the positional set of migraine genetics. Furthermore, the enrichment of the genetic sets confirms the position of the migraine genetic set. The module genes associated with migraine are PAM genes. Therefore, it should be mentioned that migraine and its related module genes overlap strongly at the position of chromosome 5q21.

We downloaded from GSEA c1: Positional genetic set corresponding to each human chromosome, c1.all.v7.5.1. Symbol and c1.all.v7.5.1. Symbols of the cytogenetic band and positional genetic set (https://www.gsea-msigdb.org/gsea/downloads.jsp). GSEA consists of three types of data: first, expression data in the text table; second,
data information in the cls file format; and finally, genes or module genes in the gmt file gmt format [22]. The analysis was carried out using the GSEA analysis tool and the migraine module gene was studied in the GSE72642 profile data.

### 2.4 Heuristic Fine Mapping

Bayesian fine mapping is performed, as well as Heuristic fine mapping [23]. The correlation between the lead SNP in each region and the remaining SNPs with $r^2 < .6$ was examined by heuristic fine mapping [23, 24]. Based on the 1000 Genome Project [25], this method was performed on FUMA GWAS [26], an online tool that merges related databases for convenient genetic analysis [24].

### 2.5 Analysis Of The Migraine Summary Statistics Database By Fuma Gwas

FUMA GWAS were used in this study. The method was carried out by examining the correlation ($r^2$) between the SNPs surrounding a lead SNP in each region and the remaining SNPs with $r^2 \geq .8$. This method was performed with FUMA, which is an online tool that merges these related databases for appropriate genetic analysis [26].

To identify independent risk locations, we combine the association results with the default parameters [26]. Furthermore, different populations of ALL, EAS, and SAS reference panels from the 1,000 genome project were used as a group for meta-analysis. [25]. Additionally, we were used and the UKB release2b, 10k white British, and the reference panel population of the FUMA website was made up of UKB release2b 10k European.

The aggregation process is as follows: lead SNP is identified as the maximum P value of lead SNPs 5e-06 and the maximum P value is 0.05. Furthermore, independent SNPs of the minimum threshold $r^2$ for a set of 0.6, and the threshold $r^2$ to define independent SNPs (<1) were used to explain the limits of genomic risk. Therefore, when an important single SNP is defined at one location, these SNPs are used to recognize the leading SNP of each location. The minimum $r^2$ for the definition of the SNP leader was established at $r^2 = 0.1$.

Independent SNPs of significant LD blocks of 250 kb and 250 kb were combined into a single genomic site. Visualization of SNPs of the results of interest and its nearby variants was generated with locus zoom [27] (http://locuszoom.org/genform.php?type=yourdata).

### 2.6 Gene Set Enrichment Analysis In Fuma Gwas

To explore whether migraine associations were enriched in the gene set enrichment analysis, MAGMA (Version 1.08) [28], implemented in the FUMA software (Version 1.4) [26] was used to perform the analysis. Furthermore, more information on tissue enrichment analysis is available on the FUMA website (https://fuma.ctglab.nl/).

### 2.7 Rs73189054 Of The Position And Associated Effects Of The Pam Gene

On the basis of the above findings, to identify rs73189054 loci and their effects. Therefore, the SNP position of rs73189054 in the PAM gene in NCBI (https://www.ncbi.nlm.nih.gov/snp/rs73189054). Furthermore, the UK Biobank (https://pheweb.org/UKB-SAIGE/variant/5:102170617-G-T) and included genome-wide associations for ICD codes from white British participants. However, the genetic associations on this website are from the FinnGen study at http://r5.finnngen.fi/variant/5-102834913-G-T#. In addition, in PheWeb of BioBank, Japan (https://pheweb.jp/variant/5:102170617-G-T) and The PheWeb of jMorp. https://jmorp.megabank.tohoku.ac.jp/dj1/pheweb/variant/5:102170617-G-T (Supplementary data)
2.8 Other Evidence On Migraine Related To Rs73189054

We used Quick SNP Lookup on an MR-based platform to identify rs73189054 by Menderlian Randomization (http://app.mrbase.org/).

Result

3.1. GSEA analysis of PAM in various migraines

Results of the gene set enrichment analysis (GSEA) to recognize positions that were significantly upregulated by PAM overexpression and details of the gene sets and signals used in this analysis. Furthermore, in the gene enrichment study, the PAM genes of position chromosome 5q21 were investigated using the gene set enrichment analysis tool [29]. Patients with migraine and normal (GSE76242) were tested for genetic expression enrichment.

On examination of the set of GSEA, C1 of the positional genes corresponding to each cytogenetic band and each human chromosome in the 5q21 module of the position chromosome is enriched in a migraine patient. Since the enrichment point is 0.50, the nominal enrichment point is 1.15, and the nominal p-value is 0.30142567. (Fig. 1, Supplementary data).

The enrichment analysis of gene position and gene set define the chromosome 5q21 module by means of position-definite modules enriched in migraine. Furthermore, analysis of the enrichment of the set of position-related chromosome 5q21 module genes in migraine and normal patients.

3.2 Analysis Of The Gwas Database Analysis By Fuma Gwas

Upon different reference panels were used for clumping in migraine summary states. For the meta-analysis, the population of the reference panel of ALL, EAS and SAS from the 1000 Genomes project [25]. And we used UKB, release2b, white British, and European on the FUMA website. The results of the clumping were identified, including the lead SNP and the mapped gene. In fact, the results were that 30 genes were matched with Lead SNPs, 33 SNPs, and set of genes with adjusted P-value < 0.05 population reference P-value < 0.05 in the SAS reference panel population (Fig. 2). Visualization of SNPs of the results of interest and its nearby variants was generated with locus zoom. Therefore, Circos plots of chromatin 5 interactions and eQTL (Fig. 3).

3.3 Analysis Of Functional Annotation And Gene Set Enrichment In Fuma Gwas

The results were that 30 genes were matched by lead SNPs, 33 SNPs, and gene sets with adjusted P-value < 0.05, population reference P value < 0.05 in the SAS reference panel population. For the expansion of output genes in gene sets, there were four Positional Gene Sets (MsigDB c1), one of the GeneSets was chromosome 5q21, N was 15, n was 2, the P value was 2.14e-4, adjusted P was 1.60e-2 and the genes were PAM, MAN2A1gene.

The PAM gene (Peptidylglycine Alpha-Amidating Monooxygenase 2) was assigned to the SNP coding area rs73189054 (lead SNP). The PAM gene encodes a multifunctional protein. The encoded pre-proprotein is processed proteolytically to generate the mature enzyme.

To enhance output, the genes in the Gene Sets were four Positional Gene Sets (MsigDB c1), one of the GeneSets was chromosome 5q21, N was 15, n was 2, the P value was 2.14e-4, the adjusted P was 1.60e-2, and the genes were PAM, MAN2A1gene. And the PAM gene (Peptidylglycine Alpha-Amidating Monooxygenase 2) was mapped by coding the area
rs73189054 SNP (lead SNP). The PAM gene encodes a multifunctional protein. The encoded pre-proprotein is processed proteolytically to generate the mature enzyme.

### 2.7 Migraine With Eqtls In Specific Tissues

On the other hand, we used FUMA GWAS GTEx data to identify the locations of migraines that can affect gene expression and identify eQTLs in certain tissues. However, it overlaps with eQTL and gene expression enriched in certain tissues.

To identify and understand the locations of migraines that can affect genetic expression, I would like to determine if the locations of migraines are affected. As a group, they are rich in the expression of specific types of GTEx tissue data in FUMA GWAS (online methods) [26, 30]. Therefore, there is evidence that the blood vessel overlaps with the eQTL at the location of the PAM (Fig. 5).

We found that tissues (after Bonferroni’s correction) significantly improved the expression of genes related to migraine. In general, expression analyzes involve blood vessels and other tissue rich in the heart [30]. (Fig. 4)

Thus, these enrichment results indicate that some genes affected by variants have a high expression in vascular tissue and that their dysfunction may play a role in migraine. The tissues most strongly enriched were part of the blood vessel system (Fig. 5).

And we have found evidence of overlap of blood vessel tissue, Artery _Tibial, Artery _Aorta, and Artery _Coronary in the PAM locus reference panel population in EAS from the 1000 Genomes project in FUMA GWAS [25, 26]. (Fig. 5)

### 3.4 Rs73189054, The Position Associated With The Pam Gene, And The Associated Effects

Based on the above findings, the SNP position of rs73189054 on the PAM gene in NCBI website (https://www.ncbi.nlm.nih.gov/snp/rs73189054 and https://www.ncbi.nlm.nih.gov/gene/50660 (Fig. 6). Instead, the rs73189054 loci in Position 5: 102,170,617 G / T in CTG-View https://vl.genoma.io/utils/karyo (Fig. 7)

However, identifying the rs73189054 loci and their effects on PheWeb in the UK Biobank (https://pheweb.org/UKB-SAIGE/variant/5:102170617-G-T ) showed that the nearest gene was PAM, the category was neurological, the phenotype was Migraine and the P-value was 2.5e-6; instead, at http://r5.finngen.fi/variant/5-102834913-G-T# of the FinnGen study show that the closest gene was the PAM gene, the category was IX diseases of the circulatory system, the phenotype was Other non-infective disorders of lymphatic vessels and lymph nodes and the P-value was 5.75e-4; https://pheweb.jp/variant/5:102170617-G-T in Biobank Japan PheWeb (PheWeb.jp) show the nearest gene was the PAM gene, Category was ICD10 I, Phenotype was Esophageal varix and the P-value was 4.54e-4; and https://jmorp.megabank.tohoku.ac.jp/dj1/pheweb/variant/5:102170617-G-T in PheWeb on jMorp (Supplementary data) (Table 1) showing that the closest gene was PAM gene, the phenotype was TGA000005-TCN000014-Cysteine full and P-value was 5.8e-4. (Supplementary data).
Table 1
Position 5: 102,170,617 G / T loci (rs73189054) and their effects on PheWeb

<table>
<thead>
<tr>
<th>Nearest gene:</th>
<th>Category</th>
<th>Phenotype</th>
<th>P-value</th>
<th>Effect Size (se)</th>
<th>Number of samples</th>
</tr>
</thead>
<tbody>
<tr>
<td>UKB-SAIGE</td>
<td>PAM</td>
<td>neurological</td>
<td>Migraine</td>
<td>2.5e-6</td>
<td>2870 / 398780</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.49 (0.10)</td>
<td></td>
</tr>
<tr>
<td>Finnish Gen</td>
<td>PAM</td>
<td>IX Diseases of the circulatory system</td>
<td>Other disorders of lymphatic vessels and lymph nodes</td>
<td>5.75e-4</td>
<td>beta: 2.2403 cases: 399 AF: 0.45% controls: 218393</td>
</tr>
<tr>
<td>BBJ</td>
<td>PAM</td>
<td>ICD10 I</td>
<td>Esophageal varix</td>
<td>4.5e-4</td>
<td>0.71 (0.20) cases: 399 controls: 218393</td>
</tr>
<tr>
<td>Megabank Tahoka</td>
<td>PAM</td>
<td>TGA000005-TCN000014-Cysteine-full</td>
<td>TGA000005-TCN000014-Cysteine-full</td>
<td>5.8e-4</td>
<td></td>
</tr>
</tbody>
</table>

Table 2
Trait diagnoses - main ICD10: The G43 migraine id was ukb-d-G43

<table>
<thead>
<tr>
<th>Trait</th>
<th>id</th>
<th>rsid</th>
<th>se</th>
<th>chr</th>
<th>position</th>
<th>beta</th>
<th>p</th>
<th>n</th>
<th>ea</th>
<th>nea</th>
<th>eaf</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diagnosis - main ICD10: G43 Migraine</td>
<td>ukb-d-G43</td>
<td>rs73189054</td>
<td>5.17E-04</td>
<td>5</td>
<td>102170617</td>
<td>1.61E-03</td>
<td>1.89E-03</td>
<td>361194</td>
<td>T</td>
<td>G</td>
<td>1.78E-02</td>
</tr>
</tbody>
</table>

3.5 Other Evidence Of Migraine Related To Rs73189054

We used Quick SNP Search on the MR base platform, inserting rs73189054, and showed 11 migraine-related entries (filtered from 17464 entries) (Fig. 6). And trait diagnoses - main ICD10: G43 migraine, ID was ukb-d-G43, se was 0.000517154, beta was 0.00160688, p was 0.00188908 and n was 361194 (http://app.mrbase.org/). (Supplementary data) (Table 2)

Discussion

In this study, we identified a new migraine biomarker, the chromosome 5q21 rs73189054 of the PAM gene could be determined in the position.

In typical migraine genetic epidemiology, there are migraine aura (MA) and migraine without aura (MO), all of which have a significant risk of family occurrence. In addition, migraine parents have 1.9 times the risk of MO and 1.4 times the risk of MA. Although the risk of MA was nearly four times higher in the first-degree lineages of MA probands than in the non-first-degree lineages of MA [31], there was no increased risk of MO [31].

Several studies have analyzed migraine pedigrees, and the inheritance of multiple factors is considered the most likely model, even in high-risk families of MA [32]. Rare monogene subtypes also exist, including migraine of the hemiplegic family, with three genetic mutations (CACNA1A, ATP1A2, and SCN1A) that are involved in glutamatergic transmission and ion transfer to synapses [32–34]. In view of the complex nature of migraines, the identification of all genes and their interactions with environmental factors that contribute to the disease is still a challenge [35].
Therefore, genome-wide association studies (GWASs) test millions of single nucleotide polymorphisms (SNPs) using microarray platforms. GWAS enables GWAS to recognize new genes and pathways through large sample sizes and multiple statistical corrections, which are less likely to produce false positives in candidate gene association studies (CGAS) [36]. To date, the most significant GWAS included 59,674 migraines and 316,078 healthy to recognize 44 mapped SNPs at 38 loci associated with common polygenic migraine [37]. Freilinger et al. added several genes associated with vascular pathways, such as TGFR2, PHACTR1 [38].

Therefore, the migraine mechanisms were of vascular origin. Migraine is the most common and complex neurovascular disease, affecting 12% of the population. The particular mechanisms that cause the beginning of migraine attacks are unclear [39]. Vascular theory was first described in the second century by Galen and then proposed by Thomas Willis at the end of the 17th century [40]. Furthermore, the generation and/or maintenance of migraine involves complex bidirectional interactions between brain vessels and their conceptual ends [39]. In addition to tremor and pulsation, the quality of headache is attributed to periodic activation of the trigeminovascular sensory afferents caused by cranial artery distension. Therefore, the artery between the head and the head plays an inflammatory role in migraine [41, 42].

On the contrary, Graham and Wolff demonstrated a positive correlation between the intensity of migraine and the amplitude of the branches of the external coronary artery, thus reducing the amplitude of pulses and the amplitude of headaches [43]. The results showed that both MMA and MCA were dilated during migraine attacks (p = 0.001) by the researchers of Asghar et al. In addition, the arterial circumference of the extracranial middle meningeal artery (MMA) and the intracranial middle cerebral artery (MCA) was dilated using a high-resolution direct magnetic resonance imaging technique [44].

Furthermore, clinical realization in the field of peripheral action antibodies targeting CGRP-related calcitonin peptides (CGRP) and its receptors to prevent migraine, we have more evidence to support the vascular hypothesis [45]. CGRP may act on blood vessels within the brain and cause vasodilation. Sensory fibers detect this change and perceive it as pain.

In this study, we found the relationship between chromosome 5q21 and migraine. Since quantitative trace link analysis formed significant links with chromosome 5q21, migraine studies have been carried out throughout the genome [46, 47].

Furthermore, Nyholt et al. point out that the region of chromosome 5 possibly contains a general headache gene of migraines most associated with pulsating headache pain (lod = 3.41) at the 10 International Headache Society (IHS) in 2005 [46, 47].

In this study, we found that the PAM gene is correlated with migraine and the position of chromosome 5q21 rs73189054. And Southern Blot analysis of human genital DNA revealed that Peptidylglycine α-Amidating Monooxygenase (PAM) encodes a single gene [46]. On the other hand, 2.2 kb PAM cDNA from humans to human metaphase chromosomes showed significant silver clustering in the 5 bands of chromosomes q14-q21 hybridized in situ hybridization was used to determine the location of the PAM gene [46].

Therefore, the gene of PAM is a glycine amide catalyzer for the conversion of glycine amides to amides and glyoxylate as a neuroendocrine processing enzyme [48]. Furthermore, PAM genes are very concentrated in the atrium and can contribute to the secretion of atrial natriuretic peptide (ANP), which is necessary to maintain liquid and BP homeostasis [49]. In addition to hypertension, polymorphisms in the PAM gene affect other risk factors. Valgerdur and Steinthorsdottir also reported that a PAM wrong variant (p.Asp563Gly and p.Ser539Trp) was associated with a moderately high risk of T2D. (OR = 1.23, P = 3.9 × 10 − 10 and OR = 1.47, P = 1.7 × 10 − 5, respectively) [50]. Furthermore, 10-month-old mice with homozygous PAM mutants die in utero with severe edema, probably due to cardiovascular deficits. It is important to use these defects, including aortic artery thrombosis and carotid artery thrombosis[51].
Furthermore, as a result of the identification of the rs73189054 loci and their effects on PheWeb in Biobank of the UK, https://pheweb.org/UKB-SAIGE/variant/5:102170617-G-T (Figure) showed that the closest gene was the PAM gene, the category was neurological, the phenotype was migraine and the P value was 2.5e-6; On the other hand, at http://r5.finnngen.fi/variant/5-102834913-G-T# of the FinnGen study, it shows that the closest gene was PAM, the category was IX diseases of the circulatory system, the phenotype was Other non-infective disorders of lymphatic vessels and lymph nodes, and the P-value was 5.75e-4; https://pheweb.jp/variant/5:102170617-G-T in BioBank Japan PheWeb (PheWeb.jp) shows that the closest gene was PAM, category was ICD10, the phenotype was Esophageal varix and the P-value was 4.54e-4; and https://jmorp.megabank.tohoku.ac.jp/dj1/pheweb/variant/5:102170617-G-T in PheWeb on jMorp show nearest gene was PAM, Phenotype was TGA000005-TCN000014-Cysteine-full and P-value was 5.8e-4. With an increase in the number of cysteines, incorrect folding and aggregation occur in the walls of small cerebral vessels, resulting in several clinical characteristics related to migraine [52] (Table 1, Supplementary data). Furthermore, due to the increase in the number of cysteines, incorrect folding and aggregation occur in the walls of small cerebral vessels, resulting in several clinical characteristics related to migraine.

**Conclusions**

In conclusion, this study provides a novel migraine biomarker, rs73189054, of PAM in the position of chromosome 5q21. Furthermore, the use of several analytical approaches and these results broaden our understanding of migraine with good diagnostic value. However, the current study was limited in that we do not have enough relevant in vitro and in vivo studies to verify its influence, which we suggest future research examines in the future. In particular, it could be determined to predict susceptibility and vulnerability in migraine.

**Abbreviations**

GEO  
Gene Expression Omnibus

NCBI  
The National Center for Biotechnology Information.

GSEA  
Gene Set Enrichment Analysis.

ICD 10  

MA  
Migraine Aura.

MO  
Migraine without Aura.

BBJ  
BioBank Japan.

GWAS  
Genome-Wide Association Studies.

SNP  
Single Nucleotide Polymorphisms.

CGAS  
Candidate Gene Association Studies.

ES  
Enrichment score.
NES
Nominal enrichment score.

PAM
Peptidylglycine Alpha-Amidating Monooxygenase

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Availability of data and materials
The authors declare that all data supporting the findings of this study are available within the paper in the main text or the supplementary materials. The accession number for GEO profile data set is Series GSE72642.

Competing interests
The authors declare no potential conflicts of interest.

Additional information
Supplementary Information.

Funding
This work do not received funding.

Authors’ contributions
HLH: Conceptualization, literature Review, writing original draft, draft manuscript preparation and editing. CHL: Conceptualization, literature Review, writing original draft, draft manuscript preparation and editing. WHL: Conceptualization, draft manuscript preparation. YSL: conceptualization, guidance, and supervision. CLW: Methodology, formal analysis, literature analysis, writing original draft, writing of the manuscript and editing, submit formats and procedure. All authors read and approved the final manuscript.

Acknowledgments
We acknowledge to Anthony Castanza, GSEA and MSigDB Team for helpful Methods. The Prof. Yung-Po Liaw of the Department of Public Health, Chung Shan Medical University for the academic support.

Author information-Authors and Affiliations

Department of Healthcare Management, Yuanpei University of Medical Technology, Hsinchu 30015, Taiwan
Hsiao-Ling Huang

Department of Public Health and Institute of Public Health, Chung Shan Medical University, Taichung 40201, Taiwan
Chun Hsiang Lin, Wen-Hsiu Liu, Chi-Ling Wu
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Supplementary Data

Supplementary data is not available with this version

Figures
Figure 1

GSEA report of GSE72642 in migraine.
Figure 2

Manhattan plot (gene-based test) Analysis of the GWAS database analysis by FUMA GWAS
Figure 3

Circos plots of chromatin 5 interactions and eQTL
Figure 4

Analyzed the expression significant enrichment in blood vessel, heart and other tissues

Figure 5

Migraine of tissue expression analysis in GTEx
Figure 6

Position of SNP rs73189054 in the PAM gene in NCBI.
Figure 7

Position 5: 102,170,617 G / T loci (rs73189054) in CTG-View

Figure 8

Fig. 6 rs73189054-related migraine by Quick SNP Search on the MR base platform

Supplementary Files

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