



TRPM7 as a Candidate Gene for Vestibular Migraine

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Objectives: Vestibular migraine (VM) is a common vestibular disorder, and familial aggregation of VM with autosomal-dominant inheritance has been described, which supports a genetic background. This study aimed to describe the clinical phenotype of a family with VM, and identify a candidate gene for VM.

Methods: We recruited six individuals (four affected and two unaffected) from three consecutive generations of a Korean family with VM, and performed whole-exome sequencing to search for candidate genes.

Results: All affected individuals presented with recurrent vertigo, headache, and nausea/vomiting that fulfilled the diagnostic criteria of VM. Two individuals also experienced transient hemiparesis or dysarthria during the episodes. The symptoms were triggered by physical or emotional stress. Interictal examinations showed uni- or bi-directional horizontal gaze-evoked nystagmus in three of the individuals. They had no causative mutations in genes causing familial hemiplegic migraine or episodic ataxia. Through whole-exome sequencing from three affected individuals, we identified a nonsense mutation c.3526C>T in *TRPM7* that encodes a cation channel selective to Ca²⁺ and Mg²⁺.

Conclusions: Alterations in intracellular Ca²⁺ and Mg²⁺ homeostasis by *TRPM7* mutation may contribute to the development of the VM phenotype. Our result suggest that *TRPM7* is a novel candidate gene for VM.

Keywords: vestibular migraine, genetics, whole-exome sequencing, TRPM7 channel, ion homeostasis

INTRODUCTION

Vestibular migraine (VM) is one of the most common vestibular disorders, affecting around 1% of the general population (1). It is characterized by recurrent attacks of vestibular symptoms, a current or previous history of migraine, and the existence of one or more migraine features during the vestibular episodes. Recently, VM has been included as a diagnostic category in the latest International Classification of Headache Disorders (ICHD) criteria (2).

Most cases of VM are considered sporadic, but familial aggregation of VM with autosomal-dominant inheritance has been described in several families, supporting a genetic background for the condition (3, 4). Genome-wide association studies (GWASs) have identified numerous single-nucleotide polymorphisms (SNPs) associated

with a genetic predisposition for migraine with or without aura (5, 6). Familial hemiplegic migraine (FHM), which is a subtype of migraine with aura, is caused by mutations in *CACNA1A*, *ATP1A2*, and *SCN1A* (7). However, no candidate gene has been validated in VM, although several genetic loci such as chromosomes 5q35, 9q13-q22, 11q, and 22q12 are known (8–11). Furthermore, previous studies have not detected pathogenic mutations in FHM or episodic ataxia (EA) genes in VM patients (12, 13).

Transient receptor potential (TRP) channels are a family of cation channels expressed mostly on the cell (14, 15). They are divided into seven subfamilies including TRPC, TRPV, TRPM, TRPA, TRPN, TRPP, and TRPML, which mediate sensory transduction such as pain, touch, hearing, and thermal sensation. In addition, TRP channels enable individual cells to respond to changes in their local environment. These ion channels have a relatively non-selective permeability to cations including Ca^{2+} and Mg^{2+} , and modulate ion entry driving forces. TRP channels have been linked to neurodegenerative disorders, kidney disease, and cancers by altering intracellular ion homeostasis (15–18). Interestingly, they have been repeatedly hypothesized to contribute to migraine via the activation of meningeal nociceptors or the release of calcitonin gene-related peptide (CGRP) (19–22).

The present study investigated the clinical phenotype of a Korean family with VM showing autosomal-dominant inheritance. Here we report one novel mutation in *TRPM7* that may explain the VM phenotype in the family.

MATERIALS AND METHODS

Subjects

Six individuals from three consecutive generations of a Korean family with VM (four affected and two unaffected individuals) were recruited at the Dizziness Clinic of Pusan National University Yangsan Hospital (**Figure 1**). VM was diagnosed based on the criteria of the Bárány Society (1). All individuals underwent full neurological and neuro-otological examinations by the author (J-HC), and the four affected individuals received

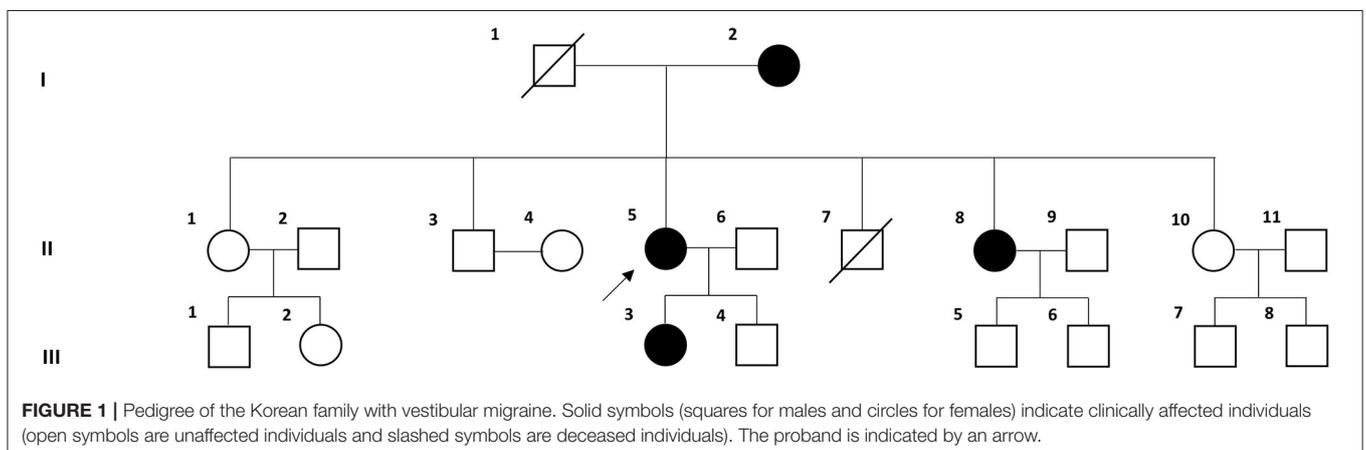
brain magnetic resonance imaging to exclude other possible causes of their symptoms.

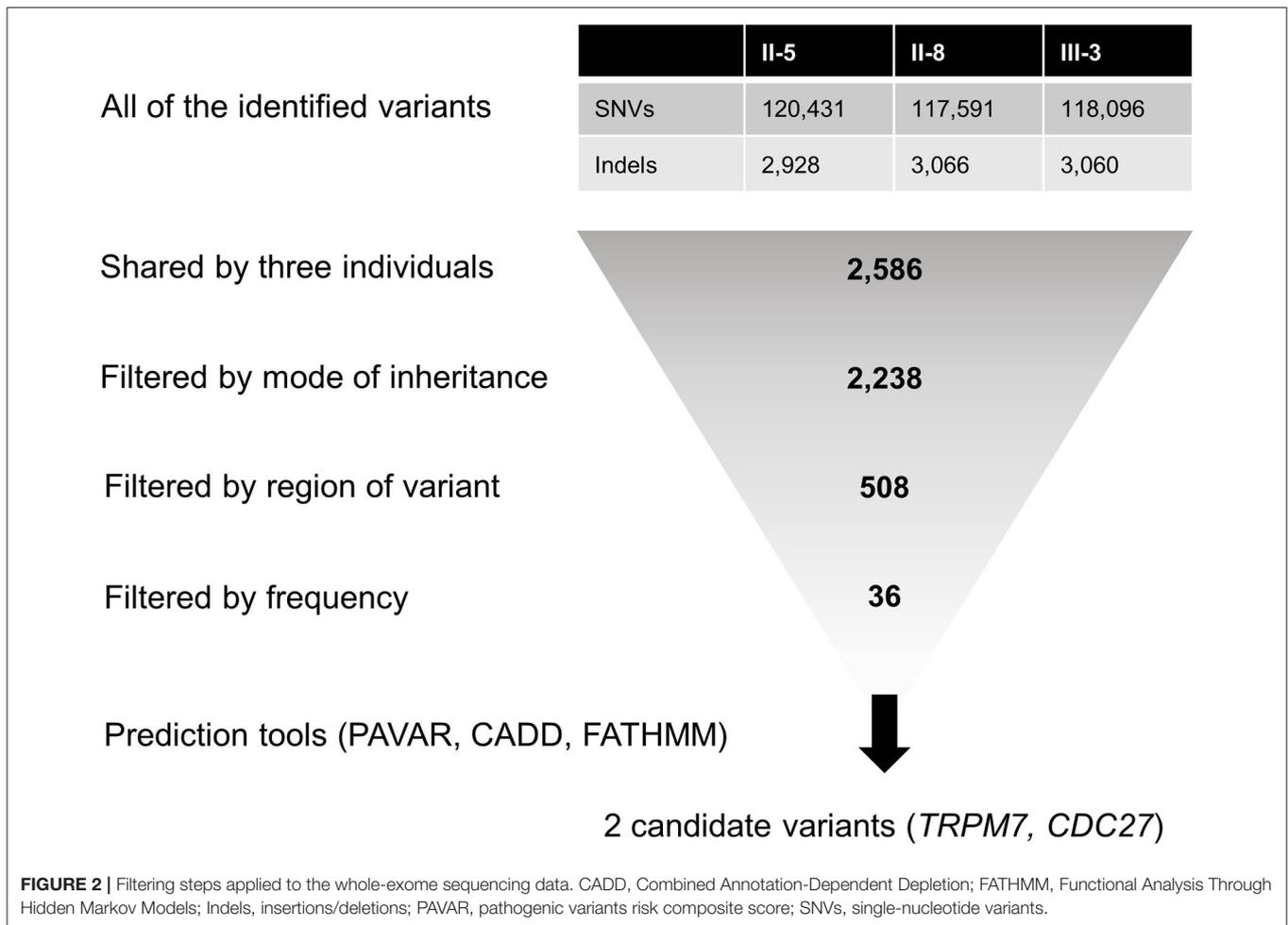
All experiments followed the tenets of the Declaration of Helsinki, and informed consents were obtained from the participants after the nature and possible consequences of this study had been explained to them. This study was approved by the institutional review boards of Pusan National University Hospital.

Whole-Exome Sequencing and Data Analysis

To systematically search for candidate genes, we applied trio exome sequencing to blood samples from three of the affected individuals (II-5, II-8, and III-3). Genomic DNA was extracted from the blood samples, and whole-exome sequencing was conducted using the SureSelect Focused Exome Kit (Agilent, Technologies, Santa Clara, CA, USA). Qualified genomic DNA samples were randomly fragmented by Covaris, followed by adapter ligation, purification, hybridization, and PCR. Captured libraries were analyzed using a bioanalyzer (Agilent 2100, Agilent Technologies) to estimate the quality, and they were loaded onto a sequencing system (Illumina HiSeq 2500, TheraGen Etex Bio Institute, Suwon, Korea). Raw image files were processed for base-calling using HCS software (version 1.4.8) with default parameters, and the sequences of each individual were generated as 100-bp paired-end reads. Sequence reads were aligned to the human reference genome sequence (GRCh37.3, hg19) using the Burrows-Wheeler Aligner (version 0.7.12). PCR duplicate reads were marked and removed using Picard tools (version 1.92). The Genome Analysis Toolkit (version 2.3-9) was used for indel realignment and base recalibration. Variation annotation and interpretation analysis were performed using SnpEff (version 4.2).

For candidate gene screening, we first filtered heterozygous single-nucleotide variants (SNVs) and insertions/deletions (indels) shared by all affected individuals (**Figure 2**). Then, variants causing non-synonymous amino acid substitutions, stop codons, indels in coding regions, and changes to splice-site sequences at exon-intron boundaries were included. Common





variants with a minor allele frequency (MAF) of >0.001 in the dbSNP147, the 1,000 Genomes Project, the NHLBI GO Exome Sequencing Project (ESP), and the Genome Aggregation Database (gnomAD) were excluded. Since the frequency of variants may differ between racial groups, we further filtered rare variants with a MAF of <0.001 in the Korean Reference Genome Database (KRGDB). Candidate variants were identified and prioritized by performing functional annotation using the following tools: (1) the pathogenic variants risk composite score (PAVAR score), which is a seven-point scoring system based on annotations using SIFT (Sort Intolerant From Tolerant), PolyPhen2 (Polymorphism Phenotyping version 2), Grantham's Matrix, GERP+ (Genomic Evolutionary Rate Profiling), MutationTaster, PhastCons and PhyloP, (2) Combined Annotation-Dependent Depletion (CADD), and (3) Functional Analysis Through Hidden Markov Models (FATHMM). Variants with PAVAR score ≥ 5 , CADD score ≥ 20 , and FATHMM score ≤ -1.5 were considered to be potentially pathogenic (23). Finally, candidate variants were interpreted according to the standards and guidelines recommended by the American College of Medical Genetics and Genomics (ACMG) (24). The gene expression patterns were analyzed using public databases such as the Genotype-Tissue Expression (GTEx), BioGPS, and Serial

Analysis of Gene Expression (SAGE), and the gene function was assessed using the HuGE Navigator, the GeneCards Human gene database, the Online Mendelian Inheritance in Man database, and PubMed. The candidate variants were validated by Sanger DNA sequencing, and were screened in another individuals within the family and 100 normal controls.

RESULTS

Clinical Phenotype

The clinical characteristics of the family are summarized in **Table 1**. All affected individuals presented with rotatory vertigo, headache, and nausea/vomiting lasting for several hours to days. All had a history of migraine with or without visual aura, and showed one or more migraine features during the vestibular episodes. Two individuals (I-2 and II-8) experienced transient hemiparesis during the attacks, one (II-8) of whom also had dysarthria and facial dysesthesia on the same side as the hemiparesis. The symptoms were triggered by physical or emotional stress. Two individuals also had auditory symptoms such as tinnitus (II-5) and ear fullness (II-8), but air-conduction audiograms showed normal hearing functions (**Supplementary Figure 1**). One individual (II-8) had a past

TABLE 1 | Clinical characteristics of the affected family members.

Patient no.	Sex/age	Age at onset	Duration	Ictal symptoms	Interictal signs	Migraine features	Additional symptoms
I-2	F/86	50	Hours-days	Vertigo, headache, nausea/vomiting, hemiplegia	Uni-directional GEN	One sided location, pulsatile quality, moderate pain intensity, nausea	(-)
II-5	F/54	53	Hours	Vertigo, headache, nausea/vomiting	Bi-directional GEN	One sided location, pulsatile quality, moderate pain intensity, photophobia, nausea	Tinnitus
II-8	F/48	30	Hours-days	Vertigo, headache, nausea/vomiting, hemiplegia, dysarthria, facial dysesthesia	(-)	One sided location, pulsatile quality	Seizure, ear fullness
III-3	F/30	19	Hours	Vertigo, headache, nausea/vomiting	Bi-directional GEN	Visual aura, moderate or severe pain intensity, aggravation by physical activity, nausea/vomiting, photophobia/phonophobia	(-)

F, female; GEN, gaze-evoked nystagmus.

TABLE 2 | Candidate variants identified using bioinformatics tools after applying filtering and prioritization processes.

Chr	Position	Gene	cDNA	Protein	Variant effect	PAVAR score	CADD	FATHMM	ACMG classification	MAF
15	50885896	<i>TRPM7</i>	c.3526C>T	p.Gln1176*	Nonsense	7	38	(-)	Pathogenic (PVS1,PS3,PM2,PP1,PP3,PP4)	NR
17	45258960	<i>CDC27</i>	c.71C>G	p.Ala24Gly	Missense	6	32	-3.23	Uncertain significance (PM2,PP1,PP3,PP4)	NR

Transcript ID: *TRPM7*, NM_017672.5; *CDC27*, NM_001114091.2.

Evidence code descriptions according to the ACMG classification: PM, pathogenic moderate; PP, pathogenic supporting; PS, pathogenic strong; PVS, pathogenic very strong. ACMG, American College of Medical Genetics and Genomics; CADD, Combined Annotation-Dependent Depletion; Chr, chromosome, FATHMM, Functional Analysis Through Hidden Markov Models; MAF, minor allele frequency; NR, not reported; PAVAR, pathogenic variants risk composite score.

history of recurrent seizure during her childhood. Between the vestibular episodes, three individuals (I-2, II-5, and III-3) showed uni- or bi-directional horizontal gaze-evoked nystagmus. The other neurological and neuro-otological examinations were unremarkable. Three individuals who received treatments showed a good response to flunarizine (II-5 and II-8) or propranolol (III-3).

Genetic Analysis

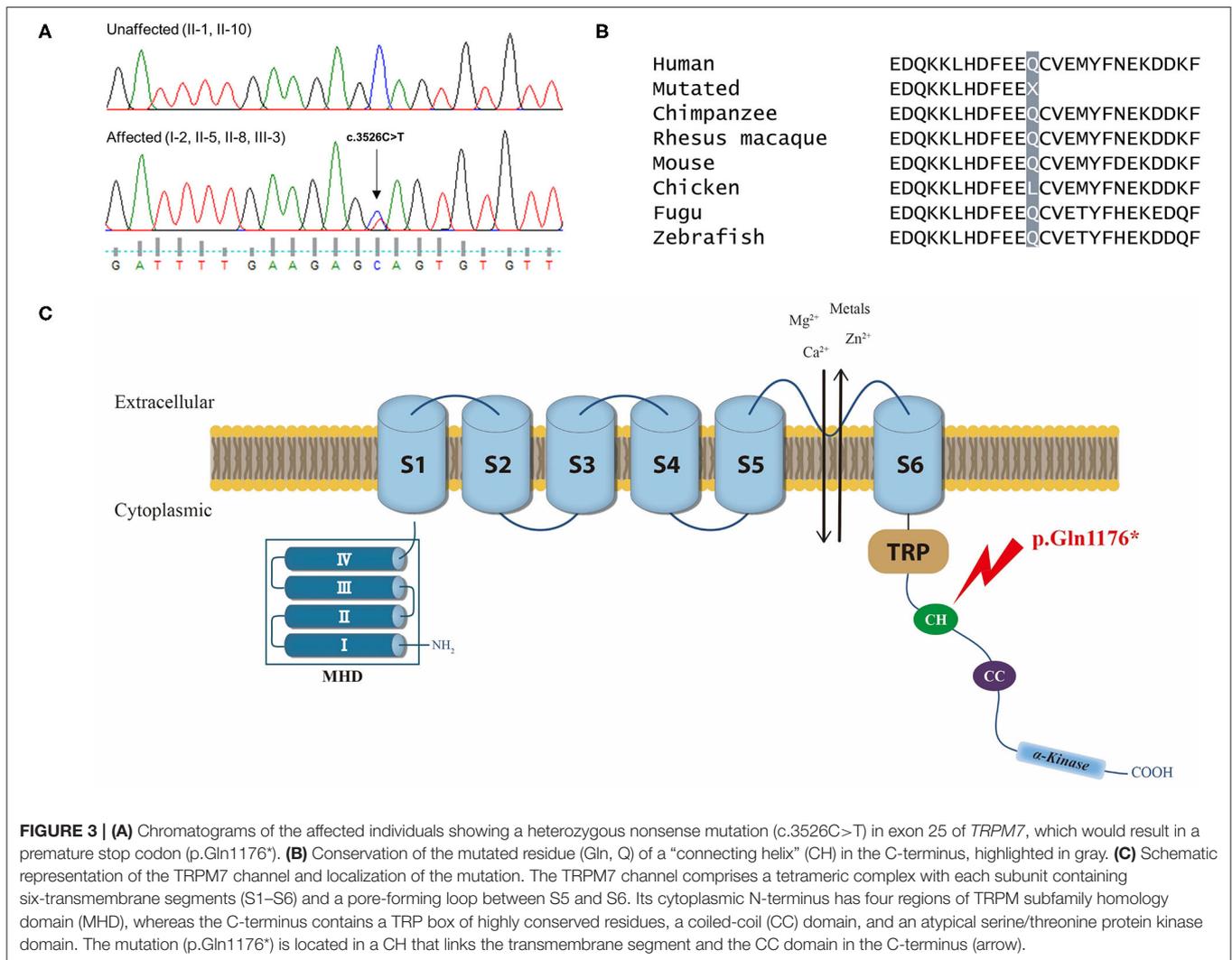
An average of 5.49 billion bases were generated per individual, with an average sequencing depth of approximately 63 in the target region, achieving the high quality of the sequencing (**Supplementary Table 1**). An initial screening of genes causing FHM and EA revealed no causative mutation in *CACNA1A*, *ATPIA2*, *SCN1A*, *KCNA1*, *CACNB4*, or *SLC1A3*.

The number of SNVs and indels identified per individual ranged from 120,657 to 123,359. Among them, a total of 2,586 variants were shared by all three individuals, and 508 of them were heterozygous non-synonymous missense variants, stop codons, coding indels, and splice-site variants at exon-intron boundaries (**Figure 2**). Next, 36 rare variants were filtered after excluding common variants with a MAF

of >0.001 in public databases including gnomAD and KRGDB (**Supplementary Table 2**), but only two candidate variants in *CDC27* and *TRPM7* were prioritized by the functional annotations (**Table 2**). Both genes were found to be widely expressed in the brain including the cerebellum in public databases such as GTEx, BioGPS, and SAGE (**Supplementary Figure 2**).

The *CDC27* variant was a missense mutation c.71C>G of exon 2, which results in the amino acid substitution of alanine by glycine at codon 24. This gene participates in regulation of the cell cycle by encoding the anaphase-promoting complex, and is known to be associated with breast and prostate cancers. However, this variant was classified as “uncertain significance” in ACMG guidelines based on only one moderate (PM2) and three supporting (PP1, PP3, PP4) pathogenic criterion. Furthermore, a literature review did not reveal any evidence for a relationship between the *CDC27* and our family’s phenotypes including migraine, vertigo, vestibular or ataxic disorders. Thus, this variant was excluded as a candidate gene for VM.

The *TRPM7* variant was a nonsense mutation c.3526C>T of exon 25 that cause a premature stop codon and loss-of-function in the protein. This variant was also present in



another affected individual (I-2), while it was absent in the unaffected individuals (II-1 and II-10), 100 normal controls, gnomAD and KRGDB (Figures 3A,B). By applying ACMG guidelines, the variant was considered “pathogenic” based on one very strong (PVC1), one strong (PS3), one moderate (PM2), and three supporting (PP1, PP3, PP4) pathogenic criterion. The *TRPM7* channel belongs to the melastatin subfamily of TRP channels, and it plays a crucial role in maintaining intracellular Ca²⁺ and Mg²⁺ homeostasis (Figure 3C). This has led to proposals that genetic variations in *TRPM7* influence the susceptibility to neurodegenerative diseases (15, 16). In addition, SNVs within some TRP genes have been linked to migraine susceptibility (5, 25–27). Therefore, the *TRPM7* variant may be a causal variant for explaining the phenotypes in the present family.

DISCUSSION

This study identified a nonsense mutation in *TRPM7* in a Korean family with VM. This variant may cause a premature stop codon

and loss-of-function in the protein, thus contributing to the development the VM phenotype by altering the homeostasis of intracellular ions.

Several hypotheses have been proposed for explaining the pathophysiology of VM, which remains unclear. The genetic susceptibility of migraine suggests ionic channelopathy involved in glutamate homeostasis as the underlying pathophysiology of VM (28, 29). Indeed, there is accumulating evidence that Ca²⁺ channels could be involved in migraine and VM pathophysiology. Mutations in *CACNA1A*, which encodes Cav2.1, the α 1A subunit of the P/Q-type voltage-gated Ca²⁺ channel, cause three neurological channelopathies: FHM type 1, EA type 2 (EA2), and spinocerebellar ataxia type 6 (30). Patients with FHM or EA2 often experience paroxysmal vertigo, and more than half of EA2 patients have migraine that meets the ICHD criteria. Some members of the present family also presented with hemiplegia and dysarthria during their episodes. Nevertheless, previous studies failed to detect mutations in patients with VM in the genes causing FHM or EA, such as *CACNA1A*, *ATP1A2*,

SCN1A, and *CACNB4* (12, 13), which is consistent with the present study.

TRPM7 reported here encodes the cation selective ion channel that is highly permeable to Ca^{2+} , Mg^{2+} , and metal ions such as Zn^{2+} (16). This channel comprises a tetrameric complex, with each subunit containing six-transmembrane segments (S1–S6) and a pore-forming loop between S5 and S6 [Figure 3C; (31)]. Its C-terminus contains a TRP box of highly conserved residues, a coiled-coil (CC) domain, and an atypical serine/threonine protein kinase domain (32). The *TRPM7* mutation identified in the present study is located in a long “connecting helix” that links the transmembrane segment and the CC domain in the C-terminus, thus predicting truncation of the C-terminus including the CC and kinase domains (32). These domains play an important role in the tetrameric assembly of the channel or in regulating channel function by Mg^{2+} nucleotides (31–34). Therefore, the mutation identified in the present study seems to affect *TRPM7* channel activity via structural instability or functional impairment. This hypothesis is supported by a previous animal study which generated knockout mice with the deletion of *TRPM7* kinase domain (35). These mice carried truncated mutation quite similar to the mutation described in this study. Although homozygous knockout mice caused embryonic lethality, heterozygous mice were viable, but showed abnormality in the regulation of Mg^{2+} homeostasis and alterations in *TRPM7* channel properties. These mice exhibited abnormal behaviors such as clasping, tremor, seizure, and violent sudden leaps as a reaction to the light and noise, similar to photophobia and phonophobia seen in VM. Furthermore, one of the affected individuals in this family had a history of recurrent seizure.

Ca^{2+} and Mg^{2+} play important roles in regulating various neuronal functions. In particular, they exert opposite effects in the signaling of the excitatory neurotransmitter glutamate: glutamate release is triggered by an influx of Ca^{2+} , whereas Mg^{2+} inhibits glutamate release by antagonizing Ca^{2+} (36). Thus, a tight balance between Ca^{2+} and Mg^{2+} is needed in order to maintain the proper excitability of neurons. Since *TRPM7* channels that are abundantly expressed in neuronal cells are highly selective to Ca^{2+} and Mg^{2+} (37, 38), mutation in *TRPM7* may cause alterations in Ca^{2+} and Mg^{2+} homeostasis and neuronal excitability. Migrainous headache is the consequence of cortical spreading depression evoked by glutamate release and N-methyl-D-aspartate (NMDA) receptor activation in the brain. These processes have been linked to low Mg^{2+} concentrations, which contribute to the hyperexcitability of the NMDA receptor (36). A beneficial effect of Mg^{2+} supplementation has also been reported in migraine patients (39). In addition, low Mg^{2+} concentrations increase the amount of substance P released, which is a neuroinflammatory mediator (40). Since the *TRPM7* channel is an important Mg^{2+} transporter, it may contribute to VM attacks by affecting intracellular Ca^{2+} and Mg^{2+} homeostasis.

Recently, several TRP channels have been linked to migraine pathophysiology, including *TRPV1*, *TRPV4*, *TRPM8*, and *TRPA1* (19). These channels are expressed on trigeminal sensory

neurons that innervate the meninges (20, 41). The activation of TRP channels promotes the excitation of nociceptive afferent fibers and potentially leads to pain and allodynia (19, 20). In addition, it can elicit the release of CGRP, causing vasodilation and neurogenic inflammation (19, 42, 43). Several SNPs in *TRPV1*, *TRPV3*, and *TRPM8* were found to be associated with migraine susceptibility in meta-analyses of observational studies and GWAS (5, 25–27). Based on these findings, TRP channels have been proposed as a therapeutic target in migraine (19, 21, 22, 44). More studies are needed to better explore the potential role for these channels including *TRPM7* in migraine pathophysiology.

This study was subjective to some potential limitations. We did not perform functional study determining pathogenicity of the candidate variants. Despite the rarity and putative pathogenicity in functional annotations, establishing the pathogenicity of the variants may be difficult without a functional assay. However, previous functional studies demonstrated that the deletion of *TRPM7* kinase domain reduced channel activity and increased its sensitivity to Mg^{2+} inhibition (33–35). Another limitation is difficulty in detecting copy number variations (CNVs) through whole-exome sequencing. CNV analysis can aid the detection of large deletions or duplications of causative genes, but whole-genome sequencing may be more suitable than whole-exome sequencing for CNV analysis. Finally, we used the hg19 as the reference genome for the reads mapping instead of hg38.

In summary, we have presented the clinical characteristics of a Korean family with VM. Whole-exome sequencing identified a potential disease-causing variant in *TRPM7*, which may cause alterations in intracellular Ca^{2+} and Mg^{2+} homeostasis and neuronal excitability. Our results highlight *TRPM7* as a novel candidate gene for VM.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Pusan National University Yangsan Hospital. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

EO conducted the experiments and interpretation of the data, and wrote the manuscript. J-HS, JC, S-YC, and K-DC contributed to the interpretation and analysis of data. J-HC conducted the design and conceptualization of the study, interpretation of the data, and revised the manuscript. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: <https://www.frontiersin.org/articles/10.3389/fneur.2020.595042/full#supplementary-material>

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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