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Original Article

The Polymorphic Analysis of the Human Potassium Channel KCNE Gene Family in Meniere's Disease-A Preliminary Study

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OBJECTIVES: To investigate the correlation between KCNE gene family and Meniere's disease (MD) in the Chinese population.

MATERIALS and METHODS: This study analyzed the single-nucleotide polymorphism (SNP) of *KCNE1* and *KCNE3* genes between the MD group and the control group and between the familial Meniere's disease (FMD) group and the sporadic Meniere's disease (SMD) group.

RESULTS: A total of 653 C/T SNPs of *KCNE1* had a statistical difference between the FMD and SMD groups ($p=0.0082<0.05$); 492 A/C SNPs of *KCNE3* were statistically different between the FMD group and the control group (genotype $p=0.037<0.05$ and allele $p=0.006<0.05$).

CONCLUSION: SNPs of *KCNE1* and *KCNE3* gene mutations were, respectively, different between the SMD and FMD groups. *KCNE3* gene polymorphism was key to FMD disease, whereas *KCNE1* was more important to the onset of SMD.

KEYWORDS: *KCNE* gene family, Meniere's disease, vertigo

INTRODUCTION

Since the first report about familial Meniere's disease (FMD) in 1941, the frequency of documenting pedigree and etiology investigation of Meniere's disease (MD) has increased [1]. As an important pathogenic factor of MD, genetics has been continuously studied in the last 20 years [2-6] ever since two independent groups of researchers found that MD onset may be the result of the interaction of one or more genetic and environmental factors [7, 8]. It is now confirmed that MD has a familial aggregation tendency [9, 10], and the mode of inheritance may be autosomal dominant inheritance with reduced penetrance [1, 11, 12]. In addition, in FMD, the siblings are approximately 10-fold at risk of MD onset [13]. Currently, FMD is well-defined as at least one other relative (first or second degree) fulfills all the criteria of MD [14] and meet the diagnostic criteria [15].

Based on the histopathological theory of endolymphatic hydrops and hypothesis of endolymphatic circulation disorder, many candidate genes have been investigated, such as AQPs [16, 17], HLA [18, 19], and COCH [20, 21]. However, there were no certain studies [7, 22-26]. Studies have also paid much attention to the *KCNE* gene family because of the vital impact of the iron channel on the lymphatic circulation of the inner ear [27]. The *KCNE* gene family, including *KCNE1*, *KCNE2*, *KCNE3*, *KCNE4*, and *KCNE5* genes, encodes protein Mink and Mink-related peptide (MIRP1-4) protein molecules that form β-subunit to constitute the functional potassium channel [28]. They are most commonly expressed in the heart, kidney, and nervous tissue. Among them, *KCNE1* gene is expressed in the human cochlea, and *KCNE3* in the lymph sac epithelial cells within the inner ear [29, 30]; thus, they may play a very important role in maintaining the stabilization of inner ear lymph circulation.

In 1997, *KCNE1* gene mutation was found to be related to long QT syndrome (LQTS), and approximately 30% of patients with LQTS were accompanied by congenital deafness, and then KCNE1 was speculated to play an important role in the K^+ regulation of the inner ear [31]. Later in 2011, KCNE3 allele mutation was found in patients with tinnitus [32]. Since 2005, the relationship between *KCNE*

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gene and MD was studied in the Japanese [33], Caucasian [34], and Finnish [35] population.

However, to date, the correlation between *KCNE* gene family and MD is not yet to be confirmed, and no mutations are found especially in the Chinese population. Therefore, the aim of this preliminary study was to compare our MD patients between the family Meniere's Disease (FMD) group and sporadic Meniere's disease (SMD) group, and further compare the results with the healthy control group.

MATERIALS AND METHODS

A total of 16 patients with MD who visited our hospital from January 2015 to January 2016 were collected. Patients were divided into eight SMD and eight FMD groups. All included patients were aged <70 years old who matched the diagnostic criteria for definite MD (Otolaryngology Head and Neck Surgery branch, Chinese Medical Association, 2006, Guiyang, China), without severe hearing loss, migraine history, or autoimmune diseases. Then, eight healthy controls from the Physical Examination Center of our hospital who have similar age and sex were selected as the control group. All candidates were informed with "MD candidate gene test informed consent" following all the guidelines for experimental investigation with human subjects required by the ethics committee of our hospital.

For single-nucleotide polymorphism (SNP) analyses, DNAs were extracted and prepared from the participants' blood, and SNP analyses were performed by a specialized corporation (Liu He Genomic Technology Co., Ltd., Beijing, China). According to cDNA library and existing research reports, we designed and synthesized the primers of *KCNE1* and *KCNE3* genes based on the *KCNE1* and *KCNE3* exon's gene sequence.

KCNE1 Primer

KCNE1 has several transcripts in humans, and the last exon of KCNE1 is already known to participate in encoding proteins.

KCNE1-exon was amplified in three sections considering its length. The length of KCNE1-exon-1 was 1051 bp, and the sense primer (5′-3′) was TGGATGGAAATAGAAGGGAA, whereas the antisense primer (5′-3′) was TGGGAAGCAGGACAAAGT. The length of KCNE1-exon-2 was 1093 bp, and the sense primer (5′-3′) was GAATCCCTGAGGACATG, whereas the antisense primer (5′-3′) was CTGGCTTCTTCCCGACT. The length of KCNE1-exon-3 was 1432 bp, and the sense primer (5′-3′) was GATGCATAGGGAGGACACCA, whereas the antisense primer (5′-3′) was GGCTGCCTCATCAAAGCATT.

KCNE3 Primer

KCNE3 has three exons. The length of KCNE3-exon-1 was 462 bp, and the sense primer (5′-3′) was AGGCTTTCGGTCTGGTC, whereas the antisense primer (5′-3′) was GGTTCCACAGTCTCACGGAG. The length of KCNE3-exon-2 was 429 bp, and the sense primer (5′-3′) was AGAGCCCACAGCAGGAC, whereas the antisense primer (5′-3′) was AAGAATGGACGCAGCAC. The length of KCNE3-exon-3 was 1534 bp, and the sense primer (5′-3′) was TAAGCCACCACGACTATCT, whereas the antisense primer (5′-3′) was CAACATCTGCCTCCAAGC.

Statistical Analysis

Statistical analysis was performed using Statistical Package for Social Sciences 16.0 version (SPSS Inc., Chicago, IL, USA). Chi-square test was used to verify whether SNP loci were in accordance with the Hardy-Weinberg genetic balance laws.

RESULTS

General Data

Our research included 24 participants, with 8 male and 16 female patients. The FMD group appears to be younger than the SMD

Table 1. General data of participants between the groups

	SMD group	FMD group	Control group	Wilcoxon test
Age (year)	42.9±17.5	31.1±10.9	30.2±10.6	
Age of vertigo onset (year)	39.0±16.3	28.5±9.8		p>0.1
Course duration (year)	4.1±3.0	2.6±1.2		p>0.1
Hearing level of sick ear (dB)	42.5	41.9		p>0.1
Vestibular function loss (cases)*	7	7		p>0.1

*Vestibular function loss has been found by caloric test in our hospital.
SMD: sporadic Meniere's disease; FMD: familial Meniere's disease

Table 2. SNP and frequency difference of KCNE1 and KCNE3 between the groups

				Frequency difference		
	Exon	Length	SNP	FMD vs. SMD	FMD vs. control	SMD vs. control
KCNE1	KCNE1-exon	3678 bp	72 A/G	p>0.05	p>0.05	p>0.05
			473 A/G	p>0.05	p>0.05	p>0.05
			653 C/T	p<0.05	p>0.05	p>0.05
KCNE3	KCNE3-exon-1	462 bp	No mutant site			
	KCNE3-exon-2	429 bp	No mutant site			
	KCNE3-exon-3	1534 bp	126 C/G	p>0.05	p>0.05	p>0.05
			450 C/T	p>0.05	p>0.05	p>0.05
			492 A/C	p>0.05	p<0.05	p>0.05
			642 C/T	p>0.05	p>0.05	p>0.05

SMD: sporadic Meniere's disease; FMD: familial Meniere's disease

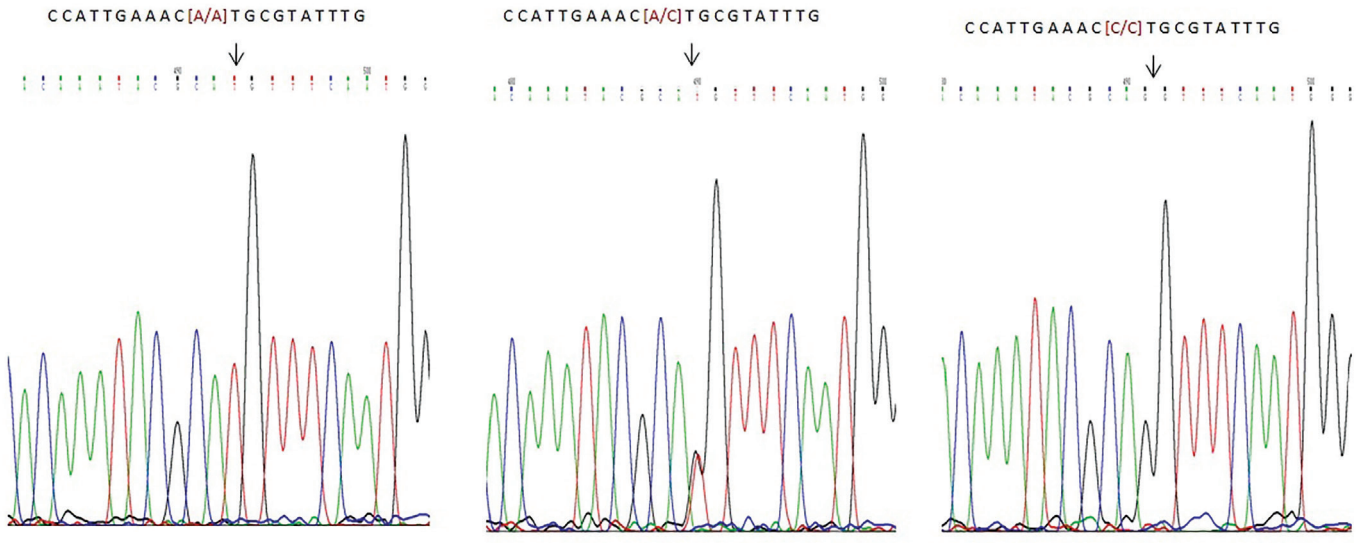

Figure 1. 492 A/C SNP genotypes.

group (Table 1). Wilcoxon test was used to compare and find that vertigo onset age and the course duration between the two groups had no statistical significance (p>0.1). In addition, there was no statistical significance in either hearing loss or vestibular function loss (p>0.1).

KCNE1

KCNE1 has 2-4 exons in several different transcripts in humans, and the last exon is already known to participate in encoding proteins (KCNE1-exon). Among the mutation loci of KCNE1-exon discovered by sequencing (Table 2), the genotype and allele frequency between groups had no statistical significance (p>0.05), except the genotype frequency of 653 C/T SNPs, which was statistically different between the FMD and SMD groups (p=0.0082<0.05). However, there was no statistical difference with the healthy control group (p=0.162>0.05) and between the SMD group and the healthy control group (p=0.318>0.05).

KCNE3

Of the three exons, only KCNE3-exon-3 had four mutation loci (Table 2), and only KCNE3-exon-3 is known to participate in encoding proteins. We found that 492 A/C SNPs were statistically significant between the groups. The genotype of 492 A/C SNPs (Figure 1) showed a frequency difference between the FMD group and the control group (p=0.037<0.05), and allele frequency was also significant (p=0.006<0.05).

The statistical analysis of 492 A/C SNPs shows that it had the highest detection rate in the FMD group. In 16 patients with MD, 6 cases had 492 A/A genotypes, 8 cases had 492 A/C, and 2 cases had 492 C/C. In 8 healthy controls, 7 cases had 492 A/A genotypes, 1 case had 492 A/C, and none had 492 C/C (Figure 2). We found that the distributions of this mutation locus in each group were in accordance with the Hardy-Weinberg equilibrium using chi-square test. The frequency of genotypes 492 A/C, 492 C/C, and mutant allele 492 C in the FMD group was obviously higher than those of the control group (Table 3).

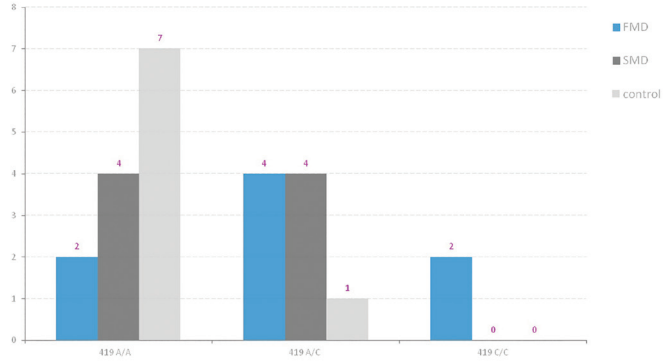

Figure 2. Frequencies of 492 A/C SNPs between the groups.

Table 3. Genotypes and allele frequency of 492 A/C SNPs between the groups

	FMD		SMD		Control		
	n	%	n	%	n	%	Sum (n)
492 A/A	2	25	4	50	7	87.5	13
492 A/C	4	50	4	50	1	12.5	9
492 C/C	2	25	0	0	0	0	2
492 A	8	50	12	75	15	93.8	35
492 C	8	50	4	25	1	6.2	13

SMD: sporadic Meniere's disease; FMD: familial Meniere's disease

Furthermore, we compared all patients with MD (including the FMD and SMD groups) with healthy controls about the 492 A/C SNPs from the frequency of genotype and allele. The results showed that the detection frequency of allele 492 C in patients with MD was higher than that in the healthy controls, and the frequency of allele C between patients with MD and the control group was statistically significant (p=0.022<0.05).

DISCUSSION

To our knowledge, this is the first research investigating the association between *KCNE* gene family and MD in China.

Within the exons of KCNE1, it is known that the last exon, where we found 653 C/T SNPs, participates in encoding protein Mink; thus, 653 C/T SNPs are the coding SNPs (cSNPs). George [36] and McDonald [37] found that KCNE1 participates in forming K^+ channel to regulate potassium current (IKs) by combining with KCNQ1 and HERG. In 1994, Lai found that the mutation of *KCNE1* gene can cause a change of K^+ channel function [38]. Splawsik reported that the *KCNE1* gene mutation relates to QT prolongation syndrome (LQTS) [31]. Then, it was found that >50% of patients with LQTS have *KCNE1* or *KCNQ1* gene mutations, of which approximately 30% of patients have congenital deafness, and speculated that KCNE1 also plays an important role in the K^+ adjustment in the inner ear. In addition, in our study, we tried to avoid this kind of interference by excluding severe to extremely severe hearing loss.

Within the three exons of KCNE3, it is known that KCNE3-exon-3, where we found 492 A/C SNPs, participates in encoding protein MIRP2. Therefore, 492 A/C SNPs are also cSNPs. Castro found that the *KCNE3* gene is expressed in the lymph sac epithelial cells to regulate the IKs [29]. It was also found that *KCNE3* gene mutations in patients with tinnitus had a family history, considering that *KCNE3* gene mutations participate in the process of tinnitus [32]. However, the inner ear function of the *KCNE3* gene and their correlation still need further study.

We found that 653 C/T SNPs of KCNE1 were statistically different between the FMD and SMD groups, especially the 653 T/T (37.5%) and 653 C/T types (37.5%) in the FMD group. The results are in accordance with Finland findings about KCNE1 and SMD. In 2012, Hietikko [35] performed gene sequencing on 59 patients with MD (38 SMD and 21 FMD), analyzed exon and line connection region of KCNE1, KCNE3, AQP2, HCFC1, COCH, and ADD1, and found gene mutation site rs1805127 of KCNE1 in three cases of patients with SMD and one patient with FMD. They speculated that the mutated gene relates to SMD ($p=0.011<0.05$) but not to FMD ($p=0.62>0.05$). However, its sample size is few.

We also found that 492 A/C SNPs of KCNE3 were statistically different between the FMD group and the control group. The result is similar with the conclusion in the Japanese population. In 2005, Doi [33] analyzed the genotype and sequence of KCNE1 and KCNE3 in 63 cases of Japanese patients with MD and found that 112 G/A SNPs in *KCNE1* gene mutations (rs1805027) and 198 T/C SNPs in *KCNE3* gene mutations (rs11702354) have a significant difference compared with the control group. The author thinks that the two genes may be MD susceptibility genes. However, their study did not distinguish between FMD and SMD; therefore, it is impossible to verify our hypothesis.

Nevertheless, Campbell [34] who verified KCNEs' genetic correlation with European patients with MD showed opposite results. They investigated exons of KCNE1 and KCNE3 in 180 cases of Caucasian patients with MD and the control group (180 healthy Caucasians) about genotype and microsatellite markers but have not found any significant differences in mutation loci with the control group; thus, the author thinks that the *KCNE* gene family has no significant correlation with MD in Caucasian patients. However, they had not divided the MD group into FMD and SMD similar to our study; therefore, it may fail to discover the respective effects of *KCNE1* gene and *KCNE3* gene.

Based on the present studies and the results of our previous experiments, we proposed the "KCNE1-SMD, KCNE3-FMD" assumption that KCNE1 encodes protein Mink, and gene mutations of its functional exon 2 affect the beta subunit synthesis of K^+ channels, thus involving the onset of the SMD process, and that KCNE3 encodes protein MIRP2, and gene mutations of its functional exon 3 affect the functional K^+ channels on the lymph sac, thus involving the onset of the FMD process. Then, all these lead to the abnormal transport and regulation of K^+ in the inner ear, which influences the maintenance of normal potential voltage difference between the internal and external lymph, and ultimately cause MD. We forecast that *KCNE3* gene polymorphism may be a relatively stable genetic mutation, which is a key factor of FMD disease, and that the mutations of KCNE1 mainly impact FMD and SMD and may not be stable genetic factors, which plays a key role in the pathogenesis of SMD. The polymorphism of the *KCNE* gene family may affect the K^+ channels of the inner ear.

However, the number of patients with MD included in our preliminary research is few. In addition, FMD was extracted from the patient's family history, without actual diagnostic confirmation of the relatives. The existing information provided by the candidate gene screening report is still limited. We will enlarge the sample size and add more methods in the future study to provide more valuable findings about the pathogenic mechanism of MD genetics in the Chinese population.

CONCLUSION

SNPs of *KCNE1* and *KCNE3* gene mutations were, respectively, different between the SMD and FMD groups. *KCNE3* gene polymorphism was key to FMD disease, whereas KCNE1 was more important to the onset of SMD. But further and more profound studies are still needed to verify it.

Ethics Committee Approval: Ethics Committee approval was received for this study from the Ethics Committee of West China Hospital.

Informed Consent: Written informed consent was obtained from the patients who participated in this study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – Q.D., H.Z., D.W.; Design - Q.D., H.Z., D.W.; Supervision - Q.D., H.Z.; Resource - Q.D., H.Z., D.W.; Materials - Q.D., H.Z., D.W.; Data Collection and/or Processing - Q.D., D.W.; Analysis and/or Interpretation - Q.D., H.Z., D.W.; Literature Search - Q.D., D.W.; Writing - Q.D., H.Z., D.W.; Critical Reviews - Q.D., H.Z. .

Conflict of Interest: The authors have no conflict of interest to declare.

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