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Variants in the KCNE1 or KCNE3 gene and risk of Ménière's disease: A meta-analysis

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Abstract.
BACKGROUND: Ménière's disease (MD) is defined as an idiopathic disorder of the inner ear characterized by the triad of tinnitus, vertigo, and sensorineural hearing loss. Although many studies have evaluated the association between variants in the KCNE1 or KCNE3 gene and MD risk, debates still exist.
OBJECTIVE: Our aim is to evaluate the association between KCNE gene variants, including KCNE1 rs1805127 and KCNE3 rs2270676, and the risk of MD by a systematic review.
METHODS: We searched the literature in PubMed, SCOPUS and EMBASE through May 2015. We calculated pooled odds ratios (OR) and 95% confidence intervals (CIs) using a fixed-effects model or a random-effects model for the risk to MD associated with different KCNE gene variants. The heterogeneity assumption decided the effect model.
RESULTS: A total of three relevant studies, with 302 MD cases and 515 controls, were included in this meta-analysis. The results indicated that neither the KCNE1 rs1805127 variant (for G vs. A: OR = 0.724, 95%CI 0.320, 1.638, $P = 0.438$), nor the KCNE3 rs2270676 variant (for T vs. C: OR = 0.714, 95%CI 0.327, 1.559, $P = 0.398$) was associated with MD risk.
CONCLUSIONS: Based on current evidence from published studies, neither of the two variants from KCNE was significantly associated with the risk of MD. Larger studies with mixed ethnicity subjects and stratified by clinical and sub-clinical characteristics are needed to validate our findings.

Keywords: Gene variant, meta-analysis, Ménière's disease, KCNE1, KCNE3

1. Introduction

Ménière's disease (MD) was first described by Prosper Ménière in 186 1as a syndrome consisting of continuous or intermittent head noises accompanied by diminution of hearing and intermittent attacks of vertigo, uncertain gait and falling accompanied by nausea, vomiting, and syncope. Incidence rates for MD are 157 per 100,000 in the United Kingdom, 46 per 100,000 in Sweden, 7.5 per 100,000 in France and 15 per 100,000 in the United States [36]. 8% to 20% of cases of MD are bilateral, rarely simultaneously [11] MD occurs in children and younger people rarely, and the majority of reported children were 10 years and older [6,10,17]. Most cases of MD are sporadic (SMD) although many patients have other family members with similar symptoms, suggesting the possibility of familial MD (FMD) [13,44]. Patients affected with FMD seem to suffer from an earlier onset and more severe manifestations of the disease [20,38,40], demonstrating that both genetic and non-genetic factors play important roles in the etiology of MD.

The most prominent and consistent pathological correlate of MD is endolymphatic hydrops (EH), a dilation of the membranous labyrinth of the inner ear. EH is thought to reflect a pressure gradient between the scala media and scala vestibuli EH is not unique to MD and can be seen with many other disorders, such

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as head trauma, mumps infection, otosyphilis, Cogan's syndrome, and labyrinth neoplasms [1,4,32].

Several studies have attempted to identify genetic factors important in MD (See [9]). Doi et al. reported that two single nucleotide polymorphisms (SNPs) in KCNE1 (21q22.12) and KCNE3 (11q13.4) were associated with MD in Japanese MD patients in 2005 [12]. These genes are members of the KCNE gene family and encode the accessory MinK proteins, MinK and MiRP2. MinK, encoded by KCNE1, associates with KCNQ1 and produces the I_{ks} current, while MiRP2, encoded by KCNE3, associates with Kv3.4 [2,34]. In the inner ear, KCNE1 is expressed at the apical membrane of vestibular dark cells and at the apical surface of marginal cells, while KCNE3 is found in the epithelium of the distal portion of the endolymphatic sac [37,39,41,46].

Campbell et al. [7] replicated the association reported by Doi et al. in a group of Caucasian MD patients accrued in the United States in 2010, but did not reach a consistent conclusion. In 2012, Hietikko et al. repeated this study in a group of Caucasian MD patients accrued in Finland [19], and the results indicated that the variant rs1805127 in the potassium channel gene, KCNE1, was associated with MD, but not rs2270676 in KCNE3.

A single study is more likely to have been underpowered to detect the effect of low-penetrance genes; a quantitative synthesis to accumulate data from different studies may provide evidence on the association of genetic variants with susceptibility to MD. Therefore, the purpose of this study was to perform a meta-analysis of the published studies and to determine whether the KCNE gene variants play roles in susceptibility to MD, as well as to quantify potential between-study heterogeneity.

2. Methods

2.1. Publication search

The bibliographic search was performed in May, 2015 in PubMed, SCOPUS and EMBASE by two investigators (Li and Jin) independently using the following terms: ("KCNE" OR "KCNE1" OR "KCNE3") AND ("genetic variant" OR "genetic variation" OR "polymorphism") AND ("Ménière's disease" OR "MD"). All the searched studies were retrieved, and their references were checked for other relevant publications. Review articles were also assessed to find additional eligible studies. The inclusion criteria were (1) evaluation of KCNE1 rs1805127 or KCNE3 rs2270676 variant and MD risk, (2) retrospective case-control studies or prospective cohort studies, (3) proper MD diagnosis criteria (AAO-HNS criteria: the diagnosis of definitive MD is exclusionary and requires documentation of at least two episodes of vertigo lasting a minimum of 20 min, documented hearing loss on at least one occasion, and tinnitus or aural fullness in the affected ear) [1]. The included studies all met these above-mentioned criteria. Any study with inconsistent data was excluded. Each article was checked by one of the authors (Xu).

2.2. Data extraction

The following information was extracted from each study: the first author, published year, country of study population, number of cases and controls, and numbers of cases and controls in different genotypes. Allele frequencies were calculated from the corresponding genotype distributions when they were not given. Documentation was extracted from all the publications, independently by two of the authors (Li and Jin). Disagreement was resolved by discussion between the authors.

2.3. Statistical methods

Pooled odds ratios (ORs) together with 95% confidence intervals (CIs) were calculated by a fixed effects model or a random effects model according to the heterogeneity assumption, which was checked by the Q test (Table 3). A P of heterogeneity (Ph) > 0.05 of a study indicated a lack of heterogeneity, and this study was analyzed using a fixed effects model; a Ph $<$ 0.05 lead to the use of a random effects model. Studies with controls not conforming to the Hardy-Weinberg equilibrium (HWE) were excluded in theory. Assessing publication bias is not necessary when there are fewer than 10 studies in a meta-analysis because the low number implies inherent weaknesses in the review. So, we did not emphasize publication bias. Statistical analyses were performed using Stata version 12.0 (Stata Corporation, College Station, TX).

3. Results

There were three papers included in our analysis [7,12,19]. There was no statistical difference in the age, race, ethnicity, and gender between MD cases and

Table 1
Characteristics of the studies included in the meta-analysis

Author	Year	Ancestry	Gene	Cases			Controls			Genotyping
				N	F%	Age	N	F%	Age	
Doi et al.	2005	Asian	KCNE1 rs1805127	63	71.4	42.5	237	71.3	35.8	RBI
			KCNE3 rs2270676				205	74.6	36.5	
Campbell et al.	2010	Caucasian	KCNE1 rs1805127	180	54	54.3	180	NA	NA	PCR
			KCNE3 rs2270676			(22.9–83.5)				
Hietikko et al	2012	Caucasian	KCNE1 rs1805127	59	NA	NA	98	NA	NA	PCR
			KCNE3 rs2270676							

F% female percentage, NA not available.

Table 2
Distribution of KCNE genotype and allele among MD patients and controls

Gene	Author	Case					Control					MAF		HWE	
		GG	G/A	AA	G	A	GG	G/A	AA	G (%)	A (%)	G %	A %	X^2	P
KCNE1	Doi K. et al	28	27	8	83	43	192	25	20	409 (86.3)	65 (13.7)	73.1	26.9	72.81	1.43E-17
rs1805127	Campbell et al.	77	81	22	235	125	67	90	23	224 (62.2)	136 (37.8)	64.6	35.4	0.73	0.39
	Hietikko et al.	20	37	2	77	41	37	41	12	115 (63.9)	65 (36.1)	64.6	35.4	0.01	0,90
		TT	T/C	CC	T	C	TT	T/C	CC	T (%)	C (%)	T %	C %	X^2	P
KCNE3	Doi et al	52	8	3	112	14	196	5	4	397 (96.8)	13 (3.2)	82.7	17.3	74.49	6.1E-18
rs2270676	Campbell et al.	144	34	2	322	38	140	38	2	318 (88.3)	42 (11.7)	92.4	7.6	0.11	0.74
	Hietikko et al.	NA	NA	NA	93	25	NA	NA	NA	153 (78.1)	43 (21.9)	92.4	7.6	NA	NA

NA not available.

control subjects in the three studies. However, no quality controls to prevent stratification by ancestry were performed. A database, including first author, published year, reference, original country, variant studied, sample size of case and control, and genotyping method was established according to the extracted information (Table 1). Genotype, allele distributions, minor allelic frequencies (MAFs) as well as HWE for each study were shown in Table 2. Note that genotype date of KCNE3 rs2270676 from the paper of Hietikko et al. was not available, resulting in a lack of different comparative results [19].

3.1. KCNE1 rs1805127

A total of 302 MD cases and 515 controls were included in the meta-analysis on the relationship between KCNE1 rs1805127 variant and risk of MD (Tables 2 and 3). Among these, two studies were carried out in Caucasian, and one in Japanese. Results of pooled ORs and heterogeneity tests for the association of variant of KCNE1 rs1805127 with MD risk in different analysis models are shown in Table 3. Overall, there was no support for an association between the KCNE1 rs1805127 variant and MD risks (for GG + G/A vs. AA: OR = 1.117, 95% CI 0.696, 1.792, Pz = 0.646; GG vs. G/A + AA: OR = 0.563, 95% CI 0.174, 1.819, Pz = 0.337; G vs. A: OR = 0.724, 95% CI 0.320, 1.638, Pz = 0.438) (Fig. 1). The comparisons of other genetic models are also shown in Table 3.

3.2. KCNE3 rs2270676

Three studies including 302 MD cases and 483 controls were in the meta-analysis on the relationship between the KCNE3 rs2270676 variant and the risk of MD (Tables 2 and 3). Due to a lack of date of genotype, we evaluated the T vs. C only, and there was no statistical evidence of an association between the KCNE3 rs2270676 variant and MD risks (T vs. C: OR = 0.714, 95% CI 0.327, 1.559, Pz = 0.398) (Fig. 1).

4. Discussion

There are several characteristics of MD that support a genetic susceptibility. Various reports indicate that women are more susceptible than men, with nearly identical age of onset for MD. There is an ethnic bias in susceptibility to MD, with the disease being extremely rare in individuals of African ancestry, slightly more prevalent in those individuals of Asian ancestry, and significantly prevalent in Caucasians. The familial clustering and the geographical and racial differences in incidence strongly suggest a certain role for genetic factors in the development of MD. Starting from rational bases for a genetic approach to MD, a number of studies focused on the fundaments of various genes involved in this disease, such as HLA, DFNA9, Chromosome 12, Macrophage migration inhibitory fac-

Table 3
Summary of different comparative results

Gene	Cases/Controls	Models		OR(95 %CI)	Ph	Pz
KCNE1 rs1805127	302/515	Dominant model(GG+G/A vs. AA)		1.117(0.696,1.792)	0.095	0.646
		Recessive model(GG vs. G/A+AA)		0.563(0.174,1.819)	0.000	0.337
		Co-dominant model	GG vs. G/A	0.477(0.125,1.819)	0.000	0.278
			GG vs. AA	0.989(0.336,2.909)	0.029	0.984
		G vs. A		0.724(0.320,1.638)	0.000	0.438
KCNE3 rs2270676	302/483	Dominant model(TT+ T/C vs. CC)		NA	NA	NA
		Recessive model(TT vs. T/C+ CC)				
		Co-dominant model	TT vs. T/C			
			TT vs. CC			
		T vs. C		0.714(0.327, 1.559)	0.005	0.398

NA not available.

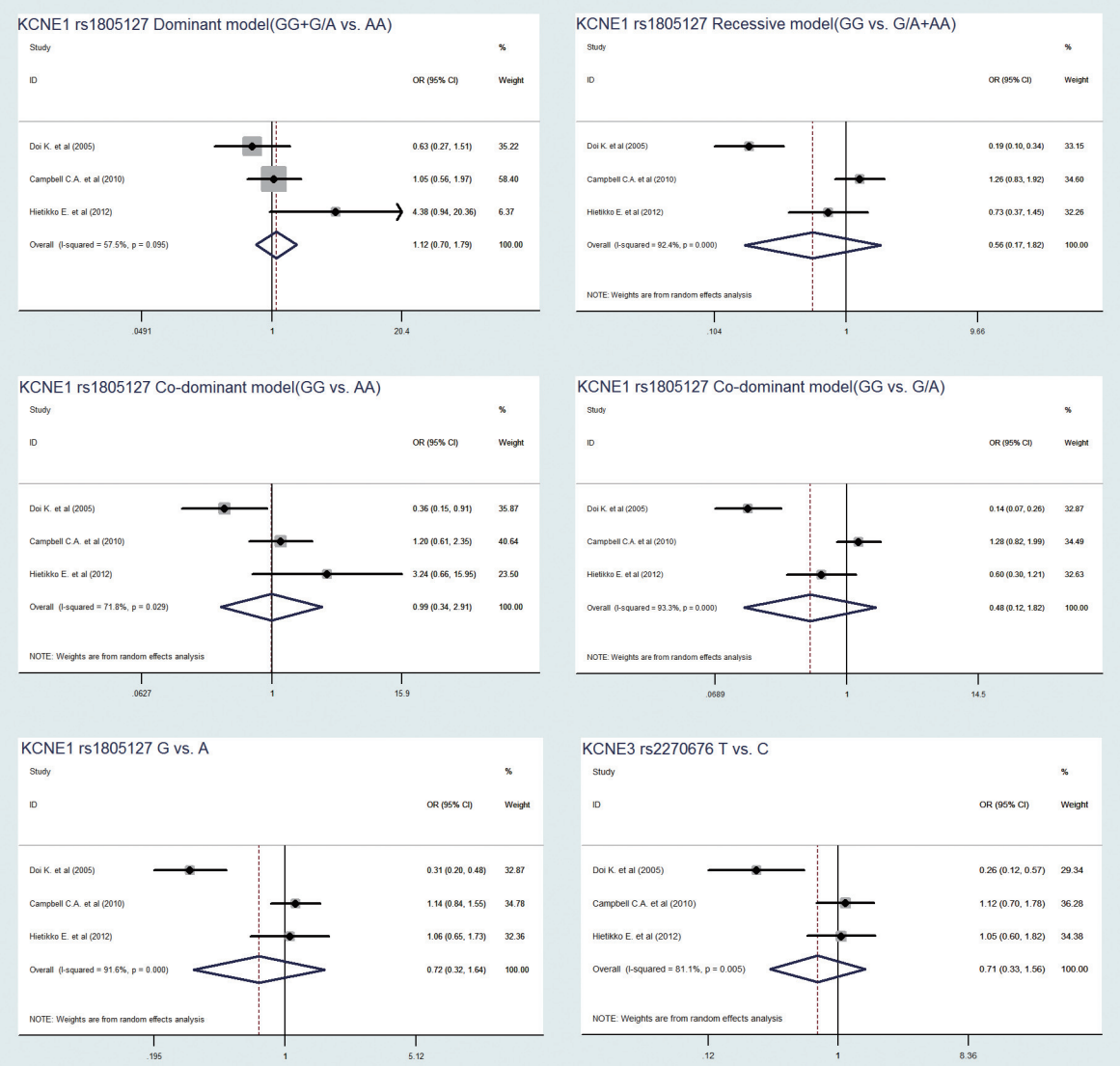

Fig. 1. Meta-analysis for the association between MD risk and the KCNE variant. The estimate of OR and its 95% confidential interval (CI) is plotted with a box and a horizontal line. ◇, pooled OR and its 95% CI. (Colours are visible in the online version of the article; http://dx.doi.org/10.3233/VES-160569)

Table 4
Reports on genetics studies on Ménière's disease

Gene	Author/year	Study design	Objective	Subjects	Ancestry	Association
12p12 *PIK3C2G*	Klar et al, 2006 [23]	Familial	Susceptibility	13/8	Caucasian	Yes
12p12.3	Hietikko et al, 2011 [18]	Familial	Susceptibility	16 families	Caucasian	No
ADD1	Teggi et al, 2008 [42]	Case-control	Susceptibility	28/48	Caucasian	Yes
AQP2	Mhatre et al, 2002 [35]	Case-control	Mutation's analysis	12	American	No
	Maekawa et al, 2010 [31]	Case-control	Gene expression study	15/9	Asian	No
AQP3	Candreia et al, 2010 [8]	Case-control	Mutation's analysis	34/100	Caucasian	No
ATQ1	Lynch et al, 2002 [30]	Case-control	Mutation's analysis	14	Australian	No
CD16A/CD32	Lopez-escamez et al, 2011 [29]	Case-control	Susceptibility	156/626	Caucasian	No
Chromosome 5	Arweiler-Harbeck et al, 2011 [5]	Familial	Susceptibility	52/29	Caucasian	Yes
*DRB1*1602*	Koyama et al, 1993 [24]	Case-control	Susceptibility	20/20	Asian	Yes
HCFC1	Vrabec et al, 2008 [45]	Case-control	Susceptibility	21/33	Caucasian	No
HLA-	Lopez-escamez et al, 2002 [26]	Case-control	Susceptibility	54/534	Caucasian	No
HLA-Cw04	Koyama et al, 1993 [24]	Case-control	Susceptibility	20/20	Asian	No
	Khorsandi et al, 2011 [22]	Case-control	Susceptibility	22/91	Caucasian	Yes
HLA-Cw07	Melchiorri et al, 2002 [33]	Case-control	Susceptibility	41/34/101	Caucasian	Yes
*HLA-DRB1*1101*	Lopez-escamez et al, 2007 [28]	Case-control	Susceptibility	80/250	Caucasian	Yes
HSPA1A	Kawaguchi et al, 2008 [21]	Case-control	Susceptibility	49/100	Asian	Yes
IL1A	Furuta et al, 2011 [14]	Case-control	Susceptibility	68/72/2202	Asian	Yes
KCNE1 – 3	Doi et al, 2005 [12]	Case-control	Susceptibility	63/237	Asian	Yes
	Campbell et al, 2010 [7]	Case-control	Susceptibility	180/180	Caucasian	No
	Hietikko et al, 2012 [19]	Case-control	Mutation's analysis	59/98	Caucasian	Yes
MIF, INFG, TFNA	Gazquez et al, 2013 [15]	Case-control	Susceptibility	580/552	Spanish/ American	No
MIF-173	Yazdani et al, 2013 [48]	Case-control	Susceptibility	72/100	Caucasian	Yes
NOS1 – NOS2A	Gazquez et al, 2011 [16]	Case-control	Susceptibility	273/550	Caucasian/American	No
PARP-1	Lopez-escamez et al, 2009 [27]	Case-control	Susceptibility	80/371	Spanish	No
PTPN22	Lopez-escamez et al, 2010 [25]	Case-control	Susceptibility	52/348	Caucasian	Yes

tor (MIF), Aquaporin (AQP), Antiquin (ATQ), Adducin (ADD), HSP70, Host cell factor C1 (HCFC1), PTPN22, Interleukin-1, as well as KCNE genes (Table 4).

Variants and polymorphisms in KCNE potassium channel genes may lead to a significant different outcome of human physiology, such as fluid homeostasis, signaling in nervous tissue, and muscular contraction [3]. It had been confirmed that the expression of the KCNE1 channel was in the stria vascularis within the inner ear, and a null variant of this gene would gradually result in an abnormal development of the endolymphatic system in the mouse cochlea as well as deafness [43]. The expression of the KCNE3 channel in the epithelium of the distal portion of the endolymphatic sac may be a key to regulating the effective volume of endolymph. Considering that KCNE channels play an essential role in transepithelial ion and water transport and that both KCNE1 and KCNE3 channels are intensely expressed in the epithelia of the stria vascularis and the endolymphatic sac, it is quite likely that variants in KCNE1 and KCNE3 genes might have a significant association with MD.

We performed a meta-analysis to analyze the associations between MD risk factor and two variants (KCNE1 rs1805127 and KCNE3 rs2270676) in the KCNE gene. The results indicated that neither of the two variants was significantly associated with MD risk. But in view of subgroup analysis, the normal expression of the KCNE1 rs1805127 and KCNE3 rs2270676 played a protective role in Asian MD patients, but not in Caucasians. The contribution of the two variants to MD risk is strongly influenced by other genes and environmental components. Variability might derive from population stratification due to ethnic admixture. That is, MD cases and controls might be unintentionally enrolled from two or more ethnic groups. In HWE analyses, the test result of Doi et al's control data did not meet the standards, which lead to the possibility for a different conclusion (Table 2). A larger study with appropriate cases and controls is needed to validate this difference.

Several studies have suggested that several genes in the major histocompatibility complex (MHC) region promote susceptibility to MD. Located in the MHC region, human leukocyte antigen (HLA) genes have been implicated in MD susceptibility. Among these studies, Xenellis et al. [47] found a significant increase in the distribution of the HLA-Cw07 allele in 41 British MD patients in comparison to the patients affected by other inner ear diseases or healthy controls, suggesting a predisposing role for the HLA-Cw07 specificities in MD. However, a study with a larger sample from Spain failed to demonstrate differences in

phenotypic frequencies of Cw07 [26], suggesting that the immunological alterations reported were probably epiphenomenon of the inner ear damage. Later, Lopez-Escamez et al. [28] observed an association between HLA-DRB1 *1101 with bilateral MD, and recently, Khorsandi et al. [22] reported the association of definite MD with the HLA-Cw04 allele. In addition to the HLA genes, some other genes have also attracted attention, such as DFNA9, several markers on chromosome 12, Macrophage migration inhibitory factor (MIF), AQP, ATQ, ADD, HSP70, Host cell factor C1 (HCFC1), PTPN22, IL1, as well as KCNE [9].

Hietikko et al's study [19], included in our analysis, reported on the screening of previously MD associated genes AQP2, KCNE1, KCNE3, COCH, HCFC1, and ADD1 on 59 individuals with a control population of 98 persons, and only rs1805127 (KCNE1) remained significant after correction for multiple testing. We did not duplicate the same result after a meta-analysis. According to the forest plot, no association with MD was observed for rs1805127 (KCNE1) (Fig. 1).

The main purpose of performing our meta-analysis was to improve statistical power and obtain more compelling results by increasing the sample size. However, some limitations of this study should be discussed. First, a lack of further adjustments for environmental risk factors, other co-variables, and potential gene environment interactions might bias the present results. Second, the controls were not uniformly defined. The different control groups might bias the risks of developing MD. Third, because of the limited availability of published results, the number of studies included in our meta-analysis is relatively small. Hopefully, more studies will become available to evaluate the association of these variants with MD risk in different ethnic groups.

In summary, we conducted a meta-analysis of the association of MD risk with genetic variants in KCNE1 and KCNE3. This gene-based analysis indicated that based on current evidence from published studies the KCNE1 rs1805127 and KCNE3 rs2270676 variants are not associated with MD risk. Further replication studies in distinct populations are required to confirm the ethnic stratification of the association.

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Conflicts of interest

The authors declare that there are no conflicts of interest.

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