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Original Article

The Association of GRM7 Single Nucleotide Polymorphisms with Age-Related Hearing Impairment in a Taiwanese Population

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OBJECTIVES: Age-related hearing impairment (ARHI) is a major disability among the elderly. This study aimed to analyze the association of single nucleotide polymorphisms (SNPs) of metabotropic glutamate receptor 7 (GRM7) gene with ARHI in an elderly population in Taiwan.

MATERIALS and METHODS: This was a community-based study performed in a metropolitan hospital. Participants ≥65 years of age were recruited. Participants with a pure tone average (PTA) of speech frequencies in the better ear of >35 decibel hearing level (dBHL) were classified into the case group, whereas those with PTA ≤25 dBHL were classified into the control group. The association of SNPs rs11928865, rs1353828, rs9814809, and rs9880404 with ARHI was analyzed.

RESULTS: In 106 cases and 190 controls, alleles of all SNPs were found not to be associated with ARHI. The genotype of rs9880404 was found to be associated with ARHI in a dominant pattern, but the genotypes of rs11928865, rs1353828, and rs9814809 were found not to be associated with ARHI.

CONCLUSION: GRM7 SNPs are associated with susceptibility to ARHI, but the significance of this finding in a Taiwanese population differed from that observed in European studies. Further studies may help to determine Taiwanese (Asian)-specific SNPs associated with ARHI.

KEYWORDS: Age-related hearing impairment, metabotropic glutamate receptor, GRM7, single nucleotide polymorphism, Asian

INTRODUCTION

Increase in the elderly population is a global issue. Many diseases may be associated with aging of an individual. Age-related hearing impairment (ARHI) is a major disability among older individuals. The prevalence of hearing impairment has been reported to be 34% in individuals 65 years of age or older, and it increases to 72% in individuals 85 years of age or older [1, 2]. In Taiwan, the prevalence of hearing impairment is reportedly as high as 78% among individuals 65 years of age or older [3]. The high prevalence of ARHI in Taiwan attracted our attention, and we initiated the present study.

Age-related hearing impairment (ARHI) is a multifactorial condition, representing the end result of multiple intrinsic (e.g., genetic predisposition) and extrinsic (e.g., noise exposure) factors acting on the inner ear leading to the accumulation of damages in the pathway of auditory signal transduction [4]. Chronic inflammation, hypoxia, noise, and toxic substances may increase oxidative stress in the inner ear, cause the production of reactive oxygen species, lead to necrosis and apoptosis of inner ear cells, and result in ARHI [4-6]. In the auditory pathway, glutamate is the primary neurotransmitter; however, overstimulation by glutamate may be toxic. Excess glutamate in the extracellular space below the inner hair cells (IHC) could result in permeability changes in the postsynaptic

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membrane of dendrites and cause osmotic imbalance, edema, and auditory dendrite destruction [7, 8]. The administration of glutamate antagonists may protect postsynaptic targets and reduce functional impairment [7], indicating that the interaction of glutamate with its receptors may be involved in the mechanism of hearing impairment. Metabotropic glutamate receptors (mGluRs) are receptors located in the neurons receiving glutamic signals from IHC and coupled to effector systems through GTP-binding proteins, which can modulate or fine-tune the activity at the synapse [9].

To date, eight subtypes of mGluRs have been identified. Some studies have reported that the single nucleotide polymorphism (SNP) of metabotropic glutamate receptor 7 (GRM7) gene is related to ARHI [10-13]. In the above studies, the SNP rs11928865 was reported to be significantly associated with susceptibility to ARHI, regardless of whether the studies were conducted in Caucasians [10, 12, 13] or Asians [11]. However, the minor allele frequency (MAF) of rs11928865 was as high as 0.32 in Caucasians, whereas it was as low as 0.14–0.20 in Asians [14]. With the high prevalence of ARHI (78%) in Taiwan and the low MAF (0.14–0.20) of rs11928865 in Asians, we hypothesized that there are some GRM7 SNPs, which have a higher MAF and are closely linked to rs11928865, associated with susceptibility to ARHI.

The goals of the present study were 1) to generate data of the genetic distribution of target SNPs in the Taiwanese population and 2) to determine common GRM7 SNPs that are associated with susceptibility to ARHI in our population. We hope that the findings of the present study can be applied in the development of screening and treatment options of ARHI in the future.

MATERIALS and METHODS

Participants

The participants of this study were clients who had undergone national annual health examinations performed by the health management center in a metropolitan hospital, from March 17 to May 19, 2015. The national annual health examinations were free of charge for participants older than 65 years of age, with funding provided by the Health Promotion Administration, Ministry of Health and Welfare, Taiwan. We recruited volunteers who were 65 years of age or older and who agreed to participate in the study and undergo additional pure tone audiometric tests and take self-reported questionnaires about the history of noise exposure and medical history of ear diseases. Participants with a history of noise exposure and/or otologic diseases were excluded from this study later during data analysis. Participants with dementia and those who could not sit independently in order to undergo the audiometric tests were also excluded from this study.

Audiometric Assessments

Pure tone audiometry was performed in sound-attenuating booths by trained technicians using standard procedures that met the requirements of the Council of Labor Affairs, Executive Yuan, Taiwan. The audiometric data were recorded at frequencies of 500, 1000, 2000, 3000, 4000, 6000, and 8000 Hz. Bone conduction (BC) audiograms were also recorded at frequencies of 500, 1000, 2000, 3000, and 4000 Hz for those whose air conduction (AC) hearing levels were >25 decibel hearing level (dBHL). The highest BC frequency achieved was 4000 Hz because of technical and physical limitations. The BC hearing levels were used for evaluating the severity of hearing loss in the older adults. For those with AC hearing levels ≤25 dBHL, the AC hearing levels were adopted. For those with BC hearing levels beyond the limit of audiometric testing capacity, the upper limit of the BC testing capacity was adopted (i.e., 65 dBHL). The BC hearing level was adopted for hearing assessments to minimize the possibility of conductive hearing loss. The speech frequency (500, 1000, 2000, and 4000 Hz) pure tone average (PTA) was calculated for each side. The PTA of the better hearing ear was used to evaluate the severity of the hearing impairment, as per the World Health Organization grading system (http://www.who.int/pbd/deafness/hearing_impairment_grades/en/). According to our earlier study, individuals may be perceptive to hearing impairment at a hearing level of >35 dBHL [3]. The participants were categorized into three groups: normal control (PTA≤25 dBHL), indolent hearing loss (PTA>25 dBHL but ≤35 dBHL), and perceptive hearing loss (PTA>35 dBHL). To identify the phenotypes more clearly, we selected the perceptive hearing loss group (ARHI group) as the case group and the normal control group as the control later for case–control analyses.

Methods

SNP selection

The target SNPs were searched using the software GLIDERS[15], with the following criteria: Asians (JPT+CHB), MAF≥0.25, linkage disequilibrium value (LD value; r^2) with rs11928865 ≥0.5, and within 20 kb to rs11928865. Three SNPs were found with the above criteria (Table 1). Four SNPs (rs1353828, rs9814809, rs9880404, and rs11928865) were adopted for genetic analysis in the present study.

Genotyping

Blood samples were obtained from all the participants with written consent. Each specimen was collected in an ethylenediaminetetraacetic acid tube and was centrifuged (2000 g, 20 min). The buffy coat was isolated, and DNA was extracted using a commercial DNA extraction kit (Gentra Corp., Minneapolis, Minn, USA). Genotypes for the selected polymorphisms were screened using the ABI TaqMan SNP genotyping assays (Applied Biosystems, Foster City,

Table 1. Target SNPs found by the searching engine GLIDERS

SNP	Chromosome	Position (bp)	MAF	Distance (from rs11928865)	r^2	D′	χ^2	p	P(BFC)
rs1353828	3	7,144,453	0.271	13kb	0.52	0.95	0.572	5.35e-30	3.17e-18
rs9814809	3	7,145,741	0.271	15kb	0.52	0.95	0.572	5.35e-30	3.17e-18
rs9880404	3	7,150,878	0.268	20kb	0.51	0.95	0.570	2.23e-29	1.32e-17

BFC: Bonferroni corrected; MAF: minor allele frequency; SNPs: single nucleotide polymorphisms

Calif., USA) The extracted DNA and genotyping assays were added to TaqMan universal PCR master mix (Roche, Branchburg, N.J., USA) according to the manufacturer's instructions. The genotyping procedures were then performed using ABI PRISM–7500 realtime PCR system (Applied Biosystems). The results were analyzed using ABI 7500 System sequence detection software, version 1.2.3 (Applied Biosystems).

Statistical Analysis

All data were analyzed using the Statistical Packages for the Social Sciences software package, version 20.0 (IBM Corp.; Armonk, NY, USA). Continuous data were analyzed using independent sample Student's t-tests. Categorical data were computed using two-sided $\chi 2$ tests. Genetic analyses were performed using the PLINK software [16]. Multivariate logistic regression analyses were used to explore the odds ratios of the genotypes on ARHI. The level of statistical significance was set at $p<0.05$.

Ethical Considerations

All participants provided written informed consent. No private personal information is identifiable in the data. This study was approved by the institutional review board of our institute (IRB approval No.: KMUHIRB-GV103069).

RESULTS

A total of 602 participants, including 325 (54.0%) males and 277 (46.0%) females, were recruited in the present study. The average age of the participants was 72.08±5.75 years. The average hearing threshold of the better ear was 29.20±12.03 dBHL. The demographic data, including the groups of hearing impairment, history of hearing hazard, and alleles and genotypes of the participants, are presented in Table 2.

Case-Control Analysis

After screening the histories of noise exposure and otologic diseases in the participants, 187 were excluded. Of the remaining participants, 106 were classified into the ARHI (case) group, whereas 190 participants with normal hearing levels were classified into the control group.

Allele Analysis

The distributions of the alleles of the target SNPs are presented in Table 3. For all four target SNPs, the proportion of the minor alleles seemed to be slightly higher in the case group. The distributions of the alleles of the target SNPs followed the Hardy–Weinberg equilibrium. However, no significant difference was found in the distributions of alleles between the case and control groups ($p>0.05$).

Genotype Analysis

The distributions of genotypes of the SNP rs1353828, rs9814809, and rs9880404 were significantly different between the case and control groups. However, there was no significant difference for rs11928865 between the groups. The patterns of the effects for the SNPs on ARHI were analyzed, and the odds ratios for the protective effects were also computed. The minor alleles of the SNP rs1353828, rs9814809, and rs9880404 were associated with hearing loss in a dominant pattern. However, after adjustment for age and sex, only rs9880404 showed statistical significance in association with susceptibility to

Table 2. Demographics of the participants

	Male	Female	Total
Number (%)	325 (54.0)	277 (46.0)	602 (100)
Age (Years)	72.30±5.84	71.83±5.66	72.08±5.75
PTA of better ear (dBHL)	32.15±12.47	27.46±11.75	29.20±12.03
Grouping			
Perceptive HL (>35 dB)	111	59	170
Indolent HL (≤35 dB, >25 dB)	92	72	164
Control (≤25 dB)	122	146	268
Hazard history†			
Noise exposure	109 (74.1)	38 (25.9)	147
Ear disease	53 (57.6)	39 (42.4)	92
	n (%)	n (%)	n (%)
Genotypes			
rs11928865			
TT	214 (65.8)	189 (68.2)	403 (66.9)
AT	102 (31.4)	80 (28.9)	182 (30.2)
AA	8 (2.5)	6 (2.2)	14 (2.3)
Undetermined	1 (0.3)	2 (0.7)	3 (0.5)
rs1353828			
AA	170 (52.3)	162 (58.5)	332 (55.1)
AC	133 (40.9)	96 (34.7)	229 (38.0)
CC	19 (5.8)	16 (5.8)	25 (5.8)
Undetermined	3 (0.9)	3 (1.1)	6 (1.0)
rs9814809			
GG	170 (52.3)	162 (58.5)	332 (55.1)
GC	133 (40.9)	96 (34.7)	229 (38.0)
CC	19 (5.8)	16 (5.8)	25 (5.8)
Undetermined	3 (0.9)	3 (1.1)	6 (1.0)
rs9880404			
CC	173 (53.2)	163 (58.8)	336 (55.8)
CT	130 (40.0)	96 (34.7)	226 (37.5)
TT	19 (5.8)	16 (5.8)	35 (5.8)
Undetermined	3 (0.9)	2 (0.7)	5 (0.8)
Alleles			
rs11928865			
T	530 (81.8)	458 (83.3)	988 (82.5)
A	118 (18.2)	92 (16.7)	210 (17.5)
rs1353828			
A	473 (73.4)	420 (76.6)	893 (74.9)
C	171 (26.6)	128 (23.4)	299 (25.1)
rs9814809			
G	473 (73.4)	420 (76.6)	893 (74.9)
C	171 (26.6)	128 (23.4)	299 (25.1)
rs9880404			
C	476 (73.9)	422 (76.7)	898 (75.2)
T	168 (26.1)	128 (23.3)	296 (24.8)

†Some participants may have both noise exposure and ear disease histories

Table 3. Analyses of alleles and genotypes between ARHI and control groups

		ARHI	Control		
Number		106	190		
Age (Years)		77.27±6.07	70.18±4.71		
PTA of better ear (dBHL)		46.12±8.41	19.01±4.52		
SNPs		**n (%)**	**n (%)**	**p†**	**Adjusted p‡**
rs11928865					
Alleles	T	175 (83.3)	320 (85.1)	0.566	0.239
	A	35 (16.7)	56 (14.9)		
Genotypes	TT	71 (67.6)	137 (72.9)	0.310	0.238
	AT	33 (31.4)	46 (24.5)		
	AA	1 (1.0)	5 (2.7)		
	Undetermined	1	2		
rs1353828					
Alleles	A	156 (74.3)	295 (78.9)	0.204	0.277
	C	54 (25.7)	79 (21.1)		
Genotypes	AA	53 (50.5)	120 (64.2)	0.004	0.029
	AC	50 (47.2)	55 (29.4)		
	CC	2 (1.9)	12 (6.4)		
	Undetermined	1	3		
rs9814809					
Alleles	G	156 (74.3)	295 (78.9)	0.204	0.277
	C	54 (25.7)	79 (21.1)		
Genotypes	GG	53 (50.5)	120 (64.2)	0.004	0.029
	CG	50 (47.2)	55 (29.4)		
	CC	2 (1.9)	12 (6.4)		
	Undetermined	1	3		
rs9880404					
Alleles	C	157 (74.8)	295 (78.9)	0.254	0.232
	T	53 (25.2)	79 (21.1)		
Genotypes	CC	54 (51.4)	120 (64.2)	0.006	0.019
	CT	49 (46.7)	55 (29.4)		
	TT	2 (1.9)	12 (6.4)		
	Undetermined	1	3		

†: Chi-square

‡: Logistic regression; adjusted for sex and age; wild type as reference

ARHI. The adjusted odds ratio of rs9880404 TT and TC genotypes to CC genotype (wild type) was 1.832 (p=0.048). The results of genotype analyses are presented in Tables 3 and 4.

The haplotypes were also analyzed. However, no specific haplotype was associated with susceptibility to ARHI.

DISCUSSION

In the present study, we found that GRM7 SNP rs9880404 is associated with susceptibility to ARHI. Compared with the CC genotype (wild type), participants with the TT and TC genotypes of SNP rs9880404 may have an increased risk for ARHI. The findings correspond to our hypothesis that some GRM7 SNPs closely related to rs11928865 are associated with susceptibility to age-related hearing loss. Although rs1353828 and rs9814809 were found not to be associated with susceptibility to AHRI, three SNPs (rs1353828, rs9814809, and rs9880404) were found to be closely related to each other. The SNPs rs1353828 and rs9814809 were in LD with r^2=1.0, where the A and C alleles in rs1353828 always correspond to the G and C alleles in rs9814809, respectively. The SNP rs9880404 was also in LD with rs1353828 and rs9814809 with r^2=0.98. The relationships among these SNPs illustrated by Haploview are presented in Figure 1.

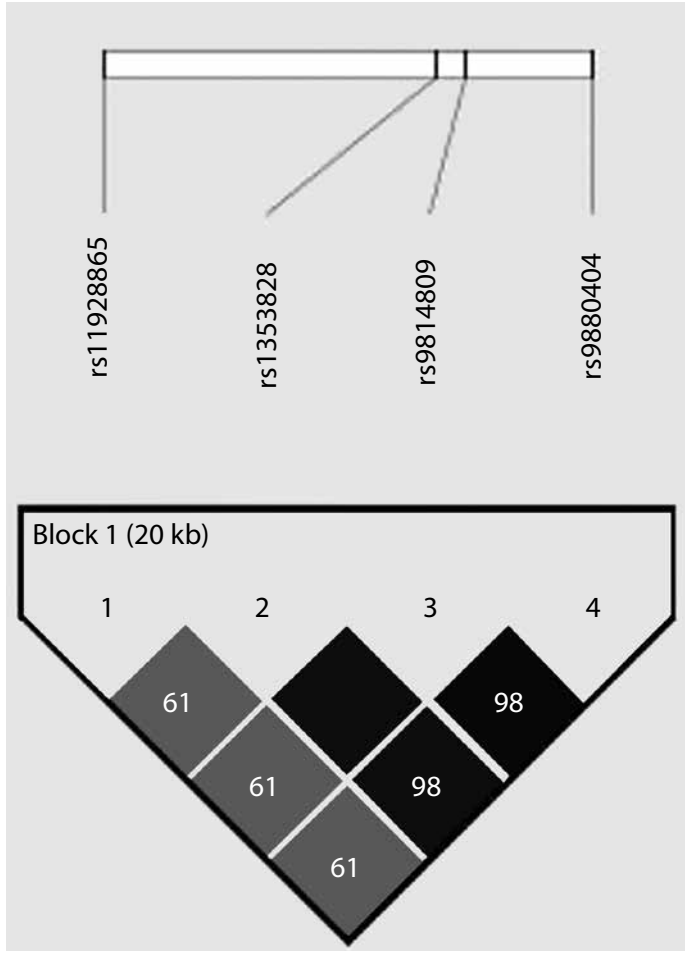

Figure 1. The relationships among single nucleotide polymorphisms (SNPs) analyzed in the present study. The numbers in the blocks indicate the r-squared between SNPs. All the LOD scores were >69 (69.39-151.91).

In the present study, however, SNP rs11928865 was found not to be associated with ARHI. This finding was different from that in other previously published studies, which confirmed that rs11928865 is associated with susceptibility to ARHI [10-13]. Ethnical differences might be the primary cause for these differing results. Reportedly, the global MAF of rs11928865 is 0.256 [14], whereas the MAFs of this SNP are 0.292 in Europeans and 0.175 in the population of the present study. In Asians, the MAF of this SNP was found to be smaller than that in Europeans. The difference in MAFs among races may interfere with the expression of clinical symptoms. In the study by Luo et al., the authors concluded that rs11928865 is associated with susceptibility to ARHI of high-tone loss audiometric patterns in a Chinese population [11]. In their study, however, rs11928865 was found not to be

Table 4. Trend analysis of hereditary patterns

	ARHI	Control	p†	OR (95% CI)	p‡ (Adjusted)	aOR (95% CI)
rs11928865						
Dominant (AA+AT):TT	34:71	51:137	0.343	0.777 (0.462–1.308)	0.181	0.643 (0.337–1.227)
Recessive AA: (AT+TT)	1:104	5:183	0.343	0.352 (0.041–3.053)	0.181	1.555 (0.815–2.966)
rs1353828						
Dominant (CC+AC):AA	52:53	67:120	0.023*	1.757 (1.081–2.855)	0.066	1.745 (0.964–3.157)
Recessive CC:(AC+AA)	2:103	12:175	0.103	0.283 (0.062–1.290)	0.166	0.305 (0.057–1.637)
rs9814809						
Dominant (CC+CG):GG	52:53	67:120	0.023*	1.757 (1.081–2.855)	0.066	1.745 (0.964–3.157)
Recessive CC:(CG+GG)	2:103	12:175	0.103	0.283 (0.062–1.290)	0.166	0.305 (0.057–1.637)
rs9880404						
Dominant (TT+CT):CC	51:54	67:120	0.034*	1.692 (1.041–2.749)	0.048*	1.832 (1.005–3.339)
Recessive TT:(CT+CC)	2:103	12:175	0.103	0.283 (0.062–1.290)	0.157	0.295 (0.055–1.598)

†: Logistic regression
‡: Adjusted for age and sex
*: $p<0.05$

associated with ARHI of flat loss audiometric patterns. Due to technical and physiological limitations, the highest BC frequency in the present study was limited to 4000 Hz. The phenotype of ARHI was defined by the speech frequency (500, 1000, 2000, and 4000 Hz) PTA of the better hearing ear, which was more similar to the flat loss audiometric pattern. Hence, the insignificant association of rs11928865 with ARHI in the present study did not conflict with the findings of earlier published studies.

The present study supported the findings of GRM7 association with ARHI [10-13]. Metabotropic glutamate receptor 7 (mGluR7) is a member of the mGluR III group. It is expressed at the highest levels in the adult brain during hippocampal formation, in the cerebral cortex, and in the cerebellum [17]. The mechanism by which mGluR7 affects hearing is still unclear. High concentrations of glutamate may cause overstimulation and excitotoxicity in the auditory system, leading to several forms of progressive hearing loss, such as noise-induced hearing loss and ARHI [8]. High concentrations of glutamate may activate the expression of mGluRs. Animal studies have found that the activation of mGluRs regulates intracellular calcium concentration in cochlear nucleus neurons [18-20]. The physical level of the calcium concentration of cochlear nucleus neurons is maintained by the mGluR-mediated activation of protein kinase A and C, whereas the deprivation or interruption of the calcium concentration-regulating mechanism are predictive of subsequent cell death [20]. The SNPs in the present study, including rs11928865, were intron variants located on chromosome 3. Perhaps the variations of these SNPs modified the expression of GRM7 in some way, or these SNPs were linked to the disequilibrium of the variants in other GRM genes. Further studies on the expressions or functional analyses of mGluRs might help answer these questions.

The major limitation of the present study is the small sample size. There were only one or two participants with the genotype of homogenous minor alleles for SNPs in the case group. Hence, a small difference in the case number may affect the statistical results enormously. Enlarging the sample size may help enhance the validity of the results in the present study. The recruitment of participants from multiple institutes in future studies should be considered.

CONCLUSION

The genetic polymorphisms of GRM7 are associated with susceptibility to ARHI. The SNP rs9880404 was found to be associated with increased risk for ARHI in a dominant pattern. SNPs rs11928865, rs1353828, and rs9814809 were found not to be associated with susceptibility to ARHI in the present study. Unlike the results of the present study, SNP rs11928865 was reported to be associated with susceptibility to ARHI in European studies. The significance of SNPs in relation to susceptibility to ARHI in the present study (Asian) differed from that in European studies. Further genome-wide association studies with a larger population in our nation may help find highly ranked SNPs associated with ARHI specifically for Taiwanese or Asians.

Ethics Committee Approval: Ethics committee approval was received for this study from the Institutional Review Board of Kaohsiung Medical University Hospital.

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

Peer-review: Externally peer-reviewed.

Author contributions: Concept – N.C.C., C.Y.D., K.Y.H.; Design – N.C.C., C.Y.D.; Supervision – K.Y.H.; Resource – W.Y.L., C.Y.D.; Materials – N.C.C., M.H.H.; Data Collection and/or Processing – H.L.Y., C.Y.C.; Analysis and/or Interpretation – N.C.C., H.L.Y.; Literature Search – N.C.C., H.M.W.; Writing – N.C.C.; Critical Reviews – C.Y.D, K.Y.H.

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

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