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Original Article

Studying the Association between Sudden Hearing Loss and DNA N-Methyltransferase 1 (DNMT1) Genetic Polymorphism

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OBJECTIVE: The aim of the present study was to investigate whether there was any relationship between some DNA N-methyltransferase 1 (DNMT1) polymorphisms and susceptibility to idiopathic sudden sensorineural hearing loss (ISSHL) in ISSHL patients.

MATERIAL and METHODS: We investigated 90 patients diagnosed with ISSHL and a control group composed of 75 age- and gender-matched healthy individuals. DNA was extracted from the blood samples by phenol-chloroform method. Polymerase chain reaction and restriction fragment length polymorphism methods were used for the genotyping analysis of 4 regions of DNMT1.

RESULTS: For rs2228612 single nucleotide polymorphism (SNP), the frequency of AA, AG, and GG genotypes were 81.4%, 9.3%, and 9.3% in controls and 82.2%, 16.7%, and 1.1% in patients, respectively. We observed a significant decrease in the frequency of GG genotype in patients with ISSHL when compared with controls (p=0.027). The frequency of GG, AG, and AA genotypes for rs2228611 SNP were 20.7%, 49.3%, and 20% in controls and 20%, 47.8%, and 32.2% in patients, respectively. There was a significantly increased frequency of the AA genotype of this SNP in the DNMT1 gene, and we found that individuals with the AA genotype had 2.47 times the risk for ISSHL development than individuals with the GG genotype (p=0.41). The GAA haplotype may constitute 2.66 times the risk for ISSHL disease (OR=2.66, 95% confidence interval: 0.28-25.03)

CONCLUSION: This study's results showed that the AA genotype in rs2228611 polymorphism was a risk factor in ISSHL patients and the GG genotype could be a protective factor in rs2228612 polymorphism.

KEYWORDS: Sudden hearing loss, DNA methyltransferase-1, polymorphism

INTRODUCTION

A hearing loss of more than 30 dB at 3 consecutive frequencies occurring within 3 days is defined as idiopathic sudden sensorineural hearing loss (ISSHL), which is a common medical emergency [1]. Since the first day it was defined, ISSHL has been a disease whose etiology and treatment methods have been controversial. Today, with the help of technological improvements and robust diagnostic tools and methods of analyses, new etiologies and treatment methods are being defined.

In ISSHL, a specific factor can be established only in 10%-15% cases [2]. Although most cases having ISSHL are considered to be idiopathic, the known causes of the disease are viral infection of the labyrinth or cochlear nerve, bacterial and protozoan infections, vascular incident, vascular occlusion, labyrinthine membrane rupture, perilymphatic hypoxia inflammatory, ototoxicity drugs, neoplastic, metabolic conditions, and genetic and autoimmune disorders [3].

The association between mutation and diseases has been studied since a long time. However, studies on the association of polymorphisms, which are epigenetic changes, and diseases have increased in recent years, and polymorphisms have been understood to have important effects on high organizational organisms. Genetic polymorphisms, considered to be the main genetic elements in the development of common and complex diseases, are responsible for inter-individual variation and diversity [4, 5]. Polymorphism is defined as a variation in the DNA sequence that occurs in a population with a frequency of 1% or higher [6]. Single nucleotide polymorphism (SNP) exemplifies the commonest polymorphism and is thought to arise every 1,000 base pairs in the human ge-

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nome. In studying the predisposition to certain traits, including diseases, SNPs are used as genetic signatures [7, 8]. DNS methylation and histone modification have been the most commonly studied types of epigenetic phenomenon. DNA methylation is a dynamic process between active methylation, mediated by DNA methyltransferases (DNMT) using *S*-adenosylmethionine as a methyl donor, and removal of methyl groups from 5-methylcytosine residues by both passive and active mechanisms. A total of 5 different forms of DNMT, namely, DNMT1, DNMT2, DNMT3a, DNMT3b, and DNMT3L, have been defined in mammals. In gene expression, DNA methyl is an important epigenetic determinant, while aberrant DNA methylation is mechanistically linked to cancer development [9]. DNA methyltransferase 1 (DNMT1) is the major enzyme involved in the somatic inheritance of DNA methylation and plays an important role in epigenomic stability. In addition, the increased expression of DNMT1 is found in various human cancers [10-12]. Our Pubmed search using the keywords "DNMT1" and "hearing loss" revealed only a few studies [13-17].

As a result, our literature search did not reveal any study on the association between ISSHL and DNMT gene polymorphism. For this reason, we aimed at studying whether there was any relationship between some DNMT1 polymorphisms and predisposition to ISSHL.

MATERIALS and METHODS

Study Population

In this study, in the patient group, we investigated 90 patients admitted to the Otorhinolaryngology Department of Cumhuriyet University and diagnosed with ISSHL between 2014 and 2015. The control group was composed of 75 healthy, age- and gender-matched, unrelated, voluntary individuals.

Having a hearing loss of at least 30 dB in 3 consecutive frequencies in 72 h was defined as ISSHL [1].

Those applying to the hospital within 1 week from the onset of the disease, receiving no previous steroid treatment, having blood samples, and undergoing pure-tone hearing test during the first visit were included in the study. Those having acute inflammation; infection; a history of otologic surgery, trauma, or barotrauma during the previous 4 weeks; having cerebellopontine angle pathology or congenital cochlear malformations; neurologic disorders predisposing to hearing loss; recent use of ototoxic medications; having neoplasm within the previous 2 years; having other major diseases (e.g., heart failure, hypertension, coronary artery disease, cor pulmonale, liver or renal dysfunction, diabetes mellitus, chronic obstructive pulmonary disease, obstructive sleep apnea, connective tissue diseases, and inflammatory bowel diseases); and any otologic disease such as otitis media during the last 4 weeks, chronic otitis media, otosclerosis, and Meniere's disease were excluded from the study. As nothing employed in the present study was harmful to the participants, none of the patients were excluded from the study during the study period, except those not meeting the inclusion criteria. No patient requested to leave the study on their own will.

A general physical examination and an audiological evaluation were carried out and blood parameters were studied in all the patients. Comprehensive ear-nose-throat and head-neck examinations of the participants were evaluated by the same researcher (KYS). Pure-tone audiometries of all the patients were performed by the same audiometrist (VO).

This study was performed in accordance with the principles of the Declaration of Helsinki. This study was approved by the Cumhuriyet University Research Ethics Committee (Decision Number: 2014-03/24; Date: 18.03.2014). Oral and written consents were obtained from all the participants.

Audiological Evaluation

Air and bone conduction thresholds of the patients were measured by a clinical audiometer device (INTERACOUSTICS AC40 clinical audiometer, Assen, Denmark) calibrated according to ISO standards. All the audiological tests were made with the non-test ear masked. Pure-tone thresholds were obtained for air conduction at 250 Hz, 500 Hz, 1 kHz, 2 kHz, 4 kHz, and 6 kHz and for bone conduction at 250 Hz, 500 Hz, 1 kHz, 2 kHz, and 4 kHz.

All of the ISSHL patients underwent standard evaluation that consisted of pure-tone speech audiometry at the baseline and after the treatment (at the end of the 4th week), and the hearing data of all the control cases obtained at the baseline were gathered. It was confirmed that hearing of all the cases in the control group composed of neurologically healthy individuals were within normal limits (0-20 dB).

Collection of Blood Samples

For genetic analysis, blood samples were taken from all the individuals participating in the study. While taking the said samples, additional blood samples were taken from ISSHL cases for routine laboratory analysis. DNA isolation of the blood samples was conducted by Cumhuriyet University, Medical Faculty, and Medical Biology Department.

DNA Extraction from Blood Samples

Four mL of peripheral whole blood samples were collected into EDTA-containing tubes from both the groups. DNA was extracted from 400 µl blood samples by phenol-chloroform method and stored at −20°C until the analysis.

Genotype Analysis

Polymerase chain reaction (PCR) and restriction fragment length polymorphism methods were used for genotyping analysis of 4 regions of DNMT1 (rs2228611, rs2228612, rs16999593, and rs8101626). Primer sets for amplification of the target sides of these genes, PCR and RFLP products, and restriction enzymes are shown in Table 1. PCR reactions were performed in a reaction volume of 25 µL containing 10 pmol of amplification primer sets, 5 nmol of 4 deoxynucleotide triphosphates (Fermentas), 10 mmoL/L of Tris-HCl (pH 8.3 at 25°C), 50 mmoL/L of KCl, 1.5 mmoL/L of $MgCl_2$, 1 unit of Taq DNA polymerase (Fermentas), and 100 ng of genomic DNA. The PCR program was as follows: an initial denaturation at 94°C for 5 min followed by 35 cycles of 94°C for 30 s, appropriate annealing temperature for each primer set for 45 s (for rs2228611, 66.5°C; for rs2228612 and rs16999593, 52°C; for rs8101626, 64.6°C), and 72°C for 45 s followed by 1 cycle of 72°C for 5 min.

In order to detect these 4 SNPs of DNMT1, 8 µL of PCR products were treated with specific 5U restriction enzyme (Table 1) and 1.5 µL reac-

Table 1. Conditions for the identification of DNMT1 polymorphisms

SNPs	Regions	Forward and primer (5′→3′)	Reverse sequences	PCR products (bp)	RE enzymes	Alleles and product size (bp)
DNMT1 (exon)	rs2228611	F: TATGTTGTCCAGGCTCGTCTC			A	232+28
		R: GTACTGTAAGCACGGTCACCTG	260	BsmAI	T	108+124+28
DNMT1 (exon)	rs2228612	F: AGAACCTGAAAAAGTAAATCCACCG			A	310+19
		R: CATGTGATTCACCCGCTTCAG	329	MspI	G	168+142+19
DNMT1 (exon)	rs16999593	F: CAGTTCTCAGCATCCTAGCC			T	440
		R: GGAATCATCTGCTCTTACGC	440	BssSI	C	268+172
DNMT1 (İntron)	rs8101626	F: CAAATGGGCCACCTAGACAC			A	640
		R: GGCAGAGATTGAGCCAGAAG	640	Alw26I	G	474+166

SNP: single nucleotide polymorphism; RE: restriction endonucleases; DNMT1: DNA methyltransferase-1; rs: single nucleotide polymorphism identification number; G: Guanine; A: Adenine; C: cytosine; T: thymine; bp: base pair

Table 2. Genotype distribution

DNMT1 Polymorphism	ISSHL patients (n=90)	Control patients (n=75)	OR (95% CI)	p
RS8101626				
A	113 (62.77)	86 (57.33)		Ref
G	67 (37.22)	64 (42.66)	0.79 (0.51-1.24)	0.314
AA	33	24		Ref
AG	47	38	0.90 (0.45-1.77)	0.759
GG	10	13	0.55 (0.21-1.48)	0.242
RS2228611				
G	79 (43.88)	83 (55.33)		Ref
A	101 (56.11)	67 (44.66)	1.58 (1.02-2.45)	0.038
GG	18	23		Ref
AG	43	37	1.48 (0.69-3.16)	0.305
AA	29	15	2.47 (1.02-5.93)	0.041
RS 2228612				
A	163 (90.55)	129 (86)		Ref
G	17 (9.44)	21 (14)	0.64 (0.32-1.26)	0.197
AA	74	61		Ref
AG	15	7	1.76 (0.67-4.06)	0.241
GG	1	7	0.11 (0.01-0.98)	0.027*
Haplotype analysis				
Polymorphism				
1 2 3				
A A A	45	30		Ref
A G A	4	6	0.44 (0.11-1.70)	0.311
A G G	7	7	0.66 (0.21-2.09)	0.486
A A G	1	1	0.66 (0.04-11.07)	0.646
G G A	28	29	0.64 (0.32-1.29)	0.213
G G G	1	0	1.02 (0.97-1.06)	0.605
G A A	4	1	2.66 (0.28-25.03)	0.353
G A G	0	1	0.96 (0.90-1.03)	0.408

DNMT1: DNA methyltransferase-1; ISSHL: idiopathic sudden sensorineural hearing loss

tion buffer (supplied with the enzyme) for each SNP in a total reaction volume of 10 mL and then incubated overnight at the optimum temperature according to the manufacturer's instruction (Table 1). All the RFLP products were run on a 3% agarose gel and imaged with UV transilluminator. To validate the genotype analysis, the DNA sequencing process was performed by ABI PRISM 377 automatic sequencer (Applied Biosystems, Foster City, CA, USA) using 15% of the PCR-RFLP products.

Statistical Analysis

All the statistical analyses were made using the Statistical Package for Social Sciences 22.0 program (IBM Corp.; Armonk, NY, USA). The statistical significance of the differences in the DNMT1 genotypes of the cases and controls were calculated by the Pearson's χ^2 test. For each odds ratio (OR), 95% confidence intervals (CI) were also calculated using the χ^2 test. The analysis of haplotype frequencies was carried out using the EH program. Here, $p<0.05$ was considered statistically significant.

RESULTS

In the present study, 90 patients with ISSHL and 75 healthy, voluntary controls were investigated. The mean ages of the patients and the controls were 44.60±12.07 years and 40.25±18.24 years, respectively (p=0.669). Here 36% (n=27) of the 75 healthy individuals in the control group were females, while 64% (n=48) were males. Out of the 90 ISSHL cases, 41.11% (n=37) were females and 58.88% (n=53) were males. The distribution of gender was similar between both the groups (p=0.502).

The genotype distributions of the 4 polymorphisms among groups fitted the Hardy-Weinberg equilibrium. The genotype frequencies and alleles for these polymorphisms of DNMT1 gene regions including rs2228611, rs2228612, and rs8101626 in patients with ISSHL and controls are shown in Table 2. It was determined that all the patients and control group individuals had TT genotype for rs16999593. Therefore, no statistical analysis was done for this region.

For rs8101626 SNP of the DNMT1 gene, we found no significant association between the controls and patients with ISSHL ($p>0.05$) (Table 2).

For rs2228612 SNP, the frequency of AA, AG, and GG genotypes were 81.4%, 9.3%, and 9.3% in the control group and 82.2%, 16.7%, and 1.1% in the patient group, respectively. We observed a significant decrease in the frequency of GG genotype in the patient group with ISSHL when compared with the controls (p=0.027; OR=0.11; 95% CI=0.01-0.98) (Table 2).

On the other hand, the frequency of GG, AG, and AA genotypes for rs2228611 SNP were 20.7%, 49.3%, and 20% in the control group and 20%, 47.8%, and 32.2% in the patient group. There was a significantly increased frequency of the AA genotype of this SNP in the DNMT1 gene, and we found that individuals with the AA genotype had 2.47 times the risk for ISSHL development than individuals with the GG genotype (p=0.41; OR=2.47; 95% CI=1.02-5.93) (Table 2).

Haplotype analyses using rs2228611, rs2228612, and rs8101626 were performed to examine the distribution of all the possible haplotypes in the patient and control groups. We observed that the GAA haplotype could constitute 2.66 times the risk for ISSHL disease (OR=2.66, 95% CI=0.28-25.03) (Table 2). The other haplotypes were found to be protective toward ISSHL. However, these results were not statistically significant (p>0.05) (Table 2).

DISCUSSION

The results obtained in the present study, where we aimed at studying the relationship between ISSHL and DNMT1 rs16999593, rs2228611, rs2228612, and rs8101626 genetic polymorphisms in the Turkish population, showed that rs2228611 and rs2228612 polymorphisms were statistically important in the patient and control groups.

Today, rapid technological improvements have led to the development of robust analyzing techniques. This has helped a more conscious and extensive approach toward analyzing genetic reasons of diseases. However, there are still a limited number of studies on the genetic factors causing sudden hearing loss.

Various studies have shown that ISSHL, which is a complex multifactorial disease, has a relationship with some genetic factors such as heat shock protein 70 (HSP70), factor V Leiden (G1691A), and prothrombin G20210A [18-20].

Based on the hypothesis that the genetic polymorphism of HSP70 are associated with susceptibility to sudden hearing loss, Chien et al. [18] studied 160 patients and 178 controls and found that there was a significant association between HSP70, rs2075800, rs1043618, and rs2763979.

In a study conducted on 362 patients and 209 healthy volunteers, Chien et al. [21] conducted sex-specific analysis to study the association of ISSHL and phosphodiesterase 4D (rs702553) known to be associated with ischemic attack and stroke. They found that phosphodiesterase 4D (rs702553) was significantly associated with the female patient group, and PDE4D gene polymorphisms could cause susceptibility for the development of ISSHL in the southern Taiwanese female population.

Corticosteroids have been known to have an anti-autoimmune effect. It has been assumed that autoimmunity may have a role in the etiology of this disease as the cases having ISSHL have a positive response to corticosteroid treatment [22]. In a study conducted on 630 ISSHL patients and 600 healthy volunteers, Liu et al. [23] studied the association between FCRL3 (rs945635, rs3761959, rs7522061, rs10489678, and rs7528684) polymorphisms and ISSHL. They found that there could be a significant association between ISSHL and rs7528684, rs3761959, and rs7522061 polymorphisms.

It is known that prothrombin G20210A is a major cause in many thromboembolic diseases. However, it is not clear whether there is an association between prothrombin G20210A mutation and ISSHL. In a study published in 2013, Liu et al. [24] noted that there could be a relationship between prothrombin G20210A mutation and ISSHL, but comprehensive studies on a larger series were needed to establish this relationship. The most recent study on the same subject was conducted by Shu et al. [25] in their meta-analysis on the European population; they found that there was no significant association between prothrombin G20210A mutation and ISSHL.

The number of studies showing that there can be an association between vascular factors and genetics in the etiology of ISSHL has been increasing. Rudack et al. [26] found elevated fibrinogen concentrations and a higher prevalence of T allele carriers of the glycoprotein (Gp) Ia C807T polymorphism in ISSHL patients. Weis et al. [27] could not obtain any results supporting the association between elevated fibrinogen concentrations and a higher prevalence of T allele carriers of the Gp Ia C807T polymorphism in ISSHL patients, but showed that Gp III and low thrombocyte concentration could have a positive effect on hearing recovery in ISSHL cases.

Our PubMed search conducted using the keywords "DNMT1" and "hearing loss" revealed that there were a limited number of studies on this issue. Among these studies, Klein et al. [13] showed that a mutation in DNMT1 decreased the enzyme activity and led to a specific form of neurodegenerative diseases with dementia and sensorineural hearing loss. Kinariwala and Dhamja[14] reported the presence of DNMT1 gene mutation in a patient having hereditary sensory and autonomic neuropathy type 1E. Similarly, Sun et al. [15] reported that there could be DNMT1 gene mutation associated with hearing loss and various neurodegenerative symptoms in patients having sensory and autonomic neuropathy type 1E.

Hu et al. [16] studied the association between noise-induced hearing loss and DNMT1 gene mutation in Chinese Han population and showed that there could be an association between susceptibility to noise-induced hearing loss and DNMT1 rs2228612. Interestingly, in another study, Hu et al. [17] failed to show an association between the said mutation and hearing loss in another study conducted in 2013 on the association between noise-induced hearing loss and DNMT1 mutation in the Chinese population. The other studies in the literature focus on the role of DNMT1 mutation in multiple neurodegenerative pathologies such as neurodegenerative diseases, dementia, cerebellar ataxia, and sensorineural hearing loss.

In the literature, there are many studies on the association between the risk factors in the etiology of ISSHL and genetic polymorphism. Some of these studies report an association between ISSHL and polymorphism, while others fail to show such an association. We would like to emphasize that the association found between polymorphisms and ISSHL cannot be proven in studies conducted on a larger

series. In our study, we found that 2 (rs222811 and rs2228612) of the 4 polymorphisms we studied were associated with ISSHL. The results we obtained show that rs2228611 could be a risk factor for ISSHL, while rs2228612 could be protecting against ISSHL. However, we believe that our results should be supported through a multicenter study to be conducted on a larger series.

As a result, the major limitations of the present study were having a limited number of cases, studying only 4 DNMT1 polymorphisms, and evaluating only the ISSHL cases seen in Sivas. The strength of the study is that it is the first study investigating the association between DNMT1 gene mutation and ISSHL and showing that there exists an association between ISSHL and the rs2228611 genotype of the DNMT1 gene.

CONCLUSION

In this study, by comparing rs8101626, rs2228611, rs2228612, and rs16999593 genotypes of the DNMT1 gene, our aim was to establish a view on whether individuals having these genotypes were susceptible to ISSHL. The results show that rs2228611 polymorphism could be a risk factor for ISSHL, while rs2228612 could protect against the said disease. Finally, we believe that further studies on a larger series are needed to investigate more DNMT1 gene polymorphisms in the mechanisms of ISSHL pathogenesis.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Cumhuriyet University, Sivas, Turkey (Decision Number: 2014-03/24; Date: 18.03.2014).

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

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