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Evaluation of angiotensin converting enzyme insertion/deletion, alpha adducin (ADD1) G460W, and IL-10 gene polymorphisms, and determination of prognostic effects in idiopathic sudden sensorineural hearing loss

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ABSTRACT

Objective: The aim of this study was to examine angiotensin converting enzyme (ACE) insertion/deletion, alpha adducin, and interleukin-10 (IL-10) gene polymorphisms (GPs) in terms of both idiopathic sudden sensorineural hearing loss (ISSNHL) risk and their potential prognostic effects.

Methods: The study group consisted of 70 patients and the control group consisted of 50 patients. Venous blood samples were analyzed for relevant GPs via kompetitive allele-specific polymerase chain reaction. Age, sex, affected side, tinnitus, and vertiginous symptom status, number of days between symptom onset and hospital admission, pure tone audiometry results at admission and after treatment were included in the study. Data were compared statistically.

Results: The D allele of ACE insertion/deletion GP was significantly more frequent in patients with ISSNHL than in the control group ($p = 0.032$). II genotype was associated with a reduced risk of ISSNHL ($p = 0.036$). The amount of hearing loss was significantly higher in patients with the TT genotype ($p = 0.027$) and T allele of the IL-10 GP ($p = 0.035$) than in the patients without this allele. Severe hearing loss was a poor prognostic factor ($p = 0.008$).

Conclusions: The D allele of ACE insertion/deletion GP may be involved in the ISSNHL etiology. Due to the association of this allele with occlusive vascular pathologies, ischemia is believed to be a common pathway in the etiopathogenesis of ISSNHL.

1. Introduction

Owing to the lack of clarity on the etiopathogenesis of ISSNHL, there is no consensus on treatment options (Chandrasekhar et al., 2019). In addition to uncertainties related to etiopathogenesis and treatment, prognostic factors associated with ISSNHL remain unclear (Cho and Choi, 2013; Edizer et al., 2015; Lionello et al., 2015; Kang et al., 2017).

The most widely studied gene polymorphism (GP) of angiotensin-converting enzyme (ACE) is the ACE insertion/deletion (ACE I/D; rs4343) GP (Turgut, 2009). This GP is associated with serum ACE level (Butler et al., 1999; Gunes et al., 2004; Huang et al., 2004; Turgut, 2009; Schüler et al., 2017). ACE I/D GP has also been associated with many diseases, especially cardiovascular diseases, and hypertension (Butler et al., 1999; Gunes et al., 2004; Huang et al., 2004; Turgut, 2009).

Adducin is a cytoskeleton protein with three subtypes, alpha, beta, and gamma. These subtypes are involved in cell signal transduction and ion transport. Alpha-adducin exerts its main effect through Na^+-K^+-ATPase activity (Zhang et al., 2019; Yermolenko et al., 2021). Alpha-adducin is encoded by a gene called ADD1. Many recent studies have investigated the relationship between alpha-adducin GPs and hypertension (Jin et al., 2019; Yermolenko et al., 2021). The most popular

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List of abbreviations

ISSNHL	Idiopathic sudden sensorineural hearing loss
ACE	Angiotensin-converting enzyme
GP	Gene polymorphism
IL-10	Interleukin-10
SNP	Single nucleotide polymorphism
AHL	Amount of hearing loss
G	Guanine
A	Adenine
T	Thymine
EDTA	Ethylenediamine tetraacetic acid
PCR	Polymerase chain reaction
KASP	Kompetitive allele specific PCR
OR	Odds ratio
HSV	Herpes simplex virus

GP of ADD1 is G460W (rs4961), which results in the exchange of glycine for tryptophan. This GP has been associated with Meniere's disease, and tinnitus (Teggi et al., 2008; Yüce et al., 2016).

Numerous GPs are known to affect interleukin-10 (IL-10) gene expression, and the effect of rs1800872 single nucleotide polymorphism (SNP) has been reported by many studies (Torres-Poveda et al., 2012; Sun et al., 2013; Palivonaite et al., 2022). Furthermore, this GP has been associated with several viral infections including enterovirus, hepatitis B virus, herpes zoster virus, and human immunodeficiency virus (Yu et al., 2017; Onishchenko et al., 2018; Fu et al., 2020; Rybicka et al., 2020).

These uncertainties in the etiopathogenesis, treatment strategies, and prognosis of ISSNHL have become the focus of many current studies. In recent years, GP studies in patients with ISSNHL have gained traction. GPs may not only provide insight into etiopathogenesis but also be helpful in determining individualized treatment strategies and predicting treatment response. To this end, the purpose of the present study was to examine ACE I/D, ADD1, and IL-10 GPs in patients with ISSNHL in terms of both ISSNHL risk and their prognostic effects. The association between ACE I/D GP and vascular pathologies, ADD1 GP, and otologic pathologies, IL-10 GP, and viral infections and the possible role of these mechanisms in the etiopathogenesis of ISSNHL formed the basis of our hypothesis that related GPs may be risk factors for ISSNHL and affect its treatment response.

2. Methods

This case-control study was performed in the Department of Otorhinolaryngology and Medical Genetics laboratory of Süleyman Demirel University. Approval was obtained from the Süleyman Demirel University Clinical Research Ethics Committee (dated November 17, 2020 and numbered 370). Patients were included in the study after obtaining their signed informed consent. This study was performed in accordance with the international ethical standards of the Declaration of Helsinki.

2.1. Patient groups

The study group consisted of patients were diagnosed with ISSNHL and subsequently received treatment in the Otorhinolaryngology clinic. The control group consisted of patients who received surgical intervention for septoplasty in the Otorhinolaryngology clinic. The control group was selected from septoplasty patients because these patients had normal ear examinations and routine blood tests. The inclusion and exclusion criteria are presented in Table 1.

2.2. Data collection and audiological evaluation

In the study group pure tone audiometry tests performed during the treatment and follow-up period, vertiginous symptoms (vertigo and/or dizziness) and tinnitus at the time of admission and age and sex information for both groups were evaluated. Pure tone averages were calculated at thresholds of 500, 1000, 2000, and 4000 Hz. Because the pure tone audiometry values of the study group before hearing loss remained unknown, the diagnosis of ISSNHL was established based on the healthy ear. The difference between the pure tone average of the healthy ear and the ear with hearing loss was evaluated as the amount of hearing loss (AHL). For the speech discrimination score, the patients were told 25 monosyllabic words, 40 dB HL above the speech reception

Table 1
Inclusion and exclusion criteria.

	Inclusion Criteria	Exclusion Criteria
Study Group	- Sensorineural hearing loss of ≥30 dB HL at three consecutive frequencies occurring within 3 days - Normal ear examination - Unilateral hearing loss - Admission to our clinic and initiation of systemic corticosteroid treatment within 14 days of the onset of symptoms - Follow-up pure tone audiometry at least 1 week after treatment	- A chronic disease requiring continuous medication use - Central neurological findings accompanying hearing loss - History of head trauma, acoustic trauma, and/or barotrauma before the onset of hearing loss - Known ear pathology - Previous ear surgery - Pathology in temporal bone contrast-enhanced magnetic resonance imaging - A history of ISSNHL - Known genetic inherited disease - A known autoimmune disease - History of malignancy - History of cerebrovascular events - History of ototoxic drug use - An active infectious disease - A systemic inflammatory disease
Control Group	- Normal ear examination - Blood sampling for routine blood tests before septoplasty - No history of hearing loss	- A chronic disease requiring continuous medication use - Known ear pathology - Previous ear surgery - Known genetic inherited disease - Known autoimmune disease - History of malignancy - History of cerebrovascular events - Active infectious disease - Systemic inflammatory disease

dB HL: Decibel Hearing Level.

threshold, and were expected to repeat them. The percentage of correct answers was considered as the speech discrimination score.

2.3. Evaluation of treatment response

In our clinic, ISSNHL patients admitted within 14 days from the onset of symptoms are treated with methylprednisolone at a dose of 1 mg/kg/day. The dose of methylprednisolone is reduced by 0.2 mg/kg/day every 3 days and treatment is completed. Response to treatment is evaluated with pure tone audiometry after treatment. Siegel Criteria were used to evaluate treatment response (Siegel, 1975). In our clinic, those who respond poorly to systemic steroid therapy and those with no response are referred to hyperbaric oxygen therapy. In the present study, patients with complete, partial, and poor response to treatment were evaluated as responders and those with no treatment response were evaluated as non-responders, and prognostic analyses were performed using the outcomes of these two groups.

2.4. Determination of gene polymorphisms

The gene encoding ACE is located on chromosome 17 at q23 and the I/D GP occurs in intron 16 (Rigat et al., 1990; Turgut, 2009; Schüler et al., 2017). The rs4343 variant of the ACE gene successfully represents I/D alteration (McKenzie et al., 2001; Schüler et al., 2017). A guanine (G) – adenine (A) exchange occurs at position 2350. Accordingly, A2350 corresponds to the I allele and 2350G corresponds to the D allele (Schüler et al., 2017). The gene encoding alpha-adducin is located at p16.2 on chromosome 4 (Matsuoka et al., 2000). In the Gly460Trp (rs4961) GP, G at position 1378 is replaced by thymine (T) and glycine at position 460 in the polypeptide chain is replaced by tryptophan (Jin et al., 2019). The IL-10 gene is located on chromosome 1 at q31-q32 (Kim et al., 1992; Eskdale et al., 1997). In the rs1800872 SNP of the IL-10 gene, a T is replaced by G (Sun et al., 2013).

In both groups, samples were collected for GP analysis after blood sampling for routine blood tests as part of the treatment and follow-up protocols of our clinic for the relevant diagnoses. Peripheral venous blood was collected in ethylenediamine tetraacetic acid (EDTA) tubes. For SNP analysis, DNA was isolated from blood samples collected in EDTA tubes using a commercial kit (PureLink Genomic DNA Mini Kit, Thermo Fisher Scientific Inc., Massachusetts, United States of America) according to the manufacturer's instructions and stored at −20 °C until further analysis. ADD1 G460W, ACE I/D, and IL10 GP variants were determined using real-time polymerase chain reaction (PCR). To this end, the kompetitive allele specific PCR (KASP) method was used. The KASP reaction was performed on an ABI StepOnePlus Real-Time PCR device (ABI StepOnePlus, Thermo Fisher Scientific Inc., Massachusetts, United States of America).

2.5. Statistical analysis

Data were transferred to IBM SPSS.23 (IBM Inc., New York, United States of America) and evaluated via statistical analysis. The relationships between categorical variables were analyzed via Chi-square test and presented with Odds ratio (OR) values. The genotype distribution of the study and control groups were analyzed through Chi-square test with values predicted through Hardy–Weinberg equilibrium. Kolmogorov–Smirnov normality test was used to check whether continuous variables were normally distributed, and homogeneity of variance was checked by Levene's test. In the causality analyses of continuous variables, non-normally distributed variables were compared between the groups using the Mann–Whitney-U test, and normally distributed variables were evaluated with independent samples *t*-test. Kruskal–Wallis-H test was used to compare non-normally distributed variables between more than two groups. Logistic regression was also performed to investigate the factors affecting treatment response. In all analyses, $p < 0.05$ indicated statistical significance.

Table 2
Age and gender distribution.

		Study Group	Control Group	
		n (%)		*p*
Gender	Female	29 (41.4)	20 (40.0)	*0.875**
	Male	41 (58.6)	30 (60.0)	
Mean ± SD (Min. – Max.)				
Age		50.44 ± 13.30 (19–76)	48.76 ± 16.01 (19–81)	*0.532*†

Table 3
The clinical and audiometric characteristics of the study group.

		Study Group (n = 70)	
		n (%)	
Side	**Left**	39 (55.7)	
	Right	31 (44.3)	
Tinnitus	**No**	7 (10.0)	
	Yes	63 (90.0)	
Vertiginous Symptoms	**No**	54 (77.1)	
	Yes	16 (22.9)	
		Min. – Max.	Mean ± SD
Day of Admission		1–14	4.04 ± 3.52
PTA of the Ear without Hearing Loss (dB HL)		0–43	15.21 ± 10.55
PTA of the Ear with Hearing Loss (dB HL)		26–110	56.05 ± 22.89
Speech Discrimination Score of the Ear without Hearing Loss (%)		48–100	91.37 ± 8.74
Speech Discrimination Score of the Ear with Hearing Loss (%)		0–92	60.46 ± 30.02
The Amount of Hearing Loss (dB HL)		26–96	40.84 ± 19.61

PTA: Pure tone average; dB HL: Decibel Hearing Level.

3. Results

Age and gender distribution of the study group and control group are presented in Table 2. The clinical and audiometric characteristics of the study group are presented in Table 3. Comparison of the study and control groups in terms of genotype and allele distribution of the three GPs are presented in Table 4. A significant intergroup difference was noted in terms of allele distribution of ACE I/D GP ($p = 0.032$). In the study and control groups, 52.1% and 66% of the alleles were A alleles and 47.9% and 34% were G alleles, respectively.

The recessive and dominant model comparison results of the groups are presented in Table 5. In ACE I/D GP, a significant intergroup difference was noted in the AA vs. AG-GG based recessive model analysis ($p = 0.036$). In the study and control groups, 25.7% and 44% of the patients in the study group had the AA genotype, respectively.

In all three GPs, no significant differences were noted in terms of genotype and allele distribution and treatment response (Table 6). After systemic corticosteroid treatment, hyperbaric oxygen therapy was recommended to 36 ISSNHL patients. Of these patients, 25 received hyperbaric oxygen therapy; however, the Siegel's classification of patients did not change.

No significant difference was noted between the genotype and allele distributions of all three GPs and whether hearing loss was accompanied by tinnitus and vertiginous symptoms in the study group patients (Table 7).

Analysis of the relationship between the AHL and GPs in the study group revealed no significant difference between genotypes and alleles in ADD1 and ACE I/D GPs and the AHL. The associated p values for the

Table 4
Genotype and allele frequencies.

			Study Group (n = 70)	Control Group (n = 50)		
			n (%)		p^a	OR
ADD1 (rs4961)	**Genotype**	GG	49 (70.0)	40 (80.0)	*0.499*	
		GT	19 (27.1)	9 (18.0)		
		TT	2 (2.9)	1 (2.0)		
	Allele	G	117 (83.6)	89 (89.0)	*0.234*	
		T	23 (16.4)	11 (11.0)		
ACE I/D (rs4343)	**Genotype**	AA	18 (25.7)	22 (44.0)	*0.087*	
		AG	37 (52.9)	22 (44.0)		
		GG	15 (21.4)	6 (12.0)		
	Allele	A	73 (52.1)	66 (66.0)	***0.032***	0.561[b]
		G	67 (47.9)	34 (34.0)		
IL-10 (rs1800872)	**Genotype**	GG	29 (41.4)	22 (44.0)	*0.936*	
		GT	39 (55.7)	27 (54.0)		
		TT	2 (2.9)	1 (2.0)		
	Allele	G	97 (69.3)	71 (71.0)	*0.775*	
		T	43 (30.7)	29 (29.0)		

[a] Chi-square test.
[b] 95% confidence interval: 0.33–0.95.

Table 5
Comparison of gene polymorphisms between groups in terms of dominant and recessive models[a].

			Study Group (n = 70)	Control Group (n = 50)		
			n (%)		p^b	OR
ADD1 (rs4961)	*GG vs TT and GT*	GG	49 (70.0)	40 (80.0)	*0.217*	
		GT, TT	21 (30.0)	10 (20.0)		
	TT vs GG and GT	TT	2 (2.9)	1 (2.0)	*0.767*	
		GT, GG	68 (97.1)	49 (98.0)		
ACE I/D (rs4343)	*GG vs AA and AG*	GG	15 (21.4)	6 (12.0)	*0.227*	
		AG, AA	55 (78.6)	44 (88.0)		
	AA vs GG and AG	AA	18 (25.7)	22 (44.0)	***0.036***	0.441[c]
		AG, GG	52 (74.3)	28 (56.0)		
IL-10 (rs1800872)	*TT vs GG and GT*	TT	2 (2.9)	1 (2.0)	*0.767*	
		GT, GG	68 (97.1)	49 (98.0)		
	GG vs TT and GT	GG	29 (41.4)	22 (44.0)	*0.779*	
		GT, TT	41 (58.6)	28 (56.0)		

[a] The dominant model is the comparison of homozygous normal genotype with homozygous and heterozygous mutant genotypes; recessive model is the comparison of homozygous mutant genotype with homozygous and heterozygous normal genotypes.
[b] Chi-square Test.
[c] 95% Confidence Interval: 0.20–0.95.

genotype and allele in the case of ADD1 GP were 0.635 and 0.893 and ACE I/D GP were 0.524 and 0.350, respectively. In IL-10 GP, a significant association was observed in genotype and allele comparisons in this regard (Table 8). The difference in genotype comparisons was attributable to differences in the mean AHL between GG and TT genotypes (p = 0.019).

The relationship between the clinical characteristics of the study group and the treatment response is presented in Table 9. The AHL and the presence of vertiginous symptoms, which appeared to affect treatment response in previous analyses, were evaluated together with the genotype distributions of ADD1, ACE I/D, and IL-10 GPs. Logistic regression analysis was performed to examine the effect of these factors. Only the AHL had a significant effect on treatment response (p = 0.008) (Table 10).

4. Discussion

Although vascular and infectious pathologies are the most commonly accused causes in the etiology of ISSNHL, immune system disorders, and intracochlear membrane rupture are considered suspected causes, the role of any factor has not been proven with concrete evidence (Hashisaki, 2021; Chandrasekhar et al., 2019; Dere et al., 2019; Satar, 2021; Genç Elden et al., 2022).

Ischemia in the cochlea owing to acute ischemic vascular pathologies is thought to result in ISSNHL (Hamidi et al., 2019; Khosravipour and Rajati, 2021; Tsuzuki et al., 2021). Studies have reported that 1 min of anoxia is enough for to initiate deterioration of cochlear functions and this damage becomes irreversible after 1 h (Yavuz et al., 2005; Khosravipour and Rajati, 2021). Atherosclerosis is the underlying cause of numerous ischemic vascular pathologies. Influence of atherosclerosis on the end arteries supplying the cochlea and the subsequent thrombus formation may lead to ISSNHL (Genç Elden et al., 2022). Fisch et al.

Table 6
Evaluation of treatment response of study group patients in terms of gene polymorphisms.

			Study Group (n = 70)		
			n (%)		
			Treatment Response		
			Responders (n = 37)	Non-Responders (n = 33)	p^a
ADD1 (rs4961)	**Genotype**	GG	23 (62.2)	26 (78.8)	*0.197*
		GT	12 (32.4)	7 (21.2)	
		TT	2 (5.4)	0 (0.0)	
	Allele	G	58 (78.4)	59 (89.4)	*0.079*
		T	16 (21.6)	7 (10.6)	
ACE I/D (rs4343)	**Genotype**	AA	7 (18.9)	11 (33.3)	*0.357*
		AG	22 (59.5)	15 (45.5)	
		GG	8 (21.6)	7 (21.2)	
	Allele	A	36 (48.6)	37 (56.1)	*0.381*
		G	38 (51.4)	29 (43.9)	
IL-10 (rs1800872)	**Genotype**	GG	15 (40.5)	14 (42.4)	*0.375*
		GT	22 (59.5)	17 (51.5)	
		TT	0 (0.0)	2 (6.1)	
	Allele	G	52 (70.3)	45 (68.2)	*0.789*
		T	22 (29.7)	21 (29.7)	

[a] Chi-square Test.

Table 7
Evaluation of tinnitus and vertiginous symptom status of the study group in terms of gene polymorphisms.

			Study Group					
			Tinnitus			Vertiginous Symptoms		
			No (n = 7)	Yes (n = 63)		No (n = 54)	Yes (n = 16)	
			n (%)		p^a	n (%)		p^a
ADD1 (rs4961)	**Genotype**	**GG**	5 (71.4)	44 (69.8)	*0.263*	36 (66.7)	13 (81.3)	*0.719*
		GT	1 (14.3)	18 (28.6)		16 (29.6)	3 (18.8)	
		TT	1 (14.3)	1 (1.6)		2 (3.7)	0 (0.0)	
	Allele	**G**	11 (78.6)	106 (84.1)	*0.702*	88 (81.5)	29 (90.6)	*0.220*
		T	3 (21.4)	20 (15.9)		20 (18.5)	3 (9.4)	
ACE I/D (rs4343)	**Genotype**	**AA**	1 (14.3)	17 (27.0)	*0.874*	15 (27.8)	3 (18.8)	*0.749*
		AG	4 (57.1)	33 (52.4)		27 (50.0)	10 (62.5)	
		GG	2 (28.6)	13 (20.6)		12 (22.2)	3 (18.8)	
	Allele	**A**	6 (42.9)	67 (53.2)	*0.463*	57 (52.8)	16 (50.0)	*0.782*
		G	8 (57.1)	59 (46.8)		51 (47.2)	16 (50.0)	
IL-10 (rs1800872)	**Genotype**	**GG**	3 (42.9)	26 (41.3)	*0.892*	21 (38.9)	8 (50.0)	*0.277*
		GT	4 (57.1)	35 (55.6)		32 (59.3)	7 (43.8)	
		TT	0 (0.0)	2 (3.2)		1 (1.9)	1 (6.3)	
	Allele	**G**	10 (71.4)	87 (69.0)	*0.855*	74 (68.5)	23 (71.9)	*0.718*
		T	4 (28.6)	39 (31.0)		34 (31.5)	9 (28.1)	

[a] Chi-square Test.

Table 8
Evaluation of study group patients in terms of IL-10 gene polymorphism according to amount of hearing loss.

			Study Group	
			Amount of Hearing Loss	
IL-10 (rs1800872)	**Genotype**	GG	35.24 ± 17.90 (26–96)	***0.027***
		GT	43.28 ± 19.27 (26–89)	
		TT	74.00 ± 12.73 (26–83)	
	Allele	G	38.47 ± 18.87 (26–96)	***0.035***
		T	46.13 ± 21.07 (26–89)	

(1972) reported that irregularities in the blood pressure of the stria vascularis occurred as a result of cochlear atherosclerosis. Endothelial dysfunction is the main mechanism at the onset of atherosclerosis (Hemmat et al., 2018). Balletshofer et al. (2005) found evidence of endothelial dysfunction in five of six ISSNHL patients. In their study, Genç Elden et al. (2022) reported that an atherosclerosis-related peptide named salusin-beta was found at a significantly higher level in patients with ISSNHL. Cortese et al. (2020), reported that N-terminal pro-B-type natriuretic peptide levels released after ischemic damage were high in patients with ISSNHL, and the authors argued that ischemic pathologies may participate in the etiopathogenesis of ISSNHL. Lin et al. (2013) evaluated 44830 patients with ISSNHL in Taiwan and reported that patients with ISSNHL had an increased risk of acute myocardial infarction compared with the control group. Similarly, patients with ISSNHL were reported to have an increased risk of stroke (Lin et al., 2008;

Table 9
The relationship between clinical characteristics of study group patients and treatment response.

Study Group (n = 70)				
		Treatment Response		
		Responders (n = 37)	Non-Responders (n = 33)	
		n (%)		p*
Tinnitus	No	3 (8.1)	4 (12.1)	*0.699*
	Yes	34 (91.9)	29 (87.9)	
Vertiginous Symptoms	No	33 (89.2)	21 (63.6)	***0.021***
	Yes	4 (10.8)	12 (36.4)	
Gender	Female	16 (43.2)	13 (39.4)	*0.744*
	Male	21 (56.8)	20 (60.6)	
		Mean ± SD		p†
Age		49.41 ± 12.96	51.61 ± 13.77	*0.493*
Day of Admission		4.08 ± 3.81	4.00 ± 3.23	*0.581*
The Amount of Hearing Loss (dB HL)		33.67 ± 12.27	48.87 ± 23.11	***0.001***

dB HL: Decibel Hearing Level.

Table 10
Results of logistic regression analysis to determine the effect of gene polymorphisms, amount of hearing loss, and vertiginous symptom status on treatment response.

	B	SE	Wald	p[a]	Exp(B)
Amount of Hearing Loss	0.053	0.02	7.08	***0.008***	1.05[b]
Vertiginous Symptom (+)	−1.045	0.76	1.92	*0.166*	0.35
ADD1- GG			0.48	*0.785*	
ADD1- GT	21.452	28254.24	0.00	*0.999*	2071874771
ADD1- TT	20.988	28254.24	0.00	*0.999*	1303229326
ACE I/D- AA			3.39	*0.184*	
ACE I/D- AG	0.640	0.812	0.62	*0.430*	1.90
ACE I/D- GG	−0.639	0.725	0.78	*0.378*	0.53
IL-10- GG			0.80	*0.671*	
IL-10- GT	−18.743	28380.87	0.00	*0.999*	0.00
IL-10- TT	−19.295	28380.87	0.00	*0.999*	0.00
Constant	−3.406	40047.20	0.00	*0.999*	0.03

SE: Standard Error; B: Variable Coefficient.
[a] Logistic Regression.
[b] 95% Confidence Interval: 1.014–1.096.

Khosravipour and Rajati, 2021). These associations suggest that predisposition to occlusive vascular pathologies may play a role in ISSNHL development.

Many GP studies have been performed to reveal the relationship between occlusive vascular pathologies and ISSNHL. Thrombosis-related gene studies such as Factor V Leiden and methylenetetrahydrofolate reductase have gained popularity in recent years and significant associations between these GPs and ISSNHL have been identified in many studies (Capaccio et al., 2005; Görür et al., 2005; Hamidi et al., 2019). In the present study, we examined ACE I/D, ADD1, and IL-10 GPs in patients with ISSNHL and found a significant difference only in terms of ACE I/D GP. Accordingly, the presence of the D allele was associated with an increased risk of developing ISSNHL and the II genotype was protective against ISSNHL. Many studies have shown that changes in pathways involving ACE predispose people to vascular pathologies such as thrombosis and atherosclerosis (Kon and Jabs, 2004). The balance between ACE and ACE2 has an important role in thrombo-inflammatory processes. ACE is responsible for the conversion of angiotensin I to angiotensin II. ACE2 converts angiotensin II into angiotensin 1-7. Disruption of the balance between these two enzymes may lead to endothelial damage and thrombosis (Kon and Jabs, 2004; Calabrese et al., 2021). A link between ACE I/D GP and serum ACE levels is known to exist. In many studies, the highest ACE levels were found in people with the DD genotype and the lowest ACE levels were found in people with the II genotype. Therefore, ACE level is increased in those with the D allele (Butler et al., 1999; Gunes et al., 2004; Huang et al., 2004). Individuals with the D allele and DD genotype of ACE I/D GP are reported to have an increased risk of occlusive vascular pathologies. Calabrese et al. (2021) examined the relationship between the risk of pulmonary embolism and ACE I/D GP in COVID-19 patients and reported that DD genotype was significantly more frequent in patients with pulmonary embolism. Güngör et al. (2011) examined patients with early arteriovenous fistula thrombosis and found that patients with DD genotype were significantly higher than the control group. Individuals with DD genotype had a 4.25-fold higher thrombosis risk than those with II and ID genotypes (Güngör et al., 2011). In a meta-analysis of 50 studies, Zhang et al. (2012) showed that the presence of the D allele resulted in an increase in the risk for ischemic stroke. High ACE levels associated with the D allele will result in increased angiotensin II levels. Angiotensin II triggers the formation of reactive oxygen products in vascular cells and causes atherosclerosis (Weiss et al., 2001). These mechanisms support the association between the D allele of the ACE I/D GP and occlusive vascular pathologies.

Another factor that may have a role in ISSNHL etiology is infectious pathologies. Viral infections have been suggested as the most probable cause of ISSNHL, especially in young patients (Gross et al., 2007). Although a history of viral infection prior to hearing loss in a significant proportion of patients points to viral etiology in ISSNHL, this still does not sufficiently explain some of the cases (Gross et al., 2007). Viruses such as mumps, measles, rubella, herpes simplex virus (HSV), cytomegalovirus, enteroviruses and varicella virus associated with ISSNHL (Mentel et al., 2004; Scalia et al., 2013; Lin et al., 2013; Cohen et al., 2014; Chen et al., 2017). Viral infections are thought to cause ISSNHL by three possible mechanisms. These are neuritis, cochleitis, and cross antibody development that will also target inner ear antigens as a result of viral infection (Wilson, 1986). In addition to these possible mechanisms, we believe that vascular pathologies triggered by viral infections may play a role in the etiopathogenesis of ISSNHL. This is because viral infections can predispose patients to occlusive vascular disorders. Occlusive vascular disorders are considered among the main mechanisms associated with ISSNHL development, and this is applicable for infective etiologies. Many studies have shown the relationship between viral infections and atherosclerosis (Libby et al., 1997; Epstein et al., 1999). Especially HSV-1 and cytomegalovirus have been associated with atherosclerosis (Epstein et al., 1999; Kotronias and Kapranos, 2005). In experiments using mice with apolipoprotein E deficiency, herpes viruses and cytomegalovirus have been shown to accelerate atherosclerosis formation (Alber et al., 2000; Hsich et al., 2001). Evidence of herpesviruses in aortic tissues of patients undergoing cardiovascular surgery has been demonstrated via electron microscopy (Gyorkey et al., 1984). In the study of Kotronias and Kapranos (2005), HSV-1, Ebstein-Barr virus, and cytomegalovirus were detected in atherosclerotic tissue. In conclusion, the fact that the D allele, which was detected more frequently in ISSNHL patients in our study, has been reported to be associated with many vascular pathologies in recent studies, the presence of findings indicating vascular pathologies in the etiopathogenesis of ISSNHL, and the relationships between viral infections and vascular pathologies suggest that ischemia may be the common pathway in the etiopathogenesis of ISSNHL.

Alpha-adducin is involved in sodium homeostasis. The Gly460Trp GP is reportedly associated with high blood pressure, cardiovascular diseases, and salt sensitivity (van Rijn et al., 2006; Cha et al., 2007; Liao et al., 2015; Jin et al., 2019). Na^+-K^+-ATPase plays an important role in the ion balance of the inner ear and provides high K^+ concentration in the endolymph (Crouch et al., 1997; Weber et al., 2001; Stephenson et al., 2021). Disruption in this ion transport prevents the formation of endocochlear potentials (Marcus et al., 2002). The increase in

Na^+-K^+-ATPase activity results in an increase in endolymph osmolarity and volume. Alpha-adducin is known to be involved in Na^+-K^+-ATPase activity (Ferrandi et al., 1999). Teggi et al. (2008) evaluated Meniere's patients in terms of Gly460Trp GP of ADD1 and found that Trp allele frequency increased in Meniere's patients. Yüce et al. (2016) examined the Gly460Trp GP of ADD1 in tinnitus and found that the Trp allele was more frequent in tinnitus patients. The Trp allele reportedly increases Na^+-K^+-ATPase activity (Ferrandi et al., 1999). The disruption in ion balance as a result of increased Na^+-K^+-ATPase activity with this GP is believed to cause hydrops and disruption of endocochlear potentials, and this GP is considered to be a predisposing factor in Meniere's disease (Teggi et al., 2008). In an experimental study by Nishiyama et al. (1994), endolymphatic hydrops was associated with impaired Na^+-K^+-ATPase activity in the stria vascularis of the guinea pigs. Therefore, changes in Na^+-K^+-ATPase activity have the potential to result in hearing loss. However, we could not find a relationship in terms of ADD1.

IL-10 is a cytokine with anti-inflammatory effects produced by T-helper 2 and B lymphocytes and macrophages (Wang et al., 2011; Li et al., 2016; Yu et al., 2017). Polymorphisms of the gene encoding IL-10 have been reported to affect gene expression. Wang et al. (2011) found that IL-10 level and the T allele frequency of the rs1800872 GP of IL-10 were correlated in patients in the control group. In the study conducted by Palivonaite et al., the mean serum IL-10 level in the control group was highest in the TT genotype and lowest in the GG genotype (Palivonaite et al., 2022). In studies examining the relationship between rs1800872 GP of IL-10 and viral infections, associations with many viruses, especially human immunodeficiency virus and hepatitis-B virus, was identified (Yu et al., 2017; Onishchenko et al., 2018; Fu et al., 2020; Rybicka et al., 2020). Yu et al. (2017) reported that the T allele increased the risk of enterovirus-induced viral encephalitis. Onishckenko et al. (2018) examined patients with herpes zoster in terms of IL-10 GP and found that the TT genotype was significantly higher frequency of occurrence in patients with herpes zoster and the presence of TT genotype was associated with more severe disease. A relationship between IL-10 level and varicella zoster relapse and severity has been reported (Shi and Cui, 2017). We analyzed this GP of IL-10, which has been shown to be associated with viral infections, in patients with ISSNHL. A study in the literature has examined the relationship between IL-10 GP and ISSNHL. Similar to the results obtained in the present study, this study found no association between IL-10 GP and ISSNHL (Hiramatsu et al., 2012). In contrast to the other study, we also examined treatment response, but found no difference in this respect. The only factor associated with IL-10 GP in the present study was the AHL. The TT genotype and T allele were associated with a higher AHL. Previous studies have shown that the T allele and TT genotype are associated with higher IL-10 levels, which in turn is associated with susceptibility to viral infections and a more severe clinical picture. This relationship between more severe hearing loss in the present study may be due to similar mechanisms.

Patients who responded poorly and those did not respond to steroid treatment according to Siegel Criteria were referred to hyperbaric oxygen therapy after steroid treatment. The Siegel's classification did not change in any of the patients receiving hyperbaric oxygen therapy. Consistent with the present study, recent studies also observed that hyperbaric oxygen treatment did not provide a significant effect in treatment (Dova et al., 2022). This may be due to the fact that all of the patients we referred to hyperbaric oxygen therapy consisted of patients who did not respond or responded poorly to steroid treatment.

Recent studies suggest that the prognosis may depend on many factors such as the age of the patient, presence of vertigo, degree of hearing loss, presence of tinnitus, audiometric configuration, and the time between the onset of hearing loss and treatment, but there is ongoing debate on this issue (Narozny et al., 2006; Cho and Choi, 2013; Wen et al., 2014; Edizer et al., 2015). In contrast to the present study, advanced age was associated with poor prognosis in the studies of Kang et al. (2017), Lionello et al. (2015), and Edizer et al. (2015). However, many studies in the literature reported no relationship between age and prognosis, support our results (Mamak et al., 2005; Ceylan et al., 2007). The presence of vertigo has been shown as a poor prognostic factor in many studies (Mamak et al., 2005; Ceylan et al., 2007; Wang et al., 2009; Korres et al., 2011). This is thought to be due to the presence of vertigo indicating more diffuse labyrinth damage (Korres et al., 2011). In more recent studies by Cho et al. (2013) and Edizer et al. (2015) no relationship was found between vertigo and prognosis. In the present study, the presence of vertiginous symptoms, which was associated with poor prognosis in univariate analyses, was found to be ineffective in multivariate analyses, and the AHL was found to be the only poor prognostic factor. In the studies of Cho et al. (2013), Chung et al. (2015), and Kang et al. (2017), excessive hearing loss has been associated with poor prognosis. A longer duration between the onset of symptoms and initiation of treatment has also been found to be a poor prognostic factor in many studies including Cho et al. (2013), Chung et al. (2015), Edizer et al. (2015), and Kang et al. (2017). Similar to Lionello et al. (2015), no significant association was found with this variable in the present study. In line with the recommendations of current guidelines, only patients admitted within the first 14 days were included in the present study. Therefore, our study consisted of patients who were considered early admissions. The difference between the literature and our study may be related to this. There are also conflicting results on the prognostic value of tinnitus (Hikita-Watanabe et al., 2010). In the studies conducted by Lionello et al. (2015) and Chung et al. (2015) comparing adult and pediatric patients in terms of prognosis, the presence of tinnitus was found to be a good prognostic criterion for both groups. In the present study, tinnitus had no effect on prognosis. Similarly, the effect of comorbid diseases on prognosis is also controversial; although there are studies suggesting that they may be associated with poor prognosis, no proofs have been found in this regard in many studies (Ceylan et al., 2007; Edizer et al., 2015; Chandrasekhar et al., 2019). In a study conducted by Kang et al. (2017), diabetes mellitus and hyperlipidemia were found to be associated with poor prognosis. In the present study, the prognostic effect of comorbid diseases such as hyperlipidemia, diabetes mellitus and hypertension could not be analyzed because patients with chronic drug use were not included. Factors such as the treatment methods, patient selection criteria, the way treatment response is evaluated, the statistical analyses performed, and the day of presentation of the patients differ in the literature. Therefore, the results in terms of prognosis may be inconsistent among different studies. However, similar to the present study, excessive hearing loss is one of the factors mostly associated with poor prognosis among the factors discussed above. In addition to these findings, we concluded that the three GPs evaluated in the present study may be ineffective in terms of prognosis.

This is the first study in the literature examining ACE I/D and ADD1 GPs in patients with ISSNHL. There is only one other study in the literature that examined IL-10 GP in patients with ISSNHL, but prognosis was not examined in this study. Therefore, our study is the first study to examine all three GPs in terms of prognosis. These are the strengths of our study. The main limitations of our study are the limited number of patients in the study and control groups and the fact that the blood levels of GP products were not analyzed. Additionally, the sample size of the subgroups in our study is small. Therefore, the relevant analyzes require confirmation by further studies.

In conclusion according to the results obtained in the present study, the D allele of ACE I/D GP indicates an increased risk of ISSNHL and the risk of ISSNHL decreased in the II genotype. This result suggests that ischemia can be common pathway in the etiopathogenesis of ISSNHL. The T allele and TT genotype of the IL-10 GP are associated with higher AHL. No association was found between all three GPs and ISSNHL prognosis. The only factor associated with prognosis was the AHL at the time of diagnosis.

Previous presentations

This study was presented as Vural Akın's specialty thesis on Otorhinolaryngology (Evaluation of Angiotensin Converting Enzyme Insertion/Deletion, Alpha Adducin (ADD1) G460W, and IL-10 Gene Polymorphisms in Idiopathic Sudden Sensorineural Hearing Loss and Determination of the Prognostic Effects of These Gene Polymorphisms - Ani İdiopatik Sensörinöral İşitme Kaybında Anjiotensin Dönüştürücü Enzim İnsersiyon/Delesyon, Alfa Addusin (ADD1) G460W ve IL-10 Gen Polimorfizmlerinin Değerlendirilmesi ve Prognostik Etkilerinin Belirlenmesi - January 11, 2023 - Süleyman Demirel University Faculty of Medicine, Isparta, Türkiye).

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Declaration of competing interest

The authors declare that they have no conflict of interest.

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