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RESEARCH ARTICLE



Genetic testing has the potential to impact hearing preservation following cochlear implantation

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ABSTRACT

Background: Recent advances in less-invasive surgery and electrode design allow for a high degree of hearing preservation (HP) after cochlear implantation (CI), although residual hearing still deteriorates in some patients. To date, the factors predictive of preserving residual hearing remain a controversial topic.

Objective: The aim of this study was to investigate the predictive factors, including the etiology of hearing loss (HL) as a patient-related factor, influencing residual HP after CI.

Methods: Forty-four patients (50 ears, 41 families) with residual acoustic hearing who underwent CI were included. Auditory thresholds before and at 6 months after initial activation were measured. Genetic testing was performed to identify the responsible genes for HL.

Results: We identified the cause of HL in 21 families (51.2%). HP was marginally correlated with age at implantation, while it was independent of pre-operative low-frequency hearing thresholds, cochlear duct length, and electrode length. We found that patients who had pathogenic variants in the *CDH23*, *MYO7A*, or *MYO15A* gene showed statistically better HP scores compared with patients with HL due to other causes ($p = .002$).

Conclusions: Identification of the etiology of HL using genetic testing is likely to facilitate the prediction of HP after implant surgery.

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Hearing preservation;
hearing loss; cochlear
implant; residual hearing

Introduction

Cochlear implantation (CI) remains a successful treatment option for patients with severe-to-profound hearing loss (HL). In the last few decades, the indication criteria for implantation have been expanded to patients with ski slope-type HL. In such individuals who have severe-to-profound high-frequency HL with only mild-to-moderate HL in the low frequencies, hearing aids cannot offer any great benefit in terms of understanding speech. To address this issue, von Ilberg and colleagues developed the concept of electric-acoustic stimulation (EAS) providing low-frequency stimulation *via* residual hearing together with electrical stimulation (ES) in the high frequencies by an inserted electrode in a single device [1,2]. The benefits of EAS in the implanted ear are well established and include improved speech recognition in noise compared with ES alone, indicating that the preservation of residual hearing in the low frequencies is important in EAS patients [1,2].

Hearing preservation (HP) was originally thought to be only necessary for EAS patients who could benefit from their residual hearing post-operatively. That being said, the benefits of HP surgical techniques are currently also

recognized for all CI patients as the concept of HP leads to the preservation of cochlear structures, which is important in expanding future treatment strategies such as gene therapy or regeneration therapy, particularly for infants.

In terms of HP surgery, a round window approach is preferable as (1) less drilling reduces acoustic trauma, (2) it ensures insertion into the Scala tympani, and (3) preserves vestibular function [3], and we first clearly demonstrated that HP can be achieved even with the electrode beneath the basilar membrane [3]. In addition to the improved surgical approach, it is necessary to optimize the electrode array design. The development of thinner and super flexible straight electrode arrays can allow for round window insertion and offer better structure and HP more comfortably [4]. Using such flexible atraumatic electrodes, we previously demonstrated that HP was achievable together with improved speech perception after EAS surgery [5].

Despite advances in less-invasive surgical techniques and electrode design, residual hearing still deteriorates in a certain number of patients after CI. Various groups have attempted to identify the factors that impact HP, with insertion depth angle, implant age, degree of residual hearing

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and cochlear duct length (CDL) being identified as potentially important factors [6–9]. While these reports are noteworthy, the factors predictive of preserving residual hearing remain a controversial topic. As patient-related factors, we hypothesized that the etiology of HL may be an important factor related to HP. In our series of studies, we performed comprehensive genetic testing, and reported that genetic etiology is a major cause of HL in CI/EAS patients [10 for review]. To evaluate the relative impact of the aforementioned variables, we approached this issue from a single institution approach with CI recipients having residual hearing in the low frequencies pre-operatively. Given the natural course of HL itself, we measured the low-frequency pure-tone average (PTA) at 6-month post-activation in comparison with the pre-operative PTA. Herein, we present our findings regarding the predictive factors impacting HP post-operatively in patients with residual hearing.

Materials and methods

Patients studied

Forty-four patients (50 ears, 41 families) who underwent implant surgery at the Department of Otorhinolaryngology, Shinshu University Hospital met the inclusion criteria for this study. The inclusion criteria were as follows: (1) age at implantation above 6 years old for the reliable assessment of pure-tone audiometric test; (2) FLEXsoft (31.5 mm), FLEX28 (28 mm) or FLEX24 (24 mm) electrode array implantation developed by MED-EL (Innsbruck, Austria); and (3) measurable residual hearing in the low frequency with a threshold less than 80 dBHL for the average of values at 125, 250, and 500 Hz before surgery. Table 1 provides a summary of patient demographic information. The median age at implantation was 36.4 years (range 6–70 years). This study was approved by the Ethics Committee of Shinshu University School of Medicine.

Table 1. Characteristics of patients evaluated in this study (N = 44).

Characteristic	Number
Sex	
Male	20
Female	24
Inheritance	
Autosomal recessive	7
Autosomal dominant or mitochondrial	12
Sporadic	20
Ambiguous	2
Total	41 ^a
Implanted ear	
Right	27
Left	23
Total	50 ^b
Inserted cochlear implant device	
FLEX ^{soft}	6
FLEX ²⁸	17
FLEX ²⁴	27
Total	50 ^b
	Mean ± SD
Age at cochlear implantation in years	36.4 ± 18.1
Preoperative LFA ^c (dB)	48.7 ± 18.3

^aTwo affected patients in three families each.

^bSix patients received bilateral EAS.

^cLFA: average low-frequency hearing thresholds at 125, 250, and 500 Hz.

CI surgical procedure

Patients included 20 males and 24 females, with 6 patients receiving implantation with a FLEXsoft electrode, 17 patients with a FLEX28 electrode, and 27 patients with a FLEX24 electrode. The CI surgery was performed as described previously [3]. Briefly, the round window approach was applied to insert the electrode array. The bony overhang of the round window was removed with a low-speed drill and the round window membrane was widely exposed. The electrode was fully inserted carefully and slowly *via* the round window membrane [3]. All participants underwent surgery by the same experienced surgeon (S.U.) and received steroids intra- and post-operatively.

HP assessment

To define the extent of hearing deterioration following CI, we measured auditory thresholds before and at 6 months after initial activation. Subsequently, to assess HP rate, we used the classification provided by Skarzynski et al. and the HEARRING group [11] with the HP scores (%) categorized as follows: complete HP, defined as greater than 75%; partial HP, 25–75%; minimal HP, 1–25%; and complete loss of hearing; 0%.

Genetic analysis

Genetic testing was performed for 41 families as described previously [12]. In brief, Amplicon libraries were constructed using an Ion AmpliSeqTM Custom Panel (Thermo Fisher Scientific, Rockford, IL) in accordance with the manufacturer's instructions for 68 genes reported to cause non-syndromic hereditary HL [12]. Subsequently, emulsion PCR and sequencing were performed with an Ion 200 sequencing kit and Ion PGM sequencer or Ion HiQ Chef kit and Ion Proton sequencer. The sequence data were mapped on the human genome sequence (build GRCh37/hg19), and the DNA variant regions were piled up with Torrent Variant Caller plug-in software. The effects of the detected variants were subsequently analyzed using ANNOVAR software. The missense, nonsense, insertion/deletion, and splicing variants were determined, and the variants were next selected as less than 1% of (1) the 1000 genome database, (2) the 6500 exome variants, (3) the Human Genetic Variation Database (dataset for 1208 Japanese exome variants), and (4) the 333 in-house Japanese normal hearing controls. For missense variants, functional prediction software, including Sorting Intolerant from Tolerant (SIFT), Polymorphism Phenotyping (PolyPhen2), Likelihood Ratio Test (LRT), Mutation Taster, Mutation Assessor, were used to assess the pathogenicity. Direct sequencing was utilized to confirm the candidate variants identified, and segregation analysis was performed for each proband and their family members. The pathogenicity of the identified variants was evaluated based on the ACMG (American College of Medical Genetics) standards and guidelines. This system classified variants into five categories; pathogenic, likely pathogenic, uncertain

significance, likely benign, and benign. Additionally, we referred to Inter Var for evaluation of the variants. A combined annotation-dependent depletion (CADD) was also used to prioritize potential causal variants.

Cochlear duct length measurement

CDL was measured by 'OTOPLAN' software for otological surgical planning developed by CAScination (Bern, Switzerland) in cooperation with MED-EL. The DICOM files from patient CT images were uploaded. We next highlighted a number of cochlear parameters, including the round window, the center of the cochlear apex and so on, according to the manufacturer's instructions. As a result, the software calculated the CDL based on cochlear diameter, width, and height for each patient.

Assessment of correlation between each factor and HP

To identify factors that impact HP, all subjects were evaluated for: (1) age at implantation; (2) pre-operative low-frequency hearing thresholds at 125, 250, and 500 Hz; (3) etiology of HL using genetic testing; and (4) CDL.

Statistical analysis

Sample sizes are noted in the figure legends. Hearing threshold data are presented as mean $\pm$ standard deviation (SD). Statistical analysis was performed using the Prism 8 software package (GraphPad, San Diego, CA). Two groups were compared using the Mann-Whitney test. For comparisons of more than two groups, one-way ANOVA was performed, followed by *post-hoc* test with Bonferroni correction of pairwise group differences. A *p* value $<.05$ was considered statistically significant.

Results

Genetic testing facilitates the diagnosis of patients with ski slope-type hearing loss

To investigate the etiology of HL, massively parallel sequencing was performed for 41 families (44 patients) with residual acoustic hearing. We identified the cause of HL in 21 families (51.2%). Of them, 19 patients received a genetic diagnosis, with the *CDH23* gene most frequently implicated, followed by *ACTG1*, *Mit1555A > G*, *MYO7A*, *MYO15A*, *SLC26A4*, and *TMPRSS3* (Table 2). Additionally, two patients were diagnosed with otosclerosis and congenital diaphragmatic hernia (Figure 1).

Low-frequency hearing threshold shift and hearing preservation scale

To define the extent of hearing deterioration following CI, we measured auditory thresholds before and at 6 months after activation. The average pre-operative air conduction hearing thresholds at 125, 250, and 500 Hz were 36.7 ± 17.2 ,

46.8 ± 20.8 , and 62.6 ± 21.8 dB, respectively. The mean LF threshold shift was 9.7 dB at 125 Hz, 15.5 dB at 250 Hz, 21.0 dB at 500 Hz, indicating that the hearing deterioration was statistically significant at 500 Hz as compared to that at 125 Hz (Figure 2). To calculate HP, we used the classification reported by Skarzynski et al. and the HEARING group [11]. The HP evaluated at 6 months after activation indicated that 20 of the 50 (40%) implanted ears completely maintained their preoperative hearing thresholds, followed by 19 with partial (38%), 8 with minimal (16%) and 3 with no measurable hearing (6%).

Assessment of predictive factors influencing residual hearing preservation

To investigate predictors that impact HP after surgery, we examined some patient-related factors (age, pre-operative LFA, CDL, and cause of HL) as well as the length of the inserted CI (FLEXsoft [31.5 mm], FLEX28 [28 mm], FLEX24 [24 mm]). We measured CDL using OTOPLAN software, and found that the mean CDL was 32.9 mm, which was independent of age. Univariate analysis of variables and the HP scale are shown in Table 3 and suggest that a younger age at implantation was moderately associated with better HP scores as compared with older patients ($R^2=0.186$), while other variables (pre-operative LFA, CDL) demonstrated negative correlations with HP scores ($R^2=0.013$, 0.0004, respectively). Additionally, the results of one-way ANOVA demonstrated no statistically significant differences in HP among the three types of electrode array used (Figure 3), indicating that HP was not dependent on inserted electrode length. As described above, eight responsible genes were found in the patients. Of them, we found that patients who had pathogenic variants in the *CDH23*, *MYO7A*, or *MYO15A* gene showed statistically better HP scores compared with patients with HL due to other causes ($p=.002$) (Figure 4), while the age at implantation in these groups was comparable (33.5 vs. 37.4 years).

Discussion

In recent years, minimally invasive surgery and flexible electrode arrays have allowed residual hearing to be preserved, leading to the preservation of cochlear structures, although the HP results remain variable on an individual level. Therefore, we analyzed the factors that have an impact on the auditory function after CI in this study. To this end, we compared pre- and 6-month post-operative auditory thresholds in patients with residual acoustic hearing. Based on the HP classification [11], complete HP was observed in 40% of patients, partial HP in 38%, minimal HP in 16% and a total loss of hearing in another 6%, which is similar to the results of previous studies [13].

We found that CI surgery impaired hearing at 500 Hz as compared to that at 125 Hz. This phenomenon was observed in another study using shorter electrode arrays (20 mm) [14], so that irrespective of the length of inserted electrode arrays, the intrinsic structural vulnerability of the basal-

Table 2. Summary of the clinical features and information of the variants identified as likely causative in this study.

Family No.	Sample ID	Gender	Implant age (years)	Gene	HGVs variant	Zygosity	CADD Phred	ACMG Criteria	Implant	Pre-op LFA (dB)	6M post-activation LFA (dB)	HP numerical scale (%)
1-I ^a	SNS5117	Female	45	CDH23	NM_022124: c.4762C > T, p.R1588W	hom	26.6	VUS	FLEX24	45.0	55.0	79.3
1-II ^a	SNS5121	Male	48	CDH23	NM_022124: c.4762C > T, p.R1588W	hom	26.6	VUS	FLEX24	60.0	71.7	65.0
2	SNS1169	Female	38	TMPR53	NM_032404: c.607C > T, p.Q203X	het	35	Pathogenic	FLEX28	55	50	95.3
3-I ^a	2885	Male	39	CDH23	NM_032404: c.778G > A, p.A260T	het	28.9	Pathogenic	FLEX24	36.7	61.7	55.9
3-II ^a	2886	Male	12	CDH23	NM_022124: c.719C > T, p.P240L	het	25.8	Pathogenic	FLEXsoft	80.0	90.0	0.0
4	SNS5142	Female	70	MYO15A	NM_022124: c.902C > T, p.R301Q	het	34	Likely pathogenic	FLEXsoft	73.3	73.3	92.3
5	SNS5791	Male	29	ACTG1	NM_022124: c.719C > T, p.P240L	het	25.8	Pathogenic	FLEXsoft	80.0	81.7	100.0
6	SNS0417	Male	39	ACTG1	NM_022124: c.719C > T, p.P240L	het	34	Likely pathogenic	FLEXsoft	80.0	81.7	100.0
7	SNS5792	Female	52	CDH23	NM_022124: c.902C > T, p.R301Q	het	25.8	Pathogenic	FLEXsoft	80.0	81.7	100.0
8	SNS5355	Male	45	TMPR53	NM_022124: c.719C > T, p.P240L	het	25.8	Pathogenic	FLEXsoft	80.0	81.7	100.0
9-I ^a	HL0186	Female	12	SLC26A4	NM_032404: c.647G > T, p.W216L	het	34	VUS	FLEX24	25.0	45.0	68.1
9-II ^a	SNS5626	Female	9	SLC26A4	NM_032404: c.771G > T, p.H257Q	het	28	VUS	FLEX24	—	—	—
10	HL0036	Female	28	MYO7A	NM_000441: c.1229C > T, p.T410M	hom	33	Pathogenic	FLEX28	63.3	70.0	70.8
11	AG6121	Female	34	CLDN14	NM_000441: c.1229C > T, p.T410M	het	33	Pathogenic	FLEX28	50.0	65.0	62.5
12	SNS5967	Male	50	CDH23	NM_000260: c.0652G > A, p.D218N	het	27.4	Likely pathogenic	FLEXsoft	66.7	71.7	75.0
13	AG5940	Male	13	SLC26A4	NM_144492: c.241C > T, p.R81C	hom	27.6	VUS	FLEX28	68.3	81.7	81.3
14	AL6787	Male	21	LOXHD1	NM_022124: c.2866C > T, p.E956K	het	34	Pathogenic	FLEX28	50.0	56.7	78.6
15	HL2709	Female	10	MYO7A	NM_022124: c.4762C > T, p.R1588W	het	26.6	VUS	FLEX28	—	—	—
16	HL0501	Male	8	MYO15A	NM_000441: c.919-2A > G	het	24.8	Pathogenic	FLEX28	78.3	81.7	100.0
17	2729259	Female	14	CDH23	NM_000441: c.1229C > T, p.T410M	het	33	Pathogenic	FLEX28	—	—	—
					NM_144612: c.6168delC	het	24.2	Pathogenic	FLEX28	33.3	66.7	37.2
					NM_000260: c.4477G > A, p.V1493I	het	24.5	VUS	FLEX24	18.3	15.0	100.0
					NM_016239: c.535G > T, p.E179X	het	36	Pathogenic	FLEX24	35.0	33.3	100.0
					NM_016239: c.9413T > A, p.L3138Q	het	24.4	Likely pathogenic	FLEX28	—	—	—
					NM_022124: c.719C > T, p.P240L	het	25.8	Pathogenic	FLEX28	56.7	48.3	100.0
					NM_022124: c.2866C > T, p.E956K	het	34	Pathogenic	—	—	—	—

^aTwo affected patients in three families each.

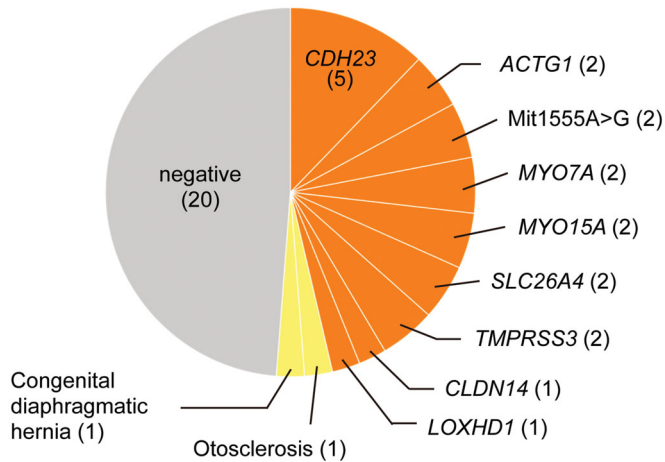


Figure 1. Etiology of patients with residual acoustic hearing. Orange indicates genetic causes of hearing loss; yellow, other causes; grey, unknown ($n = 41$).

Table 3. Univariate analysis of variables and hearing preservation scale.

Variable	Pearson's R square	p Value
Age	0.186	.001
Pre-operative LFA ^a	0.013	.404
CDL ^b	0.0004	.885

^aLFA: average low-frequency hearing thresholds at 125, 250, and 500 Hz.

^bCDL: cochlear duct length measured by OTOPLAN.

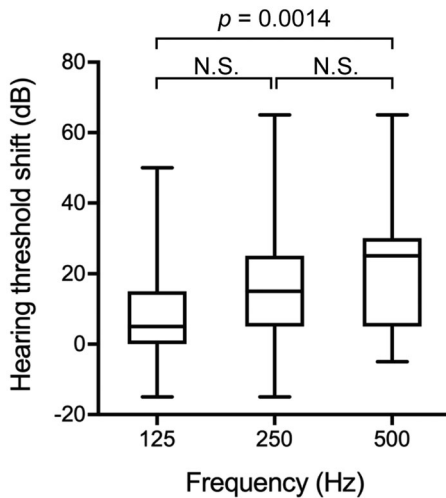


Figure 2. Comparison of hearing threshold shifts after implant surgery. Median, interquartile, minimum and maximum scores for the HP scale. Statistical analysis by one-way ANOVA with Bonferroni's correction. NS: statistically not significant.

apical turn may potentially explain this. Additionally, the HP outcomes were independent of the electrode length (24 mm vs. 28 mm vs. 31.5 mm), which was consistent with the findings that there were no differences in HP score among the insertion depth angles in our and other previous reports [7,8]. Conversely, Suhling et al. reported that 20- or 24-mm electrodes resulted in better HP than did those 28 mm in length [15]. The exact reason for this discrepancy is unclear; however, the previous studies [4,16] provided evidence that longer electrodes could offer the closest to a natural frequency match, resulting in better speech perception, which encourages surgeons to choose longer electrodes.

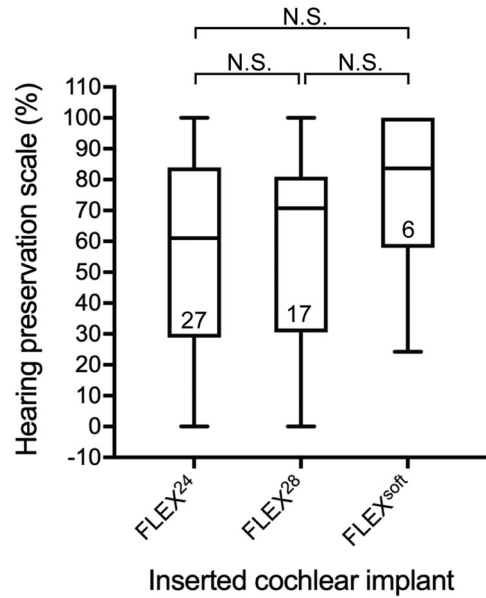


Figure 3. Comparison of HP scores among three types of CI electrode array. Median, interquartile, minimum and maximum scores for the HP scale. Statistical analysis by one-way ANOVA with Bonferroni's correction. NS: statistically not significant.

As described in our previous report [7], we demonstrated that a younger age at the time of implantation led to statistically better HP, indicating that the implant age is one of the key predictors influencing residual hearing in CI surgery (Table 3). On the other hand, we did not find that HP was associated with pre-operative LFA or CDL, which contradicts some previous studies that suggest there is a positive impact on post-operative hearing [8].

Among the studies on the predictive factors for HP in CI surgery, this report is unique as the etiology of HL was analyzed as a patient-related factor. Our data showed that the use of next-generation sequencing provided a diagnostic rate of 51.2% in this study, suggesting that genetic testing facilitates the accurate diagnosis of patients with residual hearing in the low frequencies. Interestingly, we observed statistically better HP scores in patients who had pathogenic variants in the *CDH23*, *MYO7A*, or *MYO15A* gene, which are only expressed in the stereocilia of the inner and outer hair cells (HCs) [17 for review]. In such subjects, the stereocilia function is thought to be a key component in residual hearing. Conversely, other responsible genes identified in this study are associated with other components of the cochlea; *ACTG1* with HCs and supporting cells [17], *SLC26A4* with outer sulcus cells [17], *TMPRSS3* with HCs and spiral ganglion neurons [17], *CLDN14* with the organ of Corti, Reissner's membrane, the spiral limbus and the stria vascularis [17], and *LOXHD1* with HCs and spiral ganglion neurons [17]. Based on an animal study, Reiss et al. reported that a number of inner and outer HCs were intact after implant surgery in guinea pigs, although the presynaptic ribbon and postsynaptic receptor were damaged [18], implying that CI insertion may not have an impact on the residual function of HCs. We speculated that these observations could possibly explain the phenomenon in which residual acoustic hearing after CI was well-preserved in

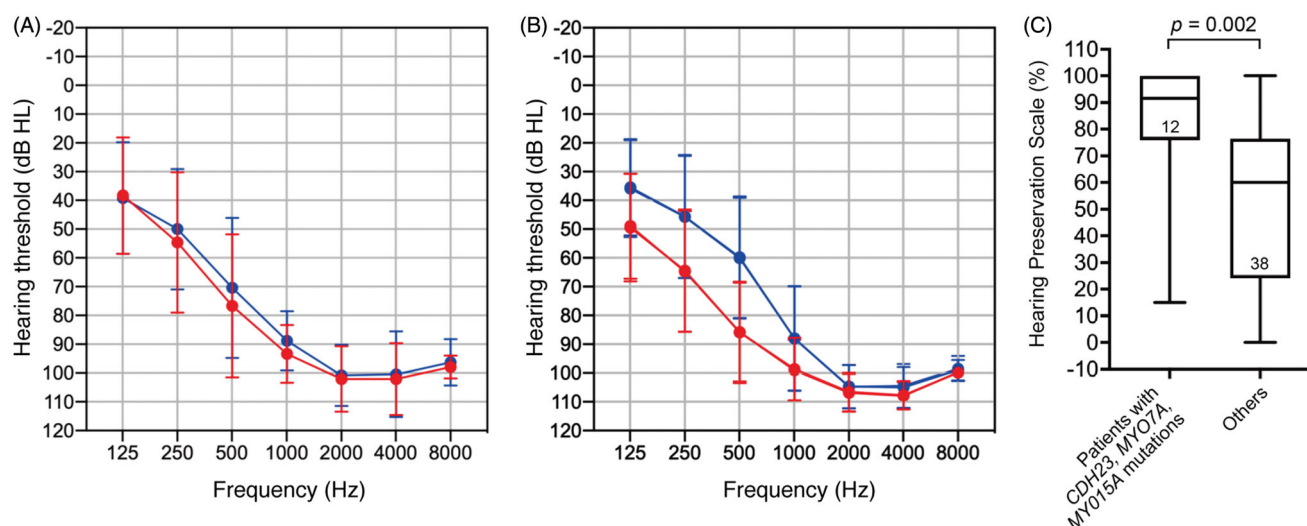


Figure 4. Average pre- (blue line) and post-operative (red line) air conduction hearing thresholds for patients with (A) pathogenic variants in the *CDH23*, *MYO7A*, or *MYO15A* gene, and (B) hearing loss due to other causes. Error bars represent the SD. (C) A comparison of HP scores in each group. Median, interquartile, minimum and maximum scores for the HP scale. Statistical analysis by Mann–Whitney test.

patients with HL caused by genes related to HCs only in comparison with patients with HL caused by mutations in other genes. As the number of subjects in this study was limited, a study employing a larger cohort will be performed to validate the present findings.

In summary, we show that HP was marginally correlated with age at implantation, which is consistent with previous reports, while HP was independent of pre-operative LFA, CDL, and electrode length. Likewise, identification of pathogenic variants in the *CDH23*, *MYO7A*, or *MYO15A* gene resulted in better HP after surgery. We reasoned that these genes are known to be expressed in the stereocilia of the inner and outer HCs of the cochlea, which may not be related to implant-induced HL. We also demonstrated that the diagnostic rate was 51.2% in patients with ski slope-type HL. Taken together, these results reveal that genetic testing facilitates not only the diagnosis of patients with HL but also the prediction of HP after CI.

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Disclosure statement

The authors declare no conflicts of interest.

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