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CASE REPORT

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Cochlear implantation in a patient with a *POU4F3* mutation

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Abstract

Cochlear implants (CIs) are generally considered useful in the treatment of hereditary hearing loss with progressive deafness. Early CI can be beneficial for maintaining social activities in *POU4F3* mutation patients.

KEYWORDS

cochlear implant surgery, *POU4F3*, progressive hearing loss, residual hearing, surgery timing

1 | INTRODUCTION

We present the first detailed report on cochlear implant (CI) surgery in a patient with *POU4F3* mutation c.896C>T: p.Pro299Leu, which causes delayed and progressive hearing loss. Speech perception with CI was better compared to a hearing aid. Early CI can be beneficial for maintaining social activities in *POU4F3* mutation patients.

The *POU4F3* gene, which has an autosomal dominant inheritance pattern, is a causative gene for nonsyndromic hearing loss (HL) (DFNA15). *POU4F3* mutations are found in 2.5% of Japanese patients with autosomal dominant hereditary HL.[1] This gene is associated with transcription factors that are specifically expressed in the inner hair cells. *POU4F3* plays an important role in the differentiation of hair cells,[2] with mutations in the gene causing delayed and progressive

HL.[3-7] In Japan, Kitano et al reported finding 12 mutations in 24 patients from 15 families.[1] Multiple studies have examined the effects of a cochlear implant (CI) on HL caused by the *GJB2* and *SLC26A4* genes.[8] In contrast, there have been no recent detailed case reports regarding the postoperative course for CI surgery in patients with *POU4F3* mutations. Here, we report a case of CI surgery that was performed in a patient with progressive HL caused by a novel mutation in *POU4F3*.

2 | CASE PRESENTATION

A 51-year-old man, who had not been previously diagnosed with HL, became aware of his binaural HL at approximately 40 years of age. He first consulted an otolaryngologist and was diagnosed with bilateral sensorineural HL, with an average hearing level of 40-50 dB. Thereafter, his HL gradually progressed, and at the age of 45 years, his average hearing level in both ears was about 60 dB. At the time of his initial examination at our hospital, he was 47 years old and had been wearing a hearing aid in his left ear from the age of 44 years and in both ears from the age of 47 years. His mother had HL starting in her 30 seconds, while his brother had HL starting in his teens (Figure 1).

At the first visit, both of his eardrums appeared normal. On pure tone audiometry (PTA), the average hearing level (500 Hz, 1 kHz, 2 kHz, and 4 kHz) was 75 dB for both the right and left ears. At this initial visit, the average hearing level recommended for use of a CI was 90 dB or higher in both ears as per the CI indication criteria established by the Otolaryngological Society of Japan. Thus, his average hearing level was out of the CI criteria range at the time of his first visit. The highest monosyllabic speech discrimination score (SDS) was 54% (100 dB HL) on the right and 52% (100 dB HL) on the left side. Auditory brainstem response thresholds were 50 dB normal hearing level (nHL) for his right and 50 dB nHL for his left ear. Auditory steady-state response thresholds for 500 Hz, 1 kHz, 2 kHz, and 4 kHz were 80, 80, 60, and 60 dB on the right and 80, 80, 70, and 60 dB on the left, respectively. No bilateral response was observed with otoacoustic emission. The aided thresholds with the use of a hearing aid (500 Hz, 1 kHz, 2 kHz, and 4 kHz) were 52 dB HL on the right and 49 dB HL on the left. SDS when using his hearing aids was 35% (65 dB sound pressure level (SPL)) and 40% (65 dB SPL) on his right and left sides, respectively. There were no abnormal findings revealed by the computed tomography of the temporal bone, or the magnetic resonance imaging of the inner ear and brain. Initially, he was able to communicate with the use of hearing aids, in addition to taking advantage of his residual hearing without the use of any hearing aid during his daily routine activities. Since there was a family history of HL, hereditary HL was suspected. As a result, he underwent a genetic test for HL in order to determine the prognosis of his progressive HL.

Thereafter, he managed his hearing by regular visits to an outpatient clinic. However, his HL gradually progressed, with his average hearing level at the age of 50 found to be 88 and 86 dB on the right and left sides, respectively. SDS with the use of hearing aids also deteriorated to 25% in both the right and left ears (65 dB SPL) (Figure 2). After we used a linear regression analysis to examine the rate of the HL progression from the initial consultation to the sudden deterioration, it was shown that his HL progressed at a relatively rapid pace (Figure 3).

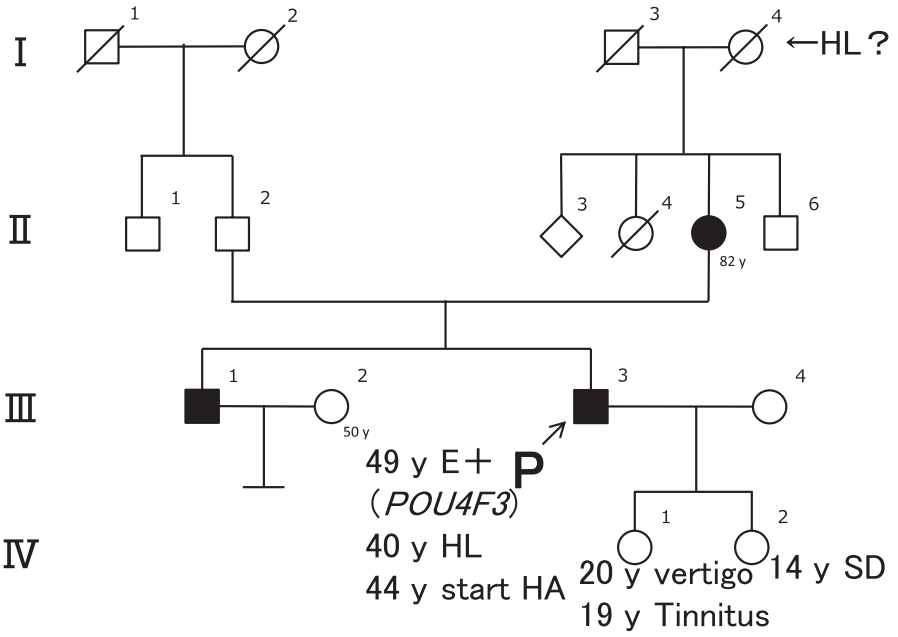

FIGURE 1 Family tree for a*POU4F3*family with hearing loss. Pedigree of a four-generation family with hearing loss. The arrow indicates the proband

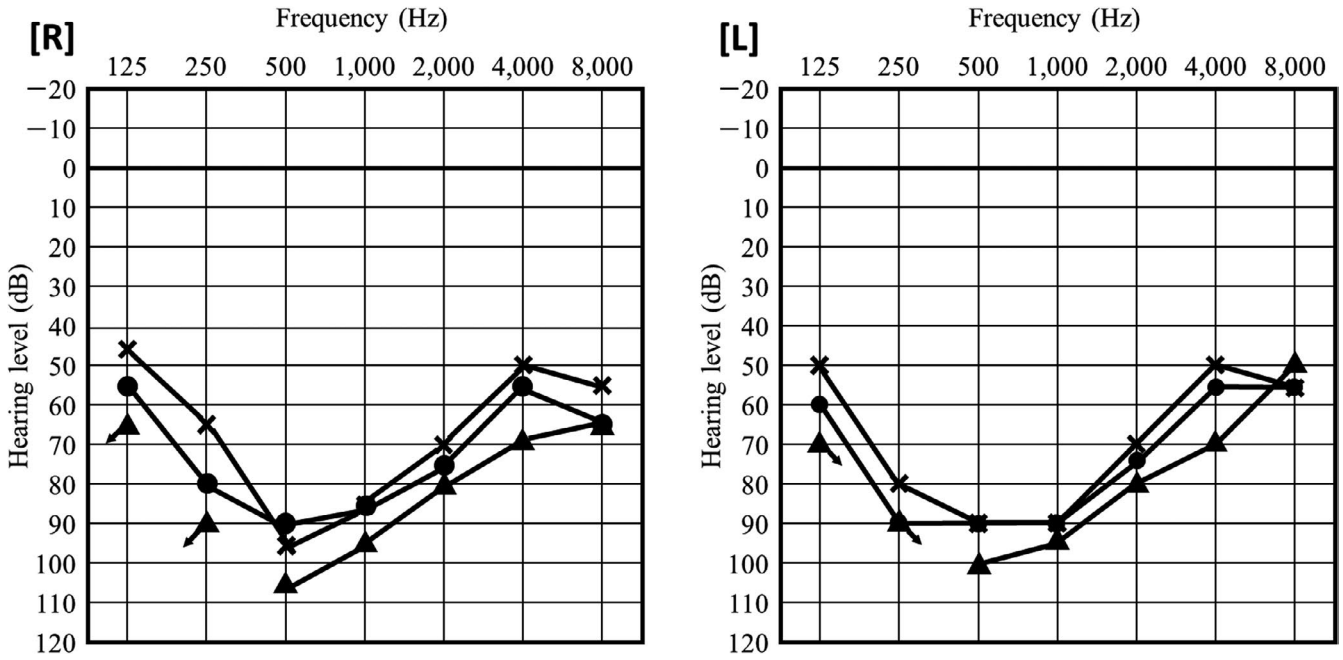

FIGURE 2 Course of the patient's preoperative PTA. PTA results are shown for the time of the initial examination (at 47 y of age;*x*on the graphs), at 49 y (● on the graphs), and for the time prior to the CI surgery (at 50 y; ▲ on the graphs). R, right ear, and L, left ear

Two years after the first visit, when the patient was 50 years old, subsequent results of a genetic analysis revealed that he had a *POU4F3* heterozygous mutation, c.896C>T: p.Pro299Leu.

At this time, he was required to communicate by writing, which led to his having to change his workplace. Thus, his HL was directly affecting his daily routine activities. Furthermore, at this time, the Otolaryngological Society of Japan had changed the average hearing level required for a CI from 90 dB to 70 dB or higher in both ears. As a result, at the age of 50 years he decided to undergo the CI surgery in his left ear (Advanced Bionics HiRes900K).

One month after the operation, the hearing threshold of the left ear when using the CI was 25 dB, while the SDS was 75% (65 dB SPL). In addition, there was significant improvement in his SDS as compared to that when he was wearing a hearing aid prior to the surgery. At 6 months after the operation, his SDS when using the CI was favorable, with 75% monosyllables, 96% words, and 90% sentences (Figure 4). Furthermore, his unaided hearing level for both ears during the periodic hearing tests 1, 3, and 6 months after the operation was found to be the same as that determined prior to the surgery. Although his unaided hearing was minimal after the CI surgery, at a few days after the 6 month anniversary of his surgical procedure, he complained that he could not hear anything from his left ear, starting from immediately after waking up in the morning. PTA evaluation showed that the unaided hearing level of his left ear was out of scale.

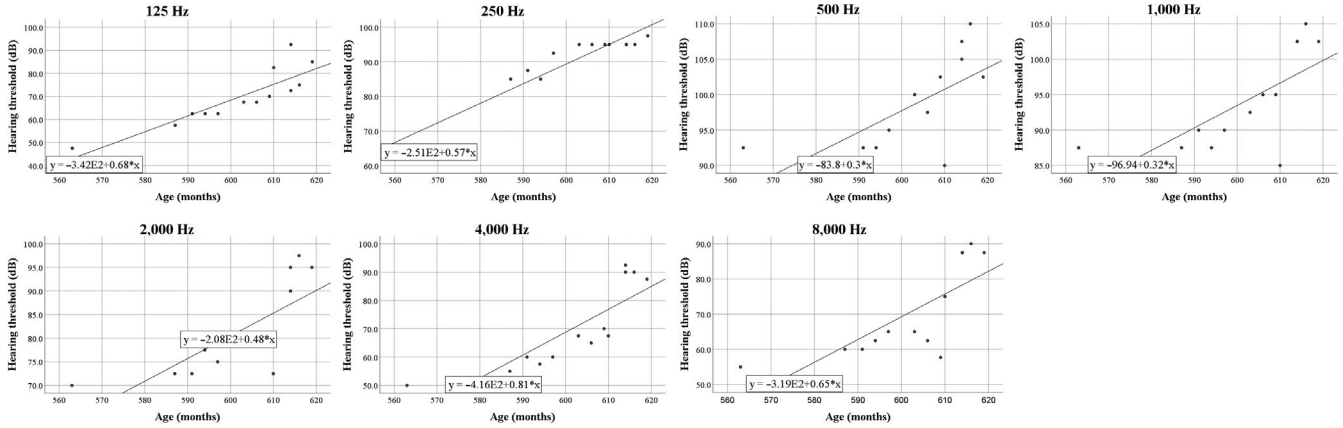

FIGURE 3 Linear regression analysis of PTA results for each frequency of the patient. For each frequency, the averaged air conduction threshold (dB) in both ears was plotted against the age in months and then analyzed by a linear regression analysis. The straight line indicates the rate of increase in the threshold per month

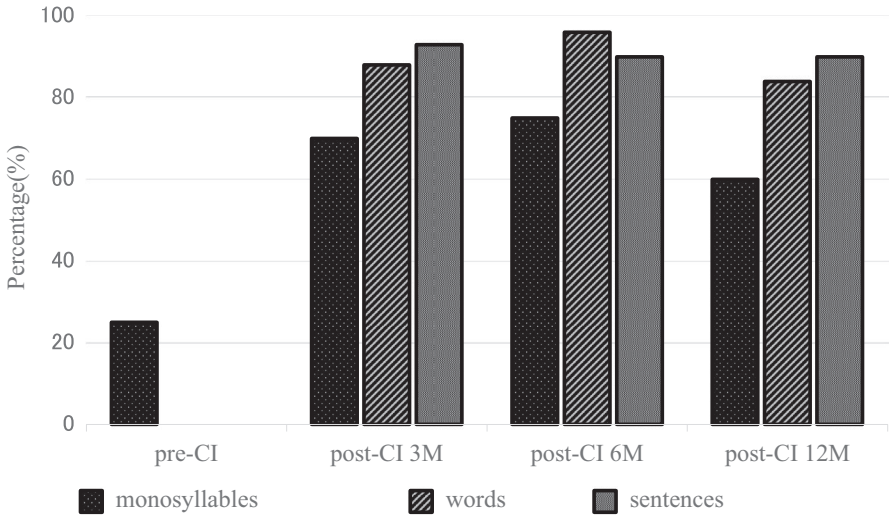

FIGURE 4 Course of the patient's speech perception. Speech perception scores of monosyllables, words, and sentences obtained prior to the cochlear implantation and at 3, 6, and 12 mo postoperatively

Although prednisolone was administered 3 days after the exacerbation, there was no observed improvement in his hearing (Figure 5). Even after the loss of his residual hearing, his hearing ability while using the CI at 1 year after surgery was still favorable, with 60% monosyllables, 84% words, and 90% sentences. At the time of the present report, he continues to use auditory-oral communication without writing during his daily activities.

3 | DISCUSSION

Mutations in *POU4F3* are known to cause progressive HL.[3] As the HL is an inner ear HL that is caused by hair cell damage, hearing ability can be recovered through the use of a CI. To the best of our knowledge, this is the first report to provide details on the hearing course and effects of using a CI in a patient with the c.896C>T: p.Pro299Leu *POU4F3* mutation. As demonstrated in this patient, even if residual hearing can be preserved after the CI surgery, there is a chance that this could subsequently disappear. These losses of residual hearing after CI surgery may be due to the progression of the HL caused by the underlying disease and invasion of the cochlea by the CI. Moreover, it has been reported that in cases of residual hearing deterioration related to the CI surgery invasion, hearing that deteriorates after the surgery will not subsequently recover.[9] In the present patient, although the residual hearing from

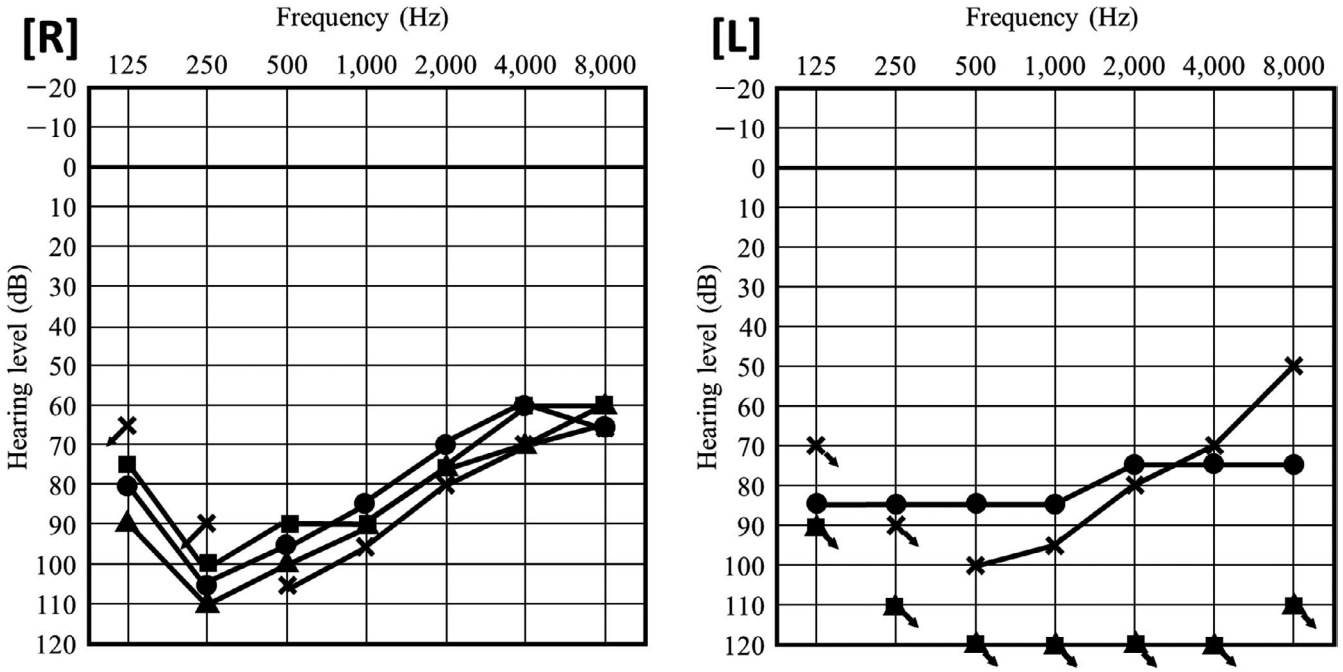

FIGURE 5 Course of the patient's postoperative PTA. PTA of both ears preoperatively (*x*), and at 1 mo (●), 6 mo (▲), and 12 mo (■) postoperatively. The patient underwent CI surgery in the left ear. R, right ear; L, left ear

1 to 6 months after the operation did not differ from that observed prior to the operation, the patient did notice a sudden HL at 1 day after the operation and at more than 6 months after the operation. Rapid progression of HL after CI surgery may be due to both delayed HL caused by the CI surgery and *POU4F3* mutation. Delayed HL due to CI surgery is often reported to gradually occur and has been less commonly reported to suddenly occur. Although there have been no previous detailed reports on the progression of the *POU4F3* mutation HL, there have been some cases of HL associated with left-right differences in the past.[1] Therefore, we cannot exclude the possibility that the natural history of *POU4F3* could potentially be the cause of the rapid progression of HL in some patients with bilateral HL.

The progression of HL in patients with *POU4F3* mutations remains unknown. The age of onset, degree of HL, and presence or absence of dizziness vary among patients. Symptoms usually begin with a cookie bite HL that mainly impairs the midrange. Subsequently, the hearing in the high frequency deteriorates, which then tends to lead to deafness due to high frequency HL.[1] The progression rate of HL was reported in a Dutch *POU4F3* p.Leu289Phe family, with the threshold shown to increase by about 0.8 dB per year at all frequencies.[4] In our present patient, bilateral severe HL occurred at 10 years after the start of the HL. Pauw et al [4] used a linear regression analysis to examine the rate of HL progression from the initial consultation to the sudden deterioration. In our patient, HL progressed at a rapid pace from the time of the first visit to the postoperative period (Figure 3). In particular, the frequency that exhibited a very rapid deterioration was 4,000 Hz, which deteriorated 9.72 times faster than that reported by Pauw et al Even the slowly deteriorating frequency (500 Hz) was shown to deteriorate 4.0 times faster than that reported by Pauw et al, and thus, the overall deterioration was much faster in the present case. In addition, there were 2 types of deafness progression in our patient, with not only a bilateral slow progression but also a unilateral rapid progression. As the rapid progression of HL is unpredictable, it is our belief that it is necessary to perform CI surgery at an early stage in order to ensure that patients will be able to continue to hear throughout their life without impairing their quality of life (QOL).

In contrast, although there was a gradual progression of the HL in the patient's right ear, we did not observe any sharp deterioration similar to that observed in his left ear, and thus, he was able to hear when using a hearing aid. However, it is conceivable that the hearing in the patient's right ear will rapidly worsen in the future, similar to that originally observed in the left ear.

Various advantages have been reported for the use of bilateral CI versus unilateral CI.[10] For example, the recognition scores of words and sentences have been found to be significantly higher in patients with bilateral versus unilateral CIs. Based on these findings, we recommended that the patient also undergoes CI surgery for his right ear. However, as he was hesitant to undergo further CI surgery due to the risk of residual hearing deterioration related to the CI, he presently continues to rely on his right ear for hearing during his daily activities. As a result, since his hearing is now primarily dependent on the left CI, the HL in his right ear is not expected to hinder his daily activities.

If a patient requires CI surgery and the procedure can be performed at an early stage in order to ensure there will be no loss in the hearing, then the timing for a second procedure can be determined at an optimal time for the subject. However, it is necessary to evaluate the appropriate time for the second CI surgery based on a comparison between the potential advantages of maintaining the residual hearing for use during daily activities versus the advantages of using binaural CI.

Determining the timing of CI surgery for progressive HL is very difficult. In our present patient, the hearing ability when using a CI was favorable, and there were no observed complications, including any deterioration of the residual hearing due to the CI surgery. Although at 6 months after CI surgery his residual hearing rapidly deteriorated, he was able to maintain his hearing when using the CI. As a result, this meant that he was able to continue his daily activities without any impact on his job. As reported in previous studies, HLs caused by *POU4F3* mutations are progressive and thus, CI surgery has proven to be useful due to the inner ear HL that occurs. In our current case, genetic testing was helpful in the determination of when the patient needed to undergo the CI surgery. Thus, once the *POU4F3* mutation is detected, early CI surgery may be of great benefit in helping to preserve the QOL as soon as the patient's hearing level meets the criteria for a CI.

4 | CONCLUSION

To our knowledge, this is the first report to provide details on the hearing history and timing of a CI in a patient with HL caused by the *POU4F3* mutation c.896C>T: p.Pro299Leu. Speech perception of the patient when using the CI was favorable. Although his residual hearing was maintained after the initial CI surgery, his hearing suddenly worsened at 6 months after the CI surgery, thereby resulting in further HL. Genetic testing was useful in helping to make decisions regarding the timing of the CI surgery. When a *POU4F3* mutation is identified, early CI surgery is useful in helping to maintain QOL.

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CONFLICT OF INTEREST

None declared.

AUTHOR CONTRIBUTION

KM: involved in investigation, and wrote, reviewed, and edited the manuscript. KS: involved in investigation, performed methodology, and wrote, reviewed, and edited the manuscript. NN: performed methodology and provided resources. SK: performed methodology, and involved in investigation and validation. YO: involved in investigation and validation. AK: involved in investigation and validation, wrote, reviewed, and edited the manuscript, and supervised the study. SU: wrote, reviewed, and edited the manuscript, and supervised the study. TK: wrote, reviewed, and edited the manuscript, and supervised the study. KT: conceptualized the study, supervised the study, wrote, reviewed, and edited the manuscript, and acquired the funding.

ETHICAL APPROVAL

This case report has been approved in writing by the patient.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author, [K.S], upon reasonable request.

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