



Published in final edited form as:

Ann Otol Rhinol Laryngol. 2015 May ; 124(1 0): 169S–176S. doi:10.1177/0003489415575042.

De novo mutation in X-linked hearing loss-associated *POU3F4* in a sporadic case of congenital hearing loss

Hideaki Moteki^{1,2,4}, A Eliot Shearer², Shuji Izumi³, Yamato Kubota³, Hela Azaiez², Kevin T Booth², Christina M Sloan², Diana L Kolbe², Richard JH Smith², and Shin-ichi Usami^{1,4}

¹Department of Otorhinolaryngology, Shinshu University School of Medicine, Matsumoto, Japan

²Department of Otolaryngology-Head and Neck Surgery, Molecular Otolaryngology & Renal Research Labs, University of Iowa Hospitals and Clinics, Iowa City, Iowa, USA

³Department of Otorhinolaryngology, Niigata University School of Medicine, Niigata, Japan

⁴Department of Hearing Implant Sciences, Shinshu University School of Medicine, Matsumoto, Japan

Abstract

Objective—In this report, we present a male patient with no family history of hearing loss, in whom we identified a novel de novo mutation in the *POU3F4* gene.

Methods—One hundred ninety-four (194) Japanese subjects from unrelated and families were enrolled in this study. We used targeted genomic enrichment and massively parallel sequencing of all known non-syndromic hearing loss genes for identifying the genetic causes of hearing loss.

Results—A novel de novo frameshift mutation of *POU3F4*, to c.727_728insA (p.N244KfsX26) was identified. The patient was a 7-year-old male with congenital progressive hearing loss and inner ear deformity. Although the patient had received a cochlear implant, auditory skills were still limited. The patient also exhibited developmental delays similar to those previously associated with *POU3F4* mutation.

Conclusion—This is the first report of a mutation in *POU3F4* causing hearing loss in a Japanese patient without a family history of hearing loss. This study underscores the importance of comprehensive genetic testing of patients with hearing loss for providing accurate prognostic information and guiding the optimal management of patient rehabilitation.

Keywords

Hearing loss; genetics; *POU3F4*; cochlear implant; massively parallel sequencing

Corresponding author: Shin-ichi Usami, MD, PhD, 3-1-1 Asahi, Matsumoto, Nagano 390-8621, Japan, TEL: +81-263-37-2666, FAX: +81-263-36-9164, usami@shinshu-u.ac.jp.

DECLARATION OF CONFLICTING INTERESTS

All authors have declared no competing financial interests.

INTRODUCTION

The majority of genetic hearing loss is autosomal inherited (autosomal recessive: approximately 75%, autosomal dominant: approximately 20%), and X-linked hearing loss is estimated to account for 1%–5 % of genetic causes.¹ To date, five loci and four genes have been implicated in X linked non-syndromic hearing loss (DFNX; Hereditary Hearing Loss Homepage, <http://hereditaryhearingloss.org/>). The most common cause of X linked hearing loss is mutation in the POU domain class 3 transcription factor 4 (*POU3F4*), which was mapped at DFNX2 loci on chromosome Xq21, and previous reports have described clinically heterogeneous disease phenotypes.^{2–4} Hearing loss is severe—profound sensorineural hearing loss (SNHL)—which varies from congenital to late onset, is often progressive, and may include a conductive hearing loss component in some cases. Anatomically, computed tomography (CT) of the temporal bone in such cases reveals an enlarged internal auditory canal that coalesces with the basal turn of the cochlea along with partial hypoplasia.⁵ With these anatomical features, perilymphatic gusher is known to occur upon stapes surgery for correcting stapedial fixation, as well as during a cochlear implant surgery.^{6, 7}

Based solely on frequency, if a male patient has hearing loss with an apparent X-linked form of inheritance segregating in the family, and/or if a temporal bone CT abnormality were found, *POU3F4* gene could be the most likely cause. However, sporadic cases of SNHL with no family history can be difficult to recognize as a candidate and move on to the sequencing of entire *POU3F4* gene. Recent advances in targeted genomic enrichment with massively parallel sequencing (TGE+MPS) have facilitated the simultaneous sequencing of all known causative genes.^{8, 9}

Here, we describe a male with no family history of hearing loss in whom we identified a novel de novo mutation in the *POU3F4* gene. This is the first report of a diagnosis of hearing caused by *POU3F4* in a patient with no family history of hearing loss and highlights the importance of comprehensive genetic testing for optimal diagnostic rates for non-syndromic hearing loss.

SUBJECTS and METHODS

Subjects

One hundred ninety-four (194) Japanese subjects (114 females) from unrelated and non-consanguineous families were ascertained through 33 otolaryngology clinics in 28 prefectures across Japan. All subjects had presumed non-syndromic hearing loss. For each proband, informed consent was obtained to participate in this study, which was approved by the human subjects ethical committee associated with each clinic.

Clinical information and blood samples were obtained from each proband and from all consenting affected and unaffected relatives.

Targeted Genomic Enrichment and Massively Parallel Sequencing

Genomic DNA was assessed for quality by gel electrophoresis and spectrophotometry (Nanodrop 1000; Thermo Fisher Scientific, Waltham, MA; 260/280 ratio of 1.8–2.2) and quantity by fluorometry (Qubit 2.0 Fluorometer; Life Technologies, Carlsbad, CA). TGE of all exons of all genes implicated in SNHL, was completed as described, targeting 89 genes as part of the OtoSCOPE® v5 platform. Libraries were prepared using a modification of the solution-based Agilent SureSelect target enrichment system (Agilent Technologies, Santa Clara, CA).¹⁰

In brief, 3µg gDNA was randomly fragmented to an average size of 250 bp (Covaris Acoustic Solubilizer; Covaris Inc., Woburn, MA), fragment ends were repaired, A-tails were added, and sequencing adaptors were ligated before the first amplification. Solid phase reverse immobilization purifications were performed between each enzymatic reaction. Hybridization and capture with RNA baits were followed by a second amplification before pooling for sequencing. Minimal amplification was used – typically 8 cycles for the pre-hybridization PCR (range 8–10 cycles) using NEB Phusion HF Master Mix (New England BioLabs Inc, Ipswich, MA) and 14 cycles for the post-hybridization PCR (range 12–16 cycles) using Agilent Herculase II Fusion DNA Polymerase. All samples were barcoded and multiplexed before sequencing on either an Illumina MiSeq or HiSeq (Illumina Inc, San Diego, CA) in pools of 4–6 or 48, respectively, using 100-bp paired-end reads.

Bioinformatics Analysis

Data were analyzed as described using a local installation of the open-source Galaxy software (<http://galaxyproject.org>) and the following open-source tools: BWA¹¹ for read mapping, Picard for duplicate removal, GATK¹² for local re-alignment and variant calling and NGSRich¹³ for enrichment statistics⁹. We reported and annotated variants with custom software.

Variant Confirmation

All pathogenic variants were confirmed by Sanger sequencing and segregation analysis with exon-specific custom primers.

RESULTS

We identified one case with a causative mutation in the *POU3F4* in the cohort of this study (194 hearing loss patients).

Case Details

The affected patient was a 7-year-old male with no particular perinatal events but failed newborn hearing screening. He was referred to Niigata University Hospital, Department of Otolaryngology for further examinations at the age of 2 months. An auditory brainstem response (ABR) revealed a bilateral hearing loss of approximately 70 dBnHL in both ear, and at least, clear responses were observed at 100 dBnHL. Behavioral observation audiometry demonstrated thresholds of 30 to 50dB between 500 and 2000Hz. Bilateral otitis media with effusion was observed with otoscopic findings. Bilateral high frequency

sloping and mild-moderate SNHL was suspected at the age of 1 year. CT findings of the middle and inner ear showed partial cochlear hypoplasia and dilatation of the fundus of the internal auditory canal, which was also incompletely separated from the basal turn of the cochlea. At 2 years of age, his parents noticed that he did not respond to their voices and had only spoken a few words. Therefore, congenital and progressive SNHL was suspected, and the patient was promptly fitted for bilateral hearing aids. However, his hearing subsequently deteriorated, and ABR was absent at the age of 3 years 6 months; the hearing aids were insufficient for adequate hearing.

Therefore, a cochlear implant (CI) surgery was performed in the left ear at the age of 4 years 3 months. Perilymphatic gusher occurred during cochleostomy, which was performed using a conventional method. The patient underwent implantation with a Nucleus 24 device and the strait array (Cochlear Ltd. Lane Cove, Australia); finally, electrode insertion was accomplished.

One year after CI, the patient's sound field threshold was 30–40 dB at low and mid frequencies, but he still could not perceive high frequency sounds with the electrode at the basal turn of the cochlea. He continued to exhibit delayed speech and low ability to interpret Japanese at 2 years after CI (age: 6 years 6 months). His limited perceptual and communicative abilities led to a diagnosis of pervasive developmental disorder (PDD).

His parents and two siblings had normal hearing, and there was no family history of hearing loss or other cognitive disorders. The patient's audiological assessment results, CT findings, and pedigree are shown in Figure 1.

Mutation analysis

We performed comprehensive genetic testing using TGE + MPS of all known non-syndromic hearing loss genes as well as non-syndromic hearing loss mimic genes, as previously described.⁹ We identified a novel frameshift mutation in the *POU3F4* gene, in which one adenine nucleotide was inserted. This mutation corresponded to c.727_728insA (NM_000307), and led to frameshift mutation and truncation (p.N244KfsX26). We also performed Sanger sequencing for family segregation study, and confirmed the gene variant in the proband. As shown in Figure 2, the Sanger sequencing revealed that the parents had no mutations, although his mother had been expected to be the carrier of the variant. Therefore, we diagnosed the patient with a de novo mutation that had resulted in hearing loss with inner ear deformity.

DISCUSSION

In this study, we identified a novel de novo *POU3F4* in a case of sporadic hearing loss. TGE + MPS allowed us to identify the causative mutation, based upon all the known hearing loss genes screened. Although there has been only one previous report of a *POU3F4* mutation in the Japanese population,¹⁴ suggesting a very rare event, many such cases have been reported in the Korean population, which harbors a very similar genetic background.^{15–17} Thus, there may be more Japanese patients harboring *POU3F4* mutations even in sporadic cases that are not identified as having X-linked inheritance mode.

As shown in Table 1, more than 30 mutations, point mutations and genomic rearrangements involving in large deletions and inversions on the upstream gene regulatory element have been reported.^{3, 18–20} However, it is difficult to detect such large genomic alterations using conventional PCR-based DNA sequencing. Anger et al. have reported normal genetic sequencing results in a DFNX2 case with chromosomal rearrangements in the vicinity of *POU3F4*, suggesting a failure of Sanger sequencing to identify mutations because of genetic causes.²¹ In contrast, it is possible to identify such genetic alterations using MPS instead of tests such as array comparative genomic hybridization and fluorescence in situ hybridization.

POU3F4 encodes a transcription factor that binds DNA using two specific domains: POU-specific domain and POU homeodomain. These domains play essential roles in inner ear development and are expressed in both the brain and neural tube. Several studies of *POU3F4* knockout and mutant mouse models have been published; Parzefall et al. have clearly described an observed shortened cochlea duct as a possible Mondini malformation in a mouse harboring a *POU3F4* mutation²². A case involving DFNX2 with *POU3F4* mutations was characterized as exhibiting an inner ear deformity of incomplete partition type III.¹⁷ Our presented case harbored the same cochlear deformity as described in previous reports and was consistent with a de novo mutation in *POU3F4* that led to congenital progressive hearing loss.

Regarding phenotypic features, previously reported manifestations and clinical histories are presented in Table 1. However, we did not observe considerable variations in the genotype-associated phenotypes. Therefore, it is difficult to determine whether these genotype–phenotype correlations exist as described in previous reports (Table 1). Cochlear deformities were observed in most cases, demonstrating mixed hearing losses that were independent of middle ear function and perilymphatic gusher. Several DFNX2 cases with large genomic deletions or chromosomal rearrangements (even single nucleotide variants) have exhibited developmental delays in addition to hearing loss (Table 1).^{7, 23, 24} PDD was diagnosed in our patient, who was suspected to exhibit some syndromic features. In general, hearing loss may impact early childhood development, and differences in hearing levels, social background, and parental factors may affect language acquisition and learning abilities. However, hearing loss-associated *POU3F4* mutation should be additionally considered as a cause of developmental delays involving communication skills, particularly in CI recipients.

Prior to cochlear implantation, we were unable to provide either genetic testing results or counseling for this patient as TGE+ MPS technologies were unavailable for common clinical usage at that time. However, these technologies are currently applicable, and the further evolution of genetic testing will facilitate the accurate diagnosis of hearing loss. Furthermore, we must also rigorously establish phenotypes with respect to the hearing loss level, progression and other manifestations. Regarding hearing loss caused by mutations in *POU3F4*, all clinicians and audiologists should provide optimal CI rehabilitation management and applicable educational supports based on the phenotypic features described herein and elsewhere. This study supports the use of comprehensive genetic diagnosis for SNHL to provide the highest chance of diagnostic success, particularly in sporadic cases.

ACKNOWLEDGEMENTS

This work was supported by NIDCD RO1s DC003544, DC002842 and DC012049 to RJHS. We thank Mr. Jim George for help with manuscript preparation.

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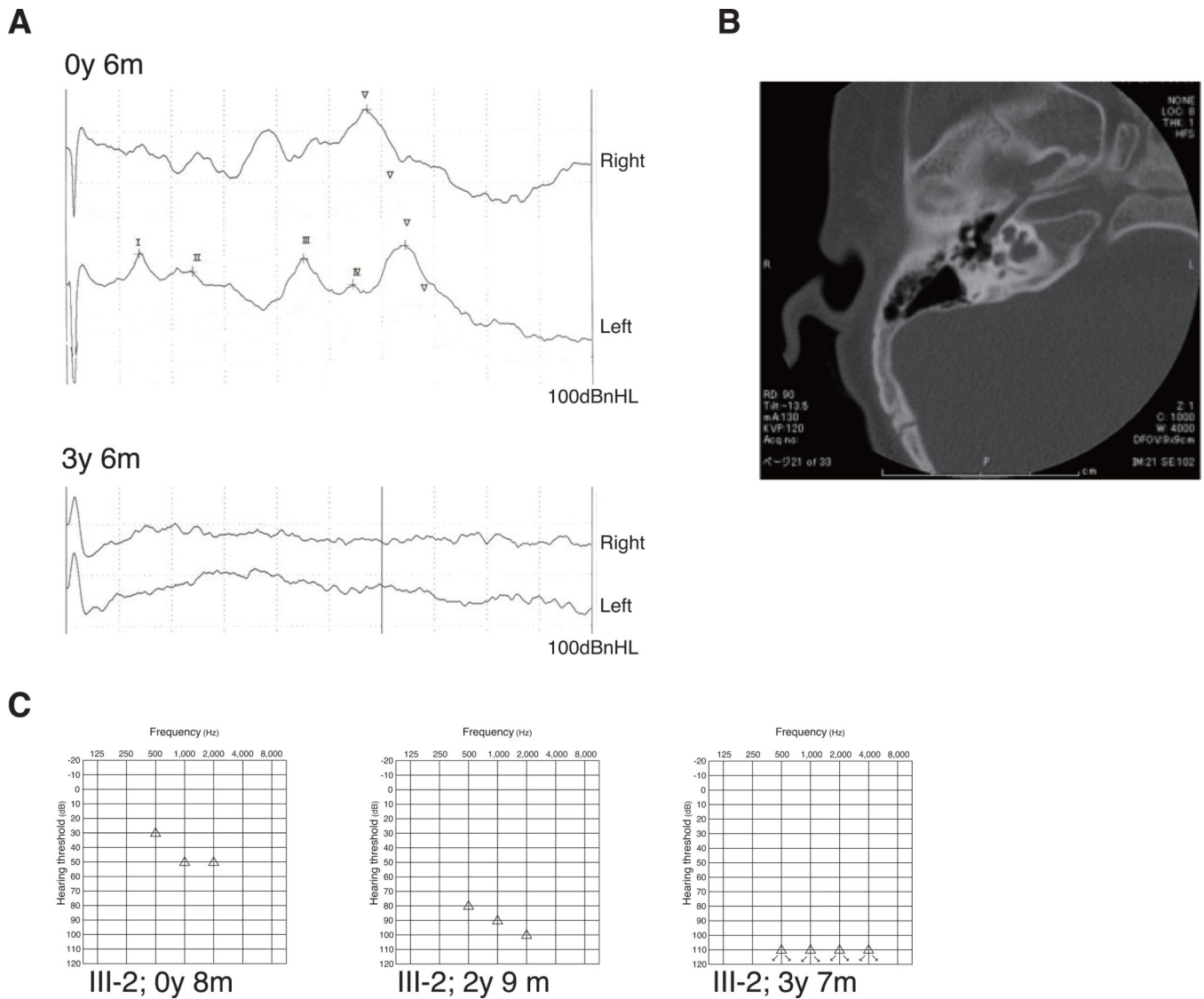
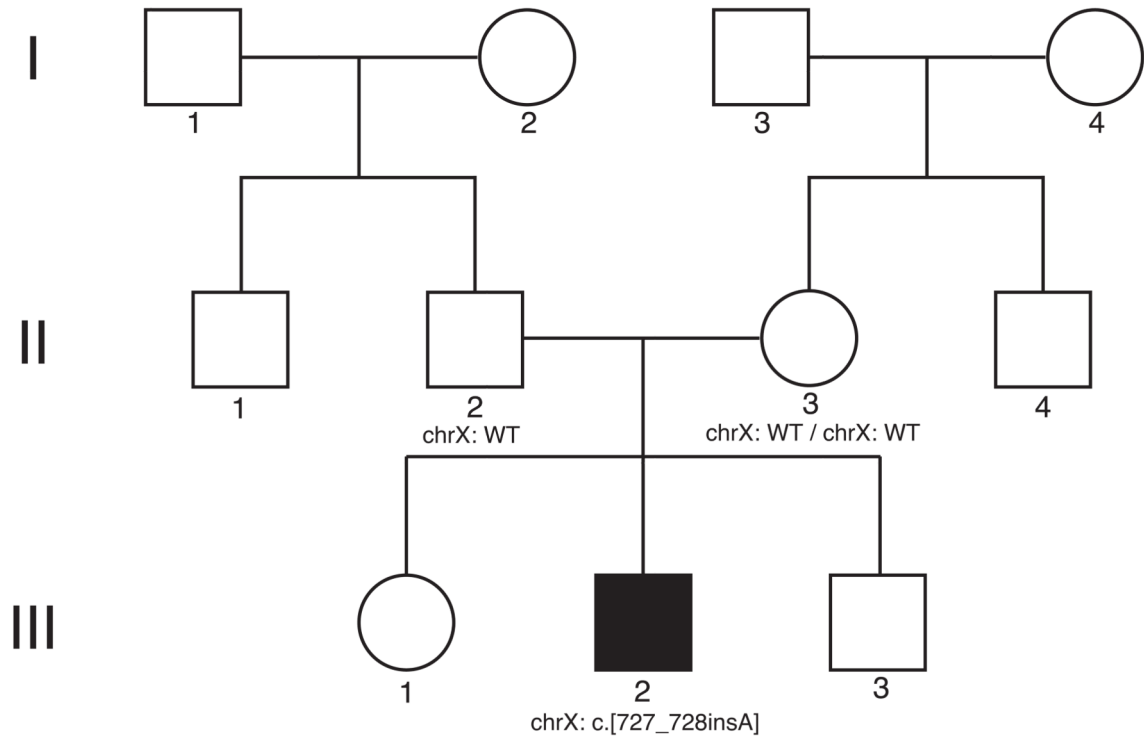


Figure 1. Clinical findings of the patient (ID 4750) (A) Auditory brain stem response (ABR) at the age of 6 months and 3 years with click stimuli at 100 dBnHL. A clear ABR was observed at the age of 6 months; however, ABR was absent in the following year. (B) Temporal bone computed tomography revealed partial cochlear hypoplasia, dilatation of the internal auditory canal fundus, and incomplete separation to the basal turn of the cochlea. (C) Behavioral observation audiometry (BOA) revealed deterioration of the threshold from 50 to 100 dB during the subsequent 3 years, suggesting progressive hearing loss.

A



B

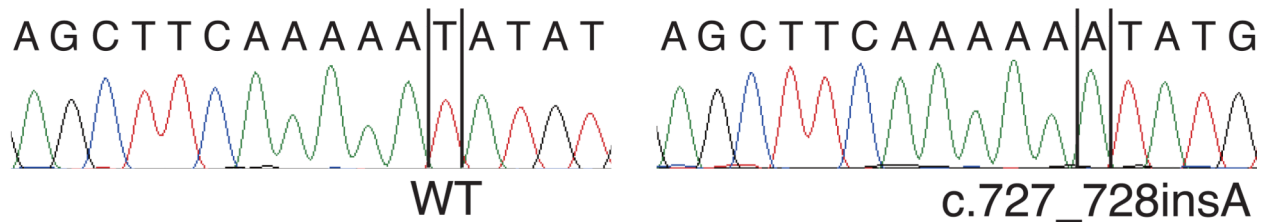


Figure 2. Pedigree of the patient (ID 4750) (A) Pedigree indicated a sporadic case in this family. (B) Electropherogram revealed a mutation only this patient (on the right) Parents (4751 and 4752) did not carry the mutation.

Table 1

Known mutations in *POU3F4* gene and associated phenotypes.

Nucleotide change	Amino acid change	Inheritance	CT findings	HL on set	Type of HL	Progression	Other features	Perilymphatic gusher	Year	Authors
	Large delation	Inherited	IP3	Congenital	Mixed	Progressive		gusher	2005	Vore
	Large delation	Inherited	Mondini	Congenital	SNHL	Progressive			2000	Arellano
	Large delation	Inherited			Mixed		Mental retardation	gusher	1996	de Kok
	Large delation	Inherited	IP3	Congenital		Progressive	Developmental delay, MR		2010	Song
	Large delation	De novo (Sporadic)	IP3						2014	Choi
	Deletion (Upstream and gene)	Inherited	Bony defect		Mixed			gusher	1996	de Kok
	Upstream delation	Inherited	Bony defect		Mixed				1996	de Kok
	Upstream delation	Inherited	IP3	Congenital	Mixed				1996	de Kok
	Upstream delation	Inherited		Congenital	SNHL	Progressive		gusher	2010	Naranjo
	Upstream delation	De novo (Sporadic)	IP3	Early		no			2010	Song
	Upstream duplication	Inherited	IP3		Mixed				1995	de Kok
	Regulatory region deletion	Inherited	Bony defect	Early	Mixed	no			2014	Stanton
	Regulatory region inversion	Inherited	IP3		Mixed	Progressive	Developmental delay		2013	Anger
c.235C>T	p.G79X	De novo (Sporadic)							2013	Parzefall
c.346delG	p.A116fs	Inherited	IP3	Congenital	Mixed		Limited verbal communication		2009	Lee PhyGen
c.383delG	p.G128fs	Inherited	IP3	Early	SNHL	Progressive			2009	Lee
c.499C>T	p.R167X	Inherited	IP3	Congenital	Mixed	no	Attention disorders, Learning delay	gusher	2010	Stankovic
c.540C>A	p.C180X	De novo (Sporadic)	IP3			no		gusher	2014	Choi
c.601-606del	p.201-202del	Inherited	Bony defect	Early	Mixed				1998	Hagiwara
c.603delA	p.K202X	Inherited	Bony defect		SNHL				1995	de Kok
c.623T>A	p.L208X	Inherited	IP3	Early	SNHL	Severe	Mental retardation		2009	Lee
c.623T>A	p.L208X	Inherited	IP3		SNHL				2013	Choi
c.632C>T	p.T211M	Inherited	IP3		Mixed				2013	Choi
c.647G>A	p.G216E	Inherited	IP3	Congenital	SNHL	Progressive			2010	Li
c.648delG	p.D215X	Inherited	Bony defect		Mixed			gusher	1995	de Kok
c.683C>T	p.S228L	Inherited	IP3	Congenital	Mixed	Progressive	Developmental delay		2005	Vore
c.686A>G	p.G229R	Inherited	IP3		SNHL				2013	Choi
c.689C>T	p.T230I		Bony defect		Mixed			gusher	1997	Friedman

Nucleotide change	Amino acid change	Inheritance	CT findings	HL on set	Type of HL	Progression	Other features	Perilymphatic gusher	Year	Authors
c.727_728insA	p.N244KfsX26	De novo (Sporadic)	IP3	Congenital	SNHL	Progressive	Pervasive developmental disorder	gusher	2014	This report
c.853-854del	p.I285Rfs43	Inherited		Early	Mixed			gusher	2013	Parzefall
c.862-866del	p.fs	Inherited			Mixed			gusher	1995	Binter-Glindzicz
c.895delA	p.L298X	Inherited						gusher	1995	de Kok
c.910C>A	p.P303H	Inherited	IP3	Congenital					2014	Choi
c.925T>C	p.S309P	Inherited	IP3	Congenital	Mixed	no			2006	Wang
c.927-929del	p.S310del	Inherited	IP3	Early	Mixed				2009	Lee PhyGen
c.927-929del	p.S310del	unknown (Adopted)	IP3	Early	Mixed	no	Learning delay	gusher	2010	Stankovic
c.935C>T	p.A312V	Inherited	Bony defect	Congenital	SNHL		Learning difficulty		1995	Binter-Glindzicz
c.950dupT	p.L317FfsX12	Inherited	IP3		Mixed				2013	Choi
c.950T>G	p.L317W	Inherited	Bony defect		Mixed				1995	de Kok
c.967C>G	p.A323G				Mixed			gusher	1997	de Kok
c.973T>A	p.W325R	Inherited	IP3	Early	SNHL	Progressive		gusher	2011	Schild
c.985C>G	p.R329G		IP3		Mixed			gusher	1997	Friedman
c.986G>C	p.R329G	Inherited	IP3	Early	Mixed	Progressive			2009	Lee PhyGen
c.990A>T	p.A330S		Bony defect		SNHL	Progressive	Growth retardation	gusher	1997	de Kok
c.1000A>G	p.K334E	Inherited	IP3		Mixed	Progressive			1995	de Kok
c.1069delA	p.T354GfsX115	Inherited	IP3		SNHL				2013	Choi
c.1084T>C	p.X362RfsX113	De novo(Sporadic)	IP3		SNHL				2013	Choi

Abbreviation: IP3, incomplete partition type III; SNHL, sensorineural hearing loss. Empty rows indicate unspecified in the reports.