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Cochlear implantation in a Chinese patient with a novel frameshift variant in *POU3F4* gene and incomplete partition type III: a case report

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Abstract

Variations in the POU Class 3 Homeobox 4 (*POU3F4*) gene are associated with X-linked mixed deafness. Here, the identification of a novel variant of *POU3F4* in a male paediatric patient (the proband) with incomplete partition type III (IP-III) hearing impairment, is described. Clinical data were collected from the proband and his biological parents. Whole exome sequencing of the proband revealed a novel frameshift insertion mutation in *POU3F4* (c.717_718ins GTGCCTTGCAG: p.Leu240Valfs*5) in a hemizygous state. This variant likely truncates the protein within the POU-specific domain, and the proband's biological mother was found to be a carrier of this variant. After excluding all contraindications, the proband underwent cochlear implantation in the right ear in June 2020. Cerebrospinal fluid (CSF) gushing was observed during surgery, but there were no postoperative complications, such as CSF leak, meningitis, or facial nerve stimulation. A novel pathogenic frameshift variant of *POU3F4* was identified, enriching the known mutation spectrum of *POU3F4*. Effective perioperative prevention and response measures should be taken to reduce the incidence of CSF gushing and meningitis in patients receiving IP-III cochlear implantation.

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Introduction

Incomplete partition type III (IP-III) is a rare cochlear malformation that accounts for approximately 2% of all inner ear anomalies.[1] First described by Nance et al. in 1971,[2] IP-III is characterized by X-linked mixed deafness, congenital fixation of the stapedial footplate, and perilymphatic gusher. In 2006, Sennaroglu et al.[3] classified the malformation as an incomplete partition deformity and named it IP-III. The diagnosis of IP-III mainly relies on computed tomography (CT) images showing a bulbous internal auditory canal, presence of interscalar septa, and complete absence of the modiolus.[1]

The POU Class 3 Homeobox 4 (*POU3F4*) gene that encodes POU domain, class 3, transcription factor 4, is located on chromosome Xq21, and its variants are associated with X-linked mixed deafness.[4] The POU3F4 protein consists of two conserved DNA-binding domains: a POU-specific domain and a POU homeodomain. Sequence variations may alter the 3-dimensional structure of these domains, thereby compromising DNA binding,[5] and mutations in *POU3F4* may cause hearing loss, with clinical features that are mainly reflected in audiology, temporal bone imaging and stapes surgery. To date, almost 100 variants of the *POU3F4* gene have been identified (Human Gene Mutation Database, http://www.hgmd.cf.ac.uk/ac/gene.php?gene=POU3F4; accessed November 2021).

Here, the case of a paediatric Chinese male patient with IP-III (the proband), who was treated with cochlear implantation, is described. Whole exome sequencing was performed and a novel variant in the *POU3F4* gene was identified in the proband and his biological mother.

Case report

This study was conducted in accordance with the Declaration of Helsinki and was approved by the ethics committee of Shanghai Children's Medical Center, School of Medicine, Shanghai Jiao Tong University (No. SCMCIRB-W2020045). The reporting of this study conforms to the CARE guidelines,[6] and all patient details were de-identified. Written informed consent for inclusion in the study and case report was obtained from all participants, including the patient's legal proxy.

A 4-year-old male patient (the proband) presented at Shanghai Children's Medical Center in May 2020 with congenital hearing loss and slow speech development. He had failed his newborn hearing screening and had worn the appropriate bilateral hearing aid for six months without any practical benefit. His parents had normal hearing. The proband and his biological parents underwent general clinical and hearing evaluation, and the family history and medical history were analysed.

All family members were negative for systemic disease, and the physical examination and otoscopy results were normal. Audiological evaluations revealed bilateral profound sensorineural hearing loss in the proband. According to temporal bone CT,

the proband exhibited the typical anomalies indicative of IP-III (Figure 1a). The absence of the modiolus was confirmed by inner ear magnetic resonance imaging (Figure 1b).

Genomic DNA was extracted from peripheral blood samples of the proband and his parents using the Gentra Puregene Blood Kit (Qiagen, Hilden, Germany) according to the manufacturer's instructions. The SureSelect Human All Exon V6 enrichment kit (Agilent, Santa Clara, CA, USA) was used to prepare the sequencing library. The experimental process included enzyme digestion of DNA fragments, library hybridization, and capture library amplification and purification. Subsequent sequencing of the library was performed on an Illumina HiSeq X Ten System (Illumina, San Diego, CA, USA) with 150 bp paired-end reads. FastQC (Babraham Research Institute, Cambridge, UK) and Fastp (Visible Genetics, Inc., Toronto, Canada) were used for data quality control and to remove the adaptor sequence. The sequencing reads were then aligned to the hg19 reference human genome using BWA alignment software with the MEM algorithm (BWA-MEM),[7] and variants were identified with the Genome Analysis Toolkit.[8] Ingenuity® Variant Analysis™ software (Ingenuity Systems, Redwood City, CA, USA) and Translational Genomics expert (TGex) platform (Geneyx, Wilmington, DE, USA) were used for mutation identification and annotation, and the MegAlign tool, version 17.1 (DNASTAR, Madison, WI, USA) was used for conservative analysis. Subsequently, a hemizygote frameshift variant (c.717_718ins GTGCCTTGCAG: p.Leu240Valfs*5) was detected in the *POU3F4* gene (NM_000307.4) from the proband and further confirmed by Sanger sequencing in the proband and his parents. The proband's mother was found to carry the same *POU3F4* variant in the heterozygous state, while the father was wild type (Figure 2). The variant was classified as pathogenic according to the American College of Medical Genetics and Genomics (ACMG) and the Association for Molecular Pathology (AMP) 2015 guidelines for variant classification and interpretation.[9]

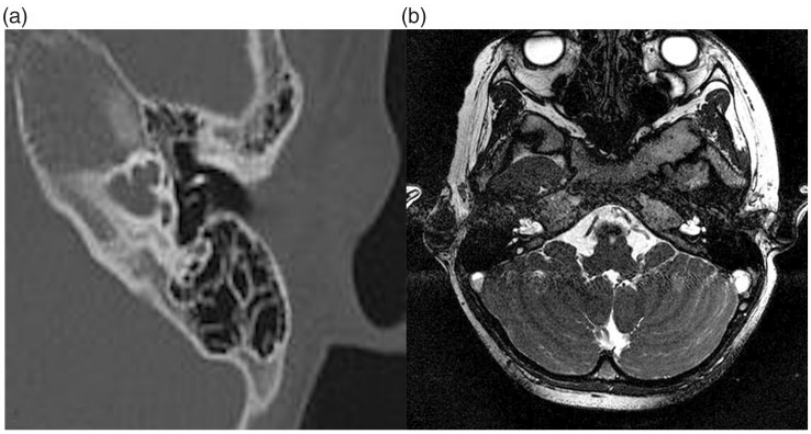

Figure 1. Imaging examination of a 4-year-old male patient (the proband) with incomplete partition type III: (a) computed tomography image of the ear showing bulbous dilatation of the lateral end of the internal auditory canal, incomplete separation of the cochlear coils from the internal auditory canal, presence of interscalar septum, and absent modiolus; and (b) magnetic resonance image showing absence of the modiolus and anomalous fusion between the basal turn and internal auditory canal.

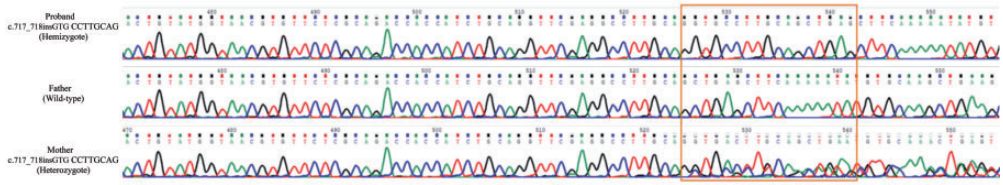

Figure 2. Identification of a novel POU Class 3 Homeobox 4 (*POU3F4*) variant. The 4-year-old male patient (the proband) was hemizygous for a variant of the *POU3F4* gene in the form of c.717_718ins GTGCCTTGCAG. The proband's mother was a heterozygous carrier of this variant, while his father was wild type.

The proband underwent a cochlear implantation (CI-1500-04 implant; Advanced Bionics, Valencia, CA, USA) in the right ear in June 2020. Cerebrospinal fluid (CSF) gushing was observed during the operation. The electrode array was partially inserted via an enlarged round window, and soft tissue harvested from the temporalis muscle was used to tightly seal the site and surround the electrode. Intraoperative medication comprised 1200 mg ceftriaxone sodium intravenously guttae once. From day 1 following surgery, the patient received 8 mg dexamethasone intravenously guttae once daily for 5 days, and 1200 mg ceftriaxone sodium intravenously guttae once daily for 7 days. Postoperative complications, such as CSF leak, meningitis, or facial nerve stimulation, were not encountered. Due to pandemic control restrictions, follow-up assessments were arranged at the nearest hospital. After 1-year of telephone follow-ups, the local hospital conducted a sound field hearing threshold test, which showed a hearing threshold of 50 dB HL. Language development remained significantly delayed for age.

Discussion

The present report describes the case of a male paediatric patient with IP-III who was found to carry a variant (c.717_718ins GTGCCTTGCAG: p.Leu240Valfs*5) in the coding region of *POU3F4*. Review of the Human Gene Mutation Database (http://www.hgmd.cf.ac.uk), Genome Aggregation Database (http://gnomad.broadinstitute.org/), Exome Aggregation Consortium (http://exac.broadinstitute.org), and the 1000 Genomes Project (http://www.1000genomes.org), revealed that this variant has not been previously reported to date, and is therefore novel. The p.Leu240 residue lies within the highly conserved POU-specific domain (Figure 3). An eleven-base insertion (GTGCCTTGCAG) between nucleotides 717 to 718 led to the substitution of leucine to valine at position 240, resulting in a truncated protein. The phenotype of the hemizygous variant carrier was highly consistent with single-gene X-linked deafness. Based on ACMG/AMP 2015 guidelines,[9] the c.717_718ins GTGCCTTGCAG (p.Leu240Valfs*5) variant is categorized as PVS1, PM2, and PP4, indicating that it is pathological.

Cerebrospinal fluid gushing during cochlear implantation has been previously reported in patients with IP-III caused by a *POU3F4* gene mutation, and profuse CSF gushing has also been observed.[10] Intraoperative repair and early postoperative detection are important factors in avoiding serious complications. The electrode arrays may be inserted via cochleostomy or a round window, and muscle tissue should be used to seal the site after electrode insertion to avoid post-operative

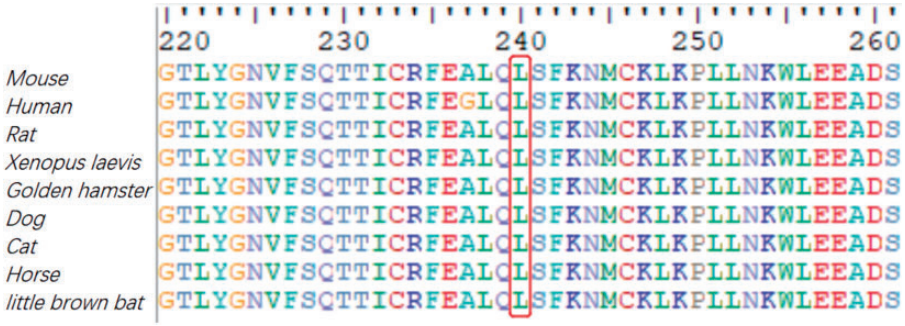

Figure 3. Protein alignment showing conservation of p.Leu240 among different species: p.Leu240 is well-conserved in the POU-specific domain.

CSF leakage or meningitis.[11–13] Lumbar drainage is sometimes used by surgeons to control profuse CSF gushing during and after the operation,[3,14,15] but mild CSF gushing, as in the present case, does not usually require lumbar drainage,[11] and was not performed in the present case.

Through whole exome sequencing, a novel pathogenic variant of the *POU3F4* gene was found in the present patient, involving a frameshift insertion. This finding enriches the known mutation spectrum of the *POU3F4* gene. In addition, in patients with IP-III who undergo cochlear implantation, effective perioperative prevention and response measures should be taken to reduce the incidence of CSF gushing and meningitis.

Availability of data and material

All data generated or analysed during this study are included in this published article.

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Author contributions

LYH and JC conceived the study; REY and YX participated in study design and coordination; and XHF and YJ helped to draft the manuscript. All authors read and approved the final manuscript

Declaration of conflicting interest

The authors declare that there is no conflict of interest.

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