A novel POU domain class 3 transcription factor 4 mutation causes X-linked non-syndromic hearing loss in a Chinese family

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To the Editor: POU domain class 3 transcription factor 4 or *BRN-4* (*POU3F4*) is a causative gene of non-syndromic X-linked hearing loss (HL), which is characterized by inner ear anomalies. To date, six X-linked non-syndromic HL loci (DFNX1-6) have been mapped to chromosome X and five of these genes have been identified: phosphoribosyl pyrophosphate synthetase 1 (*PRPS1*) (DFNX1, OMIM: 304500), *POU3F4* (DFNX2, OMIM: 304400),[1] small muscle protein, X-linked (*SMPX*) (DFNX4, OMIM: 300066), apoptosis-inducing factor, mitochondria-associated, 1 (*AIFM1*) (DFNX5, OMIM: 300614), and collagen, type IV alpha-6 (*COL4A6*) (DFNX6, OMIM; 300914). *POU3F4* mutation accounts for nearly 50% of all cases of DFNX.[2,3] The human *POU3F4* gene is located in the Xq21.1 region with only one exon, encoding 361 amino acids. *POU3F4* belongs to a superfamily of POU domain transcription factors, comprised of a POU-specific domain (75 amino acids) and a POU-homeodomain (63 amino acids), both of which influence DNA binding and specificity. The POU3F4 protein is involved in the development of the middle ear and inner ear, as well as some areas of the brain before birth.[4] However, HL is the only clinical phenotype observed in DFNX2 patients. So far, 72 different mutations in the coding region (57 mutations) and the putative regulatory element region (15 mutations) of the *POU3F4* gene have been reported to be associated with non-syndromic HL in families with DFNX2. In this study, a new non-sense mutation in *POU3F4* was analyzed and found to be associated with non-syndromic X-linked inheritance HL in a Chinese Han family.

The proband, a 20-year-old male, presented to an otolaryngology clinic with congenital bilateral severe HL. The extended family of the proband is a three-generation Chinese family with fourteen family members, including five patients (four males: II: 2, II: 7, III: 4, and III: 5; and one female: II: 1) with HL and nine individuals (five males: I: 2, II: 4, II: 6, III: 1, and III: 2; and four females: I: 1, II: 3, II: 5, and III: 3) with normal hearing [Figure 1A]. The proband was subjected to detailed clinical evaluations. The otomicroscopical examination showed intact tympanic membranes and no middle ear effusion in the proband. The auditory brainstem response was not elicited by air conduction in the left ear and right ear at 105 dB normalized hearing level (dBnHL) [Figure 1B and 1C]. Further, high-resolution axial computed tomography scan revealed that there was no abnormal density in tympanic cavity and sinus, no obvious destruction of ossicular bone and surrounding bone wall, and symmetrical internal auditory canal on both sides. Bilateral inferior gyrus of cochlea was hypoplasia, spiral plate of inferior gyrus was absent, and direct communication existed between vestibule and inferior gyrus of cochlea [Figure 1D]. For a precise diagnosis, we performed whole-exome sequencing (WES) of the proband family members (II: 3, II: 4, and III: 4) and his uncle's family (II: 1, II: 2, and III: 1). Sequence analysis of DNA identified a novel hemizygous or heterozygous mutation (*POU3F4*; NM_000307.3; c.C76>T; p.Gln26*) [Figure 1E], which changes a glutamine (CAG) to a stop code (TAG) and is predicted to result in a truncated protein lacking POU3F4 transcription factor function [Figure 1F]. Sanger sequencing was used to identify the mutation for the family members (II: 1, II: 2, II: 3, II: 4, II: 5, III: 1, III: 2, III: 4, and III: 5). This mutation co-segregates with HL in male members of this family (II: 1, III: 4, and III: 5), and carried by maternal females with normal hearing (II: 3 and II: 5). Male members with normal hearing (II: 4, III: 1, and III: 2) did not carry this mutation. Member (II: 2) also did not have this mutation, though she suffered from HL at the age of 1 year. The non-sense

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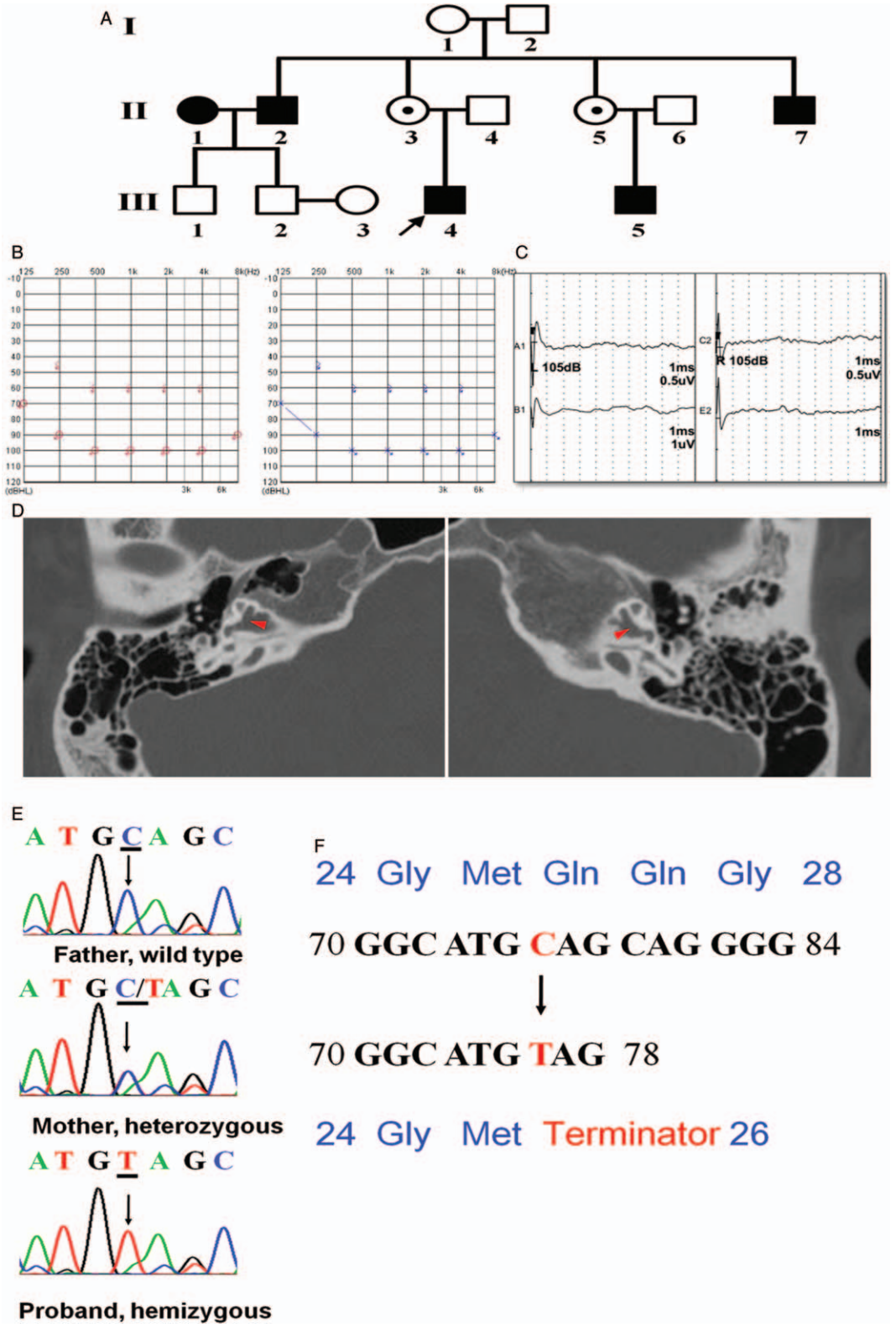

Figure 1: The clinical features of the proband and mutation analysis. (A) Pedigree of the family. Circles represent females and squares represent males. Proband is marked with arrow. Members with HL are indicated with solid squares. Carrier females are marked in the pedigree (circles with dots). The incidence pattern of the pedigree shows X-linked hereditary. (B) Audiograms of the proband. The pure tone audiometry shows belated severe to profound HL. (C) The auditory brainstem response was not elicited by air conduction in the left ear and right ear at 105 dBnHL. (D) Temporal bone computed tomography of the proband demonstrates hypoplasia of cochlea and abnormal communication between the bottom of the internal auditory canal and the vestibule (red arrow head). All the findings were symmetric. (E) Sequencing chromatograms of *POU3F4*. The Sanger sequencing of proband and his family members. A heterozygous c.C76>T mutation was found in the female carriers and hemizygotic c.C76>T mutation was detected in the affected males. (F) A stop codon created by this *POU3F4* mutation results in a truncated protein. dBnHL: dB normalized hearing level; HL: Hearing loss; *POU3F4*: POU domain class 3 transcription factor 4.

mutation in *POU3F4* was absent in the 250 healthy controls, indicating that it was not a mere polymorphism.

A lack of functional POU3F4 protein probably disrupts the normal development of structures in the middle and inner ear, leading to HL.[4] Therefore, this mutation may be the cause of disease etiology of the pedigree. Patients with severe-to-profound hearing impairment due to *POU3F* mutation can benefit from cochlear implantation.[5] The proband (III: 4) underwent cochlear implantation after genetic and clinical diagnosis. Postoperative auditory performance demonstrated that he could respond to sounds. The effects of cochlear implantation and hearing evaluation are still under observation. His cousin (III: 5) also had unilateral cochlear implantation at age of 6 years before this genetic testing, and his language ability is developing well now. A perilymphatic flow (or "gusher") is a common feature in inner ear surgery of patients with DFNX2. Based on the radiological findings and genetic diagnosis, we could properly deal with the "gusher" in cochlear implant surgery of the proband. Pedigree analysis is an important approach to search for the underlying cause of HL. However, it is not enough when small pedigrees or sporadic cases with indefinite inheritance pattern are present. WES accelerates the speed and accuracy of genetic analysis and improves the quality of genetic counseling. The younger generation members (III: 1, III: 2, and III: 3), urged to know the fate of their offspring since both of their parents exhibited congenital HL. The WES results clearly showed that they did not inherit the mutation from their father. However, they carried some potential variants from their mother. Although the cause of HL of their mother is not clear, the high-throughput sequencing technology is beneficial for medication guidance, genetic counseling, and marriage and parenting guidance, and therefore, will help to effectively prevent or reduce the occurrence of hereditary HL in this family. To our best knowledge, this novel mutation (c.C76>T; p.Gln26*) may be the first one in the coding region of the *POU3F4* gene reported so far, according to the location. Another similar mutation (c.C79>T; p.Gln27*) was reported in a family from Poland.[6] It is worth noting that, in our report, the hearing ability of female carriers was normal, while the proband's mother harboring the heterozygous p.Gln27* mutation suffered from bilateral, pre-lingual, severe, and mixed type HL. A study on phenotype and genotype in females, unrelated mothers or sisters of boys presenting with typical DFNX2 phenotype due to *POU3F4* mutants, showed that a late-onset HL was found in three of the eight patients carrying different mutants and only one had an inner ear malformation. The researchers concluded that no genotype/phenotype correlation was identified.[7] All reports on *POU3F4* mutants in Chinese families demonstrated no penetrance in the carrier female members.[8,9] In this study, a novel non-sense mutation is identified in *POU3F4* gene in a Chinese family with X-linked non-syndromic HL. Based on the results of molecular diagnosis and the clinical data, we provided genetic counseling for the family members.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

None.

References

1. de Kok YJ, Merkx GF, van der Maarel SM, Huber I, Malcolm S, Ropers HH, *et al*. A duplication/paracentric inversion associated with familial X-linked deafness (DFN3) suggests the presence of a regulatory element more than 400 kb upstream of the POU3F4 gene. Hum Mol Genet 1995;4:2145–2150. doi: 10.1093/hmg/4.11.2145.
2. de Kok YJ, van der Maarel SM, Bitner-Glindzicz M, Huber I, Monaco AP, Malcolm S, *et al*. Association between X-linked mixed deafness and mutations in the POU domain gene POU3F4. Science 1995;267:685–688. doi: 10.1126/science.7839145.
3. Li J, Cheng J, Lu Y, Lu Y, Chen A, Sun Y, *et al*. Identification of a novel mutation in POU3F4 for prenatal diagnosis in a Chinese family with X-linked nonsyndromic hearing loss. J Genet Genomics 2010;37:787–793. doi: 10.1016/S1673-8527(09)60096-5.
4. Phippard D, Lu L, Lee D, Saunders JC, Crenshaw EB. Targeted mutagenesis of the POU-domain gene Brn4/Pou3f4 causes developmental defects in the inner ear. J Neurosci 1999;19:5980–5989. doi: 10.1523/JNEUROSCI.19-14-05980.1999.
5. Smeds H, Wales J, Asp F, Lofkvist U, Falahat B, Anderlid BM, *et al*. X-linked malformation and cochlear implantation. Otol Neurotol 2017;38:38–46. doi: 10.1097/MAO.0000000000001253.
6. Pollak A, Lechowicz U, Kedra A, Stawinski P, Rydzanicz M, Furmanek M, *et al*. Novel and de novo mutations extend association of POU3F4 with distinct clinical and radiological phenotype of hearing loss. PloS one 2016;11:e0166618. doi: 10.1371/journal.pone.0166618.
7. Marlin S, Moizard MP, David A, Chaissang N, Raynaud M, Jonard L, *et al*. Phenotype and genotype in females with POU3F4 mutations. Clin Genet 2009;76:558–563. doi: 10.1111/j.1399-0004.2009.01215.x.
8. Huang BQ, Zeng JL, Yuan YY, Dai P. A novel mutation in POU3F4 in a Chinese family with X-linked non-syndromic hearing loss. J Otol 2015;10:78–82. doi: 10.1016/j.joto.2015.09.004.
9. Du W, Han MK, Wang DY, Han B, Zong L, Lan L, *et al*. A POU3F4 mutation causes nonsyndromic hearing loss in a Chinese X-linked recessive family. Chin Med J 2017;130:88–92. doi: 10.4103/0366-6999.196565.

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