Case Report

A Chinese Family with Dominant Deafness-onychodystrophy Syndrome

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Abstract
Dominant deafness-onychodystrophy syndrome (DDOD syndrome; MIM 124480) is a rare disorder characterised with congenital sensorineural hearing loss accompanied by dystrophic or absent nails. We herein report a family with two members with congenital sensorineural hearing loss and dystrophic or absent nails via autosomal dominant transmission. Genetic analysis showed an ATP6V1B2 mutation (c.1516C>T (p.Arg506X)) in the two patients. The phenotypes described in our family were similar with those reported families. Our findings supported the evidence that ATP6V1B2 gene mutation may cause DDOD syndrome; and this family's conditions were within the spectrum of DDOD, which will provide valuable hints on diagnosis of this disease.

Key words
Dominant deafness-onychodystrophy syndrome; Hearing loss; Mutation

Introduction
Dominant deafness-onychodystrophy syndrome (DDOD syndrome; MIM 124480) is a rare disorder, which is characterised mainly by congenital sensorineural hearing loss accompanied by dystrophic or absent nails.1 Up to now, ten families with DDOD syndrome in various ethnic populations have been reported.1-3 Yuan et al1 reported three unrelated Chinese DDOD pedigrees with identical phenotypes including severe congenital sensorineural hearing loss, absence of nails and aplasia of the middle phalanx in the fifth fingers. They identified a de novo mutation (c.1516C>T (p.Arg506X)) in ATP6V1B2 as the cause of DDOD syndrome in the affected patients. It's the first report on the genetic cause of DDOD syndrome.

Herein, we report a family with two members with congenital sensorineural hearing loss and dystrophic or absent nails via autosomal dominant transmission. Genetic analysis showed an ATP6V1B2 mutation (c.1516C>T (p.Arg506X)) in the two members. Clinical characteristics and molecular analysis results were described, and this report will add to the knowledge of DDOD syndrome diagnosis.

Case Report
This study has been approved by the Institutional Review Board of Children's Hospital, Zhejiang University. We have obtained a written consent for reporting this pedigree from the family members. The pedigree's data were collected from March 2014 to August 2014. The proband is a girl aged five months with hearing loss and hypoplastic nails on fingers and toes. Her mother had congenital deafness with unknown cause; her father was 23 years old with congenital hearing loss and similar hypoplastic nails on fingers and toes. Both of her parents had normal intelligence and facial appearance. The proband was born vaginally at term (38 weeks) without birth asphyxia after an uneventful...
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The girl was found with absence of nails on the first and fifth fingers and on all the toes; all fingers and toes were short and small, and aplasia of the terminal phalanx in the fifth toe was found (A&B); her father had similar features (C&D); X-ray on the daughter (E&F) and father (G&H) showed small phalanges in the first and fifth fingers, distal phalanx of the second, third and fourth fingers appeared to be thinner than normal and small phalanges of all five toes except the big toe.
five toes were all small except the big toe (Figure 1). Neuropsychiatric exam on the proband showed normal physical and intellectual development. The proband's father was found deafness since infancy, who had similar presentations with toenails completely absent with short terminal phalanxes; all fingers and toes were also short and small, and small terminal phalanx in the fifth toe was also found (Figure 1). The proband's uncle was healthy with normal hearing. Both the proband's grandparents were normal and healthy. They denied deafness in the other family members including the grandmother's five siblings and grandfather's two siblings. The proband's mother's family members were all normal with normal hearing.

Genomic DNA from the two patients and four healthy members of this family was isolated from peripheral blood; molecular analysis was done, and all exons and intron-exon boundaries of ATP6V1B2 (NM_001693.3) were amplified by PCR from genomic DNA. The variant was tested by Sanger sequencing. A heterozygous c.1516 C>T (p.Arg506X) mutation in ATP6V1B2 was found in the proband and her father. The other four healthy members showed normal results (Figure 2).

**Discussion**

"Deafness and onychodystrophy" (DOD) is a rare congenital disease with either autosomal dominant or recessive inheritance. The recessive form, DOOR syndrome (deafness, onychodystrophy, osteodystrophy, mental retardation and seizures; MIM 220500), was more severe. Differentiated from DDOR syndrome, patients with DDOD syndrome had normal intelligence and no seizures. Yuan et al firstly reported the aetiology of DDOD in three Chinese pedigrees. They identified an ATP6V1B2 c.1516 C>T mutation in three independently identified DDOD patients.

![Figure 2](A heterozygous c.1516 C>T (p.Arg506X) mutation in ATP6V1B2 was found in the proband (A) and his father (B). The other four healthy members showed normal results (C).)
which provides evidence that defect in ATP6V1B2 is the genetic aetiology for DDOD syndrome. A cochlea-specific Atp6v1b2-knockdown mouse model revealed that Atp6v1b2 deficiency leads to severe sensorineural hearing loss. Therefore, we highlighted ATP6V1B2 gene in our pedigree and found the same mutation, c.1516 C>T.

The probands in Yuan's report displayed identical phenotypes including severe congenital sensorineural hearing loss, absence of nails and aplasia of the middle phalanx in the fifth fingers. None showed inner ear malformation and intellectual disability. Our patients had very similar features with those three families. They all had hearing loss, absence of nails and aplasia of the phalanx in the fingers. Absent/hypoplastic nails and deafness were the characteristic manifestations of DDOD, which were reported in all the ten families. Bulbous swelling of terminal phalanges were found in four families, which was not found in our patients; Our family had short distal phalanges which was reported in other two DDOD families. Three families reported dental anomalies (late dentition, small or conical teeth, oligodontia), which was not found in our family as well as Yuan's three families. White and Fahey also reported dysmorphic facial features, aplasia cutis and epilepsy. Vind-Kezunovic et al indicated that when hearing loss and nail abnormalities coexist in three family members, a common cause is to be suspected; as the skin and the nails, together with the membranous labyrinth of the inner ear, are derived from the embryonic ectoderm. In the present pedigree, both father and daughter have same presentations of hearing loss and nail abnormalities. However, the other family members were all normal. We suggested that the father may have a de novo mutation and the daughter inherited from the father under an autosomal dominant way.

In summary, we identified a mutation (c.1516 C>T (p.Arg506X)) in ATP6V1B2 as the cause of DDOD syndrome in the family. The mutation was consistent with those reported in the other three Chinese families. The phenotypes described in our family were similar with those reported families though with some variants in other families. Our findings supported the evidence that ATP6V1B2 gene mutation may cause DDOD syndrome.

**Ethical Statement**

This study has been approved by Institutional Review Board of Children's Hospital, Zhejiang University. We have obtained the written consent for reporting this pedigree from the family members. The consent has been documented and reviewed by the Institutional Review Board and stored at the Institutional Review Board office. A copy of the English version of the approval has been uploaded for reviewing.

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**Conflict of Interest**

None

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**References**