Dominant deafness–onychodystrophy syndrome caused by an ATP6V1B2 mutation

Ibis Menendez¹, Claudia Carranza², Mariana Herrera², Nely Marroquin², Joseph Foster II¹, Filiz Basak Cengiz¹, Guney Bademci¹ & Mustafa Tekin¹,³

¹John P. Hussman Institute for Human Genomics, University of Miami Miller School of Medicine, Miami, Florida, USA
²Institute for Research on Genetic and Metabolic Diseases, INVEGEM, Guatemala City, Guatemala
³Department of Human Genetics, Dr. John T. Macdonald Foundation, University of Miami Miller School of Medicine, Miami, Florida, USA

Correspondence
Mustafa Tekin, Department of Human Genetics, University of Miami, 1501 NW 10th Avenue, BRB-610 M-860, Miami, FL 33136, USA. Tel: 305-243-2381; Fax: 305-243-2704; E-mail: mtekin@miami.edu

Funding Information
INVEGEM, The Rozas-Botran Foundation from Guatemala, and supported by National Institute of Health grants (R01DC009645 and R01DC012836).

Received: 8 April 2016; Revised: 25 October 2016; Accepted: 6 November 2016

Clinical Case Reports 2017; 5(4): 376–379
doi: 10.1002/ccr3.761

Key Clinical Message

Our report clarifies the role of ATP6V1B2 in patients with deafness and onychodystrophy and confirms that a recurring ATP6V1B2 c.1516C>T [p.(Arg506*)], variant causes dominant deafness–onychodystrophy (DDOD) syndrome.

Keywords
ATP6V1B2, deafness–onychodystrophy–osteodystrophy–mental retardation–seizures, dominant deafness–onychodystrophy, whole-exome sequencing, Zimmermann–Laband syndrome.

Introduction

Dominant deafness–onychodystrophy (DDOD; MIM 124480), deafness–onychodystrophy–osteodystrophy–mental retardation–seizures (DOORS; MIM 220500), and Zimmermann–Laband (ZL; MIM 135500) syndromes are characterized by the association of sensorineural deafness and onychodystrophy. DDOD and ZL are autosomal dominant conditions, and DOORS is autosomal recessive. Patients with DDOD syndrome have normal development and cognitive functions [1–3], while those with DOORS and ZL syndromes, intellectual disabilities and seizures have been reported [4, 5]. Additional findings in ZL syndrome include gingival enlargement, hypertrichosis, joint hyperextensibility, and hepatosplenomegaly. Pathogenic variants in TBC1D24 (MIM 613577) [4] and KCNH1 (MIM 603305) [5] cause DOORS and ZL syndromes, respectively. A pathogenic c.1516C>T [p.(Arg506*)] variant in ATP6V1B2 has recently been reported to cause DDOD syndrome in three simplex cases [6]. In a subsequent report, however, another ATP6V1B2 variant c.1454G>C [p.(Arg485Pro)] was reported to cause ZL syndrome in two simplex cases [5]. It remains unknown whether reported patients with DDOD syndrome and an ATP6V1B2 variant had additional findings of ZL syndrome because those details were not available in the original report [6]. Here, we describe our clinical and molecular studies in the diagnosis of a simplex patient with deafness–onychodystrophy.

Patient Report

The proband is the second child of nonconsanguineous healthy Guatemalan parents. Two sisters are healthy (Fig. 1). He was born via normal spontaneous vaginal delivery at term following an uneventful pregnancy. Birth weight was 3060 g. Initial examination revealed bilateral digital anomalies in hands and feet. Audiological examination by auditory brainstem responses (ABR) at 1 year of age indicated profound bilateral sensorineural hearing
impairment. At the age 12 years, his height, weight, and head circumference measure 146 cm (25–50 percentile), 48 kg (75–90 percentile), and 56 cm (90 percentile), respectively. He has a high forehead with dolichocephaly, bilateral triphalangeal thumbs without nails, hypoplastic fingernails from second to fifth fingers, flat feet with absent toenails (Fig. 1). He does not have gingival hyperplasia, hypertrichosis, organomegaly, or joint hyperextensibility. Neurological examination followed by EEG, brain CT scan, and MRI did not show abnormalities. He does not communicate orally, but a rudimentary sign language was present. Bilateral sensorineural severe-profound hearing loss was documented (Fig. 2). Family history was negative for deafness, nail dysplasia, and intellectual disabilities.

This study was approved by the University of Miami Institutional Review Board (USA) and Guatemala National Health Ethics Committee. After written informed consents were collected, DNA was extracted from peripheral blood samples by standard procedures. Whole-exome sequencing in the proband was performed as previously reported [7].

Figure 1. (A) Normal face, (B) X-ray of the right hand triphalangeal thumb, (C) No gingival hyperplasia, and (D and E) aplastic/hypoplastic fingernails and absent of all toenails.

Figure 2. (A) Pedigree, (B) partial sequence of exon 14 in ATP6V1B2 gene showing the heterozygous c.1516C>T [p.Arg506*] variant in the proband and the wild-type sequence, and (C) audiogram showing bilateral sensorineural hearing loss.
Whole exome sequencing (WES) was performed only in the proband [7]. Targeted exonic regions were covered 100%, 96%, and 88% in read depth of 1X, 5X, and 10X, respectively. In total, 82,594,033 number of reads, 92,131 base substitutions (synonymous, nonsynonymous, intronic), and 8277 insertions/deletions were detected. Variants were filtered as previously published [7] in all modes of inheritance patterns, followed by filtering for Mendelian genes previously reported in OMIM Morbid.

The proband was found to be heterozygous for c.1516C>T [p.(Arg506*)] in ATP6V1B2 (NM_001693.3). Sanger sequencing confirmed the variant only in the proband and excluded the variant in parents and sisters (Fig. 2). We did not test the parental identities with additional markers.

Table 1. Genetic and clinical characteristics of individuals with deafness-onychodystrophy syndrome and/or ATP6V1B2 mutations.

| No. of affected individuals | Diagnosis | Vind-Kezunovic et al. [2] | White et al. [3] | Kortüm et al. [5] |
|----------------------------|-----------|--------------------------|-----------------|------------------|
| 1                         | DDOD      | DDOD                     | DDOD            | DDOD             |
| 3                         | ATP6V1B2  | ATP6V1B2                 | ND              | ATP6V1B2         |
| 3                         | ND        | ND                       | ND              | p.(Arg485Pro)    |
| 1/1                       | De novo   | De novo                  | AD              |                  |
| 1/2                       |           |                          |                 |                  |

| Coarse facies             | –         | –                        |                 | 2/2              |
| Absent/hypoplastic finger nails | 1/1     | 3/3                      | 3/3             | 3/3              |
| Deafness                  | 1/1       | 3/3                      | 3/3             | 3/3              |
| Absent/hypoplastic toe nails | 1/1     | 3/3                      | 3/3             | NR               |
| Aplastic/hypoplastic phalanges | 1/1     | 3/3                      | 1/3             | 1/2              |
| Brachydactyly             | 1/1       | 3/3                      | 3/3             | 1/2              |
| Scoliosis                 | –         | NR                       | NR              | 1/2              |
| Gingival enlargement      | –         | NR                       | NR              | 2/2              |
| Hypertrichosis            | –         | NR                       | NR              | 2/2              |
| Intellectual disability   | –         | 1/3                      | –               | 2/2              |
| Inheritance               | De novo*  | De novo                  | AD              | De novo          |

*, absent; ND, not determined; NR, not reported finding; AD, autosomal dominant; ZLS, Zimmermann–Laband syndrome; DDOD, dominant deafness–onychodystrophy syndrome.

| *While samples from neither parent shows the variant, parental identities were not checked with DNA markers.

Discussion

Deafness and onychodystrophy, although major diagnostic findings, fail to guide specific clinical diagnosis. Seizures and intellectual disabilities are used to differentiate DOORS from DDOD [1, 4, 6, 8]. Neurological and behavioral problems are common in children with severe-profound hearing loss. For instance in our patient, severe-profound prelingual sensorineural hearing loss and a long period of auditory deprivation without specific education led to a phenotype with limited social interactions. Time of deprivation, and nutritional and socioeconomic status have been associated with developmental delay and cognitive problems in deaf individuals [9, 10]. While ZL syndrome has additional features such as gingival enlargement and hypertrichosis, differential diagnosis is not always straightforward.

Interestingly, pathogenic variants in ATP6V1B2 have been reported to cause both DDOD and ZL syndromes [5, 6]. Table 1 summarizes phenotypic findings in ATP6V1B2-related disorders. It should be noted that the information about differentiating clinical features between DDOD and ZL syndromes was missing in the report associating an ATP6V1B2 variant with DDOD syndrome [5] (Table 1). In our patient, the p.(Arg506*) variant does not cause gingival hyperplasia, hypertrichosis, or organomegaly and is associated with DDOD syndrome. Individuals with the p.(Arg485Pro) variant on the other hand were reported to develop these additional findings and are diagnosed with ZL syndrome.

Acknowledgments

Support for this research was provided by INVEGEM, The Rozas-Botran Foundation from Guatemala, and supported by National Institute of Health grants R01DC009645 and R01DC012836 to MT.

Conflict of Interest

The authors declare no conflict of interests.

Authorship

All authors contributed extensively to the work presented in this study. IM, CC, GB, and MT: performed clinical
examination, interpreted the data, and wrote the manuscript. MH, NM, JF, and FBC: draw blood samples, obtained DNA, and conducted genetic studies.

References

1. Lin, H. J., E. D. Kakkis, D. J. Eteson, and R. S. Lachman. 1993. DOOR Syndrome (Deafness, Onycho-Osteodystrophy, and Mental Retardation): a new patient and delineation of neurologic variability among recessive cases. Am. J. Med. Genet. 47:534–539.

2. Vind-Kezunovic, D., and P. M. Torring. 2013. A Danish family with dominant deafness-onychodystrophy syndrome. J. Dermatol. Case Rep. 7:125–128.

3. White, S. M., and M. Fahey. 2011. Report of a further family with dominant deafness-onychodystrophy (DDOD) syndrome. Am. J. Med. Genet. A 155:2512–2515.

4. Campeau, P. M., D. Kasperaviciute, J. T. Lu, L. C. Burrage, C. Kim, M. Hori, et al. 2014. The genetic bases of DOORS syndrome: an exome sequencing study. Lancet Neurol. 13:44–58.

5. Kortüm, F., V. Caputo, C. K. Bauer, L. Stella, A. Ciolfi, M. Alawi, et al. 2015. Mutations in KCNH1 and ATP6V1B2 cause Zimmermann-Laband syndrome. Nat. Genet. 47:661–667.

6. Yuan, Y., J. Zhang, Q. Chang, J. Zeng, F. Xin, J. Wang, et al. 2014. De novo mutation in ATP6V1B2 impairs lysosome acidification and causes dominant deafness-onychodystrophy syndrome. Cell Res. 24:1370–1373.

7. Bademci, G., J. Foster, N. Mahdieh, M. Bonyadi, D. Duman, F. B. Cengiz, et al. 2016. Comprehensive analysis via exome sequencing uncovers genetic etiology in autosomal recessive nonsyndromic deafness in a large multiethnic cohort. Genet. Med. 18:364–371.

8. James, A. W., S. G. Miranda, K. Culver, B. D. Hall, and M. Golabi. 2007. DOOR syndrome: Clinical report, literature review and discussion of natural history. Am. J. Med. Genet. A 43A:2821–2831.

9. Kutz, W., C. Wright, K. R. Krull, and S. Manolidis. 2003. Neuropsychological testing in the screening for cochlear implant candidacy. Laryngoscope 113:763–766.

10. Monteiro de Souza, A. M., J. de Franca Barros, and B. M. de Souza Neto. 2012. Postural control in children with typical development and children with profound hearing loss. Int. J. Gen. Med. 5:433–439.