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Whole exome sequencing identifies a pathogenic mutation in WFS1 in two large Chinese families with autosomal dominant all-frequency hearing loss and prenatal counseling

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ABSTRACT

Objectives: To identify the pathogenic mutation and provide prenatal counseling and diagnosis in two large Chinese families with autosomal dominant all-frequency hearing loss.
Methods: Whole exome sequencing technology was used to identify the pathogenic mutation of the two families. In addition, 298 patients with sporadic hearing loss and 400 normal controls were studied to verify the mutation/polymorphism nature of the identified variant. Prenatal diagnosis was carried out.
Results: A rare missense mutation c.2389G > A (p.D572N) in the *Wolframin syndrome 1* (*WFS1*) gene was identified. It was reported in only one previous Chinese study, and never in other populations/ethnicities. The mutation was also found in one patient with sporadic hearing loss (1/298, 0.3%). A healthy baby was born after prenatal diagnosis.
Conclusion: Our findings strongly suggest that the c.2389G > A mutation in *WFS1* is associated with all-frequency hearing loss, rather than low- or high-frequency loss. So far, the mutation is only reported in Chinese. Prenatal diagnosis and prenatal counseling is available for these two Chinese families.

1. Introduction

Hearing loss is a common sensory disorder in humans. Non-syndromic hereditary forms are known to be genetically heterogeneous [1]. To date, 149 genetic loci for non-syndromic hereditary hearing loss have been mapped, and 102 responsible genes have been identified (Hereditary Hearing Loss Homepage, http://hereditaryhearingloss.org/, March 13th, 2017). As this condition is genetically heterogeneous and the identified genes do not explain all cases, it is still necessary to pursue new genes responsible for sensorineural hearing loss, which is not an easy task. Fortunately, whole exome sequencing (WES) now provides a powerful tool for identifying new pathogenic genes that cause hereditary auditory impairment [2]. WES has been widely used to identify pathogenic genes among families with a variety of genetic diseases, using only a few patients [3–6].

As a consequence of genetic heterogeneity, different mutations in the same gene may lead to distinct clinical phenotypes. One of such genes is the *WFS1* gene, which is associated with not only autosomal recessive Wolfram syndrome (WS, a progressive neurodegenerative disorder), but also with non-syndromic low-frequency sensorineural hearing impairment (LFSNHI). Homozygous or compound heterozygous variations in *WFS1* may lead to autosomal recessive inherited WS, in which the middle and high frequencies of audiograms are typically impaired [7]. In contrast, heterozygous variations in *WFS1* gene cause LFSNHI [8], which typically affects low frequencies first, but may later affect mid and high frequencies [9–13]. LFSNHI is most often inherited as an autosomal dominant trait, but some recessive or sporadic cases have also been reported [12,14,15].

In the present study, using WES, we identified two Chinese families with ADNSHL and one patient with sporadic hearing loss, all caused by the c.2389G > A (p.D572N) mutation in the *WFS1* gene. A girl with normal hearing was born after prenatal diagnosis showed no mutation. Unlike previous reports of *WFS1* mutations associated with low- or high-frequency hearing loss, this mutation presents all-frequency hearing loss in the two families with non-syndromic sensorineural, symmetrical bilateral, mild to profound, hearing loss. This mutation has been reported by only one Chinese study [16], and not in any other population worldwide. Our findings strongly suggest that this mutation

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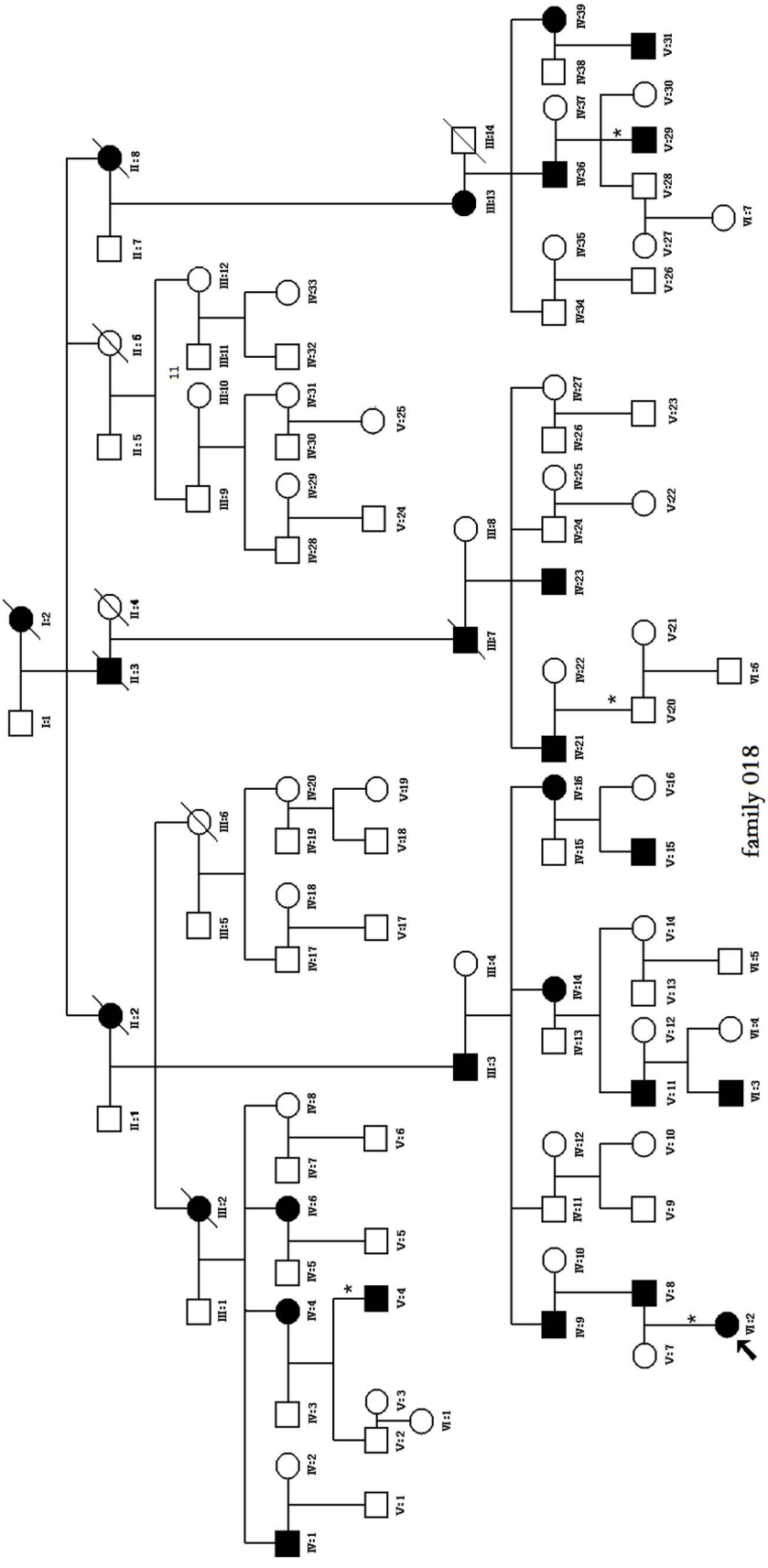

Fig. 1. Pedigree of the family 018 affected with congenital post-lingual, symmetrical, and bilateral non-syndromic sensorineural hearing loss.