THE GENOMIC ERA OF HEARING LOSS: REVISITING NON-SYNDROMIC FORMS AND THEIR MIMICS

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INTRODUCTION

Genetic hearing loss (HL) can occur as either a non-syndromic form or in association with additional clinical features (syndromic), with syndromic cases accounting for approximately 30% of genetic HL. The advent of molecular genetic testing has enabled early and accurate diagnosis of syndromes, particularly in instances of “phenotypic mimics of non-syndromic hearing loss” (NSHL). In these cases, two scenarios are commonly observed: (1) syndromic features develop later in life, or (2) some features remain subclinical or asymptomatic. Consequently, identifying a syndromic etiology in young individuals is often challenging, even when the underlying genes are known to be associated with syndromes that may manifest progressively over time.

AIM

To identify and characterize cases of apparent non-syndromic hearing loss associated with pathogenic variants or variants of uncertain significance (VUS) in genes previously reported as mimics of non-syndromic HL.

PATIENTS AND METHODS

We retrospectively analyzed genetic and clinical data from 99 individuals with HL who underwent panel sequencing. Those with variants in established syndromic genes were further evaluated through comprehensive clinical and family reassessment to detect phenotypic features indicative of the specific syndromes.

RESULTS AND DISCUSSION

Eight cases in the cohort harbored variants in five NSHL mimic genes: *USH1C*, *PEX6*, *BSND*, *HARS2*, and *WFS1* (Fig. 1).

In *USH1C*, two unrelated individuals with profound prelingual HL carried homozygous variants, but neither exhibited vestibular or ophthalmological complaints at the time of evaluation.

PEX6 compound heterozygous variants were detected in two cases; one was later diagnosed with enamel defects in permanent teeth, suggestive of Heimler syndrome, while the other was still too young for permanent teeth assessment (Fig. 2).

A *BSND* variant associated with Bartter syndrome type 4A, was identified in a patient with prenatal polyhydramnios and prelingual HL (Fig. 3).

In *HARS2*, associated with Perrault syndrome, biallelic variants were observed in a progressive HL case. Though by age 27, there were no signs of primary ovarian insufficiency.

Two individuals carried candidate variants in exon 8 of *WFS1*, potentially compatible with Wolfram-like syndrome; nonetheless, clinical confirmation was not possible.

These findings highlight that variants in NSHL mimic genes can initially manifest as isolated HL, often delaying clinical recognition, diagnosis, and management. Genetic analysis enabled early detection of syndromic cases, allowing timely referral and monitoring before other clinical features appeared.

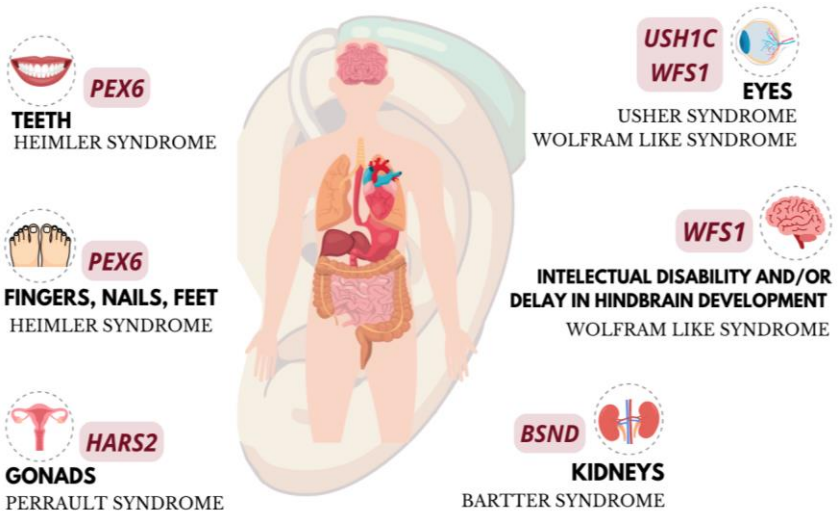

Fig. 1. Non-syndromic mimic genes implicated in hearing loss and the corresponding syndromic manifestations across various organs and tissues.

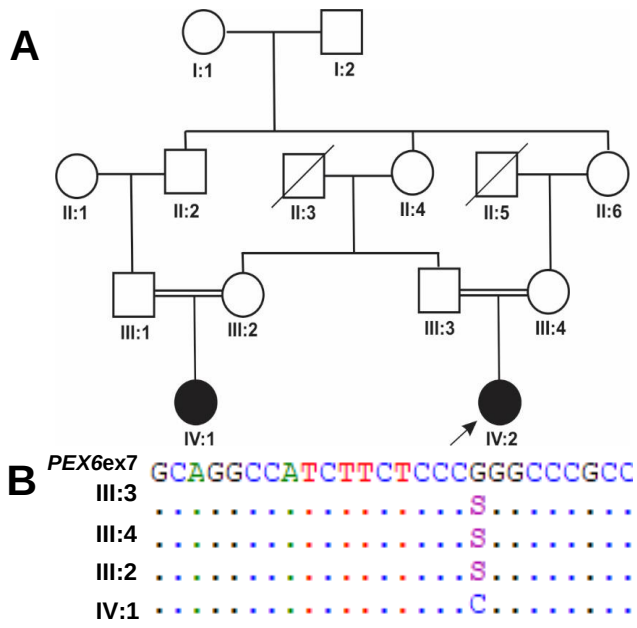

Fig. 2. A. Pedigree showing two cousins (IV:1 and IV:2) carrying a homozygous variant associated with Heimler Syndrome. **B.** Sequence alignment illustrating *PEX6* gene variants in heterozygous and homozygous states, respectively.

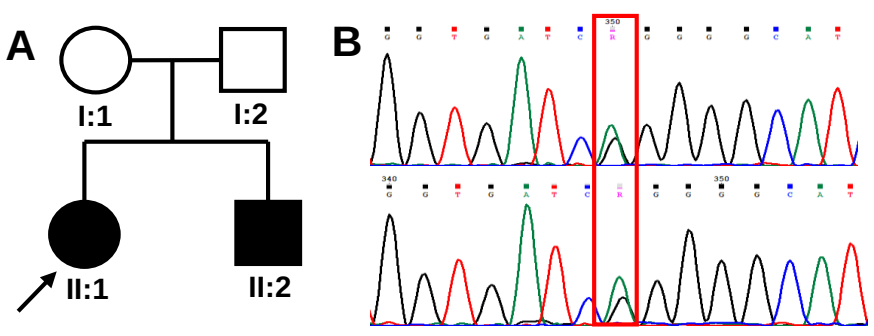

Fig. 3. A. Pedigree showing 2 brothers (II:1 and II:2) carrying a homozygous variant associated with Bartter Syndrome 4A. **B.** Chromatogram showing *BSND:* c.139G>A heterozygous variant in parents.

CONCLUSION

The identification of variants in patients initially classified as non-syndromic underscores the value of integrating clinical and genetic data. Systematic multidisciplinary reevaluation can enable earlier syndromic diagnosis and more personalized care.

REFERENCES

Vona B, 2025. Rethinking non-syndromic hearing loss and its mimics in the genomic era. *Eur J Hum Genet.* 33(2):147-150. PMID: 38443547.

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