Early Hearing Loss, Late Diagnosis: Why Genetic Testing Is Essential

S. E. Nikolova[1,2], Z. B. Kamburova[1,2], S. V. Murgova[1,2], G. I. Balchev[1,2], M. S. Tsvetkova[1,2]

[1]Medical University - Pleven, Pleven, Bulgaria, [2]Dr. Georgi Stranski University Hospital, Pleven, Bulgaria

BACKGROUNG

Congenital hearing loss is among the most common sensory disorders, affecting approximately 1–3 per 1000 live births [1]. Childhood-onset hearing loss is a clinically and genetically heterogeneous condition, which may occur as an isolated finding or as part of a syndromic disorder [2]. Hereditary causes account for approximately 50–60% of cases [3]. Differentiating acquired from hereditary etiologies may be challenging, particularly in the presence of ototoxic exposure. Usher syndrome is the most common cause of combined hereditary hereditary deaf-blindness, most frequently associated with variants in the *USH2A* gene [4].

CASE PRESENTATION

- 38-year-old female patient
- Bilateral hearing loss detected in early childhood
- History of gentamicin exposure → hearing loss initially attributed to ototoxicity
- No genetic testing was performed at that time
- In adulthood: progressive visual impairment and headaches
- Ophthalmological evaluation revealed findings consistent with retinitis pigmentosa, including attenuated retinal vessels, bone spicule pigmentation, pale optic discs, and retinal thinning on OCT

ACKNOWLEGMENTS

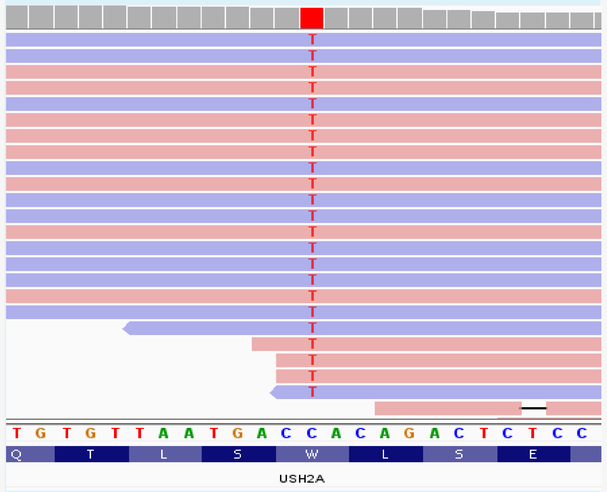
The present study was financed by the Project №18/2025 of Medical University – Pleven, Bulgaria. It was supported by Project BG16RFPR002-1.014-0002-C001, 'Centre of Competence in Personalized Medicine, 3D and Telemedicine, Robotic-Assisted and Minimally Invasive Surgery,' funded by PRIDST 2021-2027 and co-funded by the EU.

MATERIAL AND METHODS

- Next-generation sequencing (NGS) was performed using whole-exome sequencing (WES)
- Bioinformatic analysis focused on genes associated with hereditary hearing loss and retinal dystrophies
- Variant interpretation and pathogenicity classification were performed according to ACMG/AMP guidelines

RESULTS

Gene	USH2A
Variant	c.11864G>A
Protein change	p.Trp3955Ter
Zygosity	Homozygous
Variant type	Stop gained
ACMG classification	Pathogenic
Inheritance	Autosomal recessive
Disease	Usher syndrome, type 2



IGV visualization of the homozygous pathogenic *USH2A* c.11864G>A variant

INTERPRETATION

The identified homozygous *USH2A* variant is predicted to introduce **a premature stop codon**, resulting in a truncated, non-functional protein. It was classified as pathogenic according to ACMG/AMP criteria, including predicted loss of function in a gene where loss of function is a known disease mechanism **(PVS1)**, detection in the homozygous state in a patient with an autosomal recessive disorder **(PM3)** low frequency in population databases **(PM2)**, and a phenotype highly specific for the disease **(PP4)**. Variants in *USH2A* are associated with Usher syndrome, type 2, whose clinical phenotype corresponds to the patient's symptoms.

CLINICAL TIMELINE

Early childhood
Exposure to gentamicin

Early childhood
Bilateral hearing loss detected
Hearing loss attributed to ototoxicity

Adulthood
Progressive visual symptoms

Adulthood
Ophthalmological evaluation
Retinitis pigmentosa

Adulthood
Whole-exome sequencing performed

Final diagnosis
Usher syndrome type 2
(Molecular confirmation)

DISCUSSION

Childhood-onset hearing loss may present significant diagnostic challenges, particularly when potential environmental factors such as aminoglycoside exposure are present. In this patient, the history of gentamicin treatment initially supported an acquired etiology, delaying genetic evaluation for many years. The subsequent development of progressive visual impairment and retinal findings consistent with retinitis pigmentosa suggested a syndromic disorder. Molecular analysis identified a homozygous pathogenic *USH2A* variant, confirming the diagnosis of Usher syndrome, type 2. The presented case is consistent with current literature showing that variants in *USH2A* are among the most common causes of Usher syndrome, type 2. It also demonstrates the clinical utility of NGS and WES as effective diagnostic approaches in genetically heterogeneous disorders such as hereditary hearing loss. Early genetic testing may improve diagnostic accuracy, multidisciplinary management, and genetic counseling.

CONCLUSION

This case highlights the importance of early genetic testing in childhood-onset hearing loss, even when ototoxic risk factors are present. Genetic diagnosis of syndromic hearing loss enables appropriate surveillance, multidisciplinary management, and accurate genetic counseling and should be an integral part of the diagnostic workup.

REFERENCES

[1] A. E. Sutton and J. Goldman, "Syndromic Sensorineural Hearing Loss," in StatPearls, Treasure Island (FL): StatPearls Publishing, 2026. Accessed: May 28, 2026. [Online]. Available: http://www.ncbi.nlm.nih.gov/books/NBK526088/

[2] A. E. Shearer, M. S. Hildebrand, A. M. Odell, and R. J. Smith, "Genetic Hearing Loss Overview," in GeneReviews®, M. P. Adam, S. Bick, G. M. Mirzaa, R. A. Pagon, S. E. Wallace, and A. Amemiya, Eds., Seattle (WA): University of Washington, Seattle, 1993. Accessed: May 28, 2026. [Online]. Available: http://www.ncbi.nlm.nih.gov/books/NBK1434/

[3] CDC, "Data and Statistics About Hearing Loss in Children," Hearing Loss in Children. Accessed: May 28, 2026. [Online]. Available: https://www.cdc.gov/hearing-loss-children/data/index.html

[4] P. Mathur and J. Yang, "Usher syndrome: Hearing loss, retinal degeneration and associated abnormalities," Biochim. Biophys. Acta, vol. 1852, no. 3, pp. 406–420, Mar. 2015, doi: 10.1016/j.bbadis.2014.11.020.