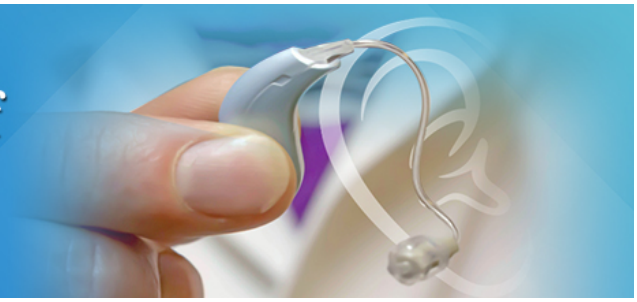
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Homozygous SLC26A5 variant in two siblings born to consanguineous parents: A case series of hereditary sensorineural hearing loss

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Abstract

Introduction: Genetic factors account for many cases of hearing loss present from birth or early childhood. The SLC26A5 gene provides instructions for making Prestin, a protein in the cochlear outer hair cells that helps amplify sound and supports normal hearing.

Case Reports: Two siblings born to consanguineous parents had bilateral sensorineural hearing loss. Case 1, an 11-year-old girl, had mild sloping Sensorineural hearing loss in the right ear and moderate sloping Sensorineural hearing loss in the left ear. Acoustic reflexes and distortion product otoacoustic emissions (DPOAEs) were absent bilaterally and auditory brainstem response (ABR) threshold estimates were in the mild to moderate range. She had used hearing aids since four years of age. Deafness gene panel testing identified a homozygous likely pathogenic nonsense variant in SLC26A5 (c.448C>T; p. Arg150Ter), consistent with autosomal recessive deafness 61 (DFNB61). Following this result, her 6.4-year-old brother (Case 2) underwent audiological evaluation despite the absence of parental concerns regarding his hearing. He had bilateral mild sensorineural hearing loss with reported mispronunciation of some speech sounds and inconsistent responses during conversation. Targeted genetic testing identified the same homozygous variant, which the laboratory classified as pathogenic. During a bilateral hearing aid trial, his aided speech discrimination score was 84%.

Conclusion: Comprehensive audiological assessment combined with molecular genetic testing helps establish the etiology of hereditary hearing loss in children. Cascade Audiological evaluation of siblings in consanguineous families can identify hearing loss that caregivers have not noticed, enabling timely intervention, rehabilitation and genetic counseling.

Keywords: SLC26A5, Prestin, Sensorineural hearing loss, Genetic testing, Early identification, Family screening

Introduction

Hearing loss is a common sensory disorder in children and can affect speech, language and communication development, particularly when identification and intervention as delayed. Genetic factors account for a substantial proportion of congenital and pre lingual hearing loss, although environmental and other acquired causes also contribute to its occurrence (Morton *et al.*, 2006; Smith *et al.*, 2005) [1, 2]. The wide range of genes associated with hereditary hearing loss makes identifying the underlying cause an important part of clinical evaluation (Shearer *et al.*, 2023) [3].

The SLC26A5 gene is of particular interest because it produces Prestin, a motor protein located in the cochlea's outer hair cells. These cells help to amplify the sound and help the ear to distinguish between frequencies (Zheng *et al.*, 2000; Dallos, 2008) [4, 5]. Changes in Prestin may disrupt these functions. However, the association of individual SLC26A5 variants with hearing loss in humans should be interpreted with caution as the evidence is not consistent across variants.

Consanguinity is essential factor for the assessment of hereditary disorders because parents related through a common ancestor are more likely to carry the same recessive disease-associated variant. If both parents carry a pathogenic variant in the same gene, their children may also inherited two altered copies and develop an autosomal recessive condition (Bittles, 2001; Hamamy, 2012) [6, 7]. Genetic testing can help establish the molecular basis of hearing loss, support clinical interpretation, and guide genetic counseling and family evaluation (Sloan-Heggen *et al.*, 2016; Shearer *et al.*, 2015) [8, 9].

Early identification of hearing loss is important for timely amplification, rehabilitation and support for speech and language development. Although newborn hearing screening and Audiological assessment are essential, a sibling may have unrecognized hearing difficulties even when caregivers have not expressed concerns. Combining Audiological evaluation with appropriate genetic testing can therefore provide clini

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cally useful information for affected children and their families (Joint Committee on Infant Hearing, 2019; Yoshinaga-Itano, 2003) [10, 11].

This case series describes two siblings born to consanguineous parents who presented with bilateral Sensorineural hearing loss and were found to carry the same homozygous SLC26A5 variant. This report highlights the role of comprehensive Audiological assessment, molecular Genetic evaluation and assessment of siblings in the clinical investigation of suspected hereditary hearing loss.

Case report

Family history

The children were born to consanguineous parents a second-degree consanguineous marriage as reported by the parents with no significant antenatal, perinatal or postnatal complications. There was no reported family history of hearing loss in previous generations. After hearing loss was identified in the elder sibling (Case 1), she underwent genetic testing, which identified a homozygous likely pathogenic variant in the SLC26A5 gene (c.448C>T; p.Arg150Ter), and audiological evaluation was advised for the younger sibling (Case 2). Parental genotypes were not available. Clinical findings are compared in Table 1 and the clinical timeline is shown in Table 2.

Case1

The elder sibling, an 11-year-old female presented with the complaint of reduced hearing sensitivity. Hearing loss was identified at the age of 4 years followed by COVID-19 infection. Previous audiological evaluation revealed bilateral moderate sensorineural hearing loss. Comprehensive audiological investigations were performed followed by genetic analysis. Appropriate audiological intervention including amplification was initiated. However no concerns were reported regarding the speech and language milestones. Otoscopic examination revealed intact tympani membrane bilaterally.

Pure Tone Audiometry revealed mild sloping sensorineural hearing loss in the right ear moderate sloping sensorineural hearing loss in the left ear (Fig 1.1). Tympanometry showed type A tympanograms with absent acoustic reflexes. Distortion product otoacoustic emissions (DPOAEs) were absent bilaterally. ABR threshold estimation click stimulus at the rate of 19.3/s using rarefaction polarity indicated mild to moderate hearing loss in both ears (Fig 1.2). Aided late latency responses showed P1-N1-P2-N2 peaks at 70dBnHL elicited with a 40ms /da/ stimulus presented at 1.1/s with alternating polarity.

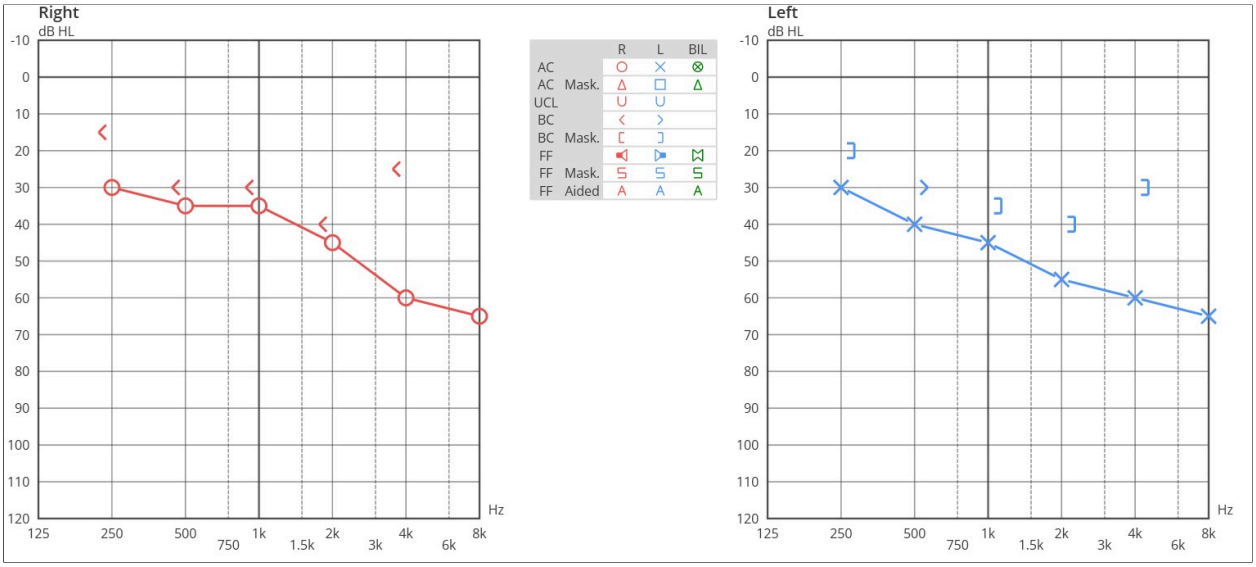


Figure 1.1. Pure tone audiogram of Case -1

Case 2

The younger sibling, a 6.4-year-old boy was referred for detailed Audiological evaluation because his parent reported mispronunciation of a few sounds and inconsistent responses during conversation. His motor and speech milestones were reported to be age appropriate. He had a history of adenoid problems and right-sided middle ear infections which were under medicated for 2 months. Genetic testing was performed (blood sample collected in June 2026) confirmed the same homozygous variant as in his sister. Pure tone audiometry revealed bilateral mild sensorineural hearing loss (Fig 1.3). Tympanometry showed type A tympanograms bilaterally. Distortion product otoacoustic emissions (DPOAEs) were absent bilaterally. ABR threshold estimation click stimulus at the rate of 19.3/s using rarefaction polarity indicated mild to moderate hearing loss in the right ear and mild hearing loss in the left ear (Fig 1.4). A hearing aid trial with bilateral receiver in canal (RIC) aids gave an aided speech awareness level of 25dBHL and a speech discrimination score of 84% with aided responses indicating audibility of the speech spectrum.

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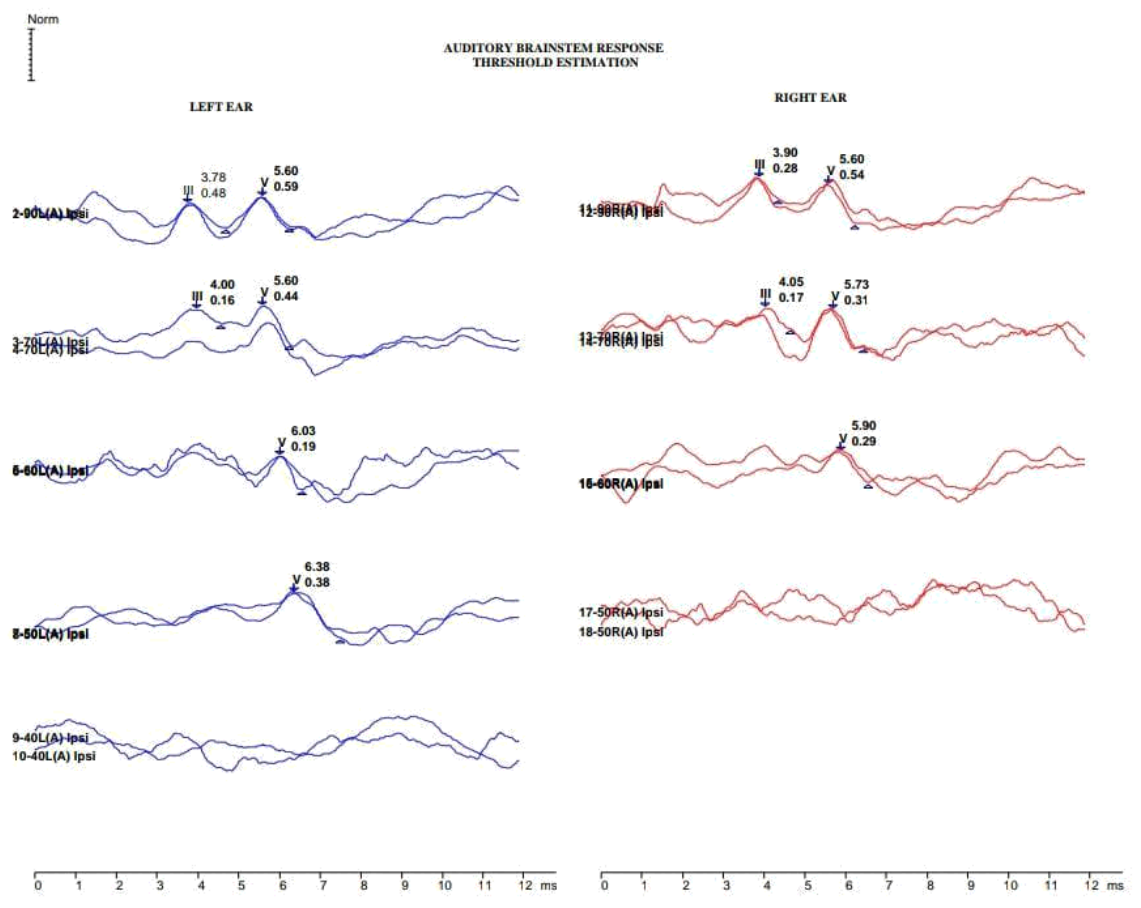


Figure 1.2. Auditory brainstem response of Case-1 (Threshold estimation)

Genetic analysis

Based on the clinical indication, deafness gene panel testing was advised by the referring clinician and performed for Case 1. It detected a homozygous nonsense variant in exon 6 of the SLC26A5 gene (c.448C>T; p.Arg150Ter). Using the available clinical scientific evidence and the American college of Medical Genetics and Genomics (ACMG) guidelines, the variant was classified as likely pathogenic. Following this, the same targeted deafness gene panel was performed for Case 2 revealed same homozygous variant (NM198999.3:c.448C>T; p.Arg150Ter; chr7:g.103411542G>A, GRCh38; read depth 88x), which the laboratory classified as pathogenic (PVS1 very strong, PM2 supporting, PP1 supporting). Homozygous pathogenic or likely pathogenic variants in SLC26A5 cause autosomal recessive deafness 61 (DFNB61). Sequencing of the parents was recommended to confirm segregation but parental genotypes were not available. Pre- and post- test genetic counseling was provided to the family, including the limitations of genetic testing and the recurrence risk in autosomal recessive inheritance (25% in each pregnancy when both parents are carriers).

Follow up and outcomes

Case 1 has used a *Signia* Pure C&G RIC hearing aid since the age of 4 years. Case 2 underwent a hearing aid trial with bilateral Rexton RIC hearing aids and bilateral fitting were recommended.

Table 1. Comparison of the clinical, audiological and genetic findings of the two siblings.

Characteristic	Case1	Case2
Age	11 years	6.4 years
Presenting complaint	Reduced hearing	Mispronunciation of certain words
Birth history	Normal	Normal
Degree of hearing loss	Mild sloping sensorineural hearing loss in right ear moderate sloping sensorineural hearing loss in left ear	Mild Sensorineural hearing loss in the both ears
Genetic analysis	Homozygous SLC26A5 variant (likely Pathogenic)	Homozygous SLC26A5 variant, same as Case 1 (Pathogenic)
Intervention	Using hearing aid from the age of 4 (*Signia* RIC)	Hearing aid trial done (Rexton RIC) ; bilateral fitting

Discussion

Several studies have demonstrated that pathogenic variants in the SLC26A5 gene are associated with impaired outer hair cell electromotility, resulting in sensorineural hearing loss (Takahashi *et al.*, 2024) [12, 13]. The clinical presentation may vary depending on the underlying variant and its effect on Prestin function (Dallos, 2008) [14].

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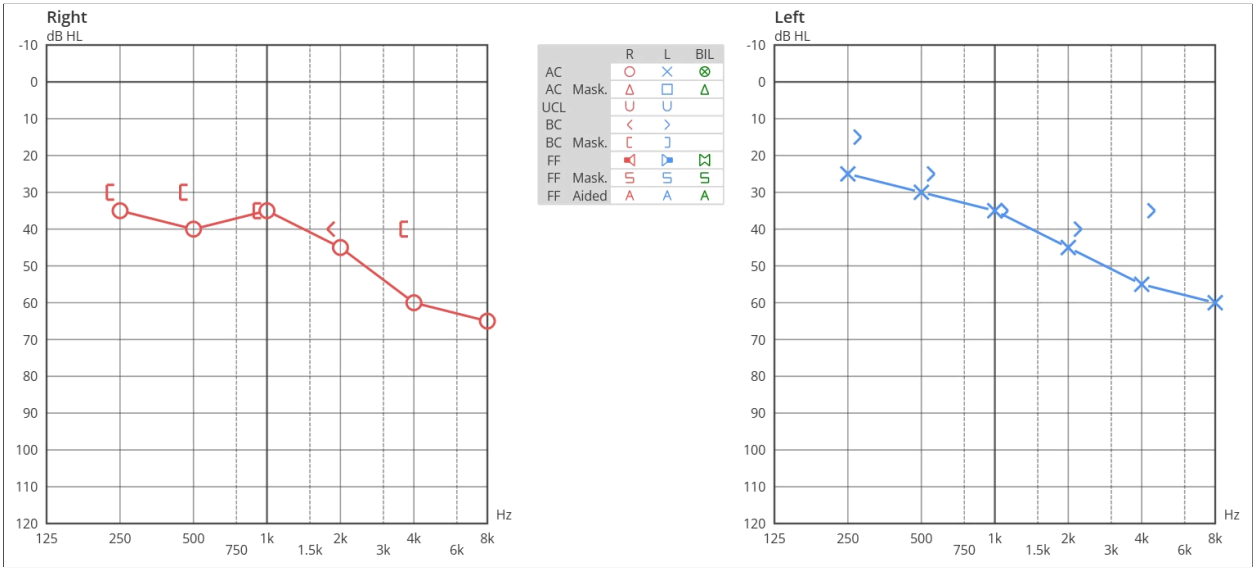


Figure 1.3. Pure tone audiogram of Case -2

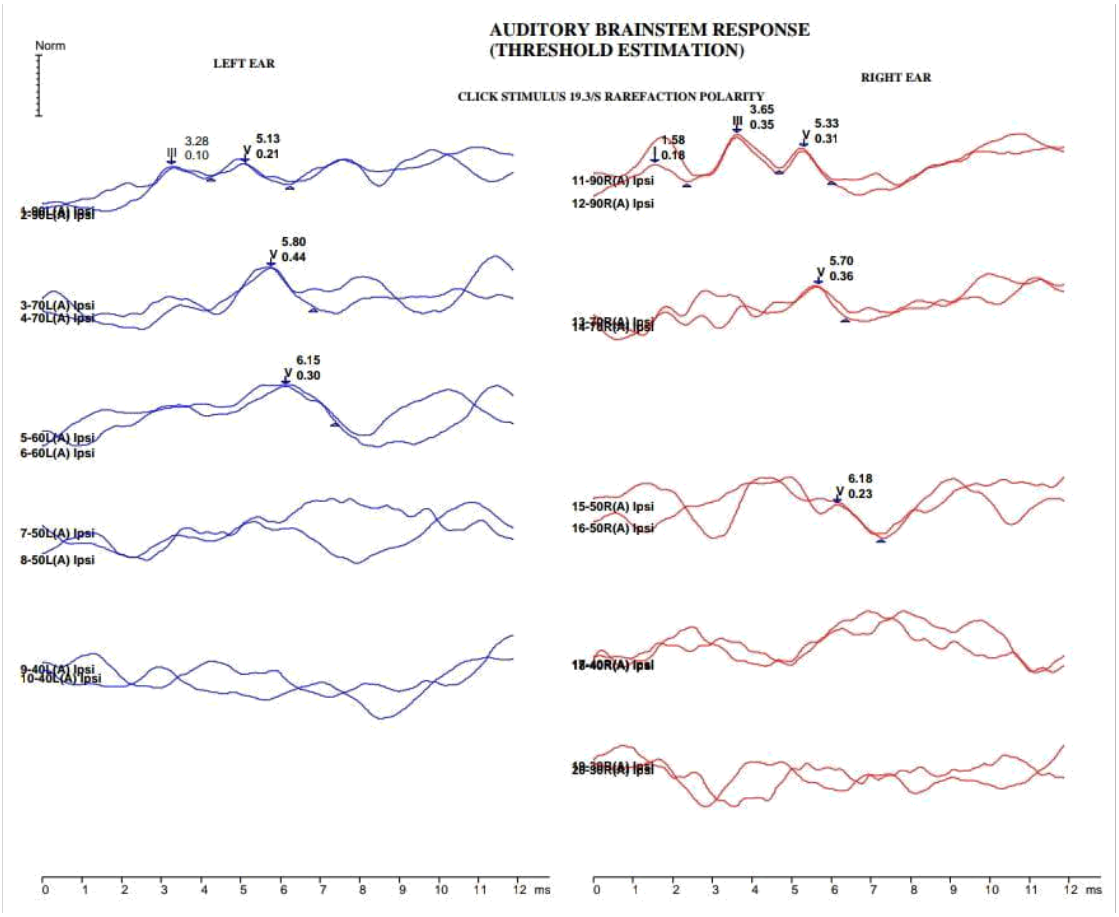


Figure 1.4. Auditory brainstem response of Case-2 (Threshold estimation)

Prestin, encoded by SLC26A5 driver outer hair cell electromotility and thereby cochlear amplification (Zheng *et al.*, 2000; Dallos, 2008) [4, 5]; loss of Prestin function is associated with autosomal recessive non-syndromic hearing loss (DFNB61) (Takahashi *et al.*, 2024) [12, 13]. In keeping with this mechanism, DPOAEs were absent bilaterally in Case 1 and suggested outer hair cell dysfunction in Case 2, while normal tympanometry in both siblings supports a cochlear rather than a middle-ear site of lesion. Absent DPOAEs indicate outer hair cell dysfunction but are not specific to SLC26A5, so the finding should be interpreted together with the genotype.

Consanguinity remains an important contributing factor to hereditary hearing loss in many populations because it increases the likelihood of homozygous pathogenic variants (Bittles *et al.*, 2010; Hamamy *et al.*, 2011) [15, 16]. In the present case series, both siblings born to consanguineous parents, were homozygous for the same SLC26A5 nonsense variant, consistent with an autosomal recessive pattern of inheritance. Parental testing, which would confirm that each parent is a carrier, was not available.

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Table 2. Clinical timeline of the two siblings.

Time point	Case 1 (elder sibling)	Case 2 (Younger sibling)
Birth	No significant antenatal, perinatal or postnatal complications	No significant antenatal, perinatal or postnatal complications
Age 4 years	Hearing loss identified; Audiological evaluation showed bilateral moderate Sensorineural hearing loss, hearing aid (*Signia* RIC) use began	-
After genetic results	Homozygous SLC26A5 variant reported; testing recommended for parents and genetic counselling provided	Same homozygous variant
Follow up	Currently she is using *Signia pure* C& G RIC hearing aid	Hearing aid trials was recommended

Genetic testing has become an important component of the diagnostic work up in children with bilateral Sensorineural hearing loss, allowing confirmation of the underlying molecular diagnosis and facilitating genetic counseling (Sloan-Heggen *et al.*, 2015; Alford *et al.*, 2014) [17, 18].

Early identification and intervention remain critical for optimizing auditory, speech, and language outcomes, highlighting the complementary roles of newborn hearing screening, comprehensive audiological assessment, and molecular genetic testing (Joint Committee on Infant Hearing, 2019; Yoshinaga-Itano, 1999) [10, 19].

A notable feature of this series is that the younger sibling was mild and came to attention through mispronunciation of a few sounds and inconsistent responses in conversation, with age -appropriate speech milestones, rather than overt hearing difficulty. Both siblings shared the same homozygous genotype and these findings support offering Audiological evaluation with periodic monitoring to siblings of children with confirmed hereditary hearing loss, particularly in consanguineous families, together with genetic testing of the affected children and parents to allow segregation analysis and recurrence-risk counseling.

Limitations

This report describes only two siblings. Parental genotypes are not available, so segregation of the variant could not be confirmed. In Case 2 the variant was identified by targeted next generation sequencing and was not confirmed by Sanger sequencing. In addition the variant was classified as likely pathogenic in the elder sibling's report and pathogenic in the younger sibling's report; clarification of this difference from the testing laboratory would strengthen the genetic interpretation.

Patient consent and ethics

Written informed consent for publication of this case series, including clinical details and images, was obtained from the parents/legal guardians of both children.

Conclusion

This case series highlights the clinical value of comprehensive audiological assessment, molecular genetic testing and family screening in identifying hereditary hearing loss associated with SLC26A5 gene mutations. Early diagnosis enables timely amplification, rehabilitation and genetic counseling.

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Authors' contributions

Author 1 contributed to data collection, evaluation, and manuscript preparation. Author 2 and Author 3 supervised the study and reviewed the manuscript.

Conflict of interest

The authors declare no conflict of interest.

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