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AUDIOLOGICAL FINDINGS IN OTOSPONDYLOMEGAEPIPHYSEAL DYSPLASIA (OSMED) ASSOCIATED WITH A NOVEL MUTATION IN *COL11A2*

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Abstract

Objective—The aim of the study was to assess the audiological findings of a 4-year-old child with a homozygous *COL11A2* mutation and to point out the role of continuous follow-ups in children with craniofacial syndromes after the newborn hearing screening.

Methods—A 4-year-old boy with otospondylomegaepiphyseal dysplasia (OSMED) was followed up after birth for hearing loss. Transient Otoacoustic Emissions (TEOAE's), Distortion Product Otoacoustic Emissions (DPOAE's), Automated and Clinical Auditory Brainstem Response (AABR and ABR) measurements, Visual Reinforcement Audiometry, immitansmetric measurements and hearing threshold measurements were performed for audiological evaluation.

Results—The patient developed sensorineural hearing loss at 11 months of age while his hearing was normal at birth. Because of auditory-verbal training with hearing aids started at 20 months of age, he now has normal verbal communication with his peers.

Conclusions—This study clearly demonstrates that hearing loss developes in infancy in patients with OSMED and underscrores the importance of contunied hearing screening beyond newborn period for early intervention of hearing impairment and communication problems.

Keywords

Newborn hearing screening; COL11A2 mutations; OSMED; sensorineural hearing loss

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Introduction

Otospondylomegaepiphyseal (OSMED; MIM 215150) dysplasia is an autosomal resessive disorder characterized by sensorineural hearing loss, shortness of the limbs, and spondyloepiphyseal dysplasia with large epiphyses [1-4]. Typical facial features are mid-face hypoplasia with depressed nasal bridge and a small nose. General view of the body is disproportionate short stature with short limbs.

A total of 12 different mutations in the *COL11A2* gene (GenBank NG_011589.1; MIM 120290) have been identified in patients with OSMED [3; according to the Human Gene Mutation Database Professional 2010.3 accessed in October 2010]. *COL11A2* is located at 6p21.3 and contains 66 exons coding for 1736 amino acids. Mutations or polymorphisms in *COL11A2* have also been reported to be associated with micrognathia, glossoptosis, nonsyndromic cleft palate, Kawasaki disease, and development of coronary artery lesions without hearing loss [5-7]. Hearing loss due to *COL11A2* mutations is the result of tectorial membrane dysfunction. A knock-out mice model with a homozygous deletion of *Col11a2* showed that the organization and strength of the fibers in the tectorial membrane were disrupted [8].

In this report we present the clinical findings with an emphasis on hearing loss associated with a novel homozygous *COL11A2* mutation in a 4-year-old child.

Clinical Report

This 4-year-old boy was born to consanguineous (second cousin) Turkish parents. Clinical features of the patient were summarized in Table 1. There was no family history of hearing loss. The study was approved by the Ethics Committee of Ankara University and by the IRB at the University of Miami. An informed consent from and permission for the publication of clinical photographs were signed by both parents.

The patient was first seen at the Pediatric Genetics Clinic of Ankara University when he was 3-1/2 months old. The diagnosis of OSMED was established based on midfacial hypoplasia with a flat nose and short upper extremities (Fig. 1a and b). Skeletal radiographs revealed shortening of the long bones and metacarpals as well as enlarged and flared metaphyses. The hights of anterior part of lower thoracal vertebral bodies were decreased (Fig. 2a, 2b and 2c). DNA sequencing of all coding exons and intron-exon boundaries of the *COL11A2* gene using a DNA sample obtained from peripheral blood of the proband revealed a homozygous c.3329delC (p.Pro1110Leufs235) mutation. Both parents were heterozygous for the mutation. The ophthalmological examination was first performed when the child was 9-1/2 months old and was normal. A recent examination showed normal findings as well.

Audiological findings

Newborn hearing screening results of the patient were normal for both Transient Evoked Otoacoustic Emissions (TEOAE's) and Automated Auditory Brainstem Response (AABR) measurements as recommended by the National Institutes of Health Consensus Development Conference in 1993 for Universal hearing screening [9]. One of them is the AABR measures average neural response to repeated sound signals, and the other is otoacoustic emissions detecting sound produced by movements of outer hair cells of the cochlea. This protocol typically has a sensitivity of % 92, and a specificity of % 98 [10].

At 3 and 1/2 months, TEOAEs and AABR measurements were bilateraly positive again. TEOAEs and Distortion Product Otoacoustic Emissions (DPOAEs) were measured with ILO-92 equipment (Institute for Laryngology and Otology, London, England). AccuScreen

PRO (MADSEN-GN Otometrics, Taastrup, Denmark) was used for AABR measurements. Bilateral midle ear pressure were 0 daPa and acoustic reflexes were positive.

At 11 months, results of TEOAEs and DPOAEs showed no emissions in either ear. Results of tympanometry were -64 daPa atmospheric pressure in the right ear, -108 daPa atmospheric pressure in the left ear. Bilateral acoustic reflex were positive.

At 17 months, hearing threshold levels were obtained with bilateral sensorineural hearing loss of 70 dB HL (with visual reinforcement audiometry), which are shown in Fig. 3. Hearing mesurement was performed within soundproof rooms, using an AC-40 audiometer (Interacoustics, Assens, Denmark). Clinical ABR threshold measurement was obtained at a threshold of 50 dB HL for click stimulation. Results of tympanometry were 0 daPa atmospheric pressure in both ears. AZ-26 (Interacoustics, Assens, Denmark) was used for immitansmetric measurements. Bilateral hearing aids were prescribed to the child at 20 months.

Current audiological findings at 4 years of age showed moderate sensorineural hearing loss of 48 dB Hearing Level (HL) in the right ear and moderate-severe sensorineural hearing loss of 60 dB HL in the left ear. Pure tone hearing threshold measurements were done between 125 and 6000 Hz, according to International Standards Organisation (ISO), 1964. Hearing thresholds of both ears are shown in Fig. 4. Speech Awereness Threshold (SAT) was 40 dB HL in the right ear and 50 dB HL in the left ear. He used hearing aids on regular basis after 20 months of age and his verbal communication was the same level as that in peers.

Clinical ABR measurements were done with ECLIPSE EP25 model Brainstem Evoked Response Audiometer (Interacoustics, Assens, Denmark). Clinical ABR outcomes were obtained for click stimulation and are shown in Fig. 5.

Educational Findings

The patient has attended auditory-verbal training with his mother regularly for two years. There were no behaviour and attention problems during the training. He was assessed in terms of general development, receptive and expressive language skills, speech intelligibility and auditory performance. Preschool Language Scale (PLS) is used to evaluate the language skills of patient and targets receptive and expressive language skills [11]. As the PLS test scores, his age of receptive and expressive language were found to be consistent with his chronologic age. Denver II is the most widely used developmental screening tests in the world and is used to evaluate the general development of the child [12]. As the Denver II test scores, his gross/fine motor, personal-social and language development were found to be consistent with his chronologic age. Speech Intelligibility Rating is a time effective global outcome measure of speech production in real-life situations [13,14]. His Speech Intelligibility Rating was 4 during the assessment, according to Speech Intelligibility Rating criteria (Table 2). His auditory performance was assessed by Categories of Auditory Performance test comprises a hierarchical scale of auditory perceptive ability [15,16]. His categories of auditory performance was 5 according to the Categories of Auditory Performance (Table 3).

Discussion

The Joint Committee on Infant Hearing determined 10 risk indicators (one of them is the presence of syndromic findings) for audiologic monitoring in infants until two years of the age with normal hearing on newborn screening [17]. Accordingly, this child was continued to be followed for hearing loss with the diagnosis of a syndrome, OSMED. As a result,

hearing loss was identified as early as possible and the child received successful intervention.

Although hearing loss is a known finding in OSMED, details of hearing phenotype are not well described. Audiological findings in this study and those of previously reported patients with *COL11A2* mutations in the literature are summarized in Table 4. Mutations in *COL11A2* are associated with two other syndromes that are autosomal dominantly inherited, nonocular Stickler syndrome type III (MIM 184840) and Weissenbacher-Zweymuller syndrome (also referred to as heterozygous OSMED; MIM 277610) and with non-syndromic autosomal dominant (DFNA13; MIM 601868) as well as autosomal recessive (DFNB53; MIM 609706) sensorineural hearing loss. Some details of hearing phenotype are missing in publications related to *COL11A2* mutations. Our study is the only one where newborn hearing screening results and ABR measurements are available, which clearly demonstrate the age of onset of sensorineural hearing loss in OSMED. An excellent outcome due to early detection and intervention of hearing loss in our patient underscores the importance of longitudinal follow ups in children with syndromic findings.

Acknowledgments

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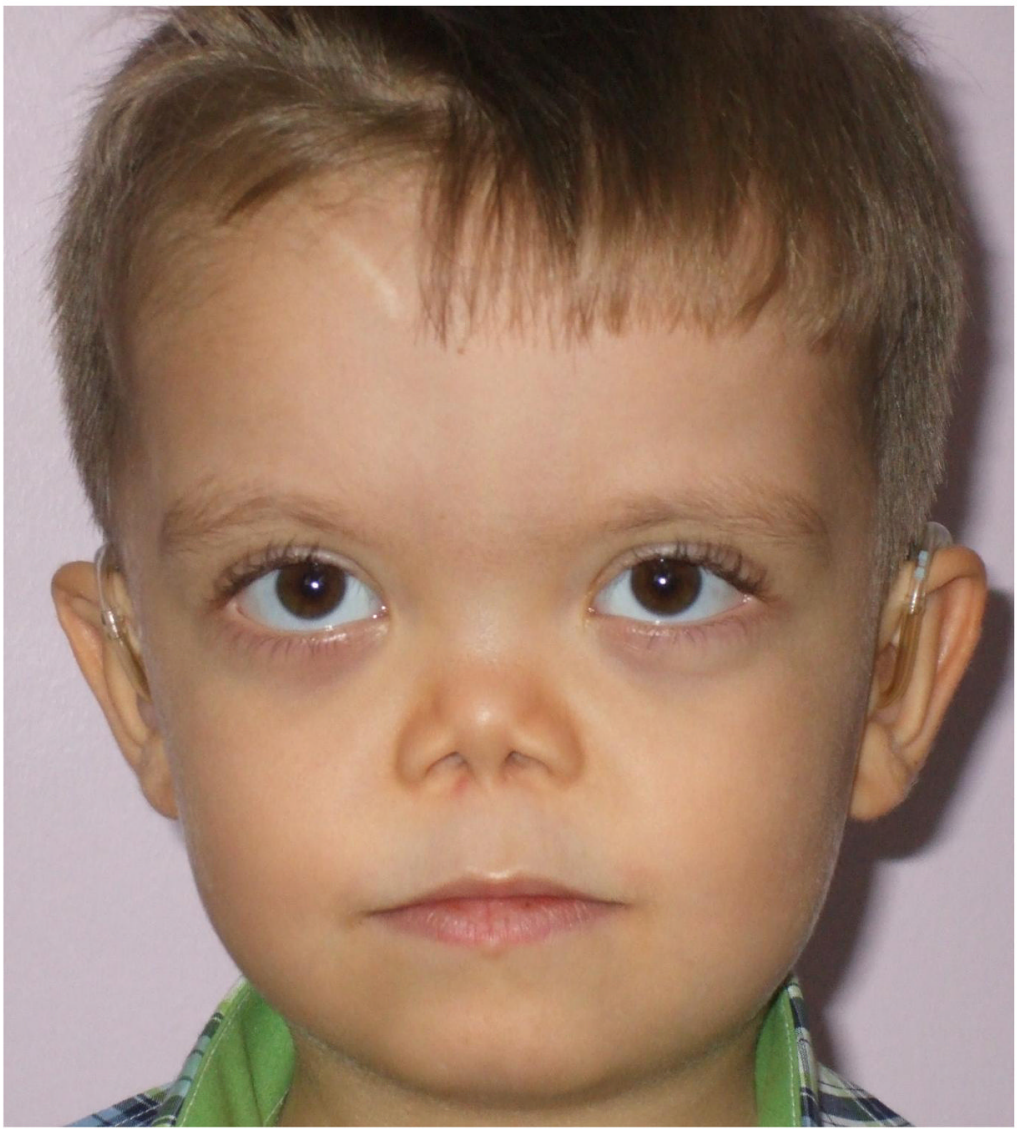


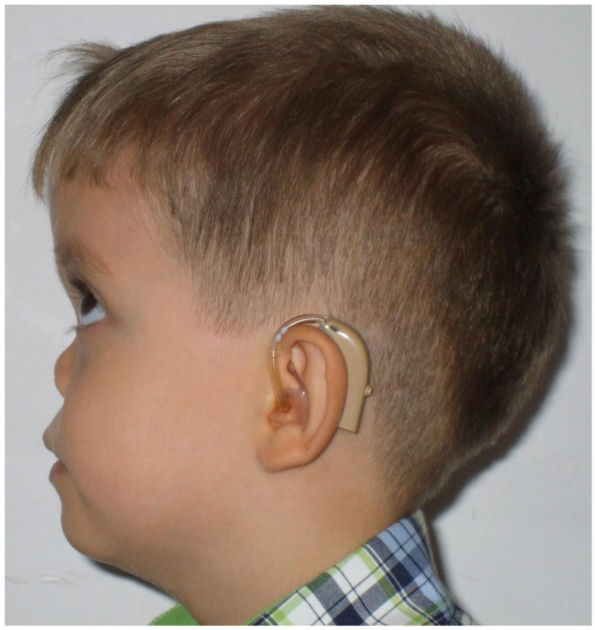
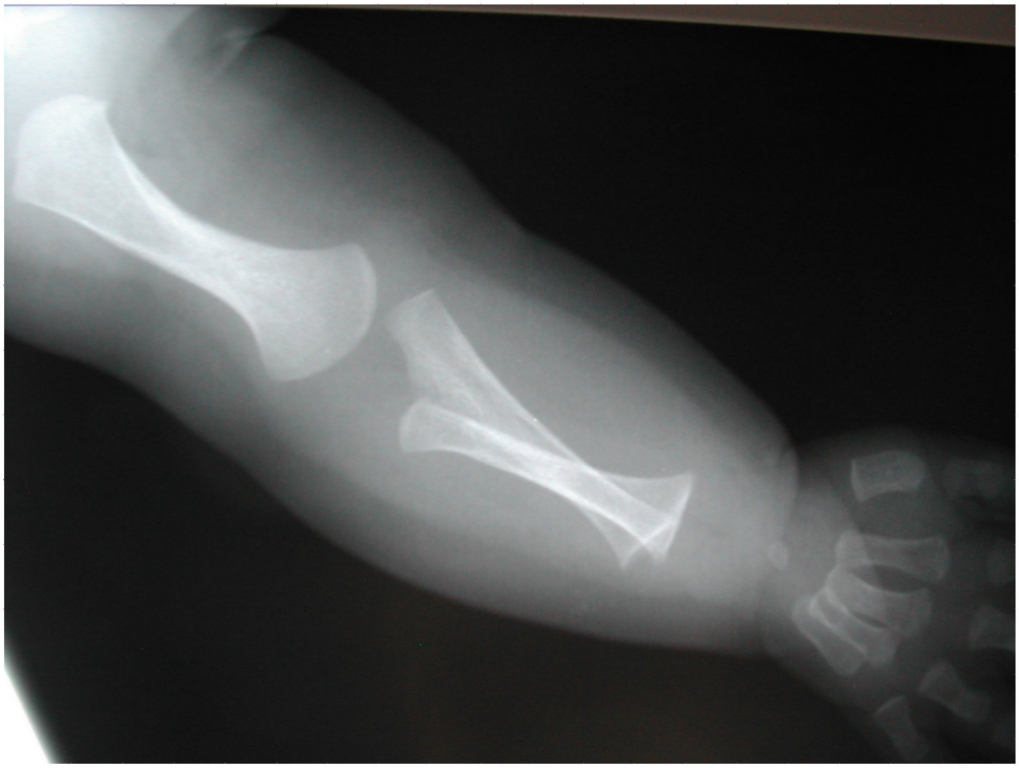


Figure 1.
a and b: Current appearance of the proband.



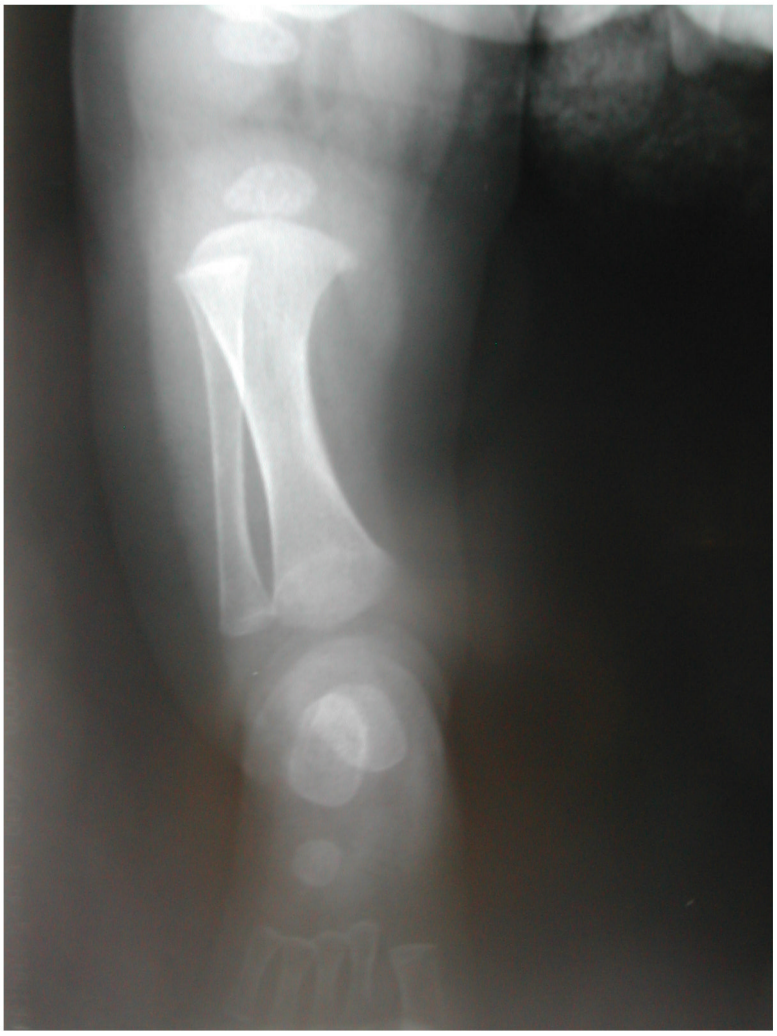


Figure 2.
a and b: Left upper and lower extremity radiographs show short and dumbbell shape humerus and tibia. Metaphyses of long bones are enlarged (megametaphyses) and flared. c: Lateral spine radiography demonstrates mild platyspondyly.

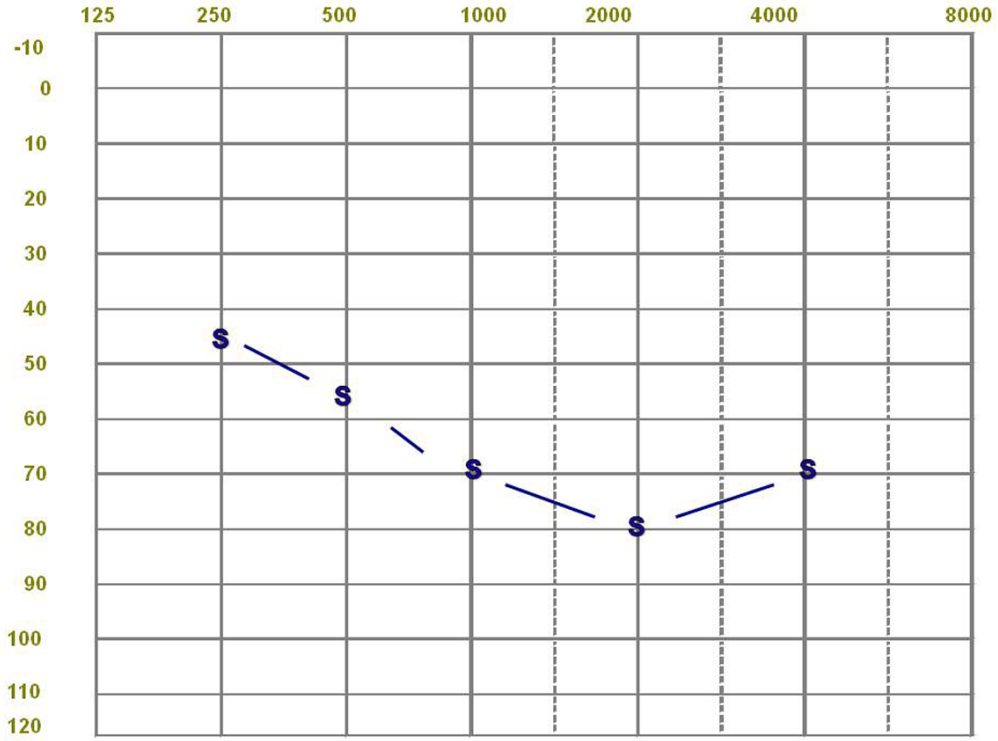


Figure 3.
Hearing thresholds of the proband with Visual Reinforcement Audiometry while the case was at 17 months.

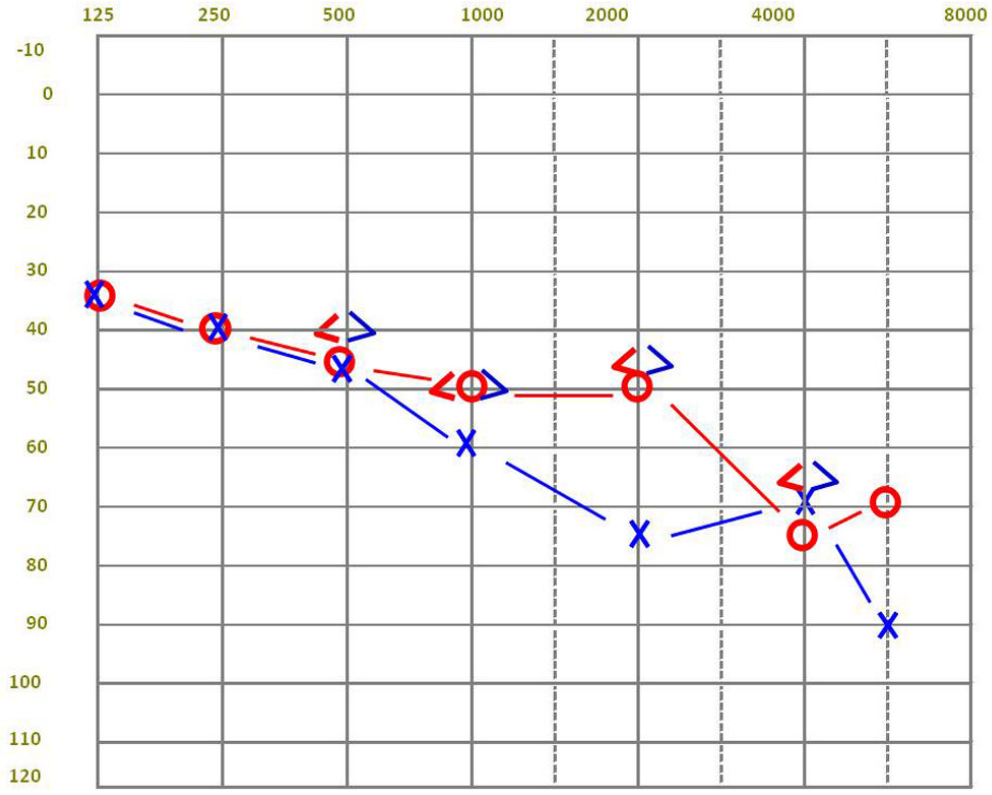


Figure 4.
Hearing thresholds of the proband at 4 years old.

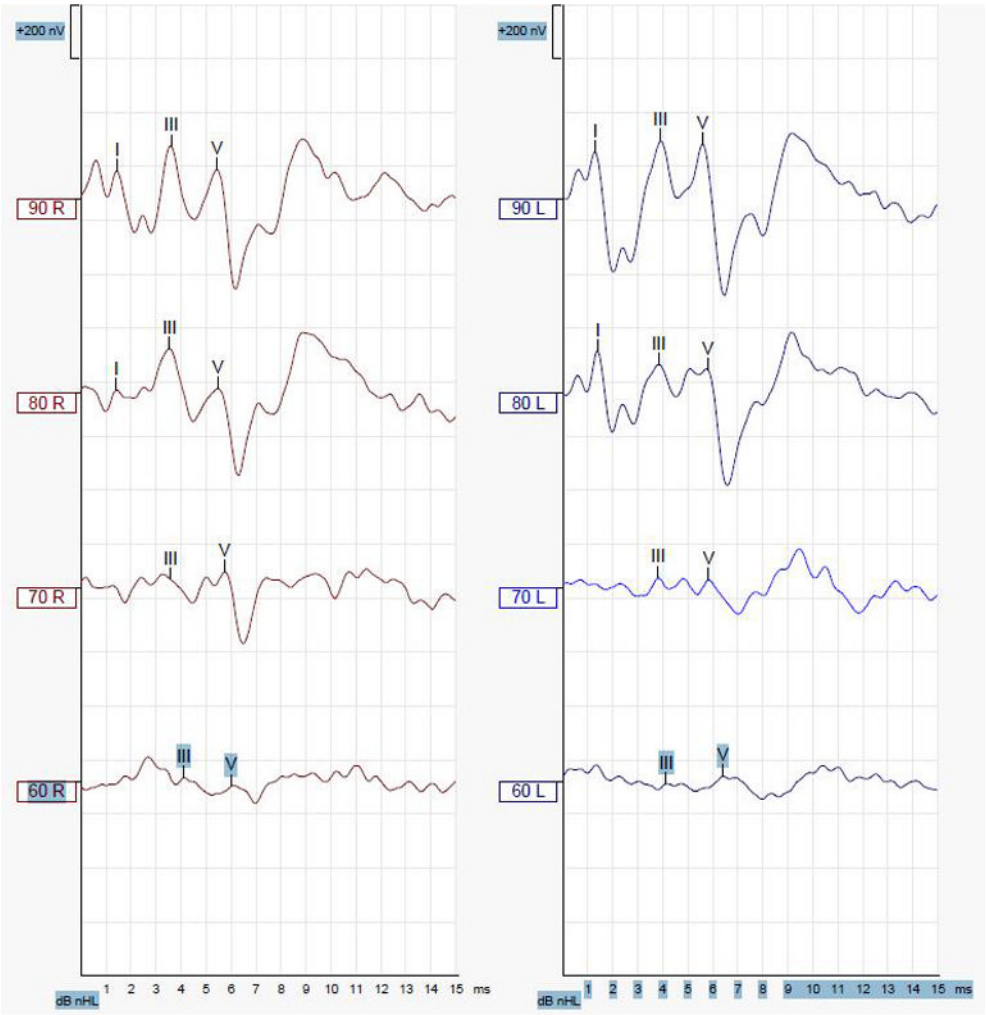


Figure 5.
Clinical ABR outcomes for click stimulation.

Table 1

Clinical features of the proband.

Characteristic	Status of the case
Age	4 years
Height	97,5 cm (between the 3rd- 10th centile)
Weight	11 kg (less than the 3rd centile)
Disproportionately short limbs	+
Cleft palate	-
Micrognathia/retrognathia	+
Midface hypoplasia	+
Nose deformities	Short nose, flat nasal bridge, anteverted nares.
Long philtrum	+
Hypertelorism	+
Midfacial hemangioma	-
Auricle deformities	Sulcus anthelix rearwards, low set ears
Sensorineural hearing loss	48 dB HL in the right, 60 dB HL in the left ear
Enlarged joints	+
Pectus excavatum	-
Vertebral body anomalies	+
Kyphosis	-
Lumbar lordosis	+
Ocular changes	-
High myopia	-

Table 2

Speech Intelligibility Rating criteria [9,10].

Category Speech Intelligibility Rating	
1	Connected speech is unintelligible. Prerecognizable words in spoken language, primary mode of communication may be manual.
2	Connected speech is unintelligible. Intelligible speech is developing in single words when context and lip-reading cues are available.
3	Connected speech is intelligible to a listener who concentrates on lip-reading.
4	Connected speech is intelligible to a listener who has little experience of a deaf person's speech.
5	Connected speech is intelligible to all listeners.

Table 3

Categories of Auditory Performance [11,12].

Categories of Auditory Performance	
1	No awareness of responds to environmental sounds/voice.
2	Awareness of responds to environmental.
3	Responds to speech sounds.
4	Recognises environmental sounds.
5	Discrimination of speech sounds.
6	Understands common phrases without lip reading.
7	Understands conversation without lip reading.
8	Can use telephone with known speaker.

Table 4

Audiological findings associated with *COL11A2* mutations.

	Present Study	**OSMED Syndrome [3,4,18,19]**	**Stickler Syndrome [20,21,22]**	**Weissenbacher-Zweymuller Syndrome [2,23]**	**DFNB53 (nonsyndromic deafness) [24]**	**DFNA13 (nonsyndromic deafness) [25,26,27,28]**
Inheritance Pattern	Autosomal Recessive	Autosomal Recessive	Autosomal Dominant	Autosomal Dominant	Autosomal Recessive	Autosomal Dominant
Number of Mutations up to date	1	12	2	1	1	2
Newborn-screening	Normal	Not available	Not available	Not available	Not available	Not available
Onset age	11 months	Early onset, early childhood, or not available.	Early childhood or not available.	5 years or not available	Prelingual	Congenital, early childhood or 2nd-4th decade
Progression	Progressed until 11 months; afterwards non progressive (thus far)	Non progressive or not available	Progressive or not available.	Not available	Non progressive	Progressive, progressive at 4th decade or non progressive
Severity	Moderate to severe	Moderate to profound	Mild to severe	Severe or not available	Profound	Mild to severe
HL type	SNHL	SNHL	Mixed or SNHL	SNHL	SNHL	SNHL
Audiogram shape	Gently slopping	Flat, high Frequencies or not available	U-shaped, flat, gently/ steply slopping or not available	Not available	Not available	Mid or High frequencies

SNHL: Sensorineural Heaing Loss

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