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Clinical Report

Hearing outcomes after cochlear implantation in two patients with *ATP6V1B2*-related deafness and onychodystrophy

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ABSTRACT

The gold standard recommendation for congenital sensorineural hearing loss (SNHL) care is cochlear implantation (CI). Adjusting for confounding factors such as developmental comorbidities is crucial when assessing expected outcomes of the procedure for the patients, their families, and their medical teams. We describe two clinical cases of the deafness and onychodystrophy (DOD) spectrum and the benefit of molecular diagnosis to underline the importance of genetic testing when evaluating potential CI outcomes in syndromic congenital SNHL.

1. Introduction

1.1. Congenital hearing loss

Congenital hearing impairment is amongst the most prevalent chronic congenital conditions in children. Of the three per mille affected by this condition, one third is diagnosed with profound sensorineural hearing loss (SNHL) (Korver et al., 2017).

Prognostic factors of congenital hearing loss include the chronology with which appropriate care is provided. Poor or absent management of prelingual SNHL can compromise language development, peer interactions, and social and academic outcomes (JCIH, 2019; O'Brien et al., 2021). In light of this, providing early care aims to enhance long-term quality of life for individuals and decrease societal costs (Neve et al., 2021). To date, care options for severe to profound SNHL most often rely on cochlear implantation (CI) before children turn 1 year old (Korver et al., 2017).

Outcome measures for CI success are oral speech and auditory perception; thus, procedure success partly depends on associated disabilities. Expected outcomes after CI must therefore be adjusted to account for confounding factors such as intellectual deficiency and neurodevelopment disorders, which interfere independently with most behavioural and developmental skills and affect 10 to 20% children with congenital SNHL (Korver et al., 2017). In such cases, and considering the invasive nature of the surgery, evaluating the anticipated benefits of CI could help manage expectations for patients' families and medical teams.

Congenital SNHL can result from multiple factors, amongst which genetic causes, intrauterine infections, or sporadic insult during foetal development (O'Brien et al., 2021). Genetic causes are monogenic diseases linked to single gene defects and manifest as isolated or syndromic forms. Associated clinical features in the latter challenges their

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classification and ensuing medical counselling.

1.2. SNHL and onychodystrophy

Association of SNHL and onychodystrophy was originally grouped under "deafness and onychodystrophy (DOD)" (Kondoh et al., 1999). Identification of novel phenotypes of the DOD spectrum later refined into 3 syndromes: dominant deafness-onychodystrophy (DDOD) (Beauregard-Lacroix et al., 2021; Kondoh et al., 1999; Li et al., 2021; Menendez et al., 2017; Yuan et al., 2014), (MIM: #124480, *ATP6V1B2* gene, autosomal dominant (AD) inheritance), deafness-onychodystrophy-osteodystrophy-mental retardation-seizures (DOORS) (Beauregard-Lacroix et al., 2021) (MIM: #220500, *TBC1D24* gene, autosomal recessive (AR) inheritance) and Zimmermann-Laband syndrome (ZLS) (Bauer et al., 2019; Chadwick et al., 1994; Chodirker et al., 1986; Inuzuka et al., 2020; Kortüm et al., 2015; Popp et al., 2017; Sawaki et al., 2012; Shaw et al., 2020) (MIM: #616455, *ATP6V1B2* gene, AD inheritance; MIM: #135500, *KCNH1* gene, AD inheritance; MIM: #618658, *KCNN3* gene, AD inheritance). Of note, DOORS syndrome has also been described in association with *ATP6V1B2* variants although this does not appear on the MIM reference (Beauregard-Lacroix et al., 2021).

DDOD was initially considered a mild, autosomal dominant form of DOD; and DOORS its severe, autosomal recessive counterpart (Kondoh et al., 1999). Their characteristics are summarised in Table 1.

We describe CI outcomes in two DOD cases, including one case with a clinical presentation suggestive of the ZLS subtype, caused by *ATP6V1B2* pathogenic variants. In the context of overlapping phenotypes and variable severity, we highlight the weight of genetic diagnosis in providing accurate prognosis to patients and their otorhinolaryngologists.

Table 1
Human ontology phenotypes in DDOD, DOORS, ZLS, P1 and P2.

HPO number	HPO term	DOORS	DDOD	ZLS	P1	P2
HP:0008625	Severe sensorineural hearing impairment	+	+	+	+	+
HP:0001817	Absent fingernail	+	+	+	+	-
HP:0001802	Absent toenail	+	+	+	+	-
HP:0008404	Nail dystrophy	+	+	+	+	+
HP:0001156	Brachydactyly	+	+	+	+	+
HP:0001250	Seizure	+	-	+	-	-
HP:0001249	Intellectual disability	+	-	+	-	-
HP:0000998	Hypertrichosis	-	+	+	+	-
HP:0001382	Joint hypermobility	-	-	+	+	-
HP:0001433	Hepatosplenomegaly	-	-	+	-	-
HP:0001263	Global developmental delay	+	-	+	-	-
HP:0000158	Macroglossia	-	-	+	-	-
HP:0000356	Abnormality of the outer ear	-	+	+	+	-
HP:0001763	Pes planus	-	+	-	-	-
HP:0000436	Abnormal nasal tip morphology	-	-	+	+	-
HP:0000343	Long philtrum	-	-	+	+	-
HP:0000698	Conical tooth	-	-	+	+	-
HP:0000684	Delayed eruption of teeth	-	+	+	+	-
HP:0001199	Triphalangeal thumb	+	+	-	-	-
HP:0006129	Drumstick terminal phalanges	-	+	+	+	-
HP:0000280	Coarse facial features	-	+	+	+	-
HP:0000169	Gingival fibromatosis	-	-	+	-	-
HP:0025707	Hypoplastic nasal bone	-	-	-	+	-
HP:0011800	Midface retrusion	-	-	-	+	-
HP:0011228	Horizontal eyebrow	-	-	-	+	-
HP:0005338	Sparse lateral eyebrow	-	-	-	+	-
HP:0002003	Large forehead	-	-	-	+	-
HP:0002705	High, narrow palate	-	-	-	+	-
HP:0032152	Keratosis pilaris	-	-	-	+	-
HP:0000960	Sacral dimple	-	-	-	+	-
HP:0001053	Hypopigmented skin patches	-	-	-	+	-

"+": presence; "-": absence.

2. Case series

2.1. Patient 1

Patient 1 (P1) is a 3-year-old female. She is the third child of an unrelated couple from Haiti. Her mother's and maternal relatives' medical histories include diabetes and idiopathic hypertension. She has two brothers, a stepsister and stepbrother on her mother's side. None present relevant medical history. Her father has 3 stepsiblings on his mother's side with unspecified intellectual deficiency.

P1 was born prematurely at 25 weeks of gestation. Birth weight was 630g (Z-score = −0.52), length was 31.5 cm (Z score = −0.05), and head circumference was 21.7 cm (Z-score = −0.45). She was diagnosed with hyaline membrane disease with severe bronchodysplasia with an Apgar score of 4 and 6, at 1 and 3 minutes respectively. She was immediately intubated and transferred to the intensive care unit where she benefited from prolonged postnatal administration of corticosteroids and nitrous oxide administrations. Cranial ultrasounds in the first 15 days of life confirmed ventricular size asymmetry with no bleeding, and an electroencephalogram at 3 days of life showed some deformed occipital delta rhythms predominantly on the left, although compatible with physiological age. She was dismissed from neonatal care and transferred to the paediatrics unit from the age of six to twelve months.

Screening at 7 months old (corrected age (CA): 3.5 months) showed absent auditory evoked potentials (AEP) in both ears.

Complete ear, nose, and throat assessment at 11 months old (CA: 7.5 months) confirmed absent auditory brain responses (ABR) in both ears at 100 dB nHL (Fig. 1A) and absent auditory steady-state responses (ASSR) at 500 and 1000 Hz, also in both ears (Fig. 1B). Behavioural audiometry concluded to bilateral profound SNHL (Fig. 1C). Auditory otoacoustic emissions (AOE) were absent in both ears with normal otoscopic examination of the right ear (Fig. 1D) and seromucous otitis in the left ear.

Video head impulse test (vHIT) and cervical vestibular evoked myogenic potentials (cVEMP) at 13 months old (CA: 9.5 months) showed no vestibular anomaly. Brain MRI and petrous bone CT scan were normal. CMV PCR was negative.

At 13 months old (CA: 9.5 months), clinical geneticists noted dysmorphic traits (Fig. 2A), delayed eruption of upper incisors with conical teeth, keratosis pilaris of the trunk with gluteal hypopigmentation, and lower limb joint hypermobility. These features are summarised in Table 1.

They also noted complete bilateral anonychia on 1st and 5th fingers and toes and bilateral 4th finger onychodystrophy, bilateral brachydactyly, and bilateral drumstick-like distal phalanges (Fig. 2A).

Hand and feet radiographies showed phalanx hypoplasia on the right hallux and complete aplasia of the remaining distal toe phalanges. She also had complete absence of 5th finger distal phalanges (Fig. 2B).

Eye fundus and ophthalmological examination were normal at 6 months old (CA: 2.5 months) and had a stable evolution.

At 13 months (CA: 9.5 months), P1 could sit, stand with assistance, swallow, and breathe independently. Her first sounds were at 11 months (CA: 7.5 months). She presented with motor delay and walked at 22 months (CA: 18.5 months), with no vestibular aetiology.

Hearing aids were introduced at 12 months old (CA: 8.5 months) and allowed her to hear up to 60 dB. She later benefited from bilateral CI (model: Cochlear CI 622, CP 1000, data logging: 10h/day) at 17 months old (CA: 13.5 months). Following the procedure, P1 attended speech therapy twice a week and psychomotor therapy once a week and could hear up to a threshold of 30-35 dB two years after implantation. Post-surgery vestibular assessment remained normal. 24 months after surgery, categories of auditory performance (CAP) and speech intelligibility

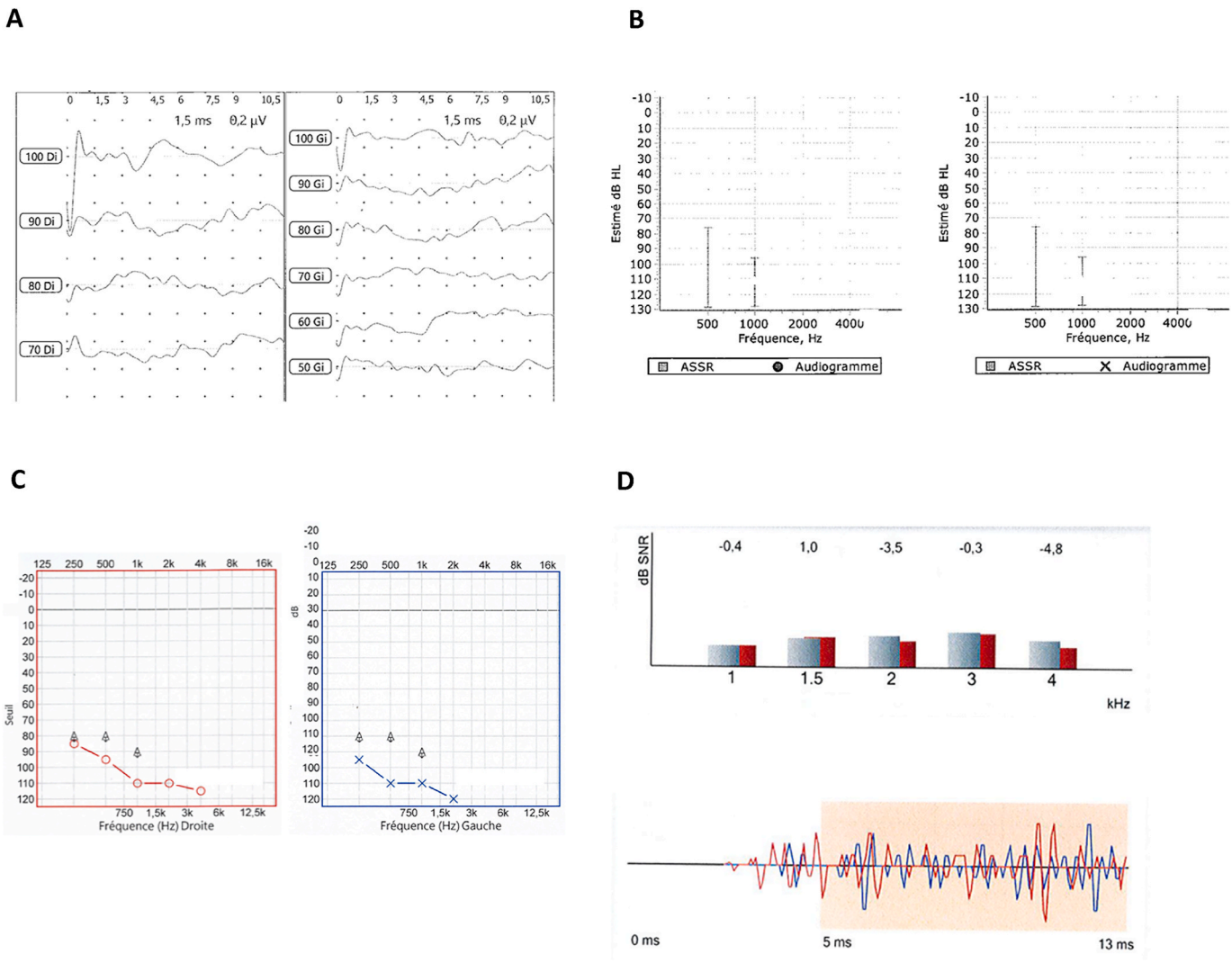

Fig. 1. Patients 1 and 2 audiology assessments. A-D: Patient 1 assessment at age 11 months. A-C: right ear shown on the left-hand side, left ear shown on the right-hand side; A: ABR. B: ASSR. C: Behavioural audiometry. D: AOE, right ear depicted, left ear not shown (seromucous otitis). E-F Patient 2 audiology assessment at different ages. E: P2 audiograms at SNHL diagnosis and follow-up (*thresholds with hearing aids). F: audiograms at 2 days pre-implantation and 55 days post-implantation.

rating (SIR) were 5 and 3 respectively.

Connected speech with words (CSW) is now full, and P1 is able to say small sentences. She has since made up for the motor delay and continues to make progress through weekly speech and psychomotor rehabilitation sessions. P1 is currently enrolled in kindergarten at her local school.

Although P1 was born premature with hyaline membrane disease and pulmonary complications, genetic origin of SNHL was considered more likely in the absence of severe neurological complications or ototoxic drug exposure, with SNHL bilaterality, and in the presence of associated onychodystrophy and dysmorphic features as described above. In light of these arguments, diagnostic hypotheses included DOORS, DDOD and ZLS.

P1 and her parents' genomes were analysed through trio genome sequencing (GS) by SeqOIA, a high-throughput sequencing platform established under the France Genomic Medicine Plan 2025. Depth for analysis was ≥15X for 96.1% of the genome with a mean of 32.7X. Genomes were interpreted under the indication of syndromic and malformative hearing loss and a *de novo*, truncating, heterozygous NM_001693.4:c.1516C > T, p.(Arg506*) variant was identified in *ATP6V1B2*, with a variant allele frequency (VAF) of 47.2%. This variant is predicted to introduce a premature stop codon in the last exon (exon 14) of *ATP6V1B2*, which would result in a truncated protein (Table 2). As per ACMG guidelines (Richards et al., 2015), GeneBe classifies this variant as pathogenic variant (PV) with PVS1_Moderate/PM2/PP5_Very_strong criteria. CADD score was 40. ClinVar also reports this variant 5 times as "pathogenic" (ClinVar: VCV000203442.5), once associated with both ZLS and DDOD, twice with DDOD alone, once with neurodevelopmental delay, and once unspecified.

ATP6V1B2 loss of function variants are associated with ZLS and DDOD (OMIM: *606939) but some cases of DOORS have also been reported (Beauregard-Lacroix et al., 2021). Despite the challenge in confirming the definitive absence of intellectual disability and seizures at such a young age, the constellation of features observed in P1 (isolated motor delay, joint hypermobility, hypertrichosis, conical teeth, long philtrum, abnormal nasal tip morphology – see Table 1) led clinical geneticists to favour a ZLS diagnosis rather than DDOD or DOORS.

In light of this collection of arguments, molecular analysis supported pathogenicity and concluded to the diagnosis of an *ATP6V1B2*-related DOD syndrome with a phenotype suggestive of the ZLS subtype.

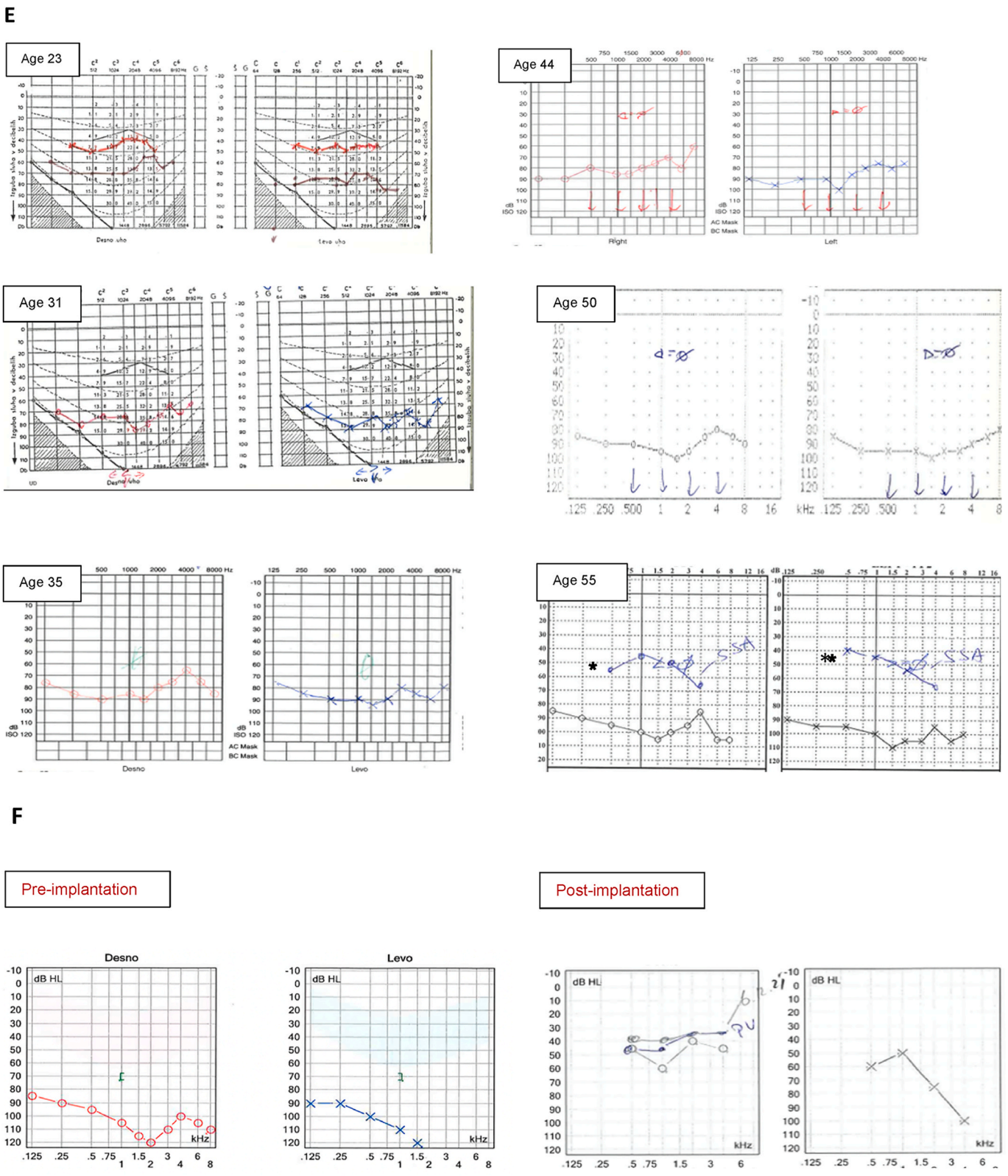

Fig. 1. (*continued*).

2.2. Patient 2

P2 is a 66-year-old white Caucasian female from Slovenia. None of her 9 siblings, her daughter, or her grandsons present with any notion of hearing loss. However, one grandson and one brother present with onychodystrophy. Further detail on family history and personal neonatal history, including birth measurements, were unavailable for this patient.

P2 was born with normal hearing and was referred to otorhinolaryngologists at age 23. She was diagnosed with a mixed bilateral severe SNHL and wore hearing aids. Her hearing loss progressed over time and evolved towards bilateral profound hearing loss at 50 years old,

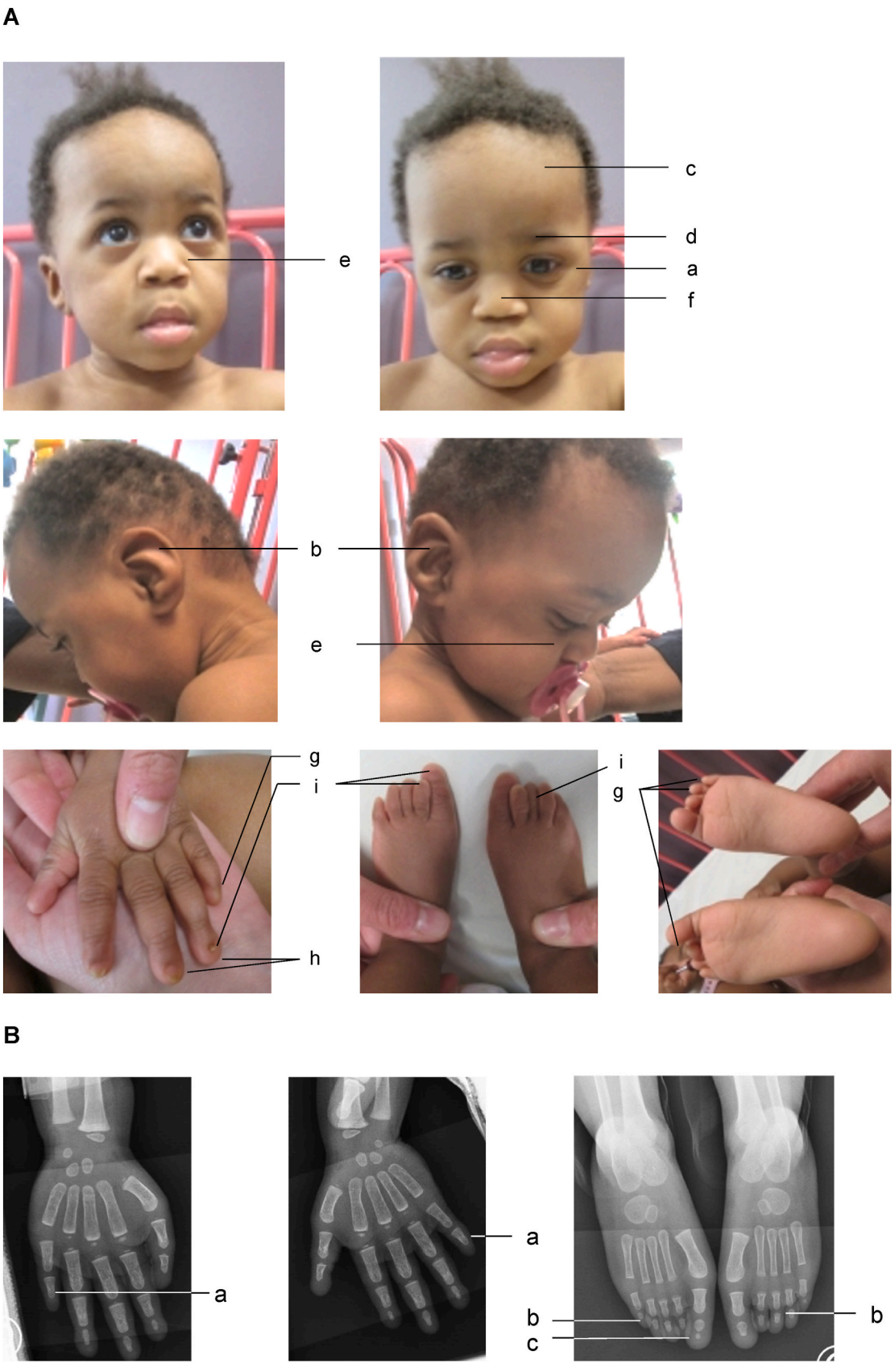

Fig. 2. Clinical and radiological findings in P1 at age 13 months. A: clinical findings. We note coarse facial features (a), bilateral conchal bowl malformation (b), large forehead (c), horizontal and sparse lateral eyebrows (d), hypoplastic nasal bone with midface retrusion (e), long philtrum (f), brachydactyly (g), drumstick-like phalanges (h) and onychodystrophy (i). B: Radiological findings. We note the absence of bilateral distal phalanges in 5th digits (a), the absence of distal phalanges in all toes of the left foot (b) and all toes except the hallux (hypoplastic distal phalanx) in the right foot (b, c).

Table 2
Variants identified in WGS for patients P1 and P2 (ClinVar accession numbers: SCV007602545-SCV007602546).

Patient	Gene	HGVS Nomenclature	VAF (%)	Transmission	Classification
P1	*ATP6V1B2*	NC_000008.11:g.20220382C > T NM_001693.4:c.1516C > T NP_001684.2:p.(Arg506Ter)	Heterozygous (47.2%)	De novo	Pathogenic
P2	*ATP6V1B2*	NC_000008.10:g.20054937G > C NM_001693.4:c.20G > C NP_001684.2:p.(Arg7Pro)	Heterozygous (NA*)	NA*	VUS

*NA: not available. ** VUS: Variant of unknown significance.

especially for higher frequencies (Fig. 1E).

P2 always used oral communication. She had no intellectual disability, no seizures, and no neurological symptoms beyond SNHL.

Because of insufficient audiological outcome through hearing aids, P2 had right ear cochlear implantation at 63 years old. Post-implantation evaluation demonstrated functional gain, with sound-field audiometry demonstrating aided thresholds reaching 40 dB across tested frequencies in the implanted ear, indicating significant auditory improvement following cochlear implantation (Fig. 1F).

During the initial consultation, clinicians had also noted morphological particularities summarised in Table 1, which included bilateral onychodystrophy and brachydactyly, on all fingers (Fig. 3). Further clinical characterisation of P2 was not available as she was lost to follow-up.

Absence of intellectual disability in P2 guided the diagnosis towards either DDOD or ZLS. Genetic testing by GS following the diagnosis of SNHL revealed a heterozygous, missense, NM_001693.4:c.20G > C, p.(Arg7Pro) variant in exon 1 of *ATP6V1B2* (Table 2). Parental samples were unavailable to conduct variant segregation. CADD score was 28.4. As per 2015 ACMG classification guidelines (Richards et al., 2015), this variant is classified as a variant of unknown significance (VUS) on hg38 InterVar and GeneBe as it checks PM2 criterion in both classifiers. This variant is not reported in ClinVar.

As previously mentioned, *ATP6V1B2* variants are found in the three syndromes. Although more arguments are required to reclassify this variant, in silico predictions combined with the absence of symptoms other than SNHL and onychodystrophy in P2 was compatible with ZLS or DDOD and P2 was diagnosed with an *ATP6V1B2*-related DOD-spectrum disorder (Table 1).

3. Discussion

In this report, we described two DOD-spectrum disorders including one case with features consistent with the ZLS subtype, an ultra-rare phenotype associating onychodystrophy and SNHL. P1 presented onychodystrophy, SNHL, joint hypermobility and dysmorphic features associated with a c.1516C > T pathogenic variant, and P2 presented onychodystrophy and SNHL associated with a c.20G > C variant of unknown significance (Table 2). SNHL was diagnosed at different ages for P1 and P2, suggesting clinical variability in DOD-associated SNHL and we note that P1 was born extremely premature with hyaline membrane disease which could serve as a confounding factor for SNHL causality. Both underwent CI and had favourable post-implantation outcomes with adequate behavioural, neurocognitive and communication skills.

3.1. Reported variants in ATP6V1B2

Despite the overlapping phenotypes of these syndromes, discrimination points exist. Unlike DOORS, DDOD does not usually present with seizures or intellectual disability. While ZLS inconstantly presents with intellectual disability and seizures, it differs from DDOD and DOORS through additional symptoms such as gingival hyperplasia and hypertrichosis. Variants in *ATP6V1B2* have been associated with all three DDOD, DOORS and Zimmerman-Laband syndromes.

To the best of our knowledge, P1 is amongst the first reported patients with a ZLS-like DOD diagnosis to present a truncating variant in *ATP6V1B2*: most ZLS cases have so far only been associated with missense variants, and the p.(Arg506*) variant has been predominantly previously reported in DOORS and DDOD cases (Beauregard-Lacroix et al., 2021; Yuan et al., 2014). The only other report of a ZLS-like truncating variant in *ATP6V1B2* describes similar features as those observed in P1: SNHL, coarse facial features, abnormal nasal tip morphology, outer ear malformation, and hypertrichosis (Clinvar ID C4225321). P1's phenotype is also consistent with previous descriptions of *ATP6V1B2* missense variants. However, contrary to other in silico prediction tools, we note that hg38 InterVar classifies this variant as a VUS with PM2/PP3/PP5 criteria. This could be due to the variant's implication in the last exon (exon 14), suggesting the possible escape of mRNA to nonsense-mediated decay (NMD) and subsequently, low PVS1 strength – encouraging functional investigation of this variant.

P2 is the first reported patient to present an *ATP6V1B2* c.20G > C variant, although we acknowledge that unpublished cases may exist. Her phenotype was coherent with prior DOD descriptions; and, to the

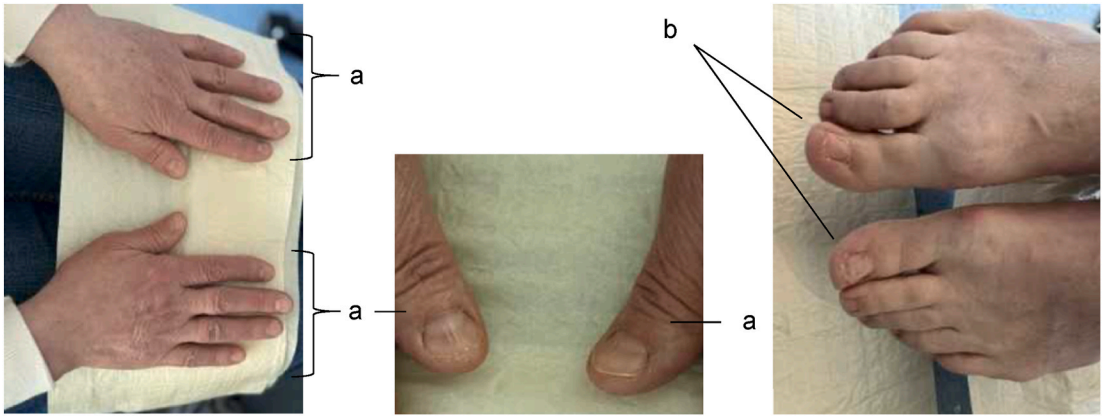

Fig. 3. Clinical findings in P2. Finger brachydactyly including both thumbs (a), toe onychodystrophy (b).

best of our knowledge, there is no published data about this variant to date. Of note, a NM_001693.4:c.19C > T, p.(Arg7Trp) missense variant affecting the same amino acid is reported as VUS in ClinVar (ClinVar: VCV003131900.1) but lacks clinical and segregation data.

Descriptions of other causal mutations identified in ZLS, and in particular of potassium channel variants such as those affecting *KCNH1*, suggest that *ATP6V1B2* phenotypes present coarser facial features and absent or mild intellectual disability (Kortüm et al., 2015) – a finding consistent with the clinical presentation of DDOD cases associated with a p.(Arg506*) *ATP6V1B2* variant (Beauregard-Lacroix et al., 2021; Yuan et al., 2014).

Furthermore, and unlike other ZLS causal genes for which SNHL is not a constant feature, *ATP6V1B2* pathogenic variants are predominantly found in forms of DDOD, DOORS and ZLS presenting with SNHL (Bauer et al., 2019; Kortüm et al., 2015). Further studies are required to determine the weight of *ATP6V1B2* in the development of an auditory phenotype similar to that of P1, P2, and those described in the literature (Gao et al., 2020; Kortüm et al., 2015; Li et al., 2021; Yuan et al., 2014).

Distribution of clinical similarities between the syndromes suggests that DDOD, DOORS and ZLS could constitute subsets of a larger phenotype, for which molecular analysis could help explain the seemingly variant-dependent clinical variability.

3.2. Role of ATP6V1B2 in hearing loss

The favourable CI outcomes observed in our two patients and in other reported cases (Yuan et al., 2014) support the hypothesis of a cochlear SNHL.

ATP6V1B2 is a 14-exon, protein-coding gene on the short arm of chromosome 8 with high cross-species conservation. It encodes a vacuolar ATPase (V-ATPase) responsible for lysosome acidification, which creates the required proton gradients for cell signalling (Qiu et al., 2021; Zhao et al., 2019) through a catalytic V1 domain and a non-catalytic V0 domain. These domains are involved in a wide array of diseases (Zhao et al., 2019).

ATP6V1B2 is highly expressed in the brain and in lysosomes and has been found to be expressed in the organ of Corti and spiral ganglion neurons in mice models (Qiu et al., 2021; Yuan et al., 2014). *ATP6V1B2* shares the expression profile of *TBC1D24* (Yuan et al., 2014), another causal gene for DOORS which also features SNHL as a cornerstone symptom (Balestrini et al., 1993).

Cochlea-specific knockdown mouse models (Yuan et al., 2014) targeting exons 13 and 14 in *ATP6V1B2* have shown dose-dependent hearing loss through progressive death of cochlear hair cells; in vitro HEK293 cell line models carrying heterozygous c.1516C > T variants are reported to result in abnormal lysosome acidification (Yuan et al., 2014). Without an acidic environment, lysosomal hydrolases are non-functional and cannot degrade autophagosomes, leading to accumulated intra and extra-lysosomal debris and triggering apoptosis through Bcl2-Bak/Bax-mediated pathways (Qiu et al., 2021).

Although non-functional cochlear hair cell lysosomes could account for the SNHL observed in P1, this model is contested by a p.Arg506* knock-in mouse model (Zhao et al., 2019) which shows normal hearing at 24 weeks. Further animal models and in vitro studies are required to determine whether spiral ganglion cells are affected by this variant, as some mice models suggest p.Arg506* injection induces spiral ganglion degeneration with normal hair cell function (Qiu et al., 2021). This could explain the absence of SNHL at 24 weeks in the p.Arg506* mouse model (Zhao et al., 2019), 24 weeks being an early cut-off to determine the effect of the time-dependent process of ganglion degeneration. As CI only benefits peripheral SNHL, this mechanism must be further studied to determine the best approach for *ATP6VB2*-induced SNHL management.

3.3. Further directions

Furthermore, the encouraging results of current clinical trials for the *DFNB9* form of congenital profound deafness (Akil et al., 2019) suggest the potential for novel therapeutic approaches targeting other genetic hearing impairments of cochlear aetiology and emphasizes the need for further functional studies in other genes, such as *ATP6V1B2*.

To conclude, we have reported two cases belonging to the DOD-spectrum, including one suspected case of the ZLS subtype, respectively caused by a truncating and a missense *ATP6V1B2* variant. Both underwent CI with favourable outcomes and neither presents with intellectual disability. This report underlines the benefit of molecular diagnosis for the assessment of projected CI outcomes in the context of syndromic SNHL.

Ethical approval

Informed consent was obtained from all participants (or their legal guardians) for the publication of their clinical data and any accompanying images.

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CRediT authorship contribution statement

Sarah Chamieh: Conceptualization, Project administration, Writing – original draft. **Pauline Marzin:** Resources, Writing – review & editing. **Sophie Achard:** Resources, Writing – review & editing. **Pierre Blanc:** Resources, Writing – review & editing. **Laurence Jonard:** Data curation, Writing – review & editing. **Saba Battelino:** Resources, Writing – review & editing. **Katarina Trebusak:** Resources, Writing – review & editing. **Margaux Serey-Gaut:** Conceptualization, Writing – review & editing. **Sandrine Marlin:** Conceptualization, Project administration, Resources, Supervision, Writing – review & editing.

Competing interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix

ABR	Auditory brain responses
AD	Autosomal dominant
AEP	Auditory evoked potentials
AOE	Auditory otoacoustic emissions
AR	Autosomal recessive

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(*continued*)

ASSR	Auditory steady-state responses
CA	Corrected age
CAP	Categories of auditory performance
CI	Cochlear implantation
CSW	Connected speech with words
cVEMP	Cervical vestibular evoked myogenic potentials
DDOD	Dominant deafness-onychodystrophy
DOD	Deafness and onychodystrophy
DOORS	Deafness-onychodystrophy-osteodystrophy-mental retardation-seizures
GS	Genome sequencing
NMD	Nonsense-mediated decay
P1	Patient 1
P2	Patient 2
PV	Pathogenic variant
SIR	Speech intelligibility rating
SNHL	Sensorineural hearing loss
vHIT	Video head impulse test
VUS	Variant of unknown significance
ZLS	Zimmerman-Laband syndrome

Data availability

No data was used for the research described in the article.

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