

## REVIEW

## Genetics of pediatric hearing loss: A functional perspective

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**Abstract**

**Objectives:** This article reviews the current role of genetics in pediatric hearing loss (HL).

**Methods:** A review of the current literature regarding the genetic basis of HL in children was performed.

**Results:** To date, 119 nonsyndromic genes have been associated with HL. There are also hundreds of syndromic causes that have HL as part of the clinical phenotype.

**Conclusions:** Identifying HL genes coupled with clinical characteristics ("genotype-phenotype") yields a more accurate diagnosis and prognosis. Although the complexity of the auditory apparatus presents challenges, gene therapy is emerging and may be a viable management option in the future.

**KEYWORDS**

deafness, exome, genetics, genome, next-generation sequencing, pediatric hearing loss, sensorineural hearing loss

**1 | INTRODUCTION**

Hearing loss (HL) is the most common congenital sensory impairment.<sup>1</sup> More than 6.1% of the world's population (466 million people) are affected by disabling HL.<sup>2</sup>

HL in children causes delay in speech and language acquisition and social development.<sup>3</sup> Early comprehensive hearing evaluation for children is crucial for diagnosing the degree, type, and etiology of HL in children.

Here, we review common genetic causes associated with pediatric HL and underscore the importance of genetic testing as a means to provide etiologic and prognostic information to guide families in long-term clinical management. Pinpointing the biological mechanisms associated with HL provides a foundation for future therapeutics.

**2 | CLASSIFICATION OF PEDIATRIC HL**

HL is classified as genetic or nongenetic, prelingual or postlingual, and syndromic or nonsyndromic.<sup>4</sup> HL be conductive, sensorineural, or

mixed. Any type or age of onset of HL may have a genetic component. The onset of the condition (congenital or later onset), the type (sensorineural, conductive, or mixed), the severity (mild, moderate, moderately severe, severe, and profound), the laterality (unilateral or bilateral), and its association with other disorders as being syndromic or nonsyndromic will guide diagnosis and management.<sup>5</sup> About 70% of genetic HL is nonsyndromic and 30% is syndromic.<sup>5</sup> Eighty percent of nonsyndromic genetic HL is autosomal recessive (AR), 15% to 20% is autosomal dominant (AD) and 1% X-linked or mitochondrial.<sup>6</sup> Hereditary deafness can be caused by mutations in a single gene, a combination of multiple mutations across various genes, as a result of de novo mutations in HL genes or germline mosaicism.

Over half of congenital SNHL has a genetic cause, with the remaining due to environmentally related causes, including congenital cytomegalovirus, ototoxic medications, noise, and trauma, and structural temporal bone anomalies. Less common etiologies include prematurity, which may be complicated by sepsis, hyperbilirubinemia, prolonged ventilation, ototoxicity, and bacterial meningitis.<sup>7</sup> Some structural abnormalities may have a genetic cause (eg, enlarged

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vestibular aqueduct [EVA] and *SLC26A4*), and there are genetic susceptibilities to some ototoxic medications.

Nonsyndromic ARHL is usually congenital, bilateral, and mild to profound. AD nonsyndromic HL (SNHL) is often postlingual and progressive.<sup>8</sup> Mutations in HL genes affect the physiology and function of the inner ear in many ways, including malfunctions in adhesion and structure, intracellular communication and transport, neurotransmitter release, and ionic homeostasis.

### 3 | NONSYNDROMIC HEARING LOSS

To date, 119 deafness (DFN) genes have been identified. Deafness genes are abbreviated using the following notation: DFN=deafness; DFNA = autosomal dominant [AD]; DFNB=autosomal recessive [AR]; DFNX=X-linked; DFNM = modifier; DFNY=Y-linked; AUN stands for auditory neuropathy spectrum disorder, ANSD., including 76 AR (DFNB), 47 AD (DFNA), and 5 X-linked (DFNX) genes.<sup>1</sup> Additional classifications include DFNM (modifier), DFNY (y-linked) and AUN (auditory neuropathy spectrum disorder, ANSD). The genes are then numbered by the order in which they were described, for example, DFNB1 describes the first recessive gene, *GJB2*. In general, the most common AR genes are *GJB2*, *SLC26A4*, *STRC*, *MYO15A*, *OTOF*, *USH2A*, *CDH23*, and *TMC1*; however, the prevalence varies markedly by population.<sup>2</sup>

The mechanotransduction of sound waves to a neural signal is highly delicate and involves a complex interplay of thousands of proteins in the inner ear. Defects in any of these steps can cause HL. The following section reviews some of the major genes implicated in according to their function within the ear.

#### 3.1 | Adhesion proteins

The inner hair cells of the cochlea feature hair-like apical projections called stereocilia. These stereocilia are linked to the tectorial membrane by adhesion proteins (tip links and horizontal top connectors) that allow for maturation and development of hair bundles as well as mechanotransduction of mechanical sound to an electrical stimulus.<sup>9</sup>

##### 3.1.1 | Whirlin (DFNB31) and harmonin (DFNB18)

Whirlin (*WHRN*) and harmonin (*USH1C*) are genes proposed to function in the organization and maintenance of stereocilia elongation and cytoskeleton assembly.<sup>10-12</sup> Mutations affecting different parts of these genes are associated with both AR SNHL and Usher syndrome type 2D.

##### 3.1.2 | Cadherin 23 (DFNB12)

Mutations in Cadherin 23 (*CHD23*) have been described in Usher syndrome type 1D (*USH1D*) and moderate-to-profound SNHL.<sup>13</sup> Specifically, *CHD23* prevents the adhesion of stereocilium to themselves

during development and, in developed hair cells, is expressed in the tip links and acts as a regulator of activity of mechanically gated ion channels during the mechanotransduction of sound.<sup>14</sup>

##### 3.1.3 | Stereocilin (DFNB16)

Stereocilin (*STRC*) is an extracellular structural protein found in the stereocilia of cochlear hair cells. *STRC* is also associated with the top connectors and the tectorial membrane attachment crowns of outer hair cells.<sup>15</sup> The prevalence of *STRC* deletions and mutations has been estimated to be between 5% and 6% of SNHL.<sup>16,17</sup> One study found *STRC* deletions in 30% of patients with mild-to-moderate HL, second only to *GJB2*.<sup>2</sup> The chromosomal region coding for *STRC* also includes a contiguous gene called *CATSPER2*, which codes for a protein in the sperm flagellum. Deletions that span both *STRC* and *CATSPER2* lead to deafness-infertility syndrome in males.

#### 3.2 | Transport proteins

Myosins are actin-binding proteins involved in inner ear transport. To date, seven unconventional myosin genes have been linked to SNHL, the most common of which are myosin 7A (*MYO7A*) and myosin 15A (*MYO15A*).

##### 3.2.1 | MYO7A (DFNA11, DFNB2)

*MYO7A* mutations are associated with both AD (DFNA11) and AR (DFNB2) SNHL, in addition to Usher syndrome 1B.<sup>18</sup> In the inner ear, myosin 7A plays a crucial role in the function of stereocilia by enabling their movement in response to sound waves. In the retina, the protein is found in the retinal pigment epithelium.<sup>18</sup> HL associated with DFNA11 begins postlingually and progresses over time. DFNB2 HL can be prelingual or postlingual and is usually severe to profound.

##### 3.2.2 | MYO15A (DFNB3)

*MYO15A* encodes an unconventional myosin protein that is a constituent of stereocilia.<sup>19</sup> Clinically, *MYO15A* mutations result in bilateral, progressive, congenital SNHL.<sup>20,21</sup>

#### 3.3 | Synaptic proteins

##### 3.3.1 | OTOF (DFNB9)

The *OTOF* gene encodes otoferlin, a protein integral for synaptic vesicle release to the afferent auditory nerve. AR *OTOF* mutations cause prelingual, profound SNHL, or may present with congenital ANSD due to aberrant synaptic vesicular transmission of glutamate.<sup>22</sup>

### 3.3.2 | *SLC17A8* (DFNA25)

*SLC17A8* encodes for a vesicular glutamate transporter called VGLUT3 that regulates the exocytosis and endocytosis of glutamate at synapses. The first study documenting successful restoration of congenital HL using adeno-associated virus (AAV)-mediated gene therapy occurred in a mouse model of VGLUT3 deafness.<sup>23,24</sup>

### 3.4 | Cytoskeletal proteins

#### 3.4.1 | *DIAPH1* (DFNA1) and *TRIOBP* (DFNB28)

*DIAPH1* is associated with AD progressive SNHL. The *DIAPH1* protein has been postulated to play a role in the regulation of actin polymerization in cochlear hair cells.<sup>25</sup> The *TRIOBP* protein affects actin cytoskeleton organization, motility, and growth.<sup>26,27</sup>

#### 3.5 | Ion homeostasis and gap junctions

To maintain the electrochemical potassium gradient between hair cells and endolymph, potassium ions must be recycled from the hair cells back to the endolymph through the epithelial cell gap junction system. Gap junction proteins form channels in cell membranes that allow ions and small molecules to be passed between adjacent cells. One of the most prominent gap junction proteins within the stria vascularis and supporting cells is the family of connexin (Cx) proteins.<sup>28</sup> It has been postulated that Cx gap junctions, through intercellular communication, affect the ionic ambience of the cochlear epithelial cells and potassium recirculation.

#### 3.5.1 | *GJB2* (DFNB1A) and *GJB6* (DFNA1B)

The most common gene associated with SNHL is the gap junction beta 2 (*GJB2*) gene at the DFNB1A locus, which accounts for up to 50% of all AR SNHL and up to 20% of all congenital HL in some populations.<sup>29,30</sup> *GJB2* SNHL generally presents as congenital, bilateral and mild-to-profound. *GJB2* encodes the gap junction protein Cx26, a component of the gap junction potassium recycling pathway in the cochlea. Generally, inactivating truncating mutations in *GJB2* lead to more severe SNHL, whereas nontruncating mutations are associated with less severe SNHL.<sup>31</sup>

#### 3.5.2 | *SLC26A4* (DFNB4)

Variants in *SLC26A4* are the second most common cause of AR SNHL.<sup>32</sup> *SLC26A4* codes for pendrin, an anion-exchange protein that transports negatively charged particles (chloride or iodide) across cell membranes that are produced in the inner ear and the thyroid gland.<sup>33</sup> HL resulting from *SLC26A4* mutations presents as SNHL alone, SNHL with EVA but

without thyroid dysfunction (DFNB4), or as Pendred syndrome, as detailed below, which includes EVA, thyroid dysfunction and goiter.

### 3.6 | Other nonsyndromic genes

#### 3.6.1 | *TMC1* (DFNA36 and DFNB7/11)

*TMC1* encodes a transmembrane protein required for normal cochlear hair cell function. Mutations may result in both AD and AR HL. The AD HL (DFNA36) is typically prelingual and bilateral severe-to-profound; the AR HL may be more moderate.<sup>34,35</sup> Recently published evidence indicates that *TMC1* may be an important component of the sensory transduction channels in auditory and vestibular hair cells.<sup>36</sup>

#### 3.6.2 | *COCH* (DFNA9)

Mutations in the *COCH* gene are related to AD progressive high frequency-onset SNHL and vestibular dysfunction. Biallelic inactivating variants in *COCH* can also cause AR congenital SNHL.<sup>37</sup> Vestibular abnormalities range from vertigo to vestibular hypofunction.<sup>38</sup>

#### 3.6.3 | *WFS1* (DFNA6/14/38)

*WFS1* codes for a protein called wolframin that is key in calcium regulation in cells. AD mutations in *WFS1* often lead to low-frequency, progressive SNHL. AR mutations have been linked to Wolfram syndrome, a rare progressive neurodegenerative syndrome characterized by diabetes insipidus, diabetes mellitus, optic atrophy, and deafness (DIDMOAD) syndrome.<sup>39</sup>

#### 3.6.4 | Mitochondrial genes

The cells of the inner ear are highly metabolically active and therefore rely heavily on mitochondria for functioning. Mutations in mitochondrial genes result in both syndromic HL and SNHL. Importantly, individuals with mitochondrial DNA mutations in the 12S rRNA gene, such as m.1555A>G and m.1494C>T, are susceptible to HL due to even brief aminoglycoside administration.<sup>40</sup>

## 4 | SYNDROMIC HL

Syndromic genetic HL is associated with additional clinical or laboratory manifestations, including abnormalities of the eyes, kidneys, thyroid, heart, musculoskeletal and nervous systems, pigmentation-related disorders, and inner ear structural abnormalities. More than 400 genetic syndromes with HL have been noted.<sup>5</sup> Some of the most common HL syndromes include Usher, Waardenburg, Pendred, branchio-oto-renal (BOR), and Jervell and Lange-Nielsen (JLN) syndrome.<sup>41</sup>

#### 4.1 | Usher syndrome

Usher syndrome (USH) is the most prevalent form of genetic deaf-blindness in children, with a pediatric population prevalence of 1 in 6000.<sup>42</sup> USH is AR and generally presents with congenital, bilateral SNHL, variable vestibular dysfunction, and a later onset of retinitis pigmentosa (RP).<sup>43,44</sup> Clinically, there are three subtypes of USH that classify the disease based on severity of the deafness, the presence of vestibular dysfunction, and the age of RP onset.<sup>44</sup> To date, at least nine genes have been identified for USH.<sup>1</sup> After *GJB2*, *SLC26A4*, and *STRC*, mutations in *USH2A* are one of the more common etiologies of bilateral mild to severe SNHL.

#### 4.2 | Waardenburg syndrome

Waardenburg syndrome (WS) is a generally AD condition associated with congenital SNHL and pigmentation anomalies of the eyes, hair, and skin. It has an estimated incidence of 1 in 40 000 and represents 2% to 5% of all cases of congenital SNHL.<sup>45,46</sup> Distinctive features of WS include different colored eyes, the presence or absence of dystopia canthorum, a white forelock (or eyelashes, eyebrows), and vitiligo. WS2 is similar to WS1 but without dystopia canthorum, WS3 shows dystopia canthorum and musculoskeletal abnormalities of the upper limbs, and WS4 shows dystopia canthorum and Hirschsprung disease. Of the four subtypes, WS1 and WS2 are the most common. To date, six causative genes that vary in inheritance, with some genes being AD and others being AR, have been described; *PAX3* causes WS1 and WSIII and *SOX10* causes WS2II and WSIV.<sup>1</sup>

#### 4.3 | Pendred syndrome

Pendred syndrome, one of the most common AR syndromic causes of HL, presents as sensorineural, mixed, or occasionally purely conductive HL and is associated with EVA, thyroid dysfunction, and variable vestibular dysfunction. Approximately 7.5% to 10% of all hereditary HL can be attributed to this disorder.<sup>47</sup> EVA is frequently associated radiographically with intracochlear partition type 2 defects of the cochlea (formerly called Mondini abnormality).<sup>48</sup> Patients may also develop a goiter due to abnormalities of organification of iodine, starting in late childhood.<sup>49,50</sup> The goiter may not develop until adolescence, so initially the condition may be deemed DFNB4.<sup>51</sup> In about 20% of cases, EVA is associated with AR mutations in *SLC26A4*; much less commonly, changes in *FOXI1* and *KCNJ10* may be associated with the clinical Pendred presentation.<sup>1</sup> Mutations in *SLC26A4* may also present as NSHL, called DFNB4, presenting with EVA but without thyroid dysfunction or goiter.

#### 4.4 | BOR syndrome

BOR syndrome is an AD disorder characterized by tissue abnormalities in the neck, kidney malformations, and HL, with an estimated

prevalence of 1 in 40 000.<sup>52</sup> Although symptoms of this disease vary substantially between individuals (even with the same mutation), defining characteristics include preauricular pits, branchial fistulas and cysts, outer/inner ear malformations, conductive, mixed, or SNHL, and renal malformation or dysfunction. Mutations in three genes, *EYA1*, *SIX5*, and *SIX1*, cause BOR syndrome.

#### 4.5 | JLN syndrome

Mutations in the genes *KCNQ1* and *KCNE1* are associated with HL and cardiac arrhythmias. Mutations in these genes cause AR JLN syndrome, characterized by bilateral congenital severe to profound SNHL and long QT intervals on electrocardiograms. The prevalence of JLN syndrome is approximately 1.6 to 6 per 1 million people worldwide.<sup>53</sup> These arrhythmias may result in associated syncope or sudden cardiac death. In the AD state, mutations in *KCNQ1* and *KCNE1* result in Romano-Ward syndrome, which generally presents with long QT but normal hearing. However, a recent study suggests that mutations in *KCNE1* could also affect hearing, suggesting a more complex phenotype-genotype.<sup>54</sup> In the inner ear, *KCNQ1* and *KCNE1* subunits form voltage-gated potassium channels.

Table 1 contains information on some of the most common syndromic and NSHL genes.

### 5 | DIAGNOSTIC GENETIC TESTING

Currently, 98.2% of newborns in the United States receive universal newborn hearing screening (UNHS), greatly reducing the age at which congenital deafness is identified.<sup>59</sup> Shearer et al recently outlined a proposal for comprehensive UNHS that urges inclusion of physiologic, genetic, and cytomegalovirus (CMV) screening, rather than solely physiologic screening.<sup>3</sup> By doing so, the screening would identify newborns at risk for deafness that may be missed by current UNHS guidelines, provide etiologic information, possibly decrease the number of children who are lost to follow up, and potentially decrease costs by reducing the need for later testing.<sup>3</sup>

After a child is identified via UNHS, diagnostic testing is the next step. With the advent of new genomic technologies, genetic testing for HL has emerged as one of the most important tests to order after history, physical examination, and audiometric testing. The newest guidelines from the American College of Medical Genetics for the evaluation and diagnosis of HL included next-generation sequencing (NGS) testing as part of the standard procedure.<sup>5</sup> The 2019 Joint Committee on Infant Hearing guidelines also recommend a genetic evaluation for newborns with congenital HL.<sup>60</sup> Prior to the advent of routine genetic testing for HL, many tests were used in the workup of children with HL. For instance, electrocardiogram (ECG) was obtained to rule out JLN, renal ultrasound and BUN/Creatinine for BOR, and urinalysis for Alport syndrome. Genetic testing as part of a comprehensive initial medical evaluation of infants and children with SNHL provides a much higher and more accurate diagnostic yield than the

**TABLE 1** Common nonsyndromic and syndromic genetic hearing loss<sup>55-58</sup>

Common nonsyndromic genes	Autosomal recessive (AR)	Autosomal dominant (AD)	X-linked	Clinical presentation
GJB2	x	Uncommonly		Generally nonsyndromic, but AD mutations are associated with skin disease
STRC	x			Generally nonsyndromic. However, deletions involving both STRC and the contiguous CATSPER2 gene result in male infertility
TECTA		x		
MYO15A	x			
TMC1	x	X (less commonly)		
OTOF	x			
TMPRSS3	x			
LOXHD1	x			
OTOA	x			
WFS1	X	X		The AD version is non-syndromic. The recessive version is syndromic and also called DIDMOAD (diabetes insipidus, diabetes mellitus, optic atrophy, deafness)
PRPS1			X	May present as non-syndromic SNHL. However, mutations may also result in CMTX5, ARTS syndromes
<b>Most common syndromes</b>				
Usher syndrome	MYO7A, USH1C, CDH23, PCDH15, SANS/USH1D (all USH1); USH2A, ADGVR1, WHRN (all USH2); CLRN1 (USH3)			Congenital hearing loss, vestibular dysfunction, retinitis pigmentosa (RP) Mutations in some genes also cause nonsyndromic SNHL or isolated RP
Pendred syndrome	SLC26A4, FOXI1, KCNJ10			SNHL, mixed or CHL, usually congenital, Enlarged vestibular aquaduct, cochlear dysplasia, euthyroid goiter
Jervell and Lange-Nielsen	KCNQ1, KCNE1			Congenital SNHL, long QT interval on ECG
Waardenburg	PAX3, EDNRB, EDN3	PAX3 (WS1,3), MITF (WS2A), SNAI2 (WS2D), SOX10 (WS2E, 4C), EDNRB (WS4A), EDN3 (WS4B)		
Treacher Collins		TCOF1, POLR1D, POLR1C		
Stickler	COL11A2,	COL2A1, COL11A1, COL11A2, COL9A1, COL9A2		
Branchio-oto-renal		EYA1, SIX5, SIX1		
Alport	COL4A3, COL4A4		COL4A5	
CHARGE		CHD7, SEMA3E		
Perrault	HSD17B4, HARS2, CLPP, LARS2, TWNK, ERAL1			
Neurofibromatosis 2		NF2		
Osteogenesis imperfecta		COLIA1, COLIA2		

routine use of these physiologic or other laboratory tests. Conversely, an abnormality in one of these routine tests, for example an abnormal U/A in a teenaged boy with HL, may lead to genetic testing for Alport syndrome.

Elucidation of the genetic etiology of HL is crucial for prognosis, family planning, developing treatment or prevention programs, and possible future access to treatment trials. Testing can include testing single genes, multi-gene sequencing panels, chromosomal microarray (CMA), whole-exome sequencing (WES) and whole genome sequencing (WGS). Single gene testing is useful if a particular genetic cause is suspected; multi-gene sequencing is useful if the etiology is unknown but a monogenetic cause is suspected. CMA can be used if looking for deletions or duplications (copy number variations), or as a first test if the patient has other syndromic features. Although Sanger sequencing (“first-generation sequencing”) has been one of the most widely used techniques for genetic sequencing, it has limitations, particularly for high-throughput applications. Therefore, a high-throughput technology known as NGS has revolutionized the field of genomics by allowing for the sequencing of millions of small DNA fragments covering the whole exome or genome at a more reasonable cost and much reduced runtime. WES is a useful tool in detecting variants in large numbers of genes, as 85% of mutations which lead to Mendelian disorders are located in the exome (the coding region of DNA segments).<sup>61</sup> In addition, multiple studies have recently reported the utilization of WES as instrumental in detecting novel, pathogenic causative variants and new candidate genes.<sup>62,63</sup> Beyond WES, WGS may be of additional benefit if WES is unrevealing and targeted sequencing is negative.

For clinicians ordering and interpreting genomic sequencing, it is important to recognize that a genetic testing laboratory’s designation of pathogenicity for a particular variant does not translate to diagnosing the patient with the disorder. A typical exome sequence identifies around 40 000 variants, from which computer algorithms filter out the variants not causal of the disease of interest, yielding a smaller group of variants with likely pathogenicity.<sup>64</sup> Combining genetic results with clinical attributes and experienced genetic counseling is the ideal way of arriving at a clinical-molecular diagnosis. However, a negative genetic test result does not necessarily mean that the HL is not genetic. For example, for NGS that uses targeted testing for only HL genes, genes or gene variants not known to be associated with HL, or not included in the analyses, will be missed. In addition, not all regions of the genome are efficiently captured or analyzed by current NGS approaches, and large deletions and duplications, in addition to copy number and structural variations, will not be detected.<sup>5</sup> Therefore, if genetic testing was “negative” many years ago, an updated approach may be worth considering.

## 5.1 | Treatment

To date, the primary treatments for HL include hearing aids and cochlear or auditory brainstem implants. These options can significantly improve the hearing of affected individuals but do not restore

normal hearing. Intriguingly, inner ear gene therapy has shown promise of translating success with animal models to patients. Strategies include correction, replacement, modifying, silencing, restoring, over-riding, or inhibit abnormal or absent gene function. Techniques to do this include gene editing, replacement genes attached to viral vectors, exon skipping, oligosense nucleotides, read-through technology, RNAi, inner ear organoids, stem cells, nanoparticles, small molecules, exosomes, and changing the genes in vivo or ex vivo. For example, a recent study using a CRISPR/Cas9 approach documented improvement in hearing thresholds in a mouse model of dominant deafness caused by a mutation in *TMC1*.<sup>65</sup> Recently, otic induction of pluripotent stem cells was reported, giving rise to the theory that generating phenotypes of inner ear cells from induced pluripotent stem cells (iPS) cells could be a useful way to assess the efficacy of drugs.<sup>66</sup> Similarly, inner ear organoids derived from iPS cells could provide a platform for gene exploration and therapeutic development.<sup>67</sup> Delivery routes into the cochlea may largely be dependent on the cell type to be targeted. In terms of modes of delivery, viral and nonviral vectors have been developed—lentivectors, adenoviruses, adeno-associated viruses, exosome-associated AAV, and so on.<sup>68</sup> Gene therapy strategies in the form of gene replacement using cDNA, gene silencing using RNA interference, or gene editing through the CRISPR/Cas9 system have appeared.<sup>69</sup>

Gene therapy delivery and hair cell regeneration have been the focus of SNHL therapeutics. However, despite potential recent success in animal models, there are still many obstacles to successful human implementation. The safety of various routes of delivery into the cochlea, the efficacy of certain drugs, potential off target effects of gene editing, possible immune responses to viral injection, along with many other questions still remain unanswered. Despite these challenges, inner ear gene therapy is promising in the near future, as there will continue to be exciting advances in the creation of novel and effective treatments for patients with genetic HL.

## 5.2 | Ethical considerations

Although clinical genetic testing may be advantageous, there are ethical questions that arise from such testing. There is the possibility that genetic testing could reveal unexpected, and sometimes upsetting results; for example, USH where the diagnosis includes retinal degeneration not yet clinically apparent in young children. Exome or genome sequencing may reveal potentially pathogenic variants in genes not necessarily related to the HL. When both parents as well as the proband are tested, nonpaternity may be uncovered. In addition, although consanguinity is generally known by the family, in some situations it may be unknown or unacknowledged. When physicians receive such incidental secondary findings, the decision on disclosure must be carefully considered, especially if the findings have actionable clinical significance. However, by doing so, the duality between patient autonomy and beneficence collide.<sup>70</sup> Clinicians should properly understand the multitude of practical and ethical considerations of such testing before ordering.

Knowing the genetic cause of HL may make the patient a candidate for a clinical trial which could stabilize, or even improve the hearing. However, there remain many questions about such trials in children, including the age of entry (before or after 18 years), risk vs benefits, the potential for off-target effects of gene therapy, and the ethical concerns about entering a genetic trial for something like HL that is life-changing but generally not life-threatening.

In some communities, deafness is considered a neutral or positive trait, with deafness contributing linguistic and cultural richness. Genetic testing may therefore be viewed from a cultural, rather than a medical, lens, and this needs to be considered when approaching any patient or family about such testing.

Finally, knowing the genetic cause may allow family planning for the parents of a child with a known mutation, or eventually that child themselves. Any discussion about assisted reproductive technology is beyond the scope of this review, but genetic counseling is always recommended before, and after any testing is contemplated and when results, and the repercussions of those results, become available.

## 6 | CONCLUSIONS

Pediatric HL is a highly heterogeneous disease. Early diagnosis provides information on prognosis, treatment, and optimal management for these children. Understanding the genetic basis of SNHL illuminates the biological pathways and mechanisms at play and provides critical information for emerging gene therapies in the near future.

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### CONFLICT OF INTEREST

The authors declare no potential conflict of interest.

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