

# The Genetic Basis of Hearing Loss: Recent Advances and Future Prospects

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## ABSTRACT

Hearing loss (HL) is a common and complex condition that can occur at any age, be inherited or acquired, and is associated with a wide number of etiologies. HL is the most common sensory deficit in newborn children. In developed countries, genetic causes are considered the most frequent etiology of HL, and are estimated to account for 75% of the causes of HL. Current estimates suggest 1% of human genes (200–250 genes) are associated with genetic HL, and to date, more than 80 genes with over 1000 mutations and 140 loci have been identified associated with non-syndromic HL. The Online Mendelian Inheritance in Man reports more than 400 syndromes with HL. Syndromic and non-syndromic HL can be caused by different mutations within the same gene. Establishing the genetic cause of HL in prelingual children facilitates the medical course of action, rehabilitation choices and long term care in children. Patients with HL of undiagnosed etiology should be evaluated by a clinical geneticist and consider genetic testing as a part of their multidisciplinary evaluation.

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## INTRODUCTION

Hearing loss (HL) is a common and complex condition that can occur at any age, be inherited or acquired, and is associated with a wide number of etiologies. Hearing loss is the most common sensory deficit in newborn children.<sup>1</sup> Studies have reported an incidence of 0.2 to 0.3% of HL in the newborn population.<sup>1</sup> Early intervention has been proven to be effective in facilitating communication and language development in hearing impaired children.<sup>2</sup> As a result, newborn hearing screening, which began in 2001, is mandated throughout the United States. Because

not all HL presents at birth, hearing screening is also recommended throughout childhood and adolescence to identify children with later onset HL and allow for early intervention.

Approximately 95% of newborns with HL identified by newborn hearing screening are born to hearing parents.<sup>3</sup> Analysis of historic data from school age children in the United States estimates that up to 60% of educationally significant congenital HL is caused by genetic factors.<sup>4</sup>

## CLASSIFICATION OF HL

Hearing loss can be classified and described in many different ways.

*Age of onset:* HL is described as congenital, prelingual (before the acquisition of speech), postlingual (after the acquisition of speech), adult onset, and presbycusis (age-related late onset HL).

*Type:* Sensorineural, conductive, mixed, or auditory neuropathy

*Laterality and Symmetry:* Unilateral or bilateral; symmetric or asymmetric

*Stability:* Progressive, nonprogressive, or fluctuating

*Degree of HL:* Mild (26–40 dB), moderate (41–55 dB), moderately severe (56–70 dB), severe (71–90 dB), or profound (91 dB or greater)

*Configuration of audiogram:* Sloping, flat, rising, or mid-frequency/cookie-bite loss

## GENETICS OF HL

In developed countries, genetic causes are considered the most frequent etiology of HL, and are estimated to account for 75% of the causes of HL.<sup>5</sup> Patients with HL of undiagnosed etiology should be evaluated by a clinical geneticist.<sup>6</sup>

An estimated 30% of genetic HL is syndromic (associated with other findings). Notable syndromes like Pendred (enlarged vestibular aqueduct, thyroid problems), Usher (retinitis pigmentosa), Waardenburg (pigmentary anomalies), and branchio-oto-renal (BOR, branchial arch and renal anomalies) syndromes account for large percentages of HL in certain populations. Syndromic HL can be transmitted in an autosomal recessive, autosomal dominant, X-linked, or mitochondrial pattern. Syndromic HL can have variable expression, with

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varying presentations of HL or associated findings. The variations can exist within and between families.

An estimated 70% of genetic HL is nonsyndromic. The majority of genetic, nonsyndromic HL is inherited in an autosomal recessive pattern, and accounts for 75% of hereditary HL.<sup>7</sup> The incidence of nonsyndromic HL is about 1.33 per 1,000 newborns, but doubles by age 5 years to 2.7 per 1,000 children.<sup>8</sup> Genetic transmission of nonsyndromic HL can be autosomal dominant (15–25%) or in a minority of cases, X-linked or mitochondrial (1–2%).<sup>9</sup>

The DFNB1 locus, which includes the gap junction beta 2 (*GJB2*) gene (gap junction protein connexin 26) and *GJB6* gene (gap junction protein connexin 30), accounts for about 50% autosomal recessive nonsyndromic HL and can account for 15 to 40% of hearing impaired individuals in a variety of populations.<sup>10</sup> More than 150 HL variants have been identified in *GJB2*, but a few mutations account for the majority of the *GJB2*-related HL. Clinically, *GJB2*-related HL is sensorineural, usually present at birth, typically bilateral and non-progressive, and can range from mild to profound in severity.<sup>11</sup>

Nonsyndromic mitochondrial HL is characterized by moderate to profound HL and is associated with mutations in the *MT-RNR1* gene (encoding mitochondrial 12S ribosomal RNA) or *MT-TS1* gene (encoding mitochondrial tRNA Ser).<sup>12</sup> Mutations in *MT-RNR1* are associated with a predisposition to aminoglycoside toxicity such that even a single dose of aminoglycoside can lead to bilateral severe to profound HL.<sup>13</sup>

As the population continues to live longer, it is estimated that by the year 2020, there will be over 1 billion people with HL in the world, approximately 10 to 20% of the world population.<sup>14</sup> A majority of the billion are projected to have age-related HL. Age-related HL is considered to be multifactorial: a combination of undetermined genetic susceptibility and environmental influences. Most of the research on presbycusis has focused on environmental etiology. However, more recent literature has discovered several susceptibility loci for presbycusis. Genes that cause increased susceptibility include genes that have been implicated in other forms of HL like *KCNQ4* and *ACTG1* (both can cause nonsyndromic genetic HL), and genes involved in oxidative stress like *GRM7*, *GRHL2*, mitochondrial oxidative genes, and glucosaminyl transferase (N-acetyltransferase).<sup>14,15</sup>

With certain exceptions, HL progresses with defined patterns. Autosomal recessive, nonsyndromic HL is generally prelingual, nonprogressive, and severe to profound. Autosomal dominant, nonsyndromic HL is generally postlingual and progressive.

Current estimates suggest 1% of human genes (200–250 genes) are associated with genetic HL.<sup>16</sup> To date,

more than 80 genes with over 1,000 mutations and 140 loci have been identified associated with nonsyndromic HL.<sup>17</sup> The Online Mendelian Inheritance in Man reports more than 400 syndromes with HL. Syndromic and nonsyndromic HL can be caused by different mutations within the same gene.<sup>18</sup>

The diverse causes of HL, combined with the highly variable and often overlapping presentations of different forms of HL and expense of genetic testing, challenge the ability of traditional clinical evaluations to arrive at an etiologic diagnosis for many hearing impaired individuals. Identifying the etiology of HL can affect clinical management, improve prognostic ability, facilitate genetic counseling, and enable assessment of the likelihood of recurrence in relatives of hearing impaired individuals. Furthermore, the identification of a previously unrecognized syndrome of HL can be particularly important because it allows early management of associated medical conditions.

## GENETIC TESTING

Data have estimated more than 3 million variants in the average human genome.<sup>19</sup> Only a small fraction of the variants are expected to be functional, and it is unclear how these genomic variations contribute to the variability in human phenotypes.<sup>20</sup> In fact, 5 to 10% of the healthy population carries a large deletion or duplication > 500 kb within their genome.<sup>21</sup>

The year 1988 marked the first reported nonsyndromic HL locus mapping to chromosome Xq using a linkage approach.<sup>22</sup> This was considered the first step in a seven-year process toward identifying the gene *POU3F4* (a cause of X-linked nonsyndromic HL). Similarly, the first autosomal locus was linked to chromosome 5q31 in 1992, leading to the identification of *DIAPH1* (a cause of autosomal dominant nonsyndromic progressive low-frequency HL) in 1997.<sup>23</sup>

Historically, molecular diagnostic testing for HL used genotyping or deoxyribonucleic acid sequencing to identify specific HL variants, to screen individual genes, or small collections of genes for changes associated with HL. The traditional approach was effective in cases where there was a single gene or a limited number of genes that were suspected to be responsible for a type of HL. Examples include the sequencing of the *SLC26A4* gene for Pendred syndrome, *PAX3* for Waardenburg syndrome type 1, *MITF* and *SOX10* for Waardenburg type II, and *MYO7A* and *USH2A* for Usher syndrome type I and II.<sup>24</sup> The traditional screening is cost-effective in a population where a single gene mutation is responsible for a significant percentage of the cases of HL, such as the *GJB2* gene in individuals who appear to have autosomal recessive nonsyndromic HL. Today, most tests are based

on next-generation sequencing. These tests use disease-targeted exon capture, whole exome sequencing, or whole genome sequencing. The advantage of the modern approach is the ability to address genetic heterogeneity in the condition of HL where different phenotypes cannot be easily differentiated.

Several next-generation sequencing tests are available clinically, but are limited by our knowledge of which genes are involved in HL. Whole exon sequencing is also based on exon capture but does not rely on a specific list of genes; rather the technique evaluates all exons in the genome for variations. Whole exon sequencing can potentially identify new HL genes. Whole genome sequencing is not limited to screening exons, and has the potential to identify changes outside known exons related to HL.<sup>25</sup> The ability of whole exon sequencing and whole genome sequencing approaches to detect a larger subset of changes associated with HL needs to be balanced with the interpretation of the data, specifically the wide number of variants and the potential for inaccurate causality.

## IDENTIFICATION OF NONSYNDROMIC HL GENES

Genetic screening is most applicable to nonsyndromic HL as these conditions very often have an indistinguishable phenotype. As new nonsyndromic HL loci are mapped, they are sequentially numbered by the order of discovery and grouped according to the inheritance pattern. Loci with dominant transmission are represented by the abbreviation DFNA followed by a HUGO gene nomenclature committee accession. Similarly, loci with a recessive inheritance are abbreviated DFNB, X-linked inheritance DFNX, modifier loci altering expression of HL genes by DFNM, and Y-linked by DFNY. To date, 141 loci have been identified. Occasionally, it has been observed that loci merge when multiple independently linked loci overlap and it is found that the same underlying gene causes HL. It has also been established that the same gene can be responsible for both the dominant and recessive forms of HL, depending on the mutation. Furthermore, some mutations in the same gene can cause nonsyndromic HL, and others cause syndromic HL.

Studies have been particularly successful in investigating the cause of nonsyndromic HL in families from regions with high rates of consanguineous marriages, and have discovered a significant number of recessive deafness genes.<sup>26</sup> It is known that the molecular epidemiology of HL can vary considerably among populations. The 35delG mutation in *GJB2* is considered the most common cause of nonsyndromic HL, and for many years was one of the few genes routinely screened in diagnostic testing

of HL patients. In HL individuals of European ethnicity, the *GJB2* mutation accounts for 28 to 63% HL.<sup>27</sup> However, in individuals with HL, who are from the Saudi Arabian, African-American, Caribbean, Hispanic, Pakistani and Moroccan populations, there is a very low incidence of *GJB2* mutations.

Current estimates suggest that 1% of human genes are necessary for hearing, and the European frequency of *GJB2* mutations is disproportionately high. As technology continues to improve, so does our understanding of nonsyndromic HL.<sup>25</sup>

## COMMON GENES

Table 1 lists bilateral nonsyndromic HL genes discovered through next-generation sequencing methods. For autosomal recessive HL, the most frequent causative genes in order of frequency are *GJB2*, *SLC26A4*, *MYO15A*, *OTOF*, *CDH23*, and *TMC1*. For each of these genes, at least 20 mutations have been reported. Autosomal dominant common mutations include *WFS1*, *MYO7A*, and *COCH*. Several of these genes are also implicated in syndromic HL.

### GJB2

The most common mutation responsible for nonsyndromic HL is a mutation of the *GJB2*. The *GJB2* gene encodes connexin 26, a gap junction protein that allows passage of potassium ions required to maintain the endocochlear potential. Immunolabeling results in the mouse show that connexin 26 is expressed by cells in the lateral wall, supporting cells in the organ of Corti and cells in the spiral limbus. More than 110 different mutations in *GJB2* have been identified. The 35delG mutation is the most frequent in the majority of Caucasian populations and may account for 70% of all *GJB2* mutations. Mutations in the *GJB2* gene produce considerable phenotypic variation, and the degree of deafness can vary from mild to profound. The HL tends to be stable. In general, bony abnormalities of the cochlea are not part of the deafness phenotype and developmental motor milestones and vestibular function are normal. Several studies have shown that children with severe-to-profound HL due to mutations in *GJB2* have excellent outcomes with cochlear implants.

### SLC26A4

Mutations in *SLC26A4* are the second most frequent cause of autosomal recessive HL, and the resulting phenotypes include Pendred syndrome, an autosomal recessive disorder characterized by sensorineural deafness and goiter, and nonsyndromic HL (DFNB4). The deafness is congenital and associated with temporal bone abnormalities that range in severity from isolated enlarged vestibular

**Table 1:** Bilateral nonsyndromic HL genes discovered through next-generation sequencing methods

Gene symbol	Gene name	DFN locus	Clinical features
Autosomal dominant inheritance			
CEACAM16	DFNA4B	Carcinoembryonic antigen-related cell adhesion molecule 16	Postlingual, progressive, SNHL
P2RX2	DFNA41	Purinergic receptor P2X, ligand gated ion channel	Postlingual, progressive moderate to severe SNHL, accelerated presbycusis
OSBPL2	DFNA67	Oxysterol binding protein-like 2	Postlingual, progressive
TBC1D24	DFNA65	TBC1 domain family, member 24	Postlingual, progressive
Autosomal recessive inheritance			
TNC	DFNB56	Tenascin C	Postlingual, progressive, severe low-frequency SNHL
ADCY1	DFNB44	Adenylate cyclase 1	Prelingual, profound, mild–moderate mixed and SNHL
BDP1	DFNB49	B double prime 1, subunit of RNA polymerase III transcription initiation factor IIIB	Prelingual progressive, moderate–severe SNHL
CABP2	DFNB93	Calcium binding protein 2	Prelingual, moderate–severe SNHL
ELMOD3	DFNB88	ELMO/CED-12 domain containing 3	Prelingual, severe–profound mixed HL
EPS8	DFNB102	Epidermal growth factor receptor pathway substrate 8	Congenital profound SNHL
GPSM2	DFNB32/82	G-protein signaling modulator 2	Prelingual, severe–profound SNHL
GRXCR2	DFNB101	Glutaredoxin, cysteine rich 2	Early onset, moderate–severe, progressive SNHL
KARS	DFNB89	Lysyl-tRNA synthetase	Prelingual, moderate–profound, stable SNHL
OTOGL	DFNB84B	Otogelin-like	Prelingual, congenital, moderate, stable SNHL
TBC1D24	DFNB86	TBC1 domain family member 24	Prelingual, profound SNHL
TMEM132E	DFNB99	Transmembrane protein 132E	Congenital, severe–profound SNHL
TPRN	DFNB79	Taperin	Prelingual, severe–profound SNHL
TSPEAR	DFNB98	Thrombospondin-type laminin G domain and EAR repeats	Congenital, profound SNHL
CLIC5	DFNB103	Chloride intracellular channel 5	Prelingual, severe–profound SNHL, vestibular areflexia
X-linked inheritance			
COL4A6	DFNX6	Collagen, type IV, alpha 6	Male: Congenital, severe SNHL female (carrier): 3rd and 4th decade onset, mild–moderate mixed or conductive HL
SMPX	DFNX4	Small muscle protein, X-linked	Male: Postlingual, severe–profound progressive SNHL Female (carrier): 2nd–4th decade onset, moderate–severe high-frequency SNHL

HL: Hearing loss; RNA: Ribonucleic acid; SNHL: Sensorineural hearing loss

aqueduct to Mondini dysplasia. The thyromegaly in Pendred syndrome is due to multinodular goitrous changes in the thyroid gland, although affected persons typically remain euthyroid. The perchlorate discharge test is often abnormal. Mutations in *SLC26A4* also cause DFNB4, a type of autosomal recessive HL in which affected persons do not have thyromegaly. Together, DFNB4 and Pendred syndrome are estimated to account for 1–8% of congenital deafness. Functional studies suggest that some of the observed phenotypic differences between Pendred syndrome and DFNB4 may be due to the degree of residual function of the encoded protein, pendrin.

### MYO15A

Mutations in *MYO15A* cause congenital severe-to-profound HL at the DFNB3 locus. *MYO15A* is encoded by 66 exons. All 28 identified mutations have been found

through linkage analysis in consanguineous families, most of which originate in Pakistan.

### OTOF

Mutations in the gene encoding otoferlin (*OTOF*) are responsible for the DFNB9 subtype of prelingual hearing impairment characterized by auditory neuropathy/auditory dissynchrony. Auditory neuropathy is a unique type of HL diagnosed when auditory brain stem responses are absent or severely abnormal; however, outer hair cell function is normal as indicated by the presence of otoacoustic emissions. Auditory testing suggests that the lesion lies at the level of the inner hair cells synapse to the afferent nerve fibers or to the auditory nerve itself. Individuals with this disorder can have various degrees of HL but generally have disproportionately poor speech understanding. Hearing aids may provide little help in

speech understanding in most individuals with auditory neuropathy. Cochlear implantation has had mixed results in speech understanding.

### CDH23

Mutations in the gene encoding cadherin-23 (*CDH23*) cause Usher syndrome (Usher) or nonsyndromic HL (DFNB12). Usher syndrome Type 1D (USH1D) is characterized by congenital severe–profound HL, adolescent onset retinitis pigmentosa, and vestibular dysfunction. DFNB12 causes moderate-to-profound progressive HL. No single *CDH23* mutation predominates as a cause of either USH1D or autosomal recessive nonsyndromic HL.

### TMC1

*TMC1* mutations are one of the more frequent causes of autosomal recessive nonsyndromic HL in non-Caucasian consanguineous populations. Twenty-one different mutations have been reported in 33 consanguineous families, only one of which was Caucasian. One mutation (c.100C>T) accounts for more than 40% of all *TMC1* mutations. *TMC1* encodes a transmembrane protein that is required for the normal function of cochlear hair cells. The reported cases show a similar phenotype characterized by prelingual severe-to-profound HL.

### WFS1

Wolfram syndrome is a progressive neurodegenerative syndrome characterized by the features diabetes insipidus, diabetes mellitus, optic atrophy, and deafness.

### MYO7A

Mutations in the gene encoding myosin VIIA (*MYO7A*) cause Usher syndrome Type 1B (USH1B), nonsyndromic deafness (DFNB2), and underlies the mouse recessive deafness mutation, *shaker-1*. Mice with *shaker-1* demonstrate typical neuroepithelial defects manifested by HL and vestibular dysfunction. Individuals with USH1B have a typical type 1 Usher syndrome, similar to USH1D (*CDH23*). Most affected individuals with DFNA11 notice HL in their first decade of life after complete speech acquisition with a subsequent gradual progressive loss. Individuals have bilateral sensorineural HL without vertigo and other associated symptoms.

### COCH

Mutations in the *COCH* gene have been identified in families with DFNA9, an autosomal dominant progressive sensorineural HL with onset in high frequencies. The phenotype is late onset HL, with parallel auditory and vestibular decline. Onset of HL in patients with DFNA9

**Table 2:** Inheritance patterns of syndromic hearing loss

Autosomal dominant	Autosomal recessive	X-linked
Waardenburg	Usher	Alport
Stickler	Pendred	Norrie
Treacher Collins	Jervell Lange-Neilson	
Brachio-oto-renal	Biotinidase	

occurs between 20 and 30 years, and is initially more profound at high frequencies. Affected individuals can have a spectrum of clinical vestibular involvement.

### “COMMON” SYNDROMES

Table 2 lists the inheritance patterns of the most common syndromic causes of HL.

#### Usher (Usher, USH)

Phenotype is characterized by concurrent HL and progressive visual impairment caused by retinitis pigmentosa. Some patients also have vestibular areflexia. Usher is the most common cause of autosomal recessive syndromic HL and affects about 1 in 6,000 to 17,000 Americans; 50% of the deaf-blind in the USA have Usher syndrome. Thirteen genes and three clinical subtypes (USH1, USH2, and USH3) are associated with Usher. Five of nine Usher genes also cause nonsyndromic HL. Individuals with USH1 are born with severe–profound deafness, severe vestibular dysfunction, and develop retinitis pigmentosa (progressive degeneration of the retina) in childhood. Individuals with USH2 are born with mild–severe HL (mild in the low frequencies and severe in the high frequencies), normal vestibular function, and retinitis pigmentosa that begins in young adulthood. USH3 is characterized by progressive HL, variable vestibular function, and variable age of onset of retinitis pigmentosa. Table 3 is a list of the types, genes, and proteins associated with Usher.

#### Pendred Syndrome

Phenotype is characterized by severe congenital sensorineural HL and euthyroid goiter. Pendred syndrome (PDS) is thought to cause about 5 to 10% of hereditary HL. A large percentage of patients have labyrinthine bony abnormalities. Some patients will have vestibular dysfunction. The goiter is due to a defect in the organification of iodine that can be demonstrated by a perchlorate test. A total of 50% of families with PDS have an *SLC26A4* gene mutation on chromosome 7q21-q34. The protein, pendrin, is involved in the transport of iodine and chloride ions.

#### Jervell and Lange–Neilson (JLNS)

Phenotype is characterized by congenital sensorineural HL and elongation of the QT interval (QT > 440 ms) on an

**Table 3:** Known Usher syndrome types, genes, and proteins

Type	Frequency	Gene locus	Gene	Protein	Function
USH1B	39–55%	11q13.5	<i>MYO7A</i>	Myosin VIIA	Motor protein
USH1C	6–8%	11p15.1-p14	<i>USH1C</i>	Harmonin	Scaffolding
USH1D	19–35%	10q21-q22	<i>CDH23</i>	Cadherin 23	Cell adhesion
USH1F	11–19%	10q11.2-q21	<i>PCDH15</i>	Protocadherin 15	Cell adhesion
USH1G	7%	17q24-q25	<i>USH1G</i>	SANS	Scaffolding
USH1J	rare		<i>CIB2</i>	Calcium and integrin binding protein 2	Calcium binding
USH2A	80%	1q41	<i>USH2A</i>	Usherin	Cell adhesion
USH2C	15%	5q14.3-q21.1	<i>GPR98</i>	VLGR1b	Signaling
USH2D	5%	9q32-q34	<i>DFNB31</i>	Whirlin	Scaffolding
USH3A		3q21-q25	<i>CLRN1</i>	Clarin-1	Scaffolding and adhesion
USH3B			<i>HARS</i>	Histidyl-tRNA synthetase	Ribonucleic acid processing

electrocardiogram. It affects 1.6 to 6 people per million worldwide. Patients may present with syncope or a family history of sudden death. Jervell and Lange-Neilson is caused by mutations in the *KVLQT1* gene (*JLNS1*), located on chromosome 11p15.5, and the *KCNE1* (*IsK*) gene (*JLNS2*), located on chromosome 21q22.1-q22.2. These genes are responsible for potassium channels.

### Branchio-oto-renal

Phenotype is characterized by HL (conductive, sensorineural, or mixed), along with branchial cleft cyst, ear anomalies, preauricular pits, and renal abnormalities like dysplasia or polycystic kidney disease. Branchio-oto-renal affects about 1 in 40,000 people. Hearing loss can be delayed in onset and affects 80% of patients. Mutations in the *EYA1* gene, on chromosome 8q13.3, account for 50% patients with BOR. Additionally, mutations on chromosome 1q31 can cause BOR.

### Stickler (STL)

Phenotype is characterized by progressive sensorineural HL, cleft palate, abnormal development of the epiphysis, vertebral anomalies, and osteoarthritis. Stickler affects 1 in 7,500 to 9,000. Stickler has three subtypes: Type 1 with progressive myopathy, vitreoretinal degeneration, and retinal detachment; type 2 with progressive myopathy and vitreoretinal degeneration, without retinal detachment; and type 3 with similar findings to type 1 and facial abnormalities. Mutations in the *COL2A1* gene (*STL1*) on chromosome 12q13.11-q13.2 are responsible for type 1; the *COL11A1* gene (*STL2*) located on chromosome 1p21 cause type 2; and *COL11A2* gene (*STL3*) on chromosome 6p21.3 cause type 3.

### Treacher Collins

Phenotype is characterized by symmetric and hypoplastic zygoma, lower palpebral fissures, malformed external ears, auditory pits, and HL (55% conductive). Treacher

Collins affects 1 in 50,000 people. There is often a *TCOF1* gene mutation on chromosome 5q32-q33.1.

### Alport

Phenotype is characterized by progressive sensorineural HL, renal dysfunction (glomerulonephritis, hematuria, and renal failure), and eye problems (lenticular and macular abnormalities). Alport affects about 1 in 50,000 individuals. Alport is X-linked in 85% of the cases, autosomal recessive in 15%, and autosomal dominant in the remaining. In the X-linked form, males are more severely affected than females. Mutations in the *COL4A5* gene on Xq22 and the *COL4A3* and *COL4A4* genes on chromosome 2q36-q37 are responsible for Alport.

### Biotinidase Deficiency

Biotinidase deficiency is due to a deficiency of the enzyme required for the normal recycling of the vitamin biotin. It affects about 1 in 60,000 infants. Affected infants have skin rashes, seizures, hair loss, hypotonia, vomiting, and acidosis in the first few months of life. If untreated, 75% affected individuals will develop HL.

### Norrie Disease

Phenotype characterized by eye disorders (pseudotumor, hyperplasia, hypoplasia or necrosis of the retina, and cataracts), developmental delays, and progressive sensorineural HL. The incidence of Norrie disease is unknown. The *Norrie* gene is located in Xp11.2 and controls vascularization in the cochlea and retina.

### Wolfram Syndrome

Rare syndrome, with an estimated prevalence of 1 in 770,000 and a carrier frequency of 1 in 354. Mutations in *WFS1* can result in the autosomal recessive Wolfram syndrome or the autosomal dominant form of nonsyndromic sensorineural HL at the *DFNA6/14/38* locus. Wolfram syndrome is characterized by high-frequency sensorineural HL.

## FUTURE

It is thought that 85% of Mendelian disease-causing mutations occur in coding splice junction regions, making targeted enrichment and massively parallel sequencing highly efficient.<sup>28</sup>

Furthermore, since 2008, the estimated costs of next-generation sequencing have decreased, and the \$1,000 genome has become a reality.<sup>29</sup> Increased affordability of gene testing makes more widespread application much more of a reality in clinical and research settings. The scientific community continues to face an ongoing problem; while it may cost \$1,000 for the genome, the complicated analysis of the data is much more expensive.<sup>30</sup> This fact has led to the term “the \$1,000 genome, the \$100,000 analysis.”<sup>30</sup> Sequencing is actually considered the cheapest and simplest part of the process. Full interpretation of the data constitutes a major expense and requires expertise from geneticists, statisticians, bioinformatics, biologists, and physicians to translate the impact of a genomic variant into clinically relevant information. The efficient analysis of the genome is the biggest area for improvement; however, effective algorithms to answer complicated statistical questions are needed. Currently, the wide availability and decreasing cost of next-generation sequencing has changed the way research is conducted. Improved habilitation, calculation of recurrence, and prognostic information are all critical components that are a result of determining the genetic diagnosis of HL. Establishing the genetic cause of HL in prelingual children facilitates the medical course of action.

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