An Overview of Hereditary Hearing Loss

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Key Words

Hereditary hearing loss · Syndromic hearing loss · Nonsyndromic hearing loss · X-linked hearing loss · Mitochondrial hearing loss

Abstract

Understanding the genetic basis of hearing loss is important because almost 50% of profound hearing loss are caused by genetic factors and more than 120 independent genes have been identified. In this review, after a brief explanation of some genetic terms (allele, heterozygosis, homozygosis, polymorphism, genotype and phenotype), classification of genetic hearing loss (syndromic versus nonsyndromic, and recessive dominant, X-linked and mitochondrial) was performed. Some of the most common syndromes (Usher, Pendred, Jervell and Lange-Nielsen, Waardenburg, branchio-oto-renal, Stickler, Treacher Collins and Alport syndromes, biotinidase deficiency and Norrie disease) causing genetic hearing loss were also explained briefly. The genes involved in hearing loss and genetic heterogeneity were presented.

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Introduction

Profound hearing loss affects almost 1 in 1,000 newborns, and more than 50% of these are caused by genetic factors [1]. More than 120 independent genes that cause hearing loss have been identified. Although the genes

causing a child to be deaf are present from the time of conception, not all forms of genetic deafness or hereditary hearing loss (HHL) are necessarily expressed at birth.

Each gene has two alleles: one comes from the mother and the other from the father. In a recessive inheritance, both alleles have to be mutated to cause hearing impairment. If the same mutation is present in both alleles, the subject is referred to as ‘homozygous’ for the mutation. Homozygous means having two identical alleles as a specific autosomal (or X chromosome in a female) gene locus. Heterozygous means having two different alleles as a specific autosomal (or X chromosome in a female) gene locus. In the case of heterozygosity, if both alleles have different disease-causing mutations, the subject is referred to as ‘compound heterozygous’ for the mutation. If only one of the alleles has the disease-causing mutation and the other allele is normal, the subject is a ‘carrier’. A recessive mutation can cause hearing impairment in both the homozygous and compound heterozygous forms. On the other hand, carriers do not have hearing impairment. According to Mendelian genetics, if a carrier is married to a normal subject, 50% of their children will possibly be carriers for the mutation.

Polymorphism means the quality or character of occurring in several different forms. Genetic polymorphism designates the occurrence together in the same population of two or more genetically determined phenotypes in such proportions that the rarest of them cannot be maintained merely by recurrent mutation. Polymorphism also refers to regions of the genome in which common sequence variations are found. Most of the polymorphisms have no detectable clinical effects and many are not even located

within the coding sequence of genes. If one of the alleles is mutated and the other allele has a polymorphism, the subject will probably not have hearing impairment.

In the dominant form, the presence of a mutation in only one of the alleles is enough for the subject to have the disease. However, penetrance of a dominant gene may differ. The term 'penetrance' means the likelihood that a person carrying a particular mutant gene will have an altered phenotype. Therefore, the presence of a dominant mutation in the parents does not always mean that the siblings will always have hearing impairment. Expression of the gene, that is the degree to which an individual has acquired the traits associated with a particular gene, is also important in inherited disorders. The expression of a disease-causing gene may be low or high, thereby causing differences in the phenotype. This may be one of the reasons why the same genotype or mutation is manifested by different phenotypes in genetic hearing loss.

Genotype means a person's genetic makeup, as reflected by his or her DNA sequences. Phenotype denotes the clinical presentation or expression of a specific gene or genes, environmental factors, or both. The genotype-to-phenotype relation in HHL is important. From the point of view of hearing impairment, phenotype is the type of hearing loss which can be figured out by means of an audiogram, and genotype means the mutation in the gene resulting in hearing impairment. As our knowledge of the relationship between genotype and phenotype increases, it will be highly likely to understand the responsible genotype alteration or mutation by looking at the phenotype or the type of hearing loss. In other words, we can better understand the correlation between genetic alteration and the degree of hearing impairment [2]. This way, possible candidate gene regions could be investigated initially without performing a genome-wide screening.

Description of genetic hearing impairments is performed according to some guidelines. Briefly, DFN, which is derived from the term 'deafness', is used to describe the locus responsible for genetic nonsyndromic hearing loss (NSHL). DFNA represents the autosomal dominant form, DFNB the autosomal recessive form of NSHL, and DFN alone represents X-linked NSHL. Numbers added after these abbreviations, like DFNB1 or DFNB30, show the chronological order in which the loci are found. Accordingly, DFNB1 is described before DFNB30. A mutation like 167delT means the presence of a deletion of T at position 167, and a mutation like 269T→C means a change of T into C at position 269. For example, a 35delG mutation that occurs in the *GJB2* gene on chromosome 13q12 results in an abnormal protein

product of connexin 26, and in nonsyndromic and recessive forms of deafness segregated with DFNB1. In this example, the responsible locus is DFNB1, the mutant gene is *GJB2*, the mutation is present in the long arm of chromosome 13 in band 12, and the mutation results from a deletion of G at position 35.

According to the pattern of inheritance, HHL can also be classified as autosomal recessive, autosomal dominant, X-linked and mitochondrial [3, 4]. In NSHL, 51 recessive, 39 dominant, and 8 X-linked loci have been mapped. According to the phenotype, HHL can be classified as nonsyndromic and syndromic hearing loss. Almost 70% of HHL are nonsyndromic, and 30% are syndromic. There are more than 70 genes involved in nonsyndromic forms and more than 400 syndromes associated with hearing loss [5]. Genetic hearing loss may be delayed in onset with different progression rates. In syndromic forms, hearing loss is mostly mild or inconsistent except for the Pendred and Jervell and Lange-Nielsen syndrome, and there may be other associated clinical findings. Differential diagnosis of syndromic and nonsyndromic hearing loss is made according to history and physical examination as well as laboratory tests and radiological assessments as indicated. This diagnostic work-up will allow us to understand the absence or presence of associated findings, and in turn a syndromic hearing loss can be distinguished from a nonsyndromic hearing loss.

Genetic Nonsyndromic Hearing Loss

NSHL has an autosomal dominant, autosomal recessive or X-linked pattern of inheritance. The autosomal recessive form accounts for 80% of all NSHL cases. The pedigree is horizontal. Hearing loss is usually prelingual and severe except for DFNB8 in which hearing loss is postlingual and rapidly progressive. Almost 25% of siblings are affected. DFNB1 is the most common cause of autosomal recessive HHL, which is responsible in almost 50% of the cases [6, 7]. It is caused by a mutation in the *GJB2* gene on chromosome 13q12-13 that codes for a gap junction protein called connexin 26. There are numerous *GJB2* mutations, the frequencies of which differ between the populations. The most common mutations are 35delG, 167delT, and 235delC, which are frequent in the Caucasian, Jewish and Asian populations, respectively [8, 9]. The 35delG mutation constitutes almost 50% of all *GJB2* mutations in the Caucasians [10–16]. Therefore, the 35delG mutation of connexin 26 is the first mutation investigated in NSHL.

Table 1. Inheritance pattern of syndromic hearing losses

Autosomal recessive	Autosomal dominant	X-linked
Usher syndrome	Waardenburg syndrome	Alport syndrome
Pendred syndrome	Branchio-oto-renal syndrome	Norrie disease
Jervell and Lange-Nielsen syndrome	Stickler syndrome	
Biotinidase deficiency	Treacher Collins syndrome	

Autosomal dominant forms constitute 18% of NSHL. The pedigree is usually vertical. Almost 50% of the siblings are affected. Hearing loss is usually postlingual except for DFNA3, DFNA6, DFNA8, DFNA12, DFNA19 and DFNA14.

X-linked NSHL constitutes 1–3% of all NSHL cases. Hearing loss is usually prelingual except for DFN6. Boys are frequently affected because they have only one X chromosome. DFN2 and DFN4 mostly cause severe prelingual sensorineural hearing loss. DFN6 starts with high-frequency hearing loss at the ages of 5–7 years. Hearing loss progressively increases, becomes severe and involves all frequencies. The type of hearing loss or phenotype is not known very well for DFN5, DFN7 and DFN8. DFN3 causes mixed hearing loss. Congenital fixation of the stapes footplate with perilymph gusher is also an X-linked disorder. The affected males have mixed or sensorineural hearing loss. They may have dilation of the internal auditory meatus. The disorder is mapped to Xq21.1. Female carriers may have mild hearing loss and less severe inner ear abnormalities. Affected males have a mutation in the *POU3F4* gene, which is a DNA-binding regulatory protein [17]. When the patient is operated and stapedectomy is performed, perilymph gusher is likely to occur.

Genetic Syndromic Hearing Loss

Syndromic hearing loss can also be inherited in an autosomal recessive, autosomal dominant and X-linked manner (table 1).

Usher Syndrome

It is the most common cause of autosomal recessive syndromic hearing loss [18]. Almost 50% of the blind and deaf people in the USA have Usher syndrome. According to genotype and phenotype differences, the syndrome has several subtypes (table 2).

Type 1. There is severe hearing loss and vestibular dysfunction. Retinitis pigmentosa (a progressive degenera-

Table 2. Mutations causing Usher syndrome

Locus	Location	Gene
USH1A	14q32	?
USH1B	11q13.5	<i>MYO7A</i>
USH1C	11p15.1	<i>USH1C</i>
USH1D	10q	<i>CDH23</i>
USH1E	21q	?
USH1F	10q21-22	<i>PCDH15</i>
USH1G	17q24-25	?
USH2A	1q41	<i>USH2A</i>
USH2B	3p23-24.2	?
USH2C	5q14.3-q21.3	?
USH3	3q21-q25	<i>USH3</i>

From van Camp and Smith [4].

tion of the retina that leads to loss of night vision, restriction of the visual fields, and blindness) starts in childhood.

Type 2. There is mild to moderate hearing loss. Vestibular function is normal. Retinitis pigmentosa occurs after childhood.

Type 3. There is progressive hearing loss and vestibular dysfunction. Retinitis pigmentosa can occur any time in life.

Pendred Syndrome

There is severe congenital hearing loss and euthyroid goiter [19]. Hearing loss is sensorineural. There may also be labyrinthine bone abnormality like Mondini dysplasia that can be seen in 86% of the cases. Vestibular dysfunction can occur. Goiter is due to a specific defect in the organification of iodine that can be demonstrated by the perchlorate test. It may be delayed in onset or clinically unapparent, and is rarely associated with hypothyroidism.

Almost 50% of the families have *SLC26A4* (*PDS*) gene mutation on chromosome 7q21-q34. The gene is responsible for sulfate transport. Its protein product, pendrin, is

Table 3. Mutations causing Waardenburg syndrome

Type	Location	Gene
WS type I (WS1)	2q35	<i>PAX3</i>
WS type II (WS2)	3p14.1-p12.3	<i>MITF</i>
WS type II (WS2)	8q11	<i>SLUG</i>
WS type III	2q35	<i>PAX3</i>
WS type IV	13q22	<i>EDNRB</i>
WS type IV	20q13.2-q13.3	<i>EDN3</i>
WS type IV	22q13	<i>SOX10</i>

From van Camp and Smith [4].

involved in the transport of iodine and chloride ions. *SLC26A4* gene mutation should be investigated in the patients who have progressive hearing loss, Mondini dysplasia or large vestibular aqueduct syndrome. The same mutation can also cause DFNB4 [20].

Jervell and Lange-Nielsen Syndrome

There is congenital hearing loss and elongation of the QT interval on electrocochleography (QT >440 ms) [21]. There may be syncope and sudden death due to a cardiac problem. If there is a family history of sudden death, this syndrome should be considered in a patient with hearing loss.

The JLNS1 locus in the *KVLQT1* gene located on chromosome 11p15.5, or the JLNS2 locus in the *KCNE1* (*IsK*) gene located on chromosome 21q22.1-q22.2 are responsible for the syndrome. These are potassium channel genes.

Biotinidase Deficiency

This condition results from the deficiency of an enzyme required for the normal recycling of the vitamin biotin. Infants with a severe deficiency are dependent on dietary sources of the vitamin. Otherwise, they will have skin rashes, seizures, hair loss, hypotonia, vomiting and acidosis within the first few months of life. If untreated, 75% of the affected infants develop hearing loss. Biotinidase deficiency is a completely preventable form of genetic deafness with supplementation of biotin [22].

Waardenburg Syndrome

Sensorineural hearing loss, pigmentation abnormality in the skin and hair, white forelock, dystrophia canthorum (lateral displacement of the inner canthi of the eyes), pinched nose and heterochromia iridis (different iris colors) can be seen. Gastrointestinal symptoms like consti-

pation and Hirschsprung disease, neural tube and limb defects may also be observed. It accounts for 1–2% of individuals with profound hearing loss, which can be bilateral or unilateral of variable severity. The syndrome has four subgroups according to the presence or absence of coexisting abnormalities and genotype (table 3).

In type 1, dystrophia canthorum is observed in every patient. In type 2, there is no dystrophia canthorum. In type 3, upper extremity abnormalities and the findings of type 1 are found. In type 4, there are pigmentation abnormalities, Hirschsprung disease and the findings of type 2.

Branchio-Oto-Renal Syndrome

Conductive, sensorineural or mixed hearing loss, branchial cleft cyst, auricle or external auditory canal abnormality, preauricular pits, and renal abnormalities like dysplasia, polycystic kidney and malformation of the calyces can be seen. Inner ear abnormalities like Mondini dysplasia and stapes fixation are possible. Almost 80% of gene carriers have some degree of hearing loss, which can be delayed in onset. In 50% of the patients, there is *EYAI* gene mutation on chromosome 8q13.3. Mutations on chromosome 1q31 may also cause this syndrome [23].

Stickler Syndrome

There is progressive sensorineural hearing loss, cleft palate, abnormal development of the epiphysis, vertebral abnormalities and osteoarthritis. It has three subgroups. In type 1, there is progressive myopathy, vitreoretinal degeneration and retinal detachment. In type 2, retina detachment is absent because of the lack of the *COL11A2* gene in the retina. The phenotypic differences between STL2 and STL1/STL3 can be explained by the absence of *COL11A2* in the vitreous [24]. In type 3, there are eye and ear findings as in type 1 and facial abnormalities.

The STL1 locus in the *COL2A1* gene located on chromosome 12q13.11-q13.2 is responsible for type 1, the STL2 locus in the *COL11A1* gene located on chromosome 1p21 is responsible for type 2, and the STL3 locus in the *COL11A2* gene located on chromosome 6p21.3 is responsible for type 3.

Treacher Collins Syndrome

Symmetric and hypoplastic zygoma, lower palpebral fissure, malformed and small ear, auditory pit, and hearing loss, which is conductive in 55% of cases, can be observed in Treacher Collins syndrome. Sensorineural hearing loss usually occurs at high frequencies. There is *TCOF1* gene mutation on chromosome 5q32-q33.1.

Table 4. Mitochondrial mutations causing syndromic hearing loss

Gene	Mutation	Phenotype
<i>TRNALeu (UUR)</i>	3243A→G	diabetes mellitus, neurologic disorder, hearing loss
<i>TRNALys</i>	8344A→G 8356T→C 8296A→G	diabetes mellitus, neurologic disorder, hearing loss
<i>tRNA^{Ser} (UCN)</i>	7512T→C	progressive myoclonic epilepsy, ataxia, hearing loss
Several	large deletion	external ophthalmoplegia, retinopathy, ataxia, arrhythmia
Several	larger deletion/duplication	diabetes mellitus
<i>TRNAGlu</i>	14709T→C	diabetes mellitus

From van Camp and Smith [4].

Alport Syndrome

Progressive sensorineural hearing loss, renal disorder (glomerulonephritis, hematuria, renal failure) and eye problems (lenticular and macular abnormalities) are observed. Almost 50% develop progressive bilateral hearing loss, which usually begins in the second decade. Hearing loss involves high frequencies initially. There may be ocular abnormalities like congenital cataract, spherophakia, retinal flecks and anterior lenticonus.

This syndrome is X-linked in 85%, autosomal recessive in 15%, and autosomal dominant in the remainders. In the X-linked form, males are more severely affected than females. The *COL4A5* gene on Xq22 and the *COL4A3* and *COL4A4* genes on chromosome 2q36–q37 are responsible for the syndrome.

Norrie Disease

We can observe eye disorders (pseudotumor, hyperplasia, hypoplasia or necrosis in the retina, and cataract), mental retardation and progressive sensorineural hearing loss in Norrie disease. *Norrin* gene mutation on Xp11.3 causes the disease. This gene is considered to control vascularization in the cochlea and retina.

Hearing Loss Inherited by a Mitochondrial Genome

Mitochondrial hearing loss constitutes less than 1% of all HHL cases. A mitochondrion has a 16,569-bp genome containing 22 tRNA and 2 rRNA, which codes for 13 proteins. Only maternal DNA is inherited to the child while paternal DNA is not. Therefore, all children are at

Table 5. Mitochondrial mutations causing NSHL

Gene	Mutation	Occasional additional findings
<i>12S rRNA</i>	1555A→G	–
	7445A→G	palmoplantar keratoderma
<i>TRNASer (UCN)</i>	7472insC	neurologic disorder, keratoderma
	7511T→C	–

From van Camp and Smith [4].

risk of having hearing impairment when the mitochondrion of the mother possesses a disease-causing mutation. Mitochondrial hearing loss may be nonsyndromic or syndromic as some other associated disorders can occur in addition to hearing loss (tables 4, 5). These disorders are neuropathy, myopathy, cardiomyopathy, retinal degeneration, diabetes mellitus, Parkinson disease, encephalopathy, lactic acidosis, epilepsy and stroke.

The mutations of 12S ribosomal RNA and tRNA may result in hearing loss in the phenotype. However, the mutation, which affects 12S ribosomal RNA, increases the susceptibility to aminoglycoside ototoxicity in addition to causing hearing loss [25]. 1555A is the binding site for aminoglycoside antibiotics in bacteria. Therefore, A1555G mutation in the human mitochondria makes this site similar to that of bacteria, thereby increasing aminoglycoside ototoxicity. A7445G, which affects tRNA, may also cause palmoplantar keratoderma in addition to hearing loss. 7472insC mutation can cause either isolated hearing loss or hearing loss may coexist with neurologic disorders like ataxia, dysarthria and myoclonus.

Table 6. Some of the genes causing hearing impairment and genetic heterogeneity

Gene	Location	Locus/syndrome
Transcriptional		
<i>PAX3</i>	2q35	Waardenburg type I–III
<i>MITF</i>	3q12	Waardenburg type II
<i>SOX10</i>	22q13	Waardenburg type IV
<i>POU4F3</i>	5q31	DFNA15
<i>POU3F4</i>	Xq21.1	DFN3, X-linked gusher
<i>EYA1</i>	8q13.3	branchio-oto-renal locus, DFNA10
<i>EYA4</i>	6q22.2-q23.3	Branchio-oto-renal, DFNA10
Intracellular		
<i>MYO7A</i>	11q13.5	DFNB2, DFNA11, Usher1B
<i>MYO6</i>	6q13	DFNA22, DFN17
<i>MYH9</i>	22q12.2-q13.3	DFNA22, DFN17
<i>MYO15</i>	17p11.2	DFNB3
<i>DIAPH1</i>	5q31	DFNA1
<i>STRC</i>	15q15	DFNB16
<i>OTOF</i>	2p23	DFNB9
<i>TCOF1</i>	5q32-q33.1	Treacher Collins
Transmembrane		
<i>KVLOT1</i>	11p15.5	JLNS1 locus/Jervell Lange Nielsen
<i>KCNE1</i>	21q22.1-q22.2	JLNS2 locus/Jervell Lange Nielsen
<i>KNCQ4</i>	1p34	DFNA2
<i>SCL26A4 (PDS)</i>	7q21-q34	DFNB23, DFNB15, DFNB4 Usher1F-III,
<i>CDH23</i>	10q21	Pendred
<i>CLDN14</i>	21q22.3	DFNB18, DFNB12, Usher1C-D
Extracellular		
<i>COL2A1</i>	12q13.11-q13.2	Stickler type 1
<i>COL11A2</i>	6p21.3	Stickler type 3, DFNA13
<i>COL11A1</i>	1p21	Stickler type 2
<i>COL4A5</i>	Xq22	Alport
<i>COL4A3</i>	2q36-q37	Alport
<i>COL4A4</i>	2q36-q37	Alport
<i>TECTA</i>	11q22	DFNA8, DFNA12, DFNB21
<i>OTOA</i>	16p12.2	DFNB22
<i>GJB2</i>	13q12	DFNB1, DFNA3, palmoplantar hyperkeratosis
<i>GJB6</i>	13q12	DFNA3
<i>GJB3</i>	1p34	DFNA2

Heterogeneity of Genetic Hearing Loss

Although genetic hearing loss is mostly caused by a mutation in a single gene, it is a heterogeneous condition [26]. Genotype-to-phenotype correlation is also important, because different mutations in the same gene can lead to different phenotypes [27]. The same mutation in a single gene can cause syndromic, nonsyndromic, recessive or dominant hearing loss. Connexin 26, connexin 31 and MYO7A mutations can cause recessive or dominant NSHL. COL11A2, PDS, MYO7A and connexin 26 mutations can cause syndromic or nonsyndromic hearing loss [28, 29]. Some of the genes that cause hearing loss and examples of genetic heterogeneity are shown in table 6.

Conclusion

The majority of deaf children are born to normal hearing parents, and understanding the attitudes of this group is necessary for optimal counseling strategies [30]. Identification of genes associated with hearing impairment will allow screening and possible therapy for the hearing impaired [31]. Although genomic DNA can be identified and is stable, mutation screening requires knowledge of the candidate gene's genomic structure [32]. Gene transfer studies have been performed and preliminary reports seem promising in HHL [33, 34].

The assessment of hearing impairment must include a thorough family history including distant and second-de-

gree relatives. The possibility of syndromes must be remembered and the patient should be assessed for possible associated findings. The study of HHL is a huge work that includes early detection of probands, identification of the

responsible genetic causes using molecular genetic techniques, genetic counseling for the families, and gene therapy in the future.

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