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Forty-six genes causing nonsyndromic hearing impairment: which ones should be analyzed in DNA diagnostics?

Nele Hilgert[1], **Richard J.H. Smith**[2], and **Guy Van Camp**[1,*]

[1] Department of Medical Genetics, University of Antwerp (UA), 2610 Antwerp, Belgium

[2] Department of Otolaryngology-Head and Neck Surgery, University of Iowa, Iowa city, IA 52242, USA

Abstract

Hearing impairment is the most common sensory disorder, present in 1 of every 500 newborns. With 46 genes implicated in nonsyndromic hearing loss, it is also an extremely heterogeneous trait. Here, we categorize for the first time all mutations reported in nonsyndromic deafness genes, both worldwide and more specifically in Caucasians. The most frequent genes implicated in autosomal recessive nonsyndromic hearing loss are *GJB2*, which is responsible for more than half of cases, followed by *SLC26A4*, *MYO15A*, *OTOF*, *CDH23* and *TMC1*. None of the genes associated with autosomal dominant nonsyndromic hearing loss accounts for a preponderance of cases. Mutations are somewhat more frequently reported in *WFS1*, *KCNQ4, COCH* and *GJB2*. Only a minority of these genes is currently included in genetic diagnostics, the selection criteria typically reflecting: 1) high frequency as a cause of deafness (i.e. *GJB2*); 2) association with another recognizable feature (i.e. *SLC26A4* and enlarged vestibular aqueduct); or 3) a recognizable audioprofile (i.e. *WFS1*). New and powerful DNA sequencing technologies have been developed over the past few years, but have not yet found their way into DNA diagnostics. Implementing these technologies is likely to happen within the next 5 years, and will cause a breakthrough in terms of power and cost efficiency. It will become possible to analyze most - if not all - deafness genes, as opposed to one or a few genes currently. This ability will greatly improve DNA diagnostics, provide epidemiological data on gene-based mutation frequencies, and reveal novel genotype-phenotype correlations.

Keywords

Hereditary hearing loss; ARNSHL; ADNSHL; *GJB2*; gene frequencies; genetic counselling

1. Introduction

Hearing loss (HL) is the most common birth defect in industrialized countries and the most prevalent sensorineural disorder. One of every 500 newborns has bilateral permanent sensorineural hearing loss ≥ 40dBHL. Before the age of 5, the prevalence increases to 2.7 per 1000 and to 3.5 per 1000 during adolescence [1]. HL is categorized in several ways: conductive HL typically implies a defect of the outer or middle ear while sensorineural HL refers to a defect of the inner ear. The co-occurrence of both conductive and sensorineural hearing loss is referred to as a mixed hearing loss. Based on the age of onset, HL can also be described as

*Corresponding author: Prof. Dr. Guy Van Camp, Department of Medical Genetics, University of Antwerp, Universiteitsplein 1, B-2610 Antwerp, Belgium, Tel.: +32-3-820-24-91, Fax: +32-3-820-25-66, guy.vancamp@ua.ac.be.

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prelingual (before speech development, sometimes referred to as congenital although not all prelingual cases are congenital) or postlingual (after speech development). It is estimated that in developed countries, genetic causes of HL can be found in at least two-thirds of prelingual cases. The remaining one-third of cases can be ascribed to environmental factors and unidentified genetic factors.

The most common environmental (non-genetic) cause of congenital hearing loss is congenital cytomegaloviral (CMV) infection. Its overall birth prevalence is 0.64%, with only about 10% of this number having symptomatic CMV. Of asymptomatic cases, 0–4.4% develops unilateral or bilateral HL before the age of six years. These figures generally apply to developed countries, although there is wide ethnic variation [2]. In addition, the diagnosis of congenital CMV is often difficult to make, especially in children over 3 weeks of age. As PCR-based techniques using dried bloodspot cards become widely available, reliable screening for *in utero* CMV exposure will be possible. Other environmental causes of hearing loss in the newborn period include bacterial infection, hyperbilirubinemia, anoxia and the use of ototoxic medications.

In most cases, inherited HL is monogenic. In 70% of neonates who fail newborn hearing screens and are presumed to have inherited HL, there are no other distinguishing physical findings and the HL is classified as nonsyndromic. In the remaining 30%, the HL is accompanied by other physical findings and is said to be syndromic [3]. Of the more than 400 syndromes in which HL is a recognized feature, Usher syndrome, Pendred syndrome and Jervell and Lange-Nielsen syndrome are the most frequent [4].

Monogenic hearing loss can be inherited in different ways. Autosomal recessive HL (ARNSHL) occurs in 80% of cases and is typically prelingual, while autosomal dominant HL (ADNSHL) accounts for about 20% of cases and is most often postlingual. In less than 1% of cases, the inheritance occurs through the X-chromosome or the mitochondria [5]. Monogenic hearing loss is an extremely heterogeneous trait, with over 100 mapped loci and 46 causally implicated genes (Hereditary Hearing Loss Homepage; http://webh01.ua.ac.be/hhh/). For over half of these loci, specific ‘deafness-causing’ genes have not yet been found. Their identification will provide further knowledge about the pathways involved in the hearing process and will allow for better genetic diagnostics. The ultimate goal is to provide better and/or new habilitation for hearing impaired persons.

Over the past decade, universal newborn hearing screening programs have been developed and implemented in many developed countries. The rationale for this initiative is based on the premise that early detection and intervention for children with hearing loss maximizes opportunities for language and speech development, thereby facilitating the acquisition of normal social, cognitive and motor skills. Stimulation of the auditory cortex before the age of 6 months is crucial for normal development of the auditory tracts. Screening is most often performed by automated auditory brainstem response (ABR) or otoacoustic emission (OAE) testing.

2. Frequency of mutations causing monogenic hearing loss

To date, 46 genes have been identified as causally related to nonsyndromic HL. Mutations in these genes do not occur at the same frequencies across ethnicities. In addition, although families with ARNSHL are found around the world, the majority of families reported with ARNSHL originate from the ‘consanguinity belt’, a region ranging from North Africa, through the Middle East to India. These consanguineous families have a large power for linkage mapping and allow locus identification on the basis of a single family. Families segregating ADNSHL, in contrast, mainly originate from Europe, North America and Australia.

To date, no overview has assessed the number of mutations reported in deafness-causing genes. The lack of this information makes it very hard to estimate the relative contribution of different genes to HL. This information is however of great importance for researchers as well as clinicians. In order to fill this gap, we performed a literature search which allowed counting the number of reported mutations in all 46 nonsyndromic deafness genes. In Table 1, we have collated these mutation numbers, both worldwide and in populations of white European ancestry (whites from Europe, North America, Canada, Australia and New Zealand), which we hereafter call 'Caucasians'. The table also lists the locus name and the presumed function of each gene. Classifying into the worldwide population and Caucasians is an oversimplification as the term 'Caucasians' does not recognize a specific ethnic subgroup. It should therefore be kept in mind that within the Caucasian population, there may be variation in mutation frequencies from country to country. Supplementary Table 1 provides information about the country of origin of the patients in which the mutation was identified, together with references to the reported articles in which the mutation was first described.

The number of reported mutations is likely biased by several factors. For example, large genes are less frequently analyzed, numbers for frequently mutated genes like *GJB2* and *SLC26A4* are likely underestimates, and some genes have distinct audioprofiles to facilitate targeted gene screening. Nevertheless, based on the number of reported mutations, we have estimated the mutation frequencies for all nonsyndromic deafness genes. For most of these genes, the number of mutations identified and the number of reported families (unrelated cases) are identical. In a few specific cases, however, the number of mutations is fewer than the number of reported cases. Examples include *GJB2*, *SLC26A4*, *OTOF*, *MT-RNR1* and *COCH*, all of which have recurrent mutations. It should also be noted that the reported mutation numbers given for Caucasians are probably not representative for all European populations and that in some cases, considerable differences in mutations frequencies may be present, even within Europe. Therefore, in-depth studies should be performed to determine the epidemiology of hearing loss in different populations.

2.1 Genes as a frequent cause of ARNSHL

For ARNSHL, the most frequent causative genes in order of frequency are *GJB2*, *SLC26A4*, *MYO15A*, *OTOF, CDH23* and *TMC1*. For these genes, at least 20 mutations have been reported. The number of mutations in the other genes is <20 and most of these mutations are reported in consanguineous families and not in Caucasians.

GJB2 mutations are the most frequent cause of ARNSHL in most world populations, in some of them accounting for up to 50% of ARNSHL cases [6]. According to the Connexin-deafness homepage (http://davinci.crg.es/deafness/index.php), 91 different mutations have been identified, some of which are very frequent, others of which are extremely rare. These mutations occur at different frequencies across populations [6]. Because mutations reported after 2003 are not listed, we completed an extensive literature search and estimate that over 220 mutations have been reported. The 35delG mutation is most frequent in the majority of Caucasian populations and may account for up to 70% of all *GJB2* mutations [7]. The carrier frequencies however differ significantly between European populations. An gradient in carrier frequency has been suggested between central-northern and southern Europe, with frequencies in the latter being roughly twice as high [8]. Other frequent mutations in specific populations are 167delT in Ashkenazi Jewish [9] and 235delC in Japanese [10]. As the number of deaf persons carrying a single *GJB2* mutation was higher than expected, a search for other mutations in or near *GJB2* led to the identification of two large deletions: del(GJB6-D13S1830) and del (GJB6-D13S1854) [11,12]. Both deletions not only truncate the neighbouring *GJB6*-gene but also abolish *GJB2* expression, possibly by deleting a currently unidentified *GJB2* regulatory element. Therefore, they are considered as *GJB2* mutations as well [13]. They are usually found

in compound heterozygosity with a *GJB2* coding mutation and cause hearing loss that is significantly worse than most other *GJB2* mutations, perhaps because expression of both copies of *GJB2* and one copy of *GJB6* is abolished [7,12]. Del(GJB6-D13S1830) seems to occur worldwide and is much more frequent than del(GJB6-D13S1854), which has mainly been found in Spain and the UK. A significant percentage of *GJB2* mutation carriers do not carry either of these deletions indicating that additional unidentified mutations/deletions may be present at DFNB1 loci.

There is a great deal of variation in the degree of hearing loss caused by *GJB2* mutations. A multicenter genotype-phenotype correlation study has shown that inactivating mutations cause a more severe phenotype than non-inactivating mutations [7]. In addition, a few common mutations (M34T, V37I, and L90P) are associated with mild-to-moderate hearing impairment. For most genotypes, however, there is considerable variation. As an example, there is striking phenotypic variability among 35delG homozygotes. While the majority does have profound HL, some 35delG homozygotes have only moderate hearing loss and in a few, the loss is only mild [7]. Most likely, this variation is caused by modifier genes, but none has been identified to date. Their identification could substantially contribute to a more accurate diagnosis and more appropriate genetic counselling.

Mutations in *SLC26A4* are the second most frequent cause of ARNSHL. The associated phenotypic spectrum ranges from Pendred syndrome at one extreme to isolated nonsyndromic HL with enlarged vestibular aqueduct (EVA) at the other (DFNB4 locus). Pendred syndrome is characterized by goiter and congenital, fluctuating, progressive hearing loss associated with Mondini dysplasia (cochlear dysplasia plus EVA) or EVA alone. It can be challenging to distinguish between Pendred syndrome and nonsyndromic HL with EVA because the goiter phenotype is usually not seen until adolescence and in some families, affected siblings can be discordant for thyroid disease [14]. In northern Europe, four mutations are found quite frequently (L236P, T416P, E384G and IVS8+1G>A) [15]. Recently, it has been reported that the *SLC26A4* promoter contains a key transcriptional regulatory element that binds *FOXI1*, a transcriptional activator of the gene. Mutations in this regulatory element as well as mutations in *FOXI1* cause Pendred syndrome and nonsyndromic hearing loss. One patient has been reported to be double-heterozygous for both an *SLC26A4* and a *FOXI1* mutation, while all other patients only carry a *FOXI1* mutation [16]. In addition, many patients carry single mutations or no mutations in *SLC26A4*, indicating that the Pendred syndrome – EVA phenotypic spectrum is not always inherited in a simple Mendelian way. No clear genotype-phenotype correlation has been reported for *SLC26A4* mutations [17].

Mutations in *MYO15A* cause congenital severe-to-profound hearing loss at the DFNB3 locus. All 28 identified mutations have been found by linkage analysis in consanguineous families, most of which originate from Pakistan. They were identified by screening 600 Pakistani consanguineous families for linkage with DFNB3 [18]. It is likely that the number of ARNSHL-causing *MYO15A* mutations is higher, as the gene is large (66 exons) and mutation analysis is rare if complementary linkage analysis has not been performed.

OTOF mutations cause prelingual, profound ARNSHL, which may initially be accompanied by auditory neuropathy in about half of cases with biallelic *OTOF* mutations [19]. Auditory neuropathy is characterized by the presence of OAE responses in absence of ABR responses. However, as the hearing loss progresses, OHC function is lost, and so is the OAE response. As *OTOF* mutations have been suggested as the major cause of auditory neuropathy, mutation screening of *OTOF* should be considered when OAE responses are present in the absence of ABR responses [19]. In addition to *OTOF*, part of the cases with DFNB59 (*PJVK*) mutations also has HL and auditory neuropathy [20]. In the Spanish population, Q829X is the most

common *OTOF* mutation identified and ranks as the third most common cause of ARNSHL in this ethnic group [19,21].

Mutations in *CDH23* cause both Usher syndrome type 1D (USH1D: hearing loss, retinitis pigmentosa and vestibular dysfunction) and moderate-to-profound progressive ARNSHL at the DFNB12 locus. Genotype-phenotype studies suggest that missense mutations or in-frame alterations cause ARNSHL, while truncating mutations cause USH1D. This correlation is not absolute, however, as six in-frame mutations have been identified in Usher patients [22] No single *CDH23* mutation predominates as a cause of either USH1D or ARNSHL.

TMC1 mutations are one of the more frequent causes of ARNSHL in populations from the consanguinity belt. Twenty-one different mutations have been reported in 33 consanguineous families, only one of which was Caucasian. One mutation, c.100C>T seems especially frequent as a cause of ARNSHL, and accounts for over 40% of all *TMC1* mutations (Hilgert et al., in press). All reported cases show a similar phenotype characterized by prelingual severe-to-profound hearing loss.

2.2 Genes as a frequent cause of ADNSHL

In contrast to ARNSHL where mutations in two genes are frequently found, none of the genes causing ADNSHL is a frequent cause of hearing loss. Based on our summary, *WFS1, KCNQ4, COCH* and *GJB2* mutations are somewhat more frequent in comparison to the other reported genes. In addition, *WFSI*, *COCH* and *TECTA* mutations cause HL with a recognizable phenotype.

Mutations in *WFS1* cause both autosomal dominant low-frequency sensorineural hearing loss (LFSNHL) at the DFNA6/14/38 locus and Wolfram syndrome, characterised by autosomal recessive hearing loss, diabetes mellitus, diabetes insipidus and optic atrophy. In addition, *WFS1* may also play a role in the susceptibility to diabetes mellitus and possibly also psychiatric disorders, although its exact role needs to be determined [23]. The hearing loss caused by dominant *WFS1* mutations is very characteristic, only affecting the low frequencies and rising to normal hearing in the high frequencies. With age, hearing in the high frequencies is lost and the audioprofile flattens. In families segregating LFSNHL, *WFS1* mutations are the most common cause, with percentages varying from 30% to 80%, depending on whether the families were preselected by linkage analysis prior to *WFS1* mutation analysis [24–26]. Interestingly, dominant mutations are nearly always found in the C-terminal domain. *WFS1* mutations causing the recessive Wolfram syndrome are numerous and distributed along the entire gene. Two mutations seem to occur recurrently in specific populations: c.424_425ins16 in Spanish people [27] and c.1362_1377del16 in Italians [28]. As a general rule, inactivating mutations cause Wolfram syndrome and missense mutations in the C-terminal domain cause the characteristic low-frequency ADNSHL [23].

KCNQ4 has been identified as one of the disease-causing genes at the DFNA2 locus. Twelve different mutations have been reported so far (10 missense mutations and 2 deletions), and a genotype-phenotype correlation has been proposed [29,30]. The missense mutations are believed to exert a dominant-negative effect by which the mutant protein interferes with the normal channel subunit. These mutations cause hearing loss with a young age of onset, affecting all frequencies. Both deletions, which are proposed to exert a pathogenic effect through haploinsufficiency, cause a milder phenotype, have an older age of onset and affect only the high frequencies. The W276S mutation in *KCNQ4* may be a mutational ‘hot spot’ as it has arisen three times independently in two European and one Japanese family [31].

Seven *COCH* mutations have been reported, all of them being missense mutations. Six mutations occur in the LCCL-domain of the protein and cause a phenotype characterized by

progressive late-onset hearing loss with vestibular impairment [32]. The late onset and the parallel auditory and vestibular decline make this a very recognizable phenotype. One mutation is present in the vWFA2 domain and causes earlier onset hearing loss, vestibular dysfunction and abnormal ocular motor responses [33]. The P51S mutation is a common cause of late onset cochleovestibular impairment in the Belgian and Dutch population through a founder effect [34].

Dominant mutations in *GJB2* have been reported predominantly in Caucasians and cause both ADNSHL and syndromic hearing loss associated with diverse skin disorders. The skin disorders are very heterogeneous and include diffuse palmoplantar keratoderma-hyperkeratosis, Vohwinkel syndrome and Keratitis –Ichthyosis –Deafness (KID) syndrome [35,36]. The particular phenotype appears to depend both on the type of mutation and its location.

TECTA mutations cause both autosomal dominant mid-frequency HL and high-frequency HL. A genotype-phenotype correlation has been established that is defined by the protein domain in which the mutation occurs and the nature of the amino acid substitution. Mutations in the zona pellucida domain of α-tectorin cause mid-frequency hearing loss, mutations in the zona adherens domain cause high-frequency hearing loss and cysteine-replacing substitutions cause progressive hearing loss [37].

2.3 X-linked and mitochondrial hearing loss

Hearing loss inherited through the X-chromosome or the mitochondria is not frequent, accounting for less than 1% of all hearing loss cases. However, these genes can be included for mutation analysis because mutations cause HL with a recognisable inheritance pattern and additional specific HL characteristics.

Mutations in *POU3F4* cause X-linked HL at locus DFN3. The HL can be mixed or purely sensorineural and may be associated with Mondini dysplasia, cochlear hypoplasia and/or stapes fixation. Identification of *POU3F4* as the deafness-causing gene is a contra-indication for stapes operations as a perilymphatic gusher may occur during surgery. Twenty different *POU3F4* mutations have been identified so far, 19 of them in Caucasians. These mutations include missense mutations in both DNA binding domains and deletions in a putative regulatory region about 900 kb upstream of the gene [38]. If HL is found to be X-linked and associated with a defect in the bony labyrinth, mutations in *POU3F4* may be suspected.

The majority of mutations in mitochondrial genes are the cause of a broad spectrum of maternally inherited multisystem disorders, which is in concordance with the fact that mitochondrial genes are expressed in every cell. However, mutations in a subset of genes, mainly *MT-RNR1* and *MT-TS1*, cause nonsyndromic HL by a currently unknown mechanism. *MT-RNR1* encodes for the 12S ribosomal RNA. One mutation in the gene, 1555G>A, is a rather frequent cause of maternally inherited nonsyndromic HL. In some 1555G>A carriers, HL may be induced by the administration of appropriate doses of aminoglycosides. The phenotypic variation caused by this mutation is very high due to the effect of modifier genes [39]. Another mitochondrial gene involved in HL is *MT-TS1*, encoding for the transfer $RNA^{Ser(UCN)}$. The penetrance is however rather low and it has been suggested that *MT-TS1* mutations on their own are an insufficient cause of HL. Other modifying factors may be involved, including aminoglycoside-exposure and the 1555G>A mutation in *MT-RNR1* [40].

3. Clinical diagnostics for hearing impairment

Diagnosing the cause of HL can be challenging. In many cases, making an accurate diagnosis requires a multidisciplinary team, with involvement of a paediatrician, otolaryngologist,

medical geneticist, ophthalmologist, and often additional specialists. Recognizing congenital HL has been facilitated by the implementation of newborn hearing screening (NBHS) in most developed countries. NBHS should be performed just after birth, preferably before hospital discharge and certainly before the age of 1 month. The test is typically either an ABR-based or OAE-based screen, which detects the presence or absence of a response at a specific threshold. If the results are abnormal, a complete ABR or auditory steady state response testing is required. For older children, behavioural or conditioned reflex audiometry can be completed. These tests should be complemented by a thorough physical examination to exclude possibly subtle dysmorphic features that may be indicative of a syndromic form of HL. In young children, an eye examination should also be obtained. Although the retinitis pigmentosa associated with USH syndrome is unlikely to be present in early childhood, many children have refractive errors that should be corrected. If the HL progresses, thin-cut computed tomography or magnetic resonance imaging of the temporal bones is required to rule out the presence of an inner ear abnormality like EVA. A thorough family history should also be obtained. Guidelines for early hearing detection and intervention programs can be found in the Year 2007 position statement by The Joint Committee on Infant Hearing [41].

4. Genetic diagnostics for hearing loss

Universal NBHS has lowered the age of detection of HL. In babies who are diagnosed with severe-to-profound HL in the absence of other abnormal findings on physical examination, the single best next diagnostic test is mutation screening for deafness at the DFNB1 locus. This screening should include DNA sequencing of *GJB2* and mutation testing for the two large *GJB6*-containing deletions, as *GJB2* mutations cause about half of all genetic hearing loss cases. Table 2 lists all genes that are currently frequently included in genetic diagnostics. All of these genes, with the exception of *GJB2*, cause a recognisable hearing loss phenotype. According to table 1, all these genes are also found to be more frequent causes of hearing loss. *SLC26A4* should be considered for mutation analysis if there has been evidence of progression of hearing loss or the presence of a goiter, EVA or Mondini dysplasia. In the absence of ABR responses in the presence of OAE responses mutation screening of *OTOF* is warranted. In case of progressive, late-onset HL combined with vestibular abnormalities, *COCH* should be tested for mutations. In the presence of HL associated with defects of the bony labyrinth, *POU3F4* mutations may be causal and *GJB2* should be screened for dominant mutations if the HL is associated with skin disorders. Mitochondrial genes may carry mutations in the case of maternal inheritance and in the presence of aminoglycoside-induced HL. *TECTA* mutations and *WFS1* mutations both cause HL with a distinct audioprofile, being moderate mid-frequency HL and low-frequency HL, respectively.

The other genes that have been identified as frequent causes of hearing loss in this review and which are not included in DNA diagnostics, all cause HL without any recognisable audioprofile. In addition, none of the genes causing ADNSHL is a frequent cause of HL and mutation analysis is therefore not cost-effective.

Establishing a genetic diagnosis has been shown to be beneficial to parents as it alleviates parental guilt and anxiety, makes accurate recurrence chance counselling possible, and provides prognostic information. For example, the parents of a child with *GJB2*-related deafness have a 25% recurrence chance to have another child with the same *GJB2* genotype. Furthermore, if their first child has mild-to-moderate HL and they do have a second hearing-impaired child, there is a 66% chance that the second child will have mild-to-moderate HL and a 34% chance that the HL will be more severe. If their child has severe-to-profound HL and receives a cochlear implant, several studies have shown that the parents can expect their child to have an excellent outcome [42].

It is important to recognize that while genetic testing is crucial, test results must be interpreted correctly and steps must be taken to ensure that parents and family members understand the information presented to them. These responsibilities often fall to paediatricians with experience in genetics and clinical geneticists, as most other health care providers are uncomfortable discussing these issues.

5. Evolution of molecular diagnostics

During the last 15 years, major achievements have been made in detecting new deafness genes. These achievements have far outpaced translation of this knowledge to improved clinical care. The gap created reflects the fact that diagnostic tests are still performed using the classical sequencing technology based on the Sanger method. These automatic DNA sequencers are very useful but are limited by slow throughput, which makes extensive sequencing of all known deafness-causing genes very expensive and time consuming. For this reason, only a very small set of genes is routinely screened for mutations with the result that in a large percentage of persons with HL, no genetic cause is identified.

An additional problem for extended diagnostic screening is that the hearing loss in a majority of AR patients is profound and congenital. Therefore, it is impossible to predict the genetic cause based on the phenotype because most responsible genes show the same phenotype. There is an urgent need for new DNA sequencing technologies which allow complete screening of all deafness genes in a quick and cost effective way. Researchers have been working on the development of a ‘deafness GeneChip’, using an Affymetrix DNA resequencing microarray platform [43]. We however believe that it is unlikely that these chips will cause a major breakthrough in molecular diagnostic testing for hearing loss, mainly because of the inaccuracy of this DNA sequencing system. More promising is the new generation of DNA sequencing technologies that have recently emerged including 454 (Roche), Solexa (Illumina) and SOLiD (Applied Biosystems). These new methods offer much higher throughput with high accuracy and potentially cheaper analyses. However, these machines have not been developed for DNA diagnostics, for which a few specific features are required: (1) high throughput for screening of selected regions; (2) high sensitivity to detect all types of mutations (missense mutations as well as large rearrangements); (3) the need for only small amounts of sample material; (4) high reliability; and (5) cost-effectiveness. Recently, the microarray-based genomic selection method has been developed, which allows selecting and enriching large human genomic target regions for resequencing [44]. Combining this technology with the new generation sequencing technologies will allow large-scale resequencing, as required for DNA diagnostics. Systematic screening of all known causative genes for a number of diseases with high genetic heterogeneity will cause a major improvement of DNA diagnostics. The benefits will be largest for hearing loss, as this trait has the highest genetic heterogeneity. When such a system will be available, all children which do not pass NBHS could be screened for the known nonsyndromic deafness genes. In addition, screening for the Usher-causing genes could then also be implemented because epidemiological studies indicate that the average prevalence of Usher syndrome among the deaf population is 10% [45]. This suggests that a significant percentage of children which do not pass NBHS and do not yet show any signs of retinitis pigmentosa do have Usher syndrome. Moreover, five of the nine Usher genes will already be included as nonsyndromic deafness genes. Such a broad-based screen of hearing-impaired persons will allow estimates of mutation frequency of deafness genes in diverse populations, reveal new genotype-phenotype correlations, and enhance the clinical care that can be offered to persons with HL and their families.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Reported number of mutations for all 46 nonsyndromic deafness genes. The number of mutations worldwide and more specifically in Caucasians are listed. The genes are ranked according to the number of mutations worldwide. For each gene, the locus and function of the encoded protein in the hearing process is mentioned, as well as the OMIM number. The table is split up in four parts, depending on the mode of inheritance: ADNSHL, ARNSHL, X-linked HL and mitochondrial HL.

ARNSHL					
Gene	**Locus**	**Number of mutations worldwide**	**Number of mutations in Caucasians**	**Function in hearing process**	**OMIM number**
GJB2	DFNB1	>220	>150	ion homeostasis	121011
SLC26A4	DFNB4	44	18	ion homeostasis	605646
MYO15A	DFNB3	28	0	hair bundle, motor protein	602666
OTOF	DFNB9	26	17	exocytosis at auditory ribon synapse	603681
CDH23	DFNB12	21	12	hair bundle, adhesion protein	605516
TMC1	DFNB7/11	20	1	unknown function	606706
TMPRSS3	DFNB8/10	16	7	unknown function	605511
TECTA	DFNB21	10	3	extracellular matrix protein	602574
TRIOBP	DFNB28	9	0	hair bundle, cytoskeletal formation	609761
TMIE	DFNB6	8	0	unknown function	607237
PJVK	DFNB59	7	2	signaling of hair cells and neurons	610219
ESPN	DFNB36	6	4	hair bundle, cytoskeletal formation	606351
PCDH15	DFNB23	5	3	hair bundle, adhesion protein	605514
ESRRB	DFNB35	5	0	transcription factor	602167
MYO7A	DFNB2	5	0	hair bundle, motor proteins	276903
GJB6	DFNB1	4	0	ion homeostasis	604418
TRIC	DFNB49	4	0	ion homeostasis	610572
TMHS	DFNB67	4	0	hair bundle, adhesion protein	609427
STRC	DFNB16	3	2	extracellular matrix protein	606440
CLDN14	DFNB29	3	1	ion homeostasis	605608
RDX	DFNB24	3	1	hair bundle, cytoskeletal formation	179410
MYO6	DFNB37	3	0	hair bundle, motor protein	600970
MYO3A	DFNB30	3	0	hair bundle, motor protein	606808
SLC26A5		2	2	molecular motor of OHC	604943

ARNSHL					
Gene	**Locus**	**Number of mutations worldwide**	**Number of mutations in Caucasians**	**Function in hearing process**	**OMIM number**
WHRN	DFNB31	2	0	hair bundle, scaffolding protein	607928
USH1C	DFNB18	2	0	hair bundle, scaffolding protein	605242
GJB3		2	0	ion homeostasis	603324
COL11A2	DFNB53	1	0	extracellular matrix protein	120290
OTOA	DFNB22	1	0	extracellular matrix protein	607038

ADNSHL					
Gene	**Locus**	**Number of mutations worldwide**	**Number of mutations in Caucasians**	**Function in hearing process**	**OMIM number**
WFS1	DFNA6/14	19	13	ion homeostasis	606201
KCNQ4	DFNA2	12	8	ion homeostasis	603537
COCH	DFNA9	12	8	extracellular matrix protein	603196
GJB2	DFNA3	11	9	ion homeostasis	121011
MYO1A	DFNA48	8	8	unknown function	601478
TECTA	DFNA8/12	8	7	extracellular matrix protein	602574
ACTG1	DFNA20/26	6	6	hair bundle, cytoskeletal formation	102560
EYA4	DFNA10	6	4	transcription factor	603550
MYH14	DFNA4	5	5	unknown function	608568
MYO6	DFNA22	5	5	hair bundle, motor protein	600970
MYO7A	DFNA11	5	4	hair bundle, motor protein	276903
ESPN		4	4	hair bundle, cytoskeletal formation	606351
DFNA5	DFNA5	4	2	unknown function	608798
GJB3	DFNA2	3	1	ion homeostasis	603324
POU4F3	DFNA15	3	2	transcription factor	602460
TMC1	DFNA36	2	2	unknown function	606706
COL11A2	DFNA13	2	2	extracellular matrix protein	120290
CRYM		2	0	ion homeostasis	123740
TFCP2L3	DFNA28	1	1	transcription factor	608576
GJB6	DFNA3	1	1	ion homeostasis	604418
MYH9	DFNA17	1	1	hair bundle, motor protein	160775

ADNSHL					
Gene	**Locus**	**Number of mutations worldwide**	**Number of mutations in Caucasians**	**Function in hearing process**	**OMIM number**
CCDC50	DFNA44	1	1	hair bundle, cytoskeletal formation	611051
DIAPH1	DFNA1	1	0	hair bundle, cytoskeletal formation	602121

X-linked hearing loss					
Gene	**Locus**	**Number of mutations worldwide**	**Number of mutations in Caucasians**	**Function in hearing process**	**OMIM number**
POU3F4	DFN3	20	19	transcription factor	300039

Mitochondrial hearing loss					
Gene	**Locus**	**Number of mutations worldwide**	**Number of mutations in Caucasians**	**Function in hearing process**	**OMIM number**
MT-RNR1	12S rRNA	9	4	RNA translation	561000
MT-TS1	$tRNA^{Ser(UCN)}$	4	1	RNA translation	590080

Table 2

Overview of genes that are frequently included in genetic diagnostics. These genes are a frequent cause of hearing loss and/or they have a recognisable phenotype. Frequent mutations in Caucasians are listed for each gene if present.

Gene	frequent mutation(s)	Diagnostic criteria
GJB2	35delG	• AR: congenital, mild to profound HL
		• AD: HL associated with skin disorders in half of the cases
SLC26A4	L236P, T416P, E384G, IVS8+1G>A for Pendred syndrome	• Pendred syndrome, AR: congenital, fluctuating, progressive HL • Often EVA and sometimes euthyroid goiter and Mondini dysplasia
		• ARNSHL associated with EVA
WFS1	c.424_425ins16 in Spain and c.1362_1377del16 in Italy for Wolfram syndrome	• AD, low-frequency hearing loss
		• AR Wolfram syndrome
OTOF	Q829X	• ARNSHL, auditory neuropathy: absence of ABR, presence of OAE • Prelingual, often severe HL
MT-RNR1	1555A>G	• Mitochondrial, aminoglycoside-induced HL; maternally inherited • Varying from severe congenital HL to normal hearing
TECTA	None	• AR, moderate-to-severe mid-frequency HL
COCH	P51S in Belgium and The Netherlands	• Progressive HL and vestibular impairment with late onset
POU3F4	none	• Mixed HL or pure sensorineural HL • Defects in the bony labyrinth e.g. Mondini dysplasia and stapes fixation • Perilymphatic gusher during stapes surgery

HL = hearing loss; AD = autosomal dominant; AR = autosomal recessive; EVA = enlarged vestibular aqueduct; ABR = auditory brainstem response; OAE = otoacoustic emission