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Hereditary hearing loss in humans: the importance of genetic approaches for clinical medicine and basic science

Causes and prevalence of hearing loss

Hearing impairment is one of the most common monogenic sensory diseases in humans. Although data on prevalence vary and depend on geographical factors, it is assumed that about one in 600 children is affected by a pronounced congenital hearing impairment [1]. In countries with relatively high standards of medical care, at least two thirds of these cases have a genetic cause, while infections (e.g. toxoplasmosis, rubella or cytomegalovirus) and perinatal complications as a cause of hearing loss are, in relative terms, decreasing. Left untreated or diagnosed too late, the effects of hearing impairment can be severe for a child and his/her social environment and may lead to severe problems in terms of cognitive and social development. In view of these problems and the prevalence of the disease, a timely diagnosis of hearing loss is desirable, particularly given the existing options in terms of medical treatment and care. The second age peak for hearing loss can be seen in the elderly. Between the ages of 60 and 70 years, around 2.5% of the population show a severe hearing loss of more than 65 decibels (dBs) [2]. This type of age-related hearing loss (presbyacusis) often leads to interaction problems, possibly causing the affected individual to withdraw from his/her social environment. Presbyacusis, however, is not a monogenic disease, like most of the forms of hearing impairment that manifest earlier, but is instead a multifactorial disease. In addition to environmental factors such as noise and ototoxic drugs, genetic factors also play an important role. In order to elucidate these largely unknown genetic predisposing factors, there is speculation that the genes that cause monogenic hearing impairment may also represent attractive "candidate genes" for presbyacusis. As such, research into the earlier-onset forms also in terms of "age-related hearing loss" as a widespread disease assumes greater relevance. This theory was first supported in an animal model showing that a functionally effective genetic polymorphism in cadherin 23, which leads to deafness in humans and in mice in the case of a complete loss of function, is responsible for the predisposition to age-related hearing impairment in various mouse strains [3].

Classifying hearing impairment

The significant genetic and clinical complexity of hearing impairment is also reflected in a variety of classification possibilities and poses a particular challenge for early genetic diagnosis. Clinical classifications are performed according to, e.g.: (i) the onset of disease, (ii) the possible progression of symptoms, (iii) the nature or localization of hearing impairment (i.e. conductive or sensorineural hearing loss) and (iv) the severity of hearing impairment measured in dBs. A genetic classification typically distinguishes between syndromic and non-syndromic forms of hearing impairment. In syndromic forms, the hearing impairment is accompanied by further anomalies and/or disorders in other organ systems [e.g. additional retinal degeneration (retinitis pigmentosa) as seen in Usher syndrome, or specific cardiac arrhythmia as seen in Jervell and Lange-Nielsen syndrome]. Several hundred such syndromes, some of which are extremely complex, are known, whereby from a medical point of view the diagnosis of hearing loss does not permit a differential diagnosis in most cases. Nevertheless, there are several syndromic forms where additional symptoms are not primarily evident, but nevertheless relevant to prognosis (as in the case of both of the above-mentioned syndromes). In contrast to syndromic hearing impairment, we speak of non-syndromic hearing loss (NSHL) when, in addition to hearing loss, there are no additional symptoms linked to the underlying disease. NSHL is mostly a sensorineural form of hearing loss. It is estimated that approximately two thirds of early-childhood cases and the majority of late-onset cases of hearing loss belong to the non-syndromic forms. Nevertheless, non-syndromic and syndromic forms of hearing loss cannot always be classified categorically. Thus, several disease genes are known whose mutations can lead within different families either to syndromic or non-syndromic hearing loss (so-called "allelic" diseases). Examples such as the allelism between forms of NSHL and Usher syndrome (hearing loss, retinitis pigmentosa and possibly impaired balance), as well as Pendred syndrome (hearing loss, inner ear malformation, struma) and Wolfram syndrome (hearing loss, optic atrophy, diabetes mel-

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litus, diabetes insipidus) warrant mention in this context.

Monogenic forms of hearing impairment

In monogenic disease, a genetic alteration of a single hereditary factor (gene) is responsible for the clinical picture. This type of disease follows a Mendelian inheritance pattern within an affected family and, from a medical point of view, often has a direct significance for other family members. In the case of complete penetrance, no other genetic factors or environmental conditions are necessary for the development of the phenotype, even though the individual onset of disease, its severity and its progression can vary (variable expressivity). It has long been known that the monogenic forms of NSHL can follow different inheritance patterns. This fact is important since, depending on the specific type of inheritance, the probability of recurrence of hearing loss in further children or descendants could be different. Obviously, this can be of great importance in terms of individual counselling. With regard to hereditary hearing loss, virtually all types of inheritance pattern have been described, including autosomal dominant, autosomal recessive, X-chromosomal recessive as well as mitochondrial inheritance patterns. Interestingly, there is even a report on a family with a Y-chromosomal inherited form of progressive hearing loss—an inheritance pattern not otherwise known, with the exception of certain forms of infertility. Further analysis of the Y-linked chromosomal region, however, has shown that an insertion/duplication of chromosomal material from chromosome 1 is probably responsible for this unusual finding [5]. Thus, in a narrower sense, this is not a case of Y-chromosomal inheritance, since there is no gene on the Y-chromosome that is causally mutated.

Of the early-childhood forms of NSHL, 80%–85% are autosomal recessive, approximately 15% autosomal dominant and 1%–3% X-chromosomally inherited. In the case of later-onset forms, it is true to say that the percentage of autosomal dominant and probably mitochondrial forms are higher. Put simply, the autosomal recessive forms are mostly more severe and account for the majority of congenital cases. On the other hand, most autosomal dominant forms are characterized by later onset and often progressive symptoms, even though severe, non-progressive and congenital forms may also occur for autosomal dominant inheritance, as has been seen in, e.g. the forms DFNA3 and DFNA8. According to the international nomenclature, "DFNA" stands for an autosomal dominant genetic locus of non-syndromic hearing loss (thus, DFNB is the abbreviation for an autosomal recessive and DFNX the abbreviation for an X-chromosomal recessive inherited form), while the subsequent, chronologically assigned number refers to the relevant specific locus. When classifying hearing loss according to the inheritance pattern, again a restriction must be made, since mutations in a gene can cause an autosomal recessive form in some families, while other mutations in the same gene can result in an autosomal dominant inherited form in other families (e.g. with the genes *MYO7A*, *GJB2* or *TMC1*).

Disease genes in non-syndromic hearing loss

NSHL is characterized by extreme (locus) heterogeneity. In other words, genetic alterations in different genes can lead to comparable or identical symptoms. It is estimated that alterations in far more than 150 different genes are responsible for the development of non-syndromic hearing loss. At present (July 2014), more than 100 autosomal recessive, 60 autosomal dominant and five X-chromosomal recessive loci have been described. The causally mutated disease gene within these chromosomal regions has already been identified in around 80 cases. This has essentially been done by positional cloning approaches [6] and the increasing use of next generation sequencing [7]. Since a detailed description of each of these disease genes lies beyond the scope of a simple review article, the reader is referred to the "Hereditary hearing loss homepage" (http://hereditaryhearingloss.org) for a comprehensive and regularly updated list of all genes and loci.

The relevance of genetic findings for basic science

The identification of this variety of NSHL genes represents an enormous increase in basic scientific knowledge. The structure of the inner ear, as well as the physiology of hearing, is complex. Even if many aspects of the hearing process are understood relatively well in terms of physiology, the molecular identity of the proteins involved was largely unknown for a long time. This was of particular relevance since "conventional" biochemical approaches were barely able to identify the functionally relevant proteins of the auditory system due to its specific features. These specific features include in particular: (i) the relatively low number of sensory cells in the organ of Corti (a few thousand hair cells compared with, e.g., more than 100 million photoreceptor cells in the retina), as well as (ii) the often low abundance of molecules in the hair cells and other structures of the inner ear. In this respect, genetic approaches represent a promising strategy for the elucidation of the molecular physiology of hearing, irrespective of cell or molecule numbers. Genetic approaches are "phenotype-driven" and analyse the correlation of "hearing loss" as a symptom at the level of the entire organism with the detection of a causal mutation in a single gene. This genetic alteration is equally detectable and analysable in all cells of an individual (and not only in the affected cells). Moreover, genetic approaches benefit from the high evolutionary conservation of molecular mechanisms and cellular as well as macroscopic structures of the auditory system, making it possible to use the analysis of hereditary hearing loss in model systems in addition to human genetic approaches. This "conception" and strengthening functioned in both directions. Thus, human genetic findings could be validated and further mechanistically analysed in suitable model systems such as the mouse, the zebra fish or the fruit fly on the one hand, whilst on the other, new human disease genes could be partially identified by the fact that human orthologues of genes, leading to hearing loss in other species, were analysed in appro-

priate groups of patients with hearing loss (see, e.g. ref. [8, 9, 10, 11]).

Overall, the findings from genetic research have strongly contributed to obtaining a detailed picture of the molecular basis of the systems and signalling pathways necessary for the specific development and functioning of the auditory system. In this context, the complexity of the hearing process is reflected by the genetic findings, and we are in a process which can lead in the long term to a nearly complete understanding of the molecular development and physiology of hearing. Many of the necessary "physiological systems" are already clearly outlined. These systems include for example: (i) specific gene regulation during inner ear development, (ii) energy balance in the inner ear, (iii) specific development of the extracellular matrix and the cytoskeleton in the hair cells, (iv) mechanotransduction and synaptic transmission, as well as (v) endocochlear ion homeostasis. Although this list is by no means exhaustive and none of the specified systems can be described extensively here, some findings or specific features of genetic studies or their implications for the understanding of molecular physiology should be discussed by way of example.

Mutations in transcription factor genes have been found in some forms of NSHL and even more often in syndromic forms of hearing loss. Since in general other organs or anatomical structures are also morphologically abnormal in syndromic forms, this finding is not unexpected. Examples include mutations of *PAX3*, *MITF* and *SOX10*. These were found in different subtypes of Waardenburg syndrome which, in addition to variable hearing loss, is characterized by pigmentation irregularities and typical facial anomalies [12]. Furthermore, transcription factor gene mutations are also found in non-syndromic hearing loss, as for example in the genes *EYA4*, *POU3F4*, *POU4F3*, *TFCP2L3* and *ESRRB*. Of interest, each causally mutated transcription factor seems to possess a relatively specific function in the development and differentiation of the inner ear, which, however, is not fully understood on the molecular level. The finding that germline mutations in the gene (not in the binding site!) of the microRNA miR-96 can lead to a non-syndromic inherited form of hearing loss in mice and humans is of particular genetic and physiological interest in terms of the regulation of gene expression in the inner ear[13, 14]. Indeed, this is the first evidence that a constitutive mutation of a specific microRNA gene can result in a monogenic disease in humans. On the other hand, it is not yet fully understood which target genes of this regulatory RNA are up- or down-regulated by the mutation to such an extent that hearing loss is caused. Nevertheless, the future elucidation of the transcriptional and post-transcriptional regulation of the inner ear-specific gene expression promises to also support, at least in some cases, the development of therapeutic approaches in the field of hearing loss.

Due to the high energy demand of the auditory system, mitochondrial dysfunction can also lead to hearing loss. Mutations in mitochondrial tRNA and rRNA genes are rarely found in early-onset forms of NSHL; nevertheless, they are important due to pharmacogenetic implications. As is well known, aminoglycoside antibiotics can cause, among other things, irreversible ototoxicity accompanied by a degeneration of sensory hair cells. This side effect can show familial clustering, whereby in some cases inheritance is maternal (mitochondrial). As early as in 1993, a causal point mutation in the gene of the mitochondrial 12S rRNA was identified in three such families [15]. Analysis of larger patient cohorts showed that mitochondrial mutations in certain populations could be responsible for a larger percentage (up to 10%) of the familial form of late-onset hearing impairment [16, 17]. This shows an age-related penetrance that can be increased by giving aminoglycosides. By identifying such mitochondrial mutations, targeted prophylaxis can be pursued in affected families by simply avoiding aminoglycosides. In the meantime, with *PNPT1* [18], *SMAC/DIABLO* [19] and possibly *MSRB3* [20], the first autosomal genes that encode for proteins with specific functions in the mitochondria and lead in the case of mutation to non-syndromic hearing loss have been identified. It is not known why only hearing impairment occurs in these specific cases of mitochondrial dysfunction, and no further symptoms in other organs with high energy demand (as for example in the brain, the heart or skeletal muscles or the retina). In general, however, syndromic hearing loss is clearly more frequently found in inherited forms of mitochondrial dysfunction, as is to be expected given the important role of mitochondria for all organs.

The central task of the inner ear is mechanotransduction, i.e. the conversion of mechanical signals into electrical signals. This process depends on the structural integrity of hair cells and their stereocilia, which depend in turn on the structure of the cytoskeleton and the surrounding extracellular matrix. Indeed, mutations are found in a variety of genes expressed in the cochlea, which encode for proteins of the cytoskeleton and hair cell bundles [e.g. actin and actin-interacting proteins (such as ACTG1, espin, TRIOBP, diaphanous 1, radixin, taperin) and atyp-

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Abstract
Hereditary hearing loss is one of the most common monogenic diseases in humans and, depending on the severity of symptoms and age of onset, dysfunction of one of the main sensory systems can cause significant problems for the affected individual and his/her social environment. The diagnostic work-up of hearing impairment is complicated by a pronounced phenotypic variability and extensive genetic heterogeneity. Nevertheless, many forms of monogenic hearing impairment have been elucidated in recent years by genetic approaches. In addition to improved counselling and medical management of patients and families, these research findings have contributed significantly to the identification of functionally relevant molecules of the inner ear and have thus helped us to better understand the molecular physiology of hearing and the pathophysiology of hearing impairment.

Keywords
Hereditary hearing loss · Deafness · Human genetics · Positional cloning · Inner ear physiology

ical myosins (such as MYO3A, MYO6, MYO7A, MYO15A, MYH9)], for proteins of the extra cellular matrix (e.g. COL11A2, stereocilin and alpha-tectorin) or for cell adhesion molecules (e.g. CDH23 and PCDH15). These genetic approaches have resulted in the identification of molecules of central importance to the function of the so-called tip links like cadherin 23 and protocadherin 15. These tip links are the linking structures between the largest stereocilium and the directly neighbouring stereocilia of the same cell, which are essential for mechanotransduction. Of equal importance, as identified by genetic analysis of Usher syndrome, is a whole network of directly interacting proteins (including MYO7A, CDH23, whirlin, USH2A, harmonin, SANS), which is essential for the structure and function of hair cell bundles. These last two findings have been described in detail elsewhere [21, 22, 23]. After converting the mechanical stimulus into electrical signals, these signals are transmitted in the form of action potentials via the auditory nerve to the brain. Indeed, genetic approaches have also been able to identify molecules that are necessary for the synaptic transmission and function of the auditory nerve (see [22, 24, 25]). In particular, the analysis of patients with so-called auditory neuropathy [26] has shown the central importance of, e.g. otoferlin, pejvakin and the vesicular glutamate transporter VGLUT3 for this transmission.

Ultimately, ion homeostasis in the inner ear plays a central role in hearing. The endolymph, which surrounds the hair cells apically, is an extracellular fluid with an unusually high potassium concentration and approximately +80 mV highly positive electric potential. Even small modifications in these characteristics lead to a loss of hearing or to irreversible damage. Hence, mutations in genes involved in the maintenance of ion homeostasis result in hereditary hearing loss (e.g. [27]). Genes involved in potassium secretion by cells of the stria vascularis and, ultimately, in the recycling of potassium, have been identified, among others. In addition to pendrin (*SLC26A4*) and the bumetanide-sensitive Na+-K+-2Cl co-transporter *NKCC1* (*SLC12A2*), the affected genes belong to the group of voltage-gated potassium channels (*KCNQ1*, *KCNQ4*, *KCNE1*, *KCNJ10*) and to the connexins [connexin 26 (*GJB2*), *GJB6* and *GJB3*]. Furthermore, a correct compartmentalisation of the different fluid-filled spaces in the inner ear is necessary for the maintenance of ion concentrations. Accordingly, mutations in genes that encode for cochlear "tight-junction" proteins (e.g., *CLDN14*, *TRIC*, *TJP2*, *ILDR1*) also result in hereditary hearing loss (see also ref. [22])

Clinical implications of genetic findings

Due to the variety of genes that can be mutated in hereditary hearing loss, a molecular genetic "standard test" of all these genes for differential diagnostic purposes would not have been possible in the past. This, however, has changed with the introduction of new sequencing technologies (see also [28]). Nevertheless, genetic findings have already contributed in the past to improving the medical management of hearing impaired patients/families. In cases where the causative mutation is identified within a family, it is possible to offer molecular diagnostics for other members of the family. This is in principle also true for prenatal diagnostics, although this has to be viewed critically in the case of NSHL due to ethical considerations. Furthermore, identifying the inheritance pattern enables specific and individualized genetic counselling on the risk of recurrence. Another advantage of the genetic identification of NSHL is the fact that further, partly invasive and stressful examinations to exclude certain syndromic forms are no longer necessary. In addition, personal risk profile analysis could mean an optimisation of prevention options, since individuals at high risk of disease could be advised to avoid further potentially ototoxic factors (e.g. noise pollution or ototoxic drugs such as the aminoglycoside antibiotics mentioned earlier or the chemotherapeutic agent cisplatin). It must be said, however, that up until recently the identification of the causative genetic alteration within a family with hereditary hearing loss was successful in only a smaller percentage of cases. Nevertheless, there is one finding which is of particular relevance in the molecular genetic diagnosis of NSHL.

It has been shown that mutations in the *GJB2* gene typically lead to an autosomal recessive form of hearing loss. The particular clinical significance of this is based on the fact that alterations in this gene are responsible in some populations—in spite of the extreme heterogeneity of NSHL—for up to 50% of cases of autosomal recessive hearing impairment; however the percentage of *GJB2*-related hearing loss in Germany seems to be lower at approximately 15%–20%. Furthermore, one of the mutations, known as 35delG (also called 30delG) occurs particularly frequently. This mutation can be found in different populations (particularly in the Mediterranean region) in 70%–85% of cases and has a heterozygote frequency of approximately 1:31 in Italy making the 35delG mutation one of the most frequent disease-causing mutations in humans. These findings make it possible to offer a quick and relatively reasonably priced genetic test for *GJB2*-related hearing loss with high medical significance, hence its frequent use in clinical practice.

In summary, (human) genetic approaches have played a significant role over the last 15–20 years in improving our understanding of the molecular mechanisms of hearing, such that we now have a very detailed picture of the molecules essential for hearing. The identification of these "key players" is also of significance in that they present attractive "targets" for therapeutic or preventive measures, as the future will hopefully show. In the meantime, however, genetic findings have already led to the fact that genetic counselling and the medical management of patients and families with hereditary hearing impairment could be expanded and, in many cases, optimised.

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Christian Kubisch has held the post of professor of human genetics and director of the Institute of Human Genetics at the University Medical Centre Hamburg-Eppendorf since April 2014. Prior to that, he was director of the Institute of Human Genetics of the University of Ulm from mid 2010 until March 2014. He held the post of professor of medical genetics at the University of Cologne from late 2004 until mid 2010. Between 1988 and 1995 he studied human medicine at the Rheinische Friedrich Wilhelms University of Bonn where, in 1995, he did his medical thesis after a 6-month research project in the INSERM U127 in Paris, on molecular mechanisms of heart hypertrophy. As a post-doctoral researcher, he worked from 1995 to 1999 at the Centre for Molecular Neurobiology Hamburg in the group of Dr. Thomas J. Jentsch, where he was closely involved in the identification and functional analysis of genetic forms of epilepsy and hearing loss. He then began to form his own group as an assistant professor at the Institute of Human Genetics of the University of Bonn; in 2003, he concluded his medical specialist training to become a specialist in medical genetics. During the following years, he and his group were critically involved in the identification and further analysis of a variety of disease genes for different monogenic and genetically complex diseases. His current research projects mainly deal with the genetic analysis of mostly neurological and sensory diseases, as well as syndromes involving signs of premature aging. He received the "Heinz-Maier-Leibnitz" prize from the German Research Foundation (DFG) in 2000 and the "Early Career Award" from the German Academy of Natural Sciences (Leopoldina) in 2010.

Conflict of interest. The corresponding author states that there are no conflicts of interest.

References

1. Morton CC, Nance WE (2006) Newborn hearing screening-a silent revolution. N Engl J Med 354:2151–2164
2. Davis AC (1989) The prevalence of hearing impairment and reported hearing disability among adults in Great Britain. Int J Epidemiol 18:911–917
3. Noben-Trauth K, Zheng QY, Johnson KR (2003) Association of cadherin 23 with polygenic inheritance and genetic modification of sensorineural hearing loss. Nat Genet 35:21–23
4. Toriello HV, Smith SD (eds) (2013) Hereditary hearing loss and its syndromes (Oxford monographs on medical genetics), 3rd edn. Oxford University Press, Oxford
5. Wang Q, Xue Y, Zhang Y et al (2013) Genetic basis of Y-linked hearing impairment. Am J Hum Genet 92:301–306
6. Altshuler D, Daly MJ, Lander ES (2008) Genetic mapping in human disease. Science 322:881–888
7. Boycott KM, Vanstone MR, Bulman DE, MacKenzie AE (2013) Rare-disease genetics in the era of next-generation sequencing: discovery to translation. Nat Rev Genet 14:681–691
8. Leibovici M, Safieddine S, Petit C (2008) Mouse models for human hereditary deafness. Curr Top Dev Biol 84:385–429
9. Vrijens K, Van Laer L, Van Camp G (2008) Human hereditary hearing impairment: mouse models can help to solve the puzzle. Hum Genet 124:325–348
10. Brown SD, Hardisty-Hughes RE, Mburu P (2008) Quiet as a mouse: dissecting the molecular and genetic basis of hearing. Nat Rev Genet 9:277–290
11. Whitfield TT (2002) Zebrafish as a model for hearing and deafness. J Neurobiol 53:157–171
12. Read AP, Newton VE (1997) Waardenburg syndrome. J Med Genet 34:656–665
13. Lewis MA, Quint E, Glazier AM et al (2009) An ENU-induced mutation of miR-96 associated with progressive hearing loss in mice. Nat Genet 41:614–668
14. Mencía A, Modamio-Høybjør S, Redshaw N et al (2009) Mutations in the seed region of human miR-96 are responsible for nonsyndromic progressive hearing loss. Nat Genet 41:609–613
15. Prezant TR, Agapian JV, Bohlman MC et al (1993) Mitochondrial ribosomal RNA mutation associated with both antibiotic- induced and non-syndromic deafness. Nat Genet 4:289–294
16. Estivill X, Govea N, Barcelo E et al (1998) Familial progressive sensorineural deafness is mainly due to the mtDNA A1555G mutation and is enhanced by treatment of aminoglycosides. Am J Hum Genet 62:27–35
17. Jacobs HT, Hutchin TP, Kappi T et al (2005) Mitochondrial DNA mutations in patients with postlingual, nonsyndromic hearing impairment. Eur J Hum Genet 13:26–33
18. Ameln S von, Wang G, Boulouiz R et al (2012) A mutation in PNPT1, encoding mitochondrial-RNA-import protein PNPase, causes hereditary hearing loss. Am J Hum Genet 91:919–927
19. Cheng J, Zhu Y, He S et al (2011) Functional mutation of SMAC/DIABLO, encoding a mitochondrial proapoptotic protein, causes human progressive hearing loss DFNA64. Am J Hum Genet 89:56–66
20. Ahmed ZM, Yousaf R, Lee BC et al (2011) Functional null mutations of MSRB3 encoding methionine sulfoxide reductase are associated with human deafness DFNB74. Am J Hum Genet 88:19–29
21. Richardson GP, Monvel JB de, Petit C (2011) How the genetics of deafness illuminates auditory physiology. Annu Rev Physiol 73:311–334
22. Dror AA, Avraham KB (2010) Hearing impairment: a panoply of genes and functions. Neuron 68:293–308
23. Petit C, Richardson GP (2009) Linking genes underlying deafness to hair-bundle development and function. Nat Neurosci 12:703–710
24. Safieddine S, El-Amraoui A, Petit C (2012) The auditory hair cell ribbon synapse: from assembly to function. Annu Rev Neurosci 35:509–528
25. Moser T, Predoehl F, Starr A (2013) Review of hair cell synapse defects in sensorineural hearing impairment. Otol Neurotol 34:995–1004
26. Del Castillo FJ, Del Castillo I (2012) Genetics of isolated auditory neuropathies. Front Biosci 17:1251–1265
27. Zdebik AA, Wangemann P, Jentsch TJ (2009) Potassium ion movement in the inner ear: insights from genetic disease and mouse models. Physiology 24:307–316
28. Alford RL, Arnos KS, Fox M et al (2014) American College of Medical Genetics and Genomics guideline for the clinical evaluation and etiologic diagnosis of hearing loss. Genet Med 16:347–355