Genetics: A New Frontier in Otology

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Abstract Molecular genetics is a rapidly expanding field with possibilities for novel diagnostic and treatment strategies for otological diseases. Gene therapy, if theory is proven practical, could eliminate disease at the molecular level, thus obviating the need for pharmacologic or surgical treatment. Recent years have seen great advances in our understanding of the molecular genetic basis of many otological disorders. Building on the success of the Human Genome Project, new technologies are in development to identify disease-causing mutations through genetic testing. A basic understanding of the genetic basis of Otological diseases is crucial to the practising Otolologist and the time has come for genetic services to be incorporated into regular Otological clinics.

Keywords Genetics · Hearing loss · Gene therapy

Introduction

Sensorineural hearing loss (SNHL) is one of the most common disabilities in humans and congenital hearing loss is the most common congenital abnormality in the new born [1]. The worldwide prevalence of congenital bilateral hearing loss is one per thousand live births and 50–70 % of them have monogenic causes [2]. Genetic factors contribute to about 50–60 % of congenital hearing loss [3]. In recent years, our knowledge about genetic causes of SNHL

has significantly advanced. Genetic hearing loss has diverse aetiologies and it is estimated that approximately 1 % of all human genes are involved in the hearing process [4]. Hereditary hearing loss can be classified into syndromic and nonsyndromic hearing loss [5].

Non-syndromic hearing loss which is not associated with a clear pattern of other physical defects accounts for more than 70 % of all hereditary hearing loss [6]. Non-syndromic hearing loss is most often sensorineural. It can be divided into DFNA (autosomal dominant deafness, ~15–20 %), DFNB (autosomal recessive deafness, ~80 %), DFN (X-linked deafness, ~1 %), and mitochondrial deafness (at least 1 %). [7, 8]. The genetic basis is highly complex.

Allelic mutations in some genes can cause recessive and dominant hearing loss, mutations in the same gene may cause syndromic or non-syndromic hearing loss, and recessive hearing loss may be caused by a combination of two mutations in different genes from the same functional group. Autosomal dominant sensorineural hearing loss (SNHL) is often post-lingual and progressive, whereas recessive SNHL is prelingual as a rule. Patients with autosomal dominant inheritance typically show progressive SNHL which begins at the age of 10–40, and the degree of hearing loss is variable while patients with autosomal recessive inheritance most frequently show congenital and severe hearing loss. Patients with mitochondrial inheritance tend to develop progressive SNHL which begins at the age of 5–50, and the degree of hearing loss is variable.

The first nonsyndromic deafness gene was discovered in 1993 [9]. Kelsell et al. [10] discovered the Gap Junction Beta 2 (GJB2), gene for nonsyndromic hearing loss. The GJB2 gene is typically transmitted in an autosomal recessive fashion, although it may also be transmitted in an autosomal dominant pattern. Mutations in the gene GJB2

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are known to account for 30–50 % of all cases with non-syndromic recessive hearing loss making it the most frequent cause of hearing loss in infants [11]. GJB2 encodes the gap junction protein, Connexin 26, found in the supporting cells, connective tissue and other cells of the cochlea. They help form intercellular gap junction or channels between cells and may play a role in the recycling of potassium ions from the hair cells to the stria vascularis [12]. More than 110 syndromic and nonsyndromic mutations of GJB2 have been reported and more than 20 widely expressed connexin proteins have been identified so far. The mutations 35delG, 167delT, and 235delC have been shown to occur most frequently in Caucasians, Ashkenazi Jews and Asian populations respectively. The specific mutation 35delG accounts for 28–63 % of the mutant alleles in Caucasians [13]. A Mutation in the gene GJB2 on one chromosome inherited along with a second mutation, usually a large deletion in the gene GJB6, located on the same chromosome (13q) will cause hearing loss.

GJB6 is responsible for encoding Connexin 30, which combine to form gap junctions with Connexin 26 [14]. More than 30 genes have been associated with recessive hearing loss, apart from the two main Connexin genes GJB2 and GJB6. Also, 24 genes associated with autosomal dominant nonsyndromic hearing loss and two genes associated with x-linked nonsyndromic hearing loss have been identified. Mitochondrial genes may also cause nonsyndromic hearing loss, particularly if an individual is exposed to aminoglycoside antibiotics [9].

Syndromic deafness is characterized by additional manifestations, such as retinitis pigmentosa (e.g., Usher syndrome), euthyroid goiter and inner ear malformations (Pendred syndrome), craniofacial dysmorphism (Treacher-Collins syndrome), marfanoid body habitus (Stickler syndrome), renal anomalies (Alport syndrome), or the presence of long QT intervals (Jervell and Lange-Nielsen syndrome). More than 400 forms of syndromic hearing loss have been characterized [15], and each syndrome may have several causative genes and about 60 genes/loci have been identified so far. Majority of patients with Pendred syndrome have mutations in SLC26A4, and these mutations also cause nonsyndromic SNHL. [16, 17]. Pendred syndrome accounts for 3 % of all congenital hearing loss and mutations in SLC26A4 including those causing nonsyndromic SNHL account for 7 % of all deaf children at age of 4 years [1]. SLC26A4 encodes a chloride-iodide cotransporter and is critical for maintaining endolymphatic ion homeostasis, which is essential to normal inner ear function. Mutations in mitochondrial DNA in patients with SNHL increases with aging. A1555G or A3243G mitochondrial DNA mutations are found in approximately 6 % of adult patients with SNHL without known causes [18, 19].

Due to tremendous genetic heterogeneity, the identification of genes and gene defects that affect the process of hearing has been challenging. Considering the complexity of the auditory system, which requires interaction of a diversity of proteins including ion channels, extracellular matrix, cytoskeletal proteins, and transcription factors, this is not surprising. The difficulty was not only due to the underlying etiological and genetic heterogeneity of deafness but also because of the limitations in the past to conduct a comprehensive genetic test of all deafness genes for each deaf individual, as a routine, in the clinic. Recent advances in technology, using NGS, have made it possible to rapidly and cost-effectively sequence all the genes of interest, including the noncoding regions. NGS is changing the face of gene identification and is making it possible to screen for mutations in hundreds of genes, allowing one to provide precise information about the genetic cause and the recurrence risk and offer precise treatment [20]. Targeted capture and next-generation sequencing (NGS), [22] is now being performed in research as well as in private laboratories, yielding impressive results.

Molecular genetic testing for hearing loss is now part of the standard protocol for etiologic diagnosis of hearing loss. Several strategies are used for genetic testing of SNHL for accurate and efficient identification of the genetic causes, and the results are used for explanation of the cause, prediction of auditory features, prevention of deafness, management of associated symptoms, determination of therapy, and genetic counselling. Identification of genetic causes provides a key to understand the mechanism of hearing loss, leads to better management of hearing loss, and facilitates functional recovery by effective rehabilitation.

Identification of causative mutations is mostly done with direct sequencing of the candidate genes using DNA extracted from blood samples. Revealing the genetic basis of hereditary HL is crucial for patients and family who are eager to know the cause of their HL. In addition, it is important in promoting the understanding of the molecular basis of HL and the auditory system, which may facilitate new methods of treatment. Molecular testing can result in an accurate and early diagnosis, which facilitates optimal cognitive development. Diagnosis of causative mutations significantly helps to provide accurate genetic counseling to the parents of hearing challenged children which primarily concerns planning of next pregnancy with the information of a recurrence risk.

Molecular analysis can be beneficial for the diagnosis of syndromic hearing loss before additional features emerge (e.g., in Pendred syndrome or Jervell and Lange-Nielsen syndrome) Hearing loss can be prevented by avoiding use of specific drugs or specific activities in genetically susceptible patients. As an example, patients with A1555G

mitochondrial DNA mutation should avoid aminoglycosides which induce or aggravate SNHL by even one injection in subjects with this mutation [23]. Another example is that detection of SLC26A4 suggests dilatation of vestibular aqueduct. Patients with this mutation should have temporal bone CT and patients who are found to have dilatation of vestibular aqueduct should avoid activities in which physical shock on their head is likely to occur. This is because such a shock tends to cause aggravation of SNHL in these patients. Identification of mutations in CACNAD in individuals who are usually initially misdiagnosed with NSHL, will guide them to be under regular cardiological care to avoid cardiac complications that are part of SANDD, a syndrome associated with sinoatrial node dysfunction and deafness [24]. Because occurrence of associated symptoms may delay more than 10 years after the onset of SNHL, many patients and even doctors who see those patients may not be able to identify the association of other conditions with SNHL and, it would be worthwhile to order for genetic testing at the time of diagnosis of SNHL. In addition, genetic tests may be valuable in substituting more stressful tests. For example, renal biopsy and/or skin biopsy are currently necessary for diagnosis of Alport syndrome which is a hereditary nephritis associated with SNHL. Mutations in COL4A3, COL4A4, COL4A5, and MYH9 are known causes of Alport syndrome. With remarkable advances in genetics, increase of sensitivity and specificity and decrease in the costs of genetic analysis are in progress. In the near future, diagnosis of Alport syndrome may be first done by clinical genetic tests, and renal and skin biopsy may be avoided in many patients [25].

Further, Identification of causative mutations is also important for clinical management of patients with auditory neuropathy. Auditory neuropathy is a distinct type of SNHL which features normal outer hair cell function and abnormal activities of auditory neurons, and a relatively frequent cause of congenital SNHL (~15 %). Development of speech and language cannot be expected by hearing aids in congenital auditory neuropathy because of poor speech recognition inherent in this disorder. Either inner hair cells or spiral ganglion neurons are affected, but current clinical tests cannot distinguish these two types. Because normal spiral ganglion neurons are necessary for success of cochlear implants, pathology underlying SNHL needs to be determined in order to evaluate the indication of cochlear implant surgery. Recent studies have shown that mutations in otoferlin (OTOF) cause auditory neuropathy by inner hair cell dysfunction and that spiral ganglion neurons are normal in patients with these mutations [26]. In agreement with the pathological mechanism of mutations in OTOF, results of cochlear implants have been successful in these group of patients [27]. According to the

recent studies, OTOF mutations may account for majority of congenital auditory neuropathy [28]. Thus, the genetic test for OTOF mutations in patients with auditory neuropathy is of high clinical importance.

Genetic factors make some people more susceptible to hearing loss as their genes make them more predisposed due to ageing, loud noises, infections, or drugs. It is estimated that between 30 and 60 % of age-related hearing loss is due to genetics. GJB2 variants may influence the expression of syndromic, environmental, progressive, and age-related hearing loss. Because GJB2 carriers have reduced hair cell function, heterozygous mutations may contribute to more severe or earlier manifestations [29]. Genotype-phenotype correlations are only now emerging and are being studied on a larger scale to determine the effect of compound heterozygous mutation sets. There may be specific missense mutations that exert an influence in the heterozygous state. Heterozygous mutations may also affect susceptibility to presbycusis or noise-induced hearing impairment through a semi-dominant effect [30]. Recently, several susceptibility loci for age-related hearing loss have been identified. Genes implicated in this process using linkage and genome-wide association studies include genes previously implicated in other forms of hearing loss (such as KCNQ4 and ACTG1), and genes involved in oxidative stress (such as GRM7, GRHL2, mitochondrial oxidative genes, and *N*-acetyltransferase).

The role of genetic factors in the development of Meniere's disease (MD) has been well documented. Most cases of MD are sporadic (SMD), but there are numerous affected persons who report other family members with similar symptoms suggesting the possibility of familial MD (FMD) [31]. No clinical differences have been reported between sporadic and familial form but patients affected with FMD seem to suffer from earlier onset and more severe manifestation of the disease [32]. Meniere's is a complex disease and, as a consequence, the genetic contribution to MD is also complex. Single locus on chromosome 12p has been reported in Swedish MD families. In addition, several inconclusive candidate-gene analyses have been performed. At the moment, knowledge of genetic factors associated with MD is modest. Genetic and clinical heterogeneity, diagnostic challenges, multifactorial origin and late onset of MD create challenges to the molecular genetic analysis of the disease. However, modern genetics may be useful in discovering new pathways associated with the pathophysiology of MD in the future. Family-based studies may assist to reduce genetic and phenotypic heterogeneity to identify molecular mechanisms or pathways involved in the pathogenesis of MD. Candidate-gene analysis is an ineffective way to study the genetics of MD and future genetic studies should emphasise the usage of linkage analyses and next-generation

sequencing as well as studying epigenetic pathways. A strong interdisciplinary research environment is needed to successfully study molecular genetics of MD. Combined efforts of highly skilled otologists, geneticists and statisticians are needed to overcome the difficulties in the molecular genetic analyses of MD.

Otosclerosis is a complex hereditary disease with relatively common monogenic forms. The majority of epidemiological studies on families with otosclerosis suggest an autosomal dominant mode of inheritance with reduced penetrance of approximately 40 %. Genetic linkage studies have demonstrated the presence of six loci (OTSC1, OTSC2, OTSC3, OTSC4, OTSC5 and OTSC7) located on chromosomes 15q, 7q, 6p, 16q, 3q and 6q respectively.

Although these loci have been mapped, no causative genes have been identified, and we have little idea of the molecular process involved in this disease. Enhanced Knowledge of these genes could lead to substantial improvements in our ability to diagnose and possibly even prevent or treat this type of hearing deterioration.

Approximately 5 % of all acoustic neuromas are familial, and are associated with neurofibromatosis Type II. The chromosome has been shown to be a deletion of the short arm of chromosome 22.

Otitis media (OM) is a very common disease in early childhood. Heritability studies suggest that there is a substantial genetic component (40–70 %) to the risk of recurrent acute otitis media and chronic otitis media with effusion. To date, only a handful of the regions/genes underlying this genetic susceptibility have been identified. These include several regions of linkage on chromosome 3p25, 10q22, 10q26, 17q12, and 19q13 identified by two genome-wide linkage scans, which appear to harbor susceptibility loci [33]. Fine mapping of these regions has yet to identify the causative genes. Several candidate genes studies have also been reported, with candidates selected on the basis of a plausible biological role in OM or through OM mouse models. Results from advanced genetic studies will identify novel genes involved in this complex disease. Identification of the genes that contribute to OM susceptibility in childhood will provide important insights into the biological complexity of this disease that could ultimately contribute to improved preventative and therapeutic strategies to reduce the incidence of this disease.

Advances in genetic testing have transformed our diagnostic approach to hearing loss in infants. Genetic testing is a complex process. It takes knowledge and experience to obtain the information needed in a time effective and cost effective manner. The clinical geneticist and genetic counsellor are indispensable to the process. It is important to remember that families are best served when genetic testing and results are presented in a genetic counselling setting by a qualified geneticist and genetic

counsellor. The main reason for genetic testing is to provide medically relevant information for the care of a child who has hearing loss.

Recent advances in therapies for hearing loss have resulted in more specific and less traumatic strategies aimed at functional restoration of the auditory system. The introduction of RNA technology has reduced off-target and nonspecific effects and has provided a potent and relatively safe strategy for targeting specific genes. Examination of stem cell viability and plasticity in the inner ear has provided us with a vehicle for cochlear cell replacement and repair [34]. Identification of damaged cells in the inner ear and the underlying mechanism by genetic testing novel and specific therapies to distinct types of SNHL. As one of such therapies, novel therapeutic approaches have been established targeting at cochlear fibrocytes which are essential for normal hearing and involved in various type of SNHL including certain types of hereditary SNHL, age-related SNHL, noise-induced SNHL and Meniere's disease [35]. Animal experiments indicate that therapeutic strategy for genetic SNHL maybe personalized, based on the cause of SNHL, using chemicals targeting at specific molecules or stem cells targeting at specific tissues for regenerative therapy [36].

Although virtually every disease in otology progresses as a combination of environment and genetics (“nature versus nurture”), the genetic contribution is now believed to play the most significant role. As we move toward personalized genomic medicine, genetic testing will be the basis for targeted molecular therapies.

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