10 Genetic Evaluation in People with Sensorineural Hearing Loss

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10.1 Introduction

Hearing loss is the most common sensory disorder affecting approximately 300 million individuals worldwide, mostly diagnosed as sensorineural hearing loss (SNHL). SNHL can be either congenital or acquired and numerous etiologies can underlie this common disorder. SNHL is diagnosed in 1–3 of 1000 newborns [1]. Newborn hearing screening program has been globally accepted after the suggestion of American Speech-Language-Hearing Association (ASHA) in 1990. By means of this program, millions of children who have hearing loss at birth have been diagnosed and treated accurately in a timely manner. Conversely, there is also a considerable amount of adult population who have SNHL.

10.2 Principles of General Evaluation

Once a person is diagnosed with SNHL, a comprehensive evaluation is needed to identify its etiology. At this point, multiple disciplines including otorhinolaryngology, audiology, radiology, and genetics collaborate. Genetic factors are regarded as one of the leading causes of SNHL in developed countries, since other causes are generally prevented by vaccines or antibiotics. Therefore appropriate assessment of these people requires a genetic evaluation. In this manner, a 3-generation family history should be obtained addressing ancestral background, family members with congenital or later onset hearing loss as well as with relevant phenotypes affecting other systems and presence of parental consanguinity. It is a good practice to obtain audiograms from first degree relatives even hearing loss is not verbally reported [2].

10.3 Genetic Etiology in Sensorineural Hearing Loss

As mentioned previously, many factors can cause SNHL. More than 50% of infants diagnosed with congenital SNHL have genetic causes. Among this population, approximately 70% are related to genetic factors, which are not associated with clinical findings of a defined syndrome (non-

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Table 10.1 Common syndromic causes of sensorineural hearing loss

Syndrome	Inheritance pattern	Clinical features	Genes
Alport	X-linked, AR, AD	Glomerulonephritis, lens abnormalities	*COL4A3, COL4A4, COL4A5*
Usher	AR	Retinitis pigmentosa	*ADGRV1, CDH23, CLRN1, HARS, MYO7A, PCDH15, SANS, USH1C, USH1E, USH2A, WHRN*
Jervell and Lange-Nielsen	AR	Long QT interval, cardiac arrhythmia	*KCNE1, KCNQ1*
Waardenburg	AD	Dystopia canthorum, heterochromia, pigmentary abnormalities of skin and hair	*PAX3, MITF, SNAI2, EDNRB, EDN, SOX10, KITLG*
Pendred	AR	Thyroid goiter, enlarged vestibular aqueduct	*SLC26A4*
Noonan	AD	Heart defects, short stature	*BRAF, KRAS, LZTR1, NRAS, PTPN11, RAF1, RIT1, SOS1, SOS2*
Branchio-Oto-renal	AD	Renal anomalies, middle/external ear anomalies, branchial fistulae/cysts	*EYA1, SIX1*
CHARGE	AD	Coloboma, heart defects, choanal atresia, retardation in growth and development, genital abnormalities	*CHD7*

AR autosomal recessive, *AD* autosomal dominant

syndromic congenital SNHL). The remaining 30% are associated with at least one additional of these syndromic causes (syndromic congenital SNHL) [3]. More than 400 forms of syndromic causes which are related to SNHL have been defined (www.omim.org).

Genetics of non-syndromic SNHL is heterogeneous with over 100 loci have already been identified. Among individuals with SNHL, autosomal recessive (AR) form is more frequent, accounting approximately 80% of cases (over 90% in countries with high rate of consanguineous marriage) and is typically congenital or prelingual-onset. The most common cause of non-syndromic SNHL in many populations is variants in the *GJB2* gene. Variants in this gene account for up to 50% of the individuals with non-syndromic AR SNHL in white populations of Europe and the USA. Mitochondrial DNA-related or X-linked forms of inheritance are rare compared to autosomal recessive and dominant forms [3].

Among many forms of syndromic causes for congenital or prelingual-onset SNHL, some are more common such as Pendred, Usher, Waardenburg, and Branchio-Oto-Renal syndromes. The responsible gene variants for several syndromes have been defined for which genetic testing is available. The clinical features and responsible genes for some common syndromic causes of SNHL are summarized in Table 10.1. Certain inner ear malformations are commonly associated with particular gene mutations; for instance, individuals who have *SLC26A4* and *POU3F4* mutations typically present with IP-II and IP-III cochlear malformations, respectively. Figure 10.1 shows three families with inner ear malformations due to mutations in the *SLC26A4*, *POU3F4*, and *EYA1* genes.

10.4 Comprehensive Genetic Testing

Mapping of the human genome and recent advances in DNA sequencing technology have created an extremely wide research area for numerous human disorders. Considering the extreme genetic heterogeneity of SNHL, comprehensive genetic testing via a set of genes (i.e., a gene panel) or whole exome/genome sequencing utilizing next-generation DNA sequencing makes a difference for the etiological evaluation of all individuals with SNHL [4]. It ideally should include all recognized genes for SNHL with both

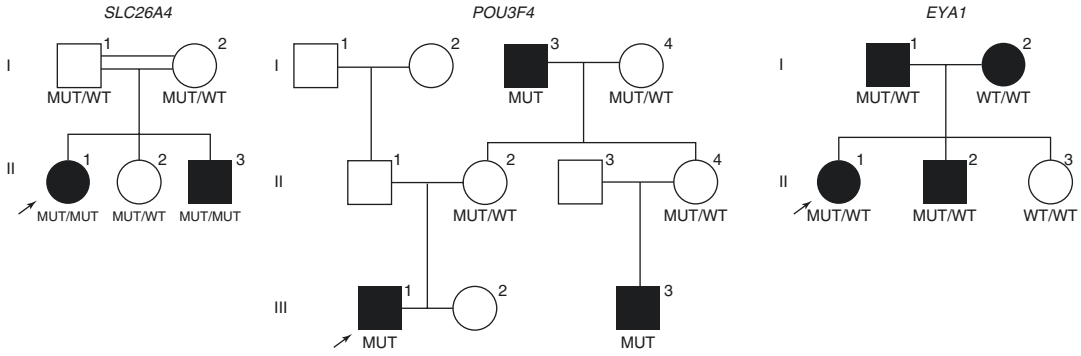

Fig. 10.1 Three families with mutations in *SLC26A4*, *POU3F4*, and *EYA1* genes. Left pedigree (autosomal recessive inheritance): two siblings with SNHL associated with IP-II cochlear anomaly are homozygous for a *SLC26A4* mutation. Unaffected sister and both parents are heterozygous for the same mutation. Double line between parents indicates parental consanguinity; Middle pedigree (X-linked inheritance): three males diagnosed with mixed hearing loss and IP-III cochlear anomaly are hemizygous for a *POU3F4* mutation. Individuals I:4, II:2, and II:4 (all females) are heterozygous for the same mutation without clinical presentation; Right pedigree (autosomal dominant inheritance): two siblings and their father have branchio-oto-renal syndrome and are heterozygous for the same *EYA1* mutation. Unaffected sister and the mother with non-syndromic hearing loss do not have the mutation. *Open circle* unaffected female, *open square* unaffected male, *closed circle or square* affected individual, *arrow* proband, *Mut* mutation, *WT* wild type

syndromic and non-syndromic forms and be performed in all cases when history and physical examination do not reveal a clear-cut environmental etiology. Comprehensive genetic testing may reveal the underlying genetic etiology even in late-onset hearing loss and aid in diagnosing syndromes even before additional symptoms appear [5].

The clinician should keep in mind that a genetic cause cannot be entirely excluded although clinical evaluation of a patient is performed with respect to the above-mentioned factors. Even when clinical findings are suggestive of a syndrome, there are often multiple genes to cause the clinically suspected syndrome. Therefore, in most cases, a next-generation sequencing gene panel or exome/genome sequencing offers a superior diagnostic yield compared to single gene testing [4].

There has been a dramatic decrease in the cost of the next-generation sequencing in the past years. It is practical, fast, accurate, and widely accepted by physicians.

Many of the recognized forms of syndromic hearing loss were reported in small number of families and sometimes in a single family. Syndromic phenotype might potentially involve any system, making a thorough review of systems and physical examination mandatory during genetic evaluation of hearing loss. Special emphasis should be placed on the clinical evaluation of the following systems:

- Visual anomalies: A full ophthalmological evaluation should be performed in every individual with SNHL as eye abnormalities involving all segments are seen in a number of syndromes. Usher and Stickler syndromes affecting the eye are among the most common forms of syndromic hearing loss with congenital/prelingual and postlingual SNHL, respectively.
- Endocrine anomalies, especially goiter and signs of hypothyroidism should be carefully evaluated, as Pendred syndrome is the most common form of syndromic hearing loss.
- Central and peripheral nervous system and general developmental history: Developmental delays and nervous system abnormalities are common in children with many syndromes as well as those with chromosomal abnormalities including copy number variants. Delay in gross motor development in an infant with severe/profound SNHL should prompt an investigation for Usher syndrome type 1 that is associated with vestibular impairment.

– Craniofacial morphology (e.g., palpebral fissures, auricules, nasal morphology, hair, sutures, etc.)
– Integumentary changes (e.g., as skin tags): especially hypo- and hyperpigmented macules should be carefully evaluated with a Wood's lamp. Waardenburg syndrome is one of the most common forms of syndromic hearing loss.
– Syncope attacks and epilepsy: individuals with Jervell and Lange-Nielsen syndrome might be misdiagnosed as having epilepsy.

Laboratory investigation

• With the recent advances in genomic sequencing technology, it is now feasible to screen mutations in most, if not all, known genes for SNHL. These tests yield underlying etiology in 20–60% of the cases depending on ethnicity, family structure, and clinical presentation. If a DNA variant known to cause only non-syndromic SNHL is identified through genetic testing, there is no need to perform costly and/or invasive clinical and laboratory investigations to rule out syndromic findings.
– Following tests should be considered based on clinical needs:

  Imaging studies (computerized tomography, magnetic resonance imaging) of the temporal bone for inner ear anomalies.

  Renal functions and morphology.

  Cardiac evaluation and EKG.

10.5 Conclusion

The etiological evaluation of individuals with SNHL requires a teamwork. As genetic factors play an important role in SNHL, appropriate and early assessment of these individuals is important to evaluate potential additional health problems, in some cases to predict the prognosis of hearing loss and to empower families to make informed decisions during planning of their families.

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