Genetics of Hearing Loss
Syndromic

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KEYWORDS

• Deafness • Hearing loss • Genetics • Genome • Sequencing

KEY POINTS

- Syndromic hearing loss (SHL) is a form of hearing loss (HL) accompanied by additional clinical features in the visual, nervous system, endocrine, and other systems. The most prevalent syndromes are Usher, Waardenburg, and Pendred.
- Genetic diagnostics can detect pathogenic variants and provide an answer regarding the cause of the HL, as well as the associated clinical symptoms of the SHL, to care for patients.
- Linkage analysis with DNA markers and polymerase chain reaction diagnostics is often used to detect these variants in clinical settings. High-throughput sequencing methods, focusing on specific genes, the exons of genes, or the entire genome of a patient, are moving into the clinic to provide more cost-effective and efficient methods for diagnostics.

INTRODUCTION

Hearing loss (HL) is the most prevalent sensory impairment in both childhood and adulthood.[1,2] According to the last update of the World Health Organization (WHO), approximately 360 million people worldwide, equaling 5% of the world's population, have a disabling HL (**Table 1**). Most of these people live in low- and middle-income countries where treatments for HL are more difficult to obtain and consanguinity increases the risk of recessive disease. HL is an etiologically heterogeneous pathology caused by different genetic and environmental factors, with half of the cases estimated to be genetic.[3] HL can also be a result of infections, injuries, and exposure to excessive noise.

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Abbreviations

ASHA	American Speech-Language-Hearing Association
ATP	Adenosine triphosphate
BOR	Branchio-oto-renal
bp	Base pair
CHARGE	Coloboma, heart defect, atresia choanae, retarded growth and development, genital hypoplasia, ear anomalies/deafness syndrome
DFN	Deafness
DFNA	Nonsyndromic deafness, autosomal dominant
DFNB	Nonsyndromic deafness autosomal recessive
DFNX	Nonsyndromic deafness, X-linked
HARS	Histidyl tRNA synthetase
HL	Hearing loss
IHC	Inner hair cell
JLNS	Jervell and Lange-Nielsen syndrome
MPS	Massive parallel sequencing
NGS	Next-generation sequencing
NIDCD	National Institute on Deafness and Other Communication Disorders
NSHL	Nonsyndromic hearing loss
OHC	Outer hair cell
OMIM	Online Mendelian Inheritance in Man
PCR	Polymerase chain reaction
PRLTS1	Perrault syndrome 1
SHL	Syndromic hearing loss
SNHL	Sensorineural hearing loss
SNP	Single nucleotide polymorphism
SNV	Single nucleotide variant
STL1	Type I Stickler syndrome
UCSC	University of California, Santa Cruz
USH1, 2, 3	Usher syndrome 1, 2, 3
WES	Whole-exome sequencing
WGS	Whole-genome sequencing
WHO	World Health Organization
WS1, 2, 3, 4	Waardenburg syndrome 1, 2, 3, 4

HEARING LOSS

Our ability to hear is orchestrated by the auditory system. The vestibular system is responsible for balance, 3-dimensional orientation, and gravity perception. The ear is a 3-chambered organ divided into the external, the middle, and the inner ear, which are all essential for the intact activity of the auditory and the vestibular systems. The external and middle ear are responsible for collecting and conducting the sound wave's energy to the inner ear.[4,5] The sensorineural end organ of hearing is the snail-shaped organ of Corti that resides in the inner ear. It is composed of a single row of inner hair cell (IHC), 3 rows of outer hair cells (OHCs), and supporting cells. The IHC act as sensory transducers, capturing stimulus energy, interpreting it as electrical responses and sending the impulses to the brain through the auditory nerve. The OHCs are responsible for enhancing the signal.[6]

According to the American Speech-Language-Hearing Association (ASHA) (see Table 1), normal hearing occurs in the range of −10 to 15 dB, with a slight HL if the range of loss is within 16 to 25 dB. Mild HL occurs when the HL ranges between 26 and 40 dB; moderate HL is when the HL ranges between 41 and 55 dB; moderate to severe HL ranges between 56 and 70 dB. Individuals with HL in these ranges are considered to be hard of hearing and can benefit from hearing aids and assistive