



Genetic Information and Precision Medicine in Hearing Loss

Doo-Yi Oh · Byung Yoon Choi

Department of Otorhinolaryngology, Seoul National University Bundang Hospital, Seongnam, Korea

Hearing loss (HL) is the most common sensory disorder, affecting at least one in 500 people in developed countries, and has the highest incidence rate of any congenital sensory organ disorder [1]. It occurs three times more often than Down syndrome or cystic fibrosis, which are especially common in western nations [2]. HL is caused by genetic and environmental factors that affect auditory pathways, such as congenital cytomegalovirus and ototoxicity caused by antibiotics [2]. Recently, with the decline in the prevalence of infectious diseases and the prevention of drug-induced HL, the proportion of patients with genetic HL has correspondingly increased, and causative genetic variants have been found both for congenital mild or moderate HL and for severe or profound HL [3,4]. In addition, congenital recessive deafness gene variants are not uncommon in patients with sporadic HL, which is not evident at the beginning of birth but becomes apparent during childhood, adolescence, or adulthood, is not uncommon to report congenital recessive deafness gene variants [5].

The accelerated discovery of causative genetic variants has been strongly influenced by the Human Genome Project, which began in 1990 and ended in 2003, and next-generation sequencing (NGS), which has enabled tremendous changes in the landscape of the genetic biomarker market since its debut in 2004. The causes of HL include aging, exposure to ototoxic drugs, environmental insults, and genetic alterations, which are considered to account for 60% of HL [6]. Owing to developments in sequencing analysis methods, the range of hereditary HL is expanding to encompass congenital sensorineural HL, presbycusis, and noise-induced HL. On top of Sanger sequencing, the lineup of current tools of precision medicine in HL includes genetic screening kits and NGS technology-based methods. NGS technology can be divided into targeted exome sequencing (panel sequencing), exome sequencing (ES) and whole genome sequencing (WGS). Establishing an ethnicity-specific variant spectrum for HL enables simultaneous and preferential screening of the genetic variants for HL in a time- and cost-saving method. In Ko-

rea, a diagnostic kit covering seven variants from three major genes (*GJB2*, *SLC26A4*, and mitochondria 12S rRNA) was developed based on microarray technology in 2009 [7], followed by the introduction of another diagnostic kit for 11 variants of five genes selected based on their prevalence in Korean HL patients in clinical settings [8]. Panel sequencing, which does not analyze the exome of the entire gene, but only analyzes the exome of genes known to be linked to deafness, has been the most popular method of HL screening since 2017. Compared to ES, panel sequencing is useful and has been established as the basic method of HL testing by clinicians, as it can analyze the sequence of genes at a much higher level with a low amount of DNA, as well as being time-saving, much less costly, and free from ethical problems derived from unwanted knowledge of genes unrelated to HL. Currently, the OtoSCOPE panel, which can analyze 152 HL genes responsible for nonsyndromic sensorineural HL, Pendred syndrome, and Usher syndrome, and the panel developed by Otogenetics Corporation, which can analyze 129 HL genes, are widely used around the world [9,10]. New HL genetic panels including all newly discovered HL genes have also been produced in Korea (e.g., Otoscan). However, if a gene has not been previously reported to cause HL, molecular diagnosis is not possible through panel sequencing due to its inherent limitations, and ES is necessary in such cases. ES is an important tool for identifying novel HL genes. The exome, which codes proteins, accounts for about 1.5% of the human genome, and the causative genetic variants for single-genetic diseases are mostly located in the exome region. By targeting only the protein-coding regions of the genome, ES reduces the time and expense compared to WGS. Numerous novel variants and HL genes in Sensorineural Hearing Loss have been identified by using ES; the first such gene was taperin (*TPRN*) [11], suggesting that ES is essential to find new HL genes. The number of new HL genes, discovered by either NGS alone or in conjunction with linkage analysis or homozygosity mapping, is expected to increase further in

the future.

With its extreme etiologic heterogeneity and recent advances in these cutting-edge sequencing technologies, such as NGS and screening kits, the field of HL has been positioned as an ideal context for adoption of the strategies of precision medicine. Recently, a growing number of studies have reported surgical outcomes of cochlear implantation (CI) in association with causative genes for HL [12,13]. This approach has been particularly entered into the spotlight for the auditory rehabilitation of auditory neuropathy spectrum disorder (ANSD), which poses a significant dilemma in terms of appropriate auditory rehabilitation tools for both patients and otologists due to the uncertain outcomes of CI in these patients. Specifically, molecular genetic testing of the p.Glu831Lys variant of *ATP1A3*, previously known to cause cerebellar ataxia, areflexia, pes cavus, optic atrophy, and sensorineural hearing loss (CAPOS) syndrome, can serve as a biomarker that allows for the identification of a subset of post-lingual-onset progressive ANSD subjects who can significantly benefit from CI, at least during short-term follow-up [14]. Without this genetic information, HL in patients with CAPOS syndrome would be considered “central” due to the accompanying deficits of the central nervous system, precluding the implementation of CI in these subjects. *OTOF*-related prelingual ANSD patients are also considered to have good prognosis for CI, if CI can be performed in a very timely fashion [15]. Considering the amount of residual hearing, it would be highly unlikely to perform early CI in those patients without the genetic information. In contrast, variants of *DFNB59* and *PCDH15* have been associated with a poor prognosis after CI [13]. Interestingly, a subset of patients with autoinflammatory inner ear diseases can show improvement of nonsyndromic HL if they carry an *NLRP3* variant and receive anakinra treatment [16,17].

Therefore, genetic information has become an important basis of auditory rehabilitation for HL patients beyond just identifying the cause of HL. Because the HL gene variant spectrum is very different in East Asian and Caucasian populations, it is not prudent to apply research results from other countries to the Korean population. In fact, many distinctive variants are exclusively found in East Asian populations or in the Korean population, warranting the establishment of ethnicity-specific variant spectra of HL.

Currently, many studies aiming to establish gene therapy for HL are at the animal testing stage. These gene therapies require a correct molecular genetic diagnosis. Successes in a subset of studies employing gene therapy, if not all, have shown improvements in cellular structure and vestibular function, as well as restoration of the neural response in the auditory cortex and recovery of behavioral responses. For example, mice with loss of *Tmc1* function, a form of hereditary HL characterized by hair cell damage that causes moderate to severe HL with post-lingual onset, were found to have restored hearing, balance, and several secondary outcomes, suggesting that inner ear gene therapy for

Tmc1 mutations may be well-suited for further development and perhaps translation to the clinical setting [18]. Gene therapy will undoubtedly change the way that HL is treated over the next few decades.

Genetic information-based, precision medicine for the diagnosis and treatment of HL is emerging as a standard and crucial part of neuro-otology. Patients will receive personalized therapies that will improve both HL prevention and our current understanding of the treatment of HL.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

ORCID

Doo-Yi Oh <https://orcid.org/0000-0003-0043-7790>

Byung Yoon Choi <https://orcid.org/0000-0001-5125-2118>

AUTHOR CONTRIBUTIONS

Conceptualization: BYC. Data curation & Formal analysis: DYO. Funding acquisition: BYC. Methodology: DYO. Project administration: BYC. Visualization: BYC. Writing—original draft: DYO. Writing—review & editing: BYC.

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Received July 27, 2020
Accepted July 30, 2020