Review paper

Diagnosis and treatment of genetic hearing loss

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Abstract

This paper discusses the potential influence of genetic research in the diagnosis and treatment of congenital hearing loss. It provides an overview of the different views in society surrounding genetic testing, especially the opinions of the hearing loss community and their families. By introducing the variety of genetic indicators of hearing loss that have been discovered, this paper highlights the technological advancements in hearing loss genetics. Furthermore, it introduces the importance of timely diagnosis and treatment to affected individuals, supporting the significance of the impact of genetic testing. Lastly, this paper presents future possibilities that genetic research can bring to hearing loss treatment, such as gene therapy. Overall, the purpose of this research is to explore the value of genetic research in this field and provide the readers with knowledge of the genetic basis in hearing loss.

Keywords

Diagnosis, Gene therapy, Genetic mutation, Genetic testing, Hearing loss, Nonsyndromic hearing loss, Syndromic hearing loss, Treatment

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Introduction

Congenital hearing loss is the most common sensorineural disorder found in 1-3 per thousand infants. While profound hearing loss is easier to recognize, it is difficult to identify mild hearing loss without professional testing. Consequently, many young children and students with mild hearing loss do not get diagnosed and begin their learning without proper hearing accommodations. Undiagnosed hearing loss can cause many long-term problems for their education and in their social life (1). Without hearing assistance, children with hearing loss are prone to learning difficulties, social isolation, and depression. These children face difficulties in interacting with their peers and taking classes, as listening, for them, is a multi-sensory task that requires much greater effort than others (2). Parents and instructors often mistake poor academic performance or social difficulties of children as lack of attention or effort, insteading of considering whether they may have hearing loss. If children are not diagnosed accurately in a timely manner, it becomes increasingly difficult to identify the problem and reduce the negative long term effects. Thus, early diagnosis is key to providing patients with appropriate treatment and care.

Hearing loss can result from abnormalities in many parts of the auditory system. The peripheral auditory system is composed of the outer ear, the middle ear, and the inner ear. The outer ear refers to the pinna, ear canal, and the eardrum (tympanic membrane), which captures sound waves and delivers them to the eardrum. The middle ear refers to the eardrum, three ossicles (small bones that communicate the eardrum movements to the inner ear), and the Eustachian tube. The inner ear refers to the cochlea, the vestibule, and the nerves connected to the brain (3). The peripheral auditory system transmits information to the central auditory system through nerve fibers that connect the organ of Corti to the auditory cortex. Two types of cells, the external and internal cilia, inhabit the Corti and are linked to nerve fibers connected to the brain. The central auditory system is where auditory information is interpreted by transmitting the sound to the brain (4-5).

Hearing loss is generally classified into two types: conductive hearing loss and sensorineural hearing loss (SNHL). Conductive hearing loss is caused by the obstruction of sound in the outer or middle ear and can usually be treated with medicine or surgery. SNHL is caused by an anomaly in the inner ear or cochlear nerves and can be caused by both genetic and environmental factors. The environmental factors of SNHL include noise levels of the environment and pharmacological factors such as ototoxic medicines (6). Ototoxic medicines can induce hearing loss by causing damage to hair cells, disruption of the cochlear fluids, toxic accumulation, etc. Some common examples of ototoxic medications include antibiotics such as aminoglycosides, chemotherapy drugs, diuretics, and nonsteroidal anti-inflammatory drugs (NSAIDs). Furthermore, SNHL can also occur as a side effect of other genetic disorders caused by variants unrelated with the inner ear, such as hyperbilirubinemia (7). Severe and prolonged hyperbilirubinemia, particularly in newborns, can lead to a condition known as

bilirubin encephalopathy or kernicterus. Kernicterus occurs when elevated bilirubin levels lead to the deposition of bilirubin in the brain, which can cause neurological damage that can include hearing loss referred to as "bilirubin-induced hearing loss." This type of hearing loss occurs when there is damage to the hair cells in the inner ear (cochlea) or the auditory nerve.

This paper will focus on genetic SNHL. As conductive hearing loss is rarely congenital, the concept of genetic testing is most relevant to sensorineural hearing loss. While hearing is affected by all the components of the auditory system, SNHL concerns the inner ear, mainly the cochlea and the hair cells. Understanding the genetics of the development of such components is important to diagnosing congenital hearing loss and informing its care (8).

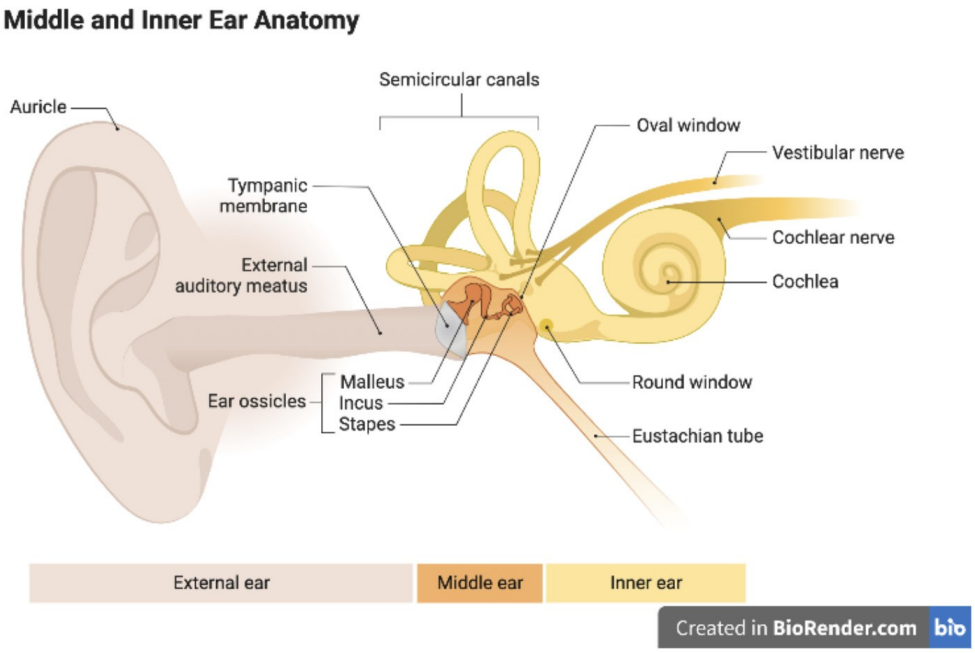

Figure 1. Diagram of the structure of the peripheral auditory system

Methods

A literature review was conducted using Google Scholar and PubMed. Government and/or medical websites provided most of the basic background information throughout the introduction. Information about the various genetic indicators were gathered through scholarly articles and the Hereditary Hearing Loss Homepage. A study conducted in China was also discussed, in elaborating how genetic testing factors into early diagnosis. Science blogs and articles were consulted when researching the future possibilities of genetic testing. Figures were recreated using BioRender and Excel.

Results and Discussion

Genetic indicators of hearing loss

Genetic hearing loss can be classified into syndromic hearing loss and nonsyndromic hearing loss (NSHL). Syndromic hearing loss is associated with medical conditions in the external ear or other organs, while NSHL is not associated with any other medical symptoms. Nearly 70% of genetic hearing loss is nonsyndromic, with genetic hearing loss accounting for the rest. Most cases of NSHL are associated with the functions of the inner ear, meaning that they can be described as sensorineural and cause permanent loss of hearing. On the other hand, most syndromic forms of hearing loss are mild or inconsistent (9-10). Many of these genes have been discovered through sequencing of patients or by conducting Genome Wide Association Studies (GWAS) (11).

The three patterns of inheritance in NSHL are autosomal dominant, autosomal recessive, and X-linked. To briefly overview the terms used to describe the different causes of NSHL, DFNA refers to the autosomal dominant form, DFNB the autosomal recessive, and DFN the X-linked. For each type, numbers added after these abbreviations refer to the order in which the loci were discovered. To date, more than 70 genes associated with NSHL have been identified. Depending on the locus, many different types of genetic mutations can cause hearing loss (10).

Autosomal recessive form is the most common, accounting for about 80% of NSHL. The most common cause of severe to profound autosomal recessive NSHL is mutations in the GJB2 gene, which is classified as DFNB1. The GJB2 gene instructs the production of connexin 26, which is a type of protein that forms gap junctions that transport potassium ions and other small molecules. Although the exact role of connexin 26 in hearing is yet to be determined, some researchers speculate that it contributes to sustaining the potassium level or that the protein plays a role in the maturation of certain cells in the cochlea. Similarly, GJB6 is another connexin gene that can cause DFNB1. The most common cause of moderate autosomal recessive NSHL is mutations in the STRC gene, classified as DFNB16. The STRC gene instructs the production of stereocilin, a protein that is also found in the inner ear, specifically in the hair cells. Stereocilin is involved in maintaining the structure of stereocilium, which is a hairlike structure that partially forms the hair cells. Stereocilia is directly related to hearing, as its movement according to sound waves stimulate the nerve impulses that get transmitted through the auditory nerves to the brain. These genetic mutations cause the majority of the autosomal recessive NSHL, and there are numerous other types of mutations that are less common and unique to certain families (14).

Autosomal dominant forms comprise about 18% of NSHL. Unlike autosomal recessive forms, autosomal dominant forms do not have a single gene that accounts for the majority of cases. However, some genes are more commonly associated than others; such as KCNQ4 and TECTA. The KCNQ4 gene codes for a protein that is a part of potassium channels. The role of KCNQ4 channels in the inner ear is maintaining appropriate potassium

levels, which affects the conversion of sound waves to electrical nerve signals that are interpreted by the brain. The TECTA gene is associated with the production of alpha-tectorin, a protein that forms the tectorial membrane. The tectorial membrane is a part of the cochlea, which is crucial to the conversion of sound waves to nerve impulses (14).

The least common forms of NSHL are X-linked and mitochondrial hearing loss. X-linked form accounts for 1-3% of NSHL. Males are more frequently and profoundly affected as they only have one X-chromosome, whereas affected females mostly suffer mild hearing loss or inner ear abnormalities. The majority of X-linked cases result from mutations in the POU3F4 gene, known to cause DFNX2. The POU3F4 gene is one of the POU domain family genes, which are genes involved in determining cell types in the central nervous system. Specifically, the POU3F4 gene instructs the production of a protein that is responsible for controlling the activity of other genes, referred to as a transcription factor. The POU3F4 gene is speculated to impact the early development of the middle to inner ear, but its exact role in hearing is yet to be determined. Mitochondrial forms of NSHL refer to mutations in the mitochondrial DNA (mtDNA). Mitochondrial forms of hearing loss are rather rare and account for less than 1% of all genetic hearing loss cases, but a few mutations in the mtDNA have been identified as indicators of hearing loss (14).

Although less common than NSHL, syndromic hearing loss accounts for about 30% of prelingual deafness, and more than 400 genetic syndromes associated with hearing loss have been identified. Syndromic hearing loss can also be differentiated into autosomal recessive, autosomal dominant, and X-linked. The following paragraphs will provide an example of each type (15).

Some major autosomal recessive syndromes are Usher syndrome, Pendred syndrome, and Jervell and Lange-Nielsen syndrome (15). Among the three, Usher Syndrome is the most common cause of syndromic hearing loss that affects nearly 50% of blind and deaf people in the United States. The main symptoms of this syndrome are retinitis pigmentosa, a vision disorder that causes progressive vision loss, and sensorineural hearing loss. Usher syndrome is differentiated into three types, type I and II accounting for 95% of the cases. Type I identifies with severe congenital hearing loss and vision loss from retinitis pigmentosa that becomes apparent from childhood. In addition, type I differs from type II in that it also associates with vestibular abnormalities, which causes balance problems. Type II is characterized by congenital hearing loss ranging from mild to severe and progressive vision loss that develops during adolescence or adulthood. Hearing loss in type II mainly affects the ability to hear high-frequency sounds. Unlike the other types, in type III, hearing loss and vision loss begins later in life. Progressive hearing loss begins after the development of speech, and most patients experience profound hearing loss by middle age. Similarly, vision loss also begins later in childhood or adolescence. Some but not all patients of type III experience vestibular abnormalities. Genetic mutations that cause the

Usher Syndrome are associated with the production of proteins that are involved in the development of hair cells (16).

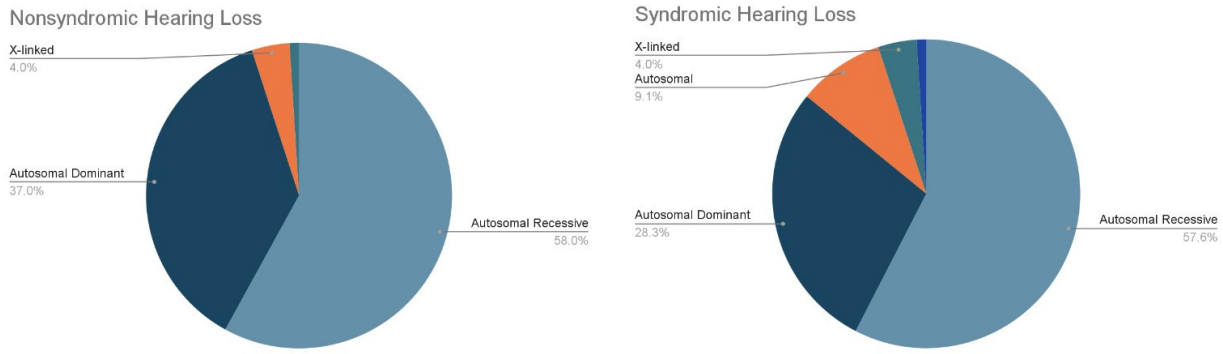

Figure 2. Genetic causes of hereditary hearing loss. The prevalence of each inheritance pattern for each nonsyndromic and syndromic hearing loss.

Autosomal dominant syndromes that cause hearing loss include Waardenburg syndrome, Treacher Collins syndrome, Stickler syndrome, branchio-oto-renal syndrome (Melnick-Fraser syndrome), neurofibromatosis type 2, osteogenesis imperfecta, and otosclerosis (15). Waardenburg syndrome is the most common, accounting for 2 to 5% of congenital hearing loss. The primary feature of this syndrome is abnormalities in the pigmentation of hair, skin, and eyes. While many people with the syndrome do not experience hearing loss, sensorineural hearing loss is one of the possible symptoms, varying from moderate to profound. Waardenburg syndrome is distinguished into four different types. Types I and II are common, and types III and IV are rare. Types I and II are very similar, but differ from each other in that the majority of people affected by type I have widely spaced out eyes. Hearing loss is more prevalent in type II. Type III is associated with hearing loss, changes in bodily pigmentation, and abnormalities of the arms and hands. Waardenburg syndrome is caused by the mutation of genes that are involved in the production of pigmentation cells called melanocytes. Melanocytes produce melanin, a pigment that plays a vital role in the inner ear (17).

Lastly, the three major X-linked syndromes that cause hearing loss are Alport syndrome, Norrie Syndrome, and otopalatodigital syndrome (14). Alport syndrome is characterized by kidney disease, hearing loss, and vision abnormalities. Many people affected by the Alport syndrome suffer sensorineural hearing loss during late childhood or early adolescence. Like most X-linked syndromes, the symptoms are more common in affected males than females. Alport syndrome is caused by mutations in genes that are involved in the production of type IV collagen, a protein associated with the kidney, inner ear, and

retina. This protein plays an important role in the organ of Corti in the inner ear that translates sound into nerve impulses. Moreover, mutations in related genes can cause sensorineural hearing loss (18).

Genetic Testing in Hearing Loss Diagnosis

At least half of congenital or early childhood hearing loss cases have genetic causes. As researchers continue to discover genetic causes of hearing loss, the potential impact genetic testing can have on the hearing loss community should be acknowledged.

For those with hereditary hearing loss, genetic testing can be of great benefit, as it helps to identify the etiology and provides them with an early diagnosis necessary for treatment (19). Recognizing the importance of early detection and intervention, newborn hearing screening programs (NBHS) have been globally employed since the 1990s. An example of NBHS in the United States is the Early Detection and Hearing Intervention (EDHI). EDHI includes infant screening for hearing loss and aims to provide families across the US with accurate information and appropriate hearing assistance. Newborn screening utilizes otoacoustic emissions and auditory brainstem response (20-21). However, there are significant limitations to the conventional newborn screening, as it cannot detect mild or delayed hearing loss. Thus, genetic testing is anticipated to be an important addition to the current process in order to increase the accuracy of the testing and inform early treatment (22).

Massively parallel sequencing (MPS) techniques have revolutionized the field of genetic testing and have become invaluable tools in diagnosing various genetic disorders, including congenital hearing loss (23). These techniques have expanded the scope of genetic testing beyond individual genes, allowing for the identification of both common and rare genetic variants associated with hearing loss. The integration of MPS into clinical practice has improved the understanding of the genetic basis of congenital hearing loss, leading to more accurate diagnoses, personalized treatment strategies, and improved counseling for affected individuals and their families.

MPS, also known as next-generation sequencing (NGS), allows for the simultaneous sequencing of multiple DNA fragments in a massively parallel manner (23). This high-throughput sequencing technology enables the rapid analysis of large amounts of genetic data at a relatively low cost. In the context of congenital hearing loss, MPS techniques have been instrumental in identifying the genetic variants responsible for various forms of the condition. There are two main MPS approaches commonly employed in diagnosing congenital hearing loss: targeted gene panel sequencing and whole-exome sequencing.

Targeted Gene Panel Sequencing: This approach involves sequencing a predefined set of genes known to be associated with hearing loss. By focusing on a specific set of genes, targeted gene panel sequencing allows for a more cost-effective and efficient analysis of relevant genetic variants.

Whole-Exome Sequencing (WES): WES involves sequencing the protein-coding regions of the entire genome, known as the exome. The exome represents approximately 1-2% of the total genome but contains a vast majority of disease-causing variants. WES allows for a broader analysis of genetic variants beyond the known hearing loss genes, which can be particularly useful in cases where the genetic cause is unknown or suspected to be rare.

Once the sequencing is complete, the resulting data undergoes bioinformatics analysis to identify potential disease-causing variants. This involves aligning the sequenced reads to a reference genome, identifying genetic variants , and prioritizing the variants based on their potential pathogenicity by comparing the patient's genetic data to databases and literature resources to identify known pathogenic variants and to assess the significance of novel variants. Clinicians and geneticists can then assess the identified variants in the context of the patient's clinical features, family history, and available literature and databases. Functional studies, such as *in vitro* or *in vivo* experiments, may also be conducted to further validate the pathogenicity of the identified variants (23).

As mentioned in the last section, mutations in GJB2 and GJB6 genes are the most common causes of nonsyndromic hearing loss, and more than half of infants with hereditary hearing loss will only have identifiable mutations in those genes. Moreover, one of the suggestions regarding genetic testing is selective gene screening for GJB2 and GJB6. Relevant mutations are usually associated with moderate to profound, congenital, and nonprogressive hearing loss. GJB2/GJB6 testing can also provide information about the hearing loss - such as severity and prognosis - according to the type of mutation identified. Lastly, GJB2/GJB6 testing can eliminate the need for unnecessary testing, as patients with GJB2/GJB6 detrimental mutations will most probably have hearing loss associated hearing loss associated with these mutations. Without this knowledge, all infants that were tested to have hearing loss would have to consider the possibility of having a genetic syndrome that comes with other physical conditions. Many symptoms of such syndromes are hidden in newborn stages and discovered later in life, which means that it will require extensive surveillance and additional testing such as electrocardiograms, serial ophthalmological evaluations, renal ultrasounds, urine testing, and complicated thyroid studies. Incorporating GJB2/GJB6 testing to the NBHS will save time and effort for many families by providing specific information about the etiology of the hearing loss (24).

Although it seems safe to assert that genetic testing will strengthen the screening programs and has many benefits, it is yet to be widely employed in many countries. There are many aspects to be considered, such as the timing/method of testing, necessary resources, follow-up, genetic counseling, etc. As a result, many studies and statistics regarding genetic testing have been limited to targeted screening of small samples. However, a recent study that discusses the nationwide genetic screening in China provides meaningful data that reflects the benefits of testing. The study demonstrates

a quantitative review of the genetic testing results of ~1.2 million newborns (25).

Data of 1,172,234 newborns that underwent genetic screening from March 2012 to September 2017 were evaluated. The method of limited genetic testing was adopted, genotyping 20 variants in GJB2, SLC26A4, MT-RNR1, and GJB3. Screening was performed by collecting blood clot specimens via heel stick onto filter paper according to the routine newborn screening protocol. The screening results were classified into three types: positive (biallelic variants in either GJB2 or SLC26A4), inconclusive (a heterozygous variant in GJB2 or SLC26A4, or presence of any GJB3 variant), at-risk (any mitochondrial variant), and negative (none of the 20 screened variants identified). Guardians of newborns that were identified with at least one variant between March 2012 and December 2016 were subject to follow-up phone interviews. Newborns that were tested negative with no variants were excluded from the follow-up. The comprehensive results found 360 (0.03%) positive, 2638 (0.23%) at-risk, 52,979 (4.52%) inconclusive, and 1,116,257 (95.22%) negative. 55,977 newborns were identified with at least one of the mutations screened, and 19,125 of them were successfully contacted. A total of 12,778 newborns were eligible for primary analysis, which found 112 (0.9%) positive, 11,591 (90.7%) inconclusive, and 1075 (8.4%) at-risk for ototoxicity. By the time of the last interview, 107 subjects were diagnosed to have hearing loss (25).

The statistics of this study demonstrates specific benefits of genetic screening. Of the 107 subjects reported to have hearing loss, only 95 were diagnosed in the conventional NBHS program. This result indicates 13% increase in hearing loss detection, diagnosing 12 subjects that were not identified by risk factor–indicated audiologic monitoring. Positive genetic testing results indicate that the child will eventually develop hearing loss, even if it isn't during early childhood. Such prognosis can inform parents and encourage surveillance and extensive care. In addition, genetic testing discovered 2,638 (0.23% of total) newborns with genetic risk of ototoxicity undetectable by hearing screening. With this information, 41 families with a self-reported family history of drug-induced hearing loss were able to prevent the development of hearing loss by avoiding exposure to aminoglycoside antibiotics. Even the limited genetic screening of 20 variants made a change in NBHS results and provided a timely diagnosis that allowed early intervention. Considering that many subjects were not contacted for follow-up investigation, it can be deduced that reducing the lost-to-follow-up/documentation rates and providing genetic counseling to a greater number of families would significantly heighten the clinical effectiveness of NBHS. Furthermore, this study evidences many positive prospects and potential of genetic testing in hearing loss screening (25).

The future of genetic testing in NBHS includes not only selective gene testing but full sequencing to capture all mutations in a larger number of genes. Otological Sequence Capture Of Pathogenic Exons is an example of a massively parallel sequencing platform that utilizes targeted sequence capture and next-

generation sequencing for genetic testing of hearing loss. Many other next-generation sequencers are being developed, and with continued research in this field, it is anticipated that there will be improvements to the cost and speed of DNA sequencing technologies (25).

Potential of Gene Therapy in Hearing Loss Treatment

The future of genetics in hearing loss extends beyond genetic indicators and diagnosis. As genetic technology advances, researchers are looking for ways to target genes for hearing loss treatment. Gene therapy has proved to be effective in other organs such as the retina, and there are experimental findings from murine studies that support the possibility of the same application in the inner ear (27-29). However, research about gene therapy is limited by unmet needs, such as adequate animal models for testing. The mouse is an ideal model for mammalian hearing loss and has been integral to the progress of a century of research. However, for many recent discoveries of genes for human hearing loss, no viable mouse model yet exists (29). For some of these genes, mouse models were generated that recapitulate the human genotype but do not recapitulate the human hearing loss. In other cases, knock-out mice for hearing-loss associated genes do not survive long enough to assess hearing loss.While mouse models cannot be directly translated to human treatment, current research in gene therapy seems promising. With additional experiments and modifications, it seems possible that gene therapy could soon be incorporated as hearing loss treatment for humans, and even become a cure (30).

There are largely three types of gene therapy to be discussed that may alleviate hearing loss from inherited mutations: functional rescue by restoration of genes, functional rescue by inhibition or editing, and *in utero* gene therapy. Currently, these methods are being tested in murine models (31).

Functional rescue by restoration would be applicable to most recessively inherited genetic hearing loss, as treatment would require compensation of the missing gene or gene product. In a recent experiment, a null allele of SLC17A8 was rescued by selective insertion of a wild-type SLC17A8 gene into the genomes of the inner hair cells using AAV1-mediated transfection. This functional rescue lasted over a year in some cases after the delivery of viruses when the mice were less than 2 weeks of age (31).

On the other hand, functional rescue by inhibition or editing is applicable to dominantly inherited hearing loss. The idea behind this method is to inhibit the dominant mutation so that the remaining copy of the gene product can restore function. This form of gene therapy was demonstrated on mice with a dominant mutation in the gene GJB2. This study was able to restore the hearing of the mice by co-transfection of an siRNA that targeted the dominant negative construct. Such results conjecture that the elimination of dominant genes products could be a therapeutic method for dominantly inherited hearing loss (31).

In utero gene therapy is another method that may be possible in the distant future. *In utero* gene therapy is a form of gene therapy that

alters the developmental processes that occur in the embryo during gestation (32). This method has been used in mouse models, such as in utero electroporation applied to inhibit GJB6 with short hairpin RNAs. Additionally, there are ongoing clinical trials that explore gene therapy on patients with hearing loss. For instance, Decibel Therapeutics is one of the companies that are developing gene therapies using AAV delivery systems to target otoferlin, GJB2, and cisplatin related hearing loss. Their trials are mostly in early stages (phase 1/2) with one trial (DB-OTO), now beginning phase 3 (33). Lastly, attempts to prevent a wide variety of genetic disorders by editing gametes before in vitro fertilization are being studied, and in principle this could be done for SNHL causing variants as well. However, there are still many technical and ethical challenges faced by these types of gene therapy (34).

While genetic research in hearing loss presents many benefits and possibilities, it is important to note the social controversy around genetic testing and treatment. Opinions on genetic testing (especially prenatal diagnosis) are greatly affected by the culture and identity of the individual.

One key aspect to consider is the different stances regarding hearing loss and deafness. While hearing loss and deafness is commonly treated as a disease or disability in the medical world, many people in the Deaf community believe it to be a distinct part of their identity. The Deaf community is now considered as a unique population with their own customs and language. Consequently, people who identify as culturally deaf often express discomfort about genetic testing, in fear that its intent is to eradicate their culture by attempting to "cure" what is simply a part of their identity. The rejection of the medical definition of hearing loss as a defect that needs to be cured shapes the perspective of the Deaf community. For instance, a survey conducted at a conference on the "Deaf Nation" in the United Kingdom found majority of the respondents holding a negative view on genetic testing, and another much larger survey of 644 Deaf, 143 hard of hearing and deafened, and 527 hearing subjects with either a Deaf parent or a Deaf child also demonstrated that culturally deaf respondents showed a higher tendency to disapprove of genetic testing (34).

On the other hand, studies of parental attitudes on genetic testing demonstrate that the majority of hearing parents of deaf children hold a positive stance in genetic testing. While there are different reasons to why parents are interested in genetic testing of their children, some common reasons are: to identify the cause of their child's hearing loss and to promote accommodation or treatment of their child. A study by Steinberg et al. examined the parental narratives on genetic testing by interviewing 24 parents of diverse racial and socio-economic status whose children were referred for genetic testing but yet to be tested. It was noted that many parents did not have extensive knowledge about the genetic basis behind hearing loss, and misunderstood the mechanics of genetic transmission. Awareness on the syndromic causes of hereditary hearing loss was also very low. Even parents with experience in genetic testing did not have increased knowledge, and were unaware of what genetic counseling is, uncovering the

need for accurate information and analysis in order for genetic testing to be utilized effectively. Furthermore, genetic testing also impacted the parents' perspectives on the reason behind their child's hearing loss. As the participants of the study held different religious and cultural beliefs, the impact of genetic testing also differed; for some parents, a genetic cause for hearing loss alleviated self-blame, while for others a genetic origin implied greater personal responsibility. The parents in the survey also voiced hope that genetic testing could be of help to the family, as it can help them prepare to accommodate their child with hearing loss or deafness. Another perspective was that their child being diagnosed with genetic hearing loss felt far worse, as it felt permanent and incurable. Despite the Deaf community's concern for selective reproduction, none of the parents considered terminating the pregnancy due to genetic testing results (35). It is evident from such surveys that genetic testing is still a topic of controversy that stems from different cultures and beliefs.

As a part of the hearing loss community, the author recognizes that it is important for affected individuals to know about the genetic basis of their condition. Through such information, individuals can gain knowledge about the etiology, prognosis, and inheritance possibilities of their hearing loss. Regardless of the varying perspectives surrounding genetic research, it is crucial to be aware of the options that science will be able to provide. The incorporation of genetic studies will need careful consideration of numerous issues; among them being culturally respectful to the Deaf community.

Conclusions

Early targeted genetic testing in neonates for mutations in GJB2 and GJB6 genes (which are the most common causes of nonsyndromic hearing loss) has the potential to detect and to mitigate some of the risk factors that can predisopose to congenital hearing loss. These include avoiding exposure to ototoxic medicines such as aminoglycoside antibiotics and monitoring hyperbilirubinemia. Gene therapies currently in clinical or animal testing can alleviate hearing loss from inherited mutations by three methods: functional rescue by restoration of genes, functional rescue by inhibition or editing, and *in utero* gene therapy. GWAS and MPS have revolutionized the identification of genes that may play a role in the causation chain but an unmet need for adequate animal models for testing still exists. As an example, the Gjb2 deletion mouse model shows embryonic lethality. The prospects for a cure for congenital hearing loss appear good as gene therapy progresses through clinical trials, and the detection limit for accurate diagnoses decreases.

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