Genetics of Childhood Hearing Loss

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KEYWORDS

• Genomics • Genetics • Newborn hearing screening
• Single nucleotide variant interpretation • Copy number variant interpretation
• Precision medicine • Hereditary hearing loss • Early intervention

KEY POINTS

- Using genomic sequencing (GS), in addition to physiologic screening of audition, is a more effective approach to identify newborns having, and at risk to develop, hearing loss.
- The addition of GS to newborn hearing screening (NBHS) will optimize treatment and outcomes for infants and children with congenital hearing loss.
- GS provides beneficial etiologic information to families and clinicians.
- GS has the potential to decrease significantly the number of children lost to follow-up from NBHS and identify newborns with genetic hearing loss who pass NBHS due to nonpenetrance at birth.

INTRODUCTION

Hearing loss is recognized as the most common birth defect diagnosed in children in developed countries.[1] Permanent hearing loss creates challenges during development for individuals who are deaf and hard of hearing (DHH) and affects quality of life.[2] Early diagnosis and intervention have been shown to reduce developmental deficits among children who are DHH and financial burden on families, the education system, and health care systems.[3] For this reason, universal newborn hearing screening (NBHS) has been widely implemented in the United States for moderate-to-severe

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hearing loss since the Joint Committee of Infant Hearing endorsed NBHS in 1994.[4] According to the Centers for Disease Control and Prevention, greater than 98% of US newborns are screened for hearing loss and approximately 1.6 per 1000 screened newborns have some level of hearing loss.[5] By school age, this number increases to 3 to 4 children per 1000.[6] Childhood hearing loss is an etiologically heterogeneous trait with many recognized genetic and environmental causes.[6] **Fig. 1** shows the landscape of the causes contributing to childhood hearing loss diagnoses. Although injuries, infections, and exposure to excessive noise[7] can all contribute to development of hearing loss in children, between 50%[8] and 60%[6] of congenital and childhood hearing loss has a genetic origin,[9] and more than 1000 genes have been estimated to underlie hearing.[10]

GENETIC CAUSES OF CHILDHOOD HEARING LOSS

Genetic hearing loss can be categorized into 2 phenotypes: nonsyndromic and syndromic. Nonsyndromic sensorineural hearing loss is most commonly caused by autosomal recessive inheritance and accounts for at least 80% of congenital genetic hearing loss.[11] Syndromic hearing loss involves various other organ systems[12]—not uncommonly eye and kidney with varied modes of inheritance. Mitochondrial deafness is inherited through matrilineal relatives and is well

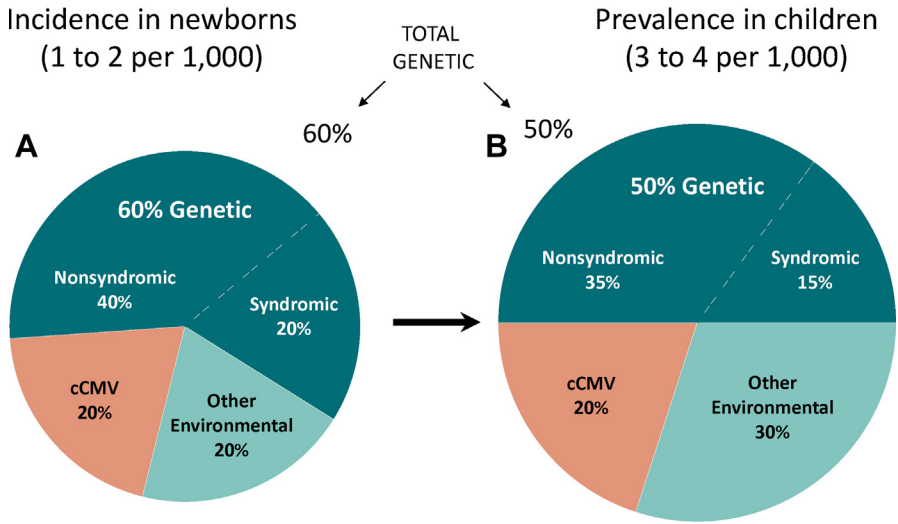

Fig. 1. Landscape of causes of DHH at birth and in childhood. (*A*) Incidence in newborns. Approximately 60% of congenital DHH is of genetic origin. Of genetic deafness, 30% is syndromic and 70% is nonsyndromic. Environmental factors contribute to 40% of congenital DHH diagnoses. As great as 20%[1,4] of environmental causes of deafness is attributed to congenital cytomegalovirus infections. Other environmental causes include prematurity, prenatal and postnatal infections, head trauma, subarachnoid hemorrhage, and pharmacologic ototoxicity.[6] (*B*) Prevalence in children. By childhood, the prevalance of DHH increases from 1 to 2 infants per 1000 to 3 to 4 children per 1000. Approximately 50% of DHH diagnosed in childhood is of genetic origin, and 20% is due to CMV infections. Other environmental factors including infections and structural anomalies contribute approximately 30%[8] of DHH. (*Adapted from* Morton CC, Nance WE. Newborn Hearing Screening — A Silent Revolution. *New England Journal of Medicine*. 2006;354(20):2151-2164. https://doi.org/10.1056/nejmra050700.)

recognized for genetic variants predisposing to ototoxicity from exposure to aminoglycosides.[13] Of note, some genes cause both syndromic and nonsyndromic deafness disorders and can display both autosomal dominant and autosomal recessive modes of inheritance.

SYNDROMIC HEARING LOSS

Hereditary forms of syndromic hearing loss are less prevalent than nonsyndromic forms.[9] Syndromic hearing loss has been associated with more than 400 syndromes, including Branchiootorenal syndrome, CHARGE syndrome, neurofibromatosis type 2, Stickler syndrome, Waardenburg syndrome, and Treacher Collins syndrome.[9,12] Pendred syndrome (PS), the most common autosomal recessive form of syndromic hearing loss, is caused by pathogenic variants in *SLC26A4* and affects between 7.5 and 10 individuals per 1000.[9] PS has been estimated to account for as much as 10% of hereditary deafness,[9] usually presenting as congenital severe-to-profound bilateral hearing loss. Pathogenic variants in *SLC26A4* are also the cause of a type of nonsyndromic autosomal recessive deafness (DFNB4).[9] Other common syndromes associated with autosomal recessive syndromic hearing loss are Jervell and Lange-Nielsen syndrome (prolonged QT syndrome), Usher syndrome, Perrault syndrome, biotinidase deficiency, and Refsum disease.[9,12]

NONSYNDROMIC HEARING LOSS

Nonsyndromic deafness is more prevalent than syndromic deafness, accounting for 70% of hereditary hearing loss.[9] Most of the genetic variants are missense and rare.[14] Consequently, 90% of DHH children are born into families without any history of hearing loss.[15] Approximately 15% to 20% of nonsyndromic hearing loss is inherited in an autosomal dominant pattern. X-linked and mitochondrial variations account for 1% to 1.5%, respectively.[11] To date, more than 50 autosomal dominant, more than 75 autosomal recessive, and 5 X-linked genes are known to cause nonsyndromic hearing loss[16] with more awaiting discovery. Current information and novel gene discoveries for hearing can be found on the Hereditary Hearing Loss homepage[16] (https://hereditaryhearingloss.org). Nomenclature for nonsyndromic genetic deafness is DFN (for deafness), followed by an A (dominant) or B (recessive), and a consecutive number based on order of discovery. X-linked deafness is designated as DFN followed by an X and an ascending number for its sequence in identification.

AUTOSOMAL RECESSIVE NONSYNDROMIC HEARING LOSS

Autosomal recessive nonsyndromic hearing loss usually presents prelingually and results in severe-to-profound hearing loss. Accounting for up to 50% of diagnoses,[17] the most prominent cause of severe-to-profound autosomal recessive hearing loss in most populations is caused by *GJB2* (DFNB1) variants.[18] Pathogenic variants in *SLC26A4* (DFNB4) are the second most common cause of autosomal recessive hearing loss and can also cause syndromic hearing loss in Pendred syndrome, manifesting with enlarged vestibular aqueducts.[9,12,17] Variants in *STRC* (DFNB16) are a major contributor of mild-to-moderate autosomal recessive nonsyndromic hearing loss.[18] Identification of hearing loss due to *STRC* variants is clinically relevant, as contiguous deletions can affect the *CATSPER2* gene nearby and cause Deafness Infertility syndrome in men. Because of repeated DNA segments at the locus, *STRC* is predisposed to copy number variants (CNVs),[9] which complicates variant interpretation.

AUTOSOMAL DOMINANT HEARING LOSS

Frequently, autosomal dominant hearing loss is postlingual, progressive, and milder than recessive forms.[9] Unlike autosomal recessive hearing loss where *GJB2 and SLC26A4* are the most prevalent causes, in autosomal dominant hearing loss there is no single gene that accounts for a significant proportion of etiologic diagnoses.[17] Pathogenic variants in *COCH* (DFNA9), *KCNQ4* (DFNA2), *DFNA5,* and *POU4F3* (DFNA16) are associated with high-frequency hearing loss.[9] Other autosomal dominant pathogenic variants cause mid-frequency deficits such as *TECTA* (DFNA8/12) and *COL11A2* (DFNA13) and low-frequency deficits with *WFS1* (DFNA6/14/38).[9,17]

SEX CHROMOSOME–LINKED HEARING LOSS

To date, 5 X-linked genes have been associated with hearing loss with the most common due to variants in *POU3F4* (DFNX2).[9,17] Pathogenic variants in *COL4A5* cause Alport syndrome, a syndromic form of X-linked hearing loss with kidney pathology that usually presents late in childhood.[9] Another X-linked syndromic form is Mohr-Tranebjærg syndrome caused by genetic variants in *TIMM8A.*[9] Only one locus to date has been assigned to the Y chromosome, DFNY1, discovered in 2004 in a large Chinese family and caused by an insertion of chromosome 1 DNA sequence into the Y chromosome.[19] DFNY1 has also been observed in one other Chinese family presenting with similar audiologic characteristics.[19]

MITOCHONDRIAL HEARING LOSS

Mitochondrial diseases most often involve multiple organ systems, and syndromic hearing loss is present in approximately 70% of affected individuals.[9] MELAS (mitochondrial encephalopathy, lactic acidosis, and strokelike episodes) syndrome, MERRF (myoclonic epilepsy with ragged-red fibers syndrome, Kearns-Sayre syndrome, and MIDD (maternally inherited diabetes and deafness) result in mitochondrial hearing loss.[9] One common nonsyndromic form of mitochondrial deafness is due to a variant in the mitochondrial 12S ribosomal ribonucleic acid gene. This variant, A1555G, has been estimated to be present in as many as 1 in 500 Caucasians.[17] Individuals with this variant are at risk to develop severe hearing loss from exposure to ototoxic aminoglycosides.[20] Maternal relatives harboring *MT-RNR1* variants are susceptible to ototoxicity given mitochondrial maternal inheritance and should avoid aminoglycoside antibiotics.[13] The PALOH (Pharmacogenetics to Avoid Loss of Hearing) study conducted recently in the United Kingdom implemented point-of-care genetic testing to intervene with potential ototoxicity in infants being treated in the neonatal intensive care unit. This study found that incorporating genetic testing in time sensitive, acute situations could avoid as many as 180 cases of aminoglycoside-induced ototoxicity in the United Kingdom each year.[21]

DISCUSSION

Precision medicine offers personalized treatments for individuals using their genetic information. With more than 15 countries currently providing novel genomic sequencing projects[22] since the completion of the Human Genome Project in 2003, an appreciation for the impact of molecular genomics on disease frequency has enabled implementation of genomics in diagnostic care. Personalized therapeutics and interventions can be developed using information from *genome sequencing* that encompasses assessing variants in all of an individual's 3×10^9 base pairs of DNA, *exome sequencing* that provides DNA sequence of 1% to 2% of the genome

encoding proteins, or *gene panels* of selected genes of interest relevant to the condition under study. Advancements made in the past 2 decades have facilitated rapid and low-cost diagnostics for patients with hearing loss.[7] Today, various genetic panels are used in the diagnosis of congenital and childhood hearing loss. These panels, spanning from 23 to 252 genes,[1] provide assessment of genes associated with inheritance patterns of autosomal dominant, autosomal recessive, X-linked and mitochondrial deafness, and syndromic and nonsyndromic forms.

HEARING IN GENERATION GENOME: COMPREHENSIVE NEWBORN HEARING SCREENING

Before implementation of next-generation sequencing (NGS), most diagnostic laboratories analyzed a limited number of hearing loss genes, beginning with *GJB2* given its high prevalence among DHH individuals and yielding a diagnosis in about 10% to 20% of cases.[23] In recent years, advances in gene discovery and analysis increased the diagnostic yield range from 39%[18] to 50%.[24] A recent review reports that using congenital cytomegalovirus (cCMV) analysis and targeted NGS panels for hearing loss has increased the diagnostic yield for congenital bilateral loss to 77.9%,[25] depending on the DHH population being studied.

Determining the cause of a child's hearing loss can provide prognostic information as well as predict the chance of familial reoccurrence.[9] Studies have described the benefits of using genetic testing as a prognostic tool, such as the outcome performance shown by cochlear implant recipients with *GJB2* and *SLC26A4* related deafness.[26,27] In 2002, Green and colleagues[26] found that effective rehabilitation is possible for individuals with profound hearing loss due to *GJB2* deafness through cochlear implantation. More recent data provide further insight into benefits of cochlear implantation in a variety of deafness-causing genes including *GJB2*, *SLC26A4*, *OTOF*, *CACNA1D*, *CABP2*, *SLC17A8*, *DIAPH3*, *OPA1*, and *ROR1*.[28] Using genetic testing to predict cochlear implant outcomes will lead to better clinical management for individuals with genetic deafness.[29]

The prevalence of hearing loss continues to increase in childhood up to school age.[6] An explanation for this is, in part at least, because of limitations of current NBHS practices. Although NBHS is often successful in identifying infants with congenital hearing loss, it does not adequately detect mild or delayed onset loss or children with auditory neuropathy and has a high false-positive rate[4] and high loss-to-follow-up rate in the United States (~26% for recent data[5,30]). By implementing genomic sequencing (GS) into NBHS, Wang and colleagues found a decrease in the loss-to- follow-up rate among families with a genetic cause.[13] Shearer and colleagues proposed comprehensive NBHS with the addition of genetic testing and cCMV testing alongside standard physiologic NBHS. Including genomic sequencing in NBHS would identify newborns with genetic hearing loss missed on physiologic NBHS, allowing for a comprehensive analysis of causes including common genes known to cause hearing loss and viral infections such as cCMV.[4] Comprehensive NBHS would lead to improved diagnostic yields, earlier intervention, and thus, better outcomes for DHH babies and children.

SEQaBOO (SEQuencing A BABY FOR AN OPTIMAL OUTCOME): GENOME SEQUENCING FOR NEWBORN SCREEN

A study initiated in Boston, Massachusetts, SEQaBOO (SEQuencing a Baby for an Optimal Outcome), aims to identify genetic variants for deafness and be at the forefront of precision medicine treatments for newborns and children who are DHH.

Participants are recruited from 3 Harvard Medical School affiliated hospitals: Brigham and Women's Hospital (BWH), Boston Children's Hospital (BCH), and the Massachusetts Eye and Ear (MEE). Parents and newborns referred following a positive NBHS at BWH or at confirmatory diagnostic audiometry at BCH or MEE can elect to receive comprehensive genomic sequencing and interpretation of curated genes for hearing loss. Parents can additionally obtain ACMG v3.0 secondary findings for themselves. ACMG v3.0 secondary genes are a group of 73 genes proposed by the American College of Medical Genetics and Genomics[31] for which an individual might pursue some intervention, were it to be discovered that a pathogenic variant was present (eg, colonoscopy at an earlier age than otherwise recommended). Alternatively, parents can enroll only for annual surveys administered to all participating families to ascertain evolving attitudes on genomic testing in addition to family medical history and health information.

SEQaBOO MANCHESTER: PANEL TESTING AVAILABLE THROUGH THE NATIONAL HEALTH SERVICE

Running in parallel, SEQaBOO Manchester, England plans to use the National Health Service (NHS) hearing loss panel that reports on 115 genes associated with hearing loss. This panel was introduced in April 2021 to parents of newborns identified to have hearing loss by the national newborn hearing screening program. Approval to begin recruitment at 4 Manchester University NHS Trust hospitals has been granted. Parents who enroll in SEQaBOO Manchester will take part in annual surveys aimed at assessing evolving attitudes and opinions on genomic testing in addition to family medical history and health information.

IMPLICATIONS OF CURRENT PHYSIOLOGIC NEWBORN HEARING SCREENING

Since implementation of NBHS in the 1990s, many children who are DHH were discovered at a much earlier age than would have occurred without NBHS, allowing for timely interventions. However, NBHS is not designed to identify all infants who are at risk for hearing loss. For example, infants with normal or mild hearing loss at birth might develop delayed onset or progressive hearing loss not identified by current physiologic NBHS approaches.

Given the extreme heterogeneity of hearing loss, current NBHS is ineffective in as many as 25% to 50%[13,32–35] of positive genetic cases because they pass contemporary NBHS. Screening a limited number of the most common variants in *GJB2* and *SLC26A4* has shown to benefit detection of DHH individuals. Genetic screening would be a valuable adjunctive screen to current physiologic NBHS. In a study of 180,469 neonates in Beijing, China using concurrent hearing and genetic screening, Dai and colleagues[32] found 9 neonates with etiologic variants in *GJB2* and 1 with a homozygous pathogenic variant in *SLC26A4* who passed both initial and secondary hearing screens (**Table 1**). Further follow-up indicated 9 of the children suffered from varying degrees of hearing loss (mild to severe), suggesting that approximately 27% of infants with pathogenic combinations of *GJB2* variants and about 14% of infants with pathogenic combinations of *SLC26A4* variants will pass NBHS and most of them will develop hearing loss by age 5 years.[32] **Fig. 2** shows the approximate 27% of DHH individuals harboring biallelic variants in *GJB2* who are not likely to be identified using current physiologic NBHS.

Another study in China analyzed 1,172,504 newborns and found that incorporating genetic testing into NBHS leads to an increase in detection rate of 13%[13] by 3 months of age. Notably, of the positive genetic cases, 42% would not benefit from physiologic

Table 1
Pathogenic variants for DHH nonpenetrant on functional newborn hearing screening

Newborn	Gene	Variants	Phenotype of DHH
1.	*GJB2*	c.299delAT/c.299delAT	Mild/severe bilateral
2.	*GJB2*	c.235delC/c.235delC	Lost to follow-up
3.	*GJB2*	c.176del16/c.235delC	Moderate bilateral
4.	*GJB2*	c.235delC/c.299delAT	Severe bilateral
5.	*GJB2*	c.235delC/c.299delAT	Moderate bilateral
6.	*GJB2*	c.235delC/c.235delC	Moderate bilateral
7.	*GJB2*	c.235delC/c.299delAT	Mild bilateral
8.	*GJB2*	c.235delC/c.235delC	Moderate bilateral
9.	*GJB2*	c.235delC/c.235delC	Moderate bilateral
10.	*SLC26A4*	c.919A>G/c.919A>G	Mild unilateral

Data obtained from Dai and co-authors in concurrent hearing and genetic screening study[32]; 10 neonates with pathogenic variants in *GJB2* and *SLC26A4* passed newborn hearing screening and nine were confirmed to be DHH with one lost to follow up.

NBHS alone. Wang and colleagues highlight the improvement in diagnostic yield allowing for earlier interventions and better outcomes by using concurrent genetic testing along with physiologic NBHS.[13] These data are consistent with other studies; for example, Guo and colleagues[35] found that 31% of individuals with positive genetic results passed NBHS. An earlier study by Minami and colleagues[34] suggests that the number of individuals who are DHH and harbor biallelic *GJB2* variants nonpenetrant on NBHS is much larger than that reported in previous studies; their study found 57% of patients with biallelic *GJB2* variants passed NBHS to be diagnosed later as DHH. Wu and colleagues also noted a large percentage of newborns passing NBHS, with 56.1%[33] of newborns having conclusive genetic diagnoses for their

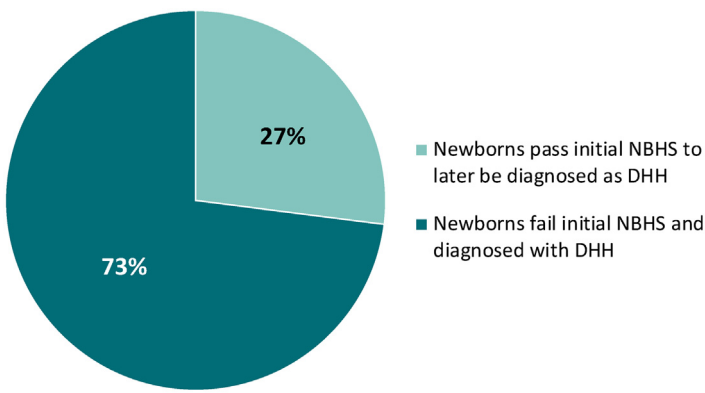

Fig. 2. Percentage of newborns harboring etiologic pathogenic *GJB2* variants. This chart highlights the percentage of newborns harboring etiologic pathogenic *GJB2* variants that will be missed by standard NBHS alone. These data obtained from Dai and colleagues[32] demonstrate the importance of concurrent hearing and genetic screening in newborns to yield the highest diagnostic rate for DHH individuals. Nine of thirty-three newborns harboring etiologic *GJB2* variants passed the initial hearing screen and later were diagnosed as DHH.

hearing loss. These data indicate the need to implement universal genetic testing for such variants that are likely to be missed on standard NBHS.

A recent initiative in Victoria, Australia using the platform of the Victorian Childhood Hearing Impairment Longitudinal Databank, which provides natural history data on development and resource use for DHH, translation of genetic findings can be accomplished to improve care for DHH children. Through this platform, the Melbourne Genomics Health Alliance offered targeted exome sequencing.[36] A population cohort of bilateral moderate, severe, or profound hearing loss was recruited to join the Baby Beyond Hearing Project.[37] Of 106 infants who underwent genetic testing, 56% received a diagnosis, with 21% harboring pathogenic variants in *GJB2* or *GJB6*.[37] The most common causative genes in addition to *GJB2* were *SLC26A4* (5%), *MYO15A* (5%), and *STRC* (4%).[38] Downie and colleagues found that 81% of diagnoses were inherited in an autosomal recessive pattern. As part of a larger aim of the study, analyzing parents' opinions and the psychosocial impact of offering additional findings for their newborns, the investigators noted that personal values and circumstances affected the level of information parents seek to obtain from genomic sequencing.[37,39] A cost-effectiveness analysis was completed on this cohort of DHH individuals that provides evidence that genetic testing is valuable at preventing further investigation and creating more efficient and timely clinical management.[40]

As part of Ontario's Infant Hearing Program, hearing loss risk factor screening was initiated into universal NBHS in July 2019. Dried blood spots are screened for cCMV and variants in *GJB2*, *GJB6*, and *SLC26A4*[41,42] to identify DHH individuals early to limit scenarios where DHH children go undetected by current physiologic NBHS methods. More children are identified and provided with services earlier due to recognition of genetic and environmental causes leading to improved understanding of cause and improved surveillance mechanisms. For example, using dried blood spots enabled risk factor screening to proceed during the COVID-19 pandemic when standard NBHS was suspended ensuring that fewer DHH newborns were missed. Knowing the genotype allows for surveillance for screen positives with genetic variants to be monitored for developing hearing loss later during childhood[43] (information obtained via personal communication with Marie Pigeon).

COPY NUMBER VARIANT ANALYSIS IS ESSENTIAL IN DETERMINING ETIOLOGIC DIAGNOSES FOR GENETIC HEARING LOSS

Copy number variation is a large source of variation in the human genome, resulting in a 1.2% difference in comparison to the reference genome.[44] Previous studies have reported the importance of incorporating CNV analysis into genomic interpretation for efficient diagnosis of cause of childhood and congenital hearing loss.[45] CNVs are causal or contributory for an etiologic diagnosis in greater than 15% of DHH individuals.[18,44,45] More than 20 genes for hearing have been identified to have copy number deletions or duplications,[45] indicating the powerful influence of CNV detection in genetic hearing loss diagnoses. **Table 2** highlights the most prevalent hearing loss–associated genes with known CNVs.

COMPREHENSIVE NEWBORN HEARING SCREENING INCLUDES CONGENITAL CYTOMEGALOVIRUS ANALYSIS

In developed countries, cytomegalovirus is the most common intrauterine virus[46] with a highly variable presentation, and many newborns are asymptomatic. cCMV is the most common nongenetic cause of hearing loss,[23] and approximately 10% of otherwise asymptomatic cCMV cases develop congenital hearing loss.[46] Estimates

Table 2
Most prevalent DHH genes identified with copy number variants[45]

Gene	Phenotype
STRC	ARNSHL, deafness infertility syndrome (DIS)
OTOA	ARNSHL
GJB2	ARNSHL, ADNSHL
GJB6	ARNSHL, ADNSHL
SLC26A4	ARNSHL, Pendred syndrome (PS)
PCDH15	ARNSHL, Usher syndrome type 1F (USH1F)
POU3F4	XLNSHL
TMC1	ARNSHL

Data from Shearer AE, Kolbe DL, Azaiez H, et al. Copy number variants are a common cause of non-syndromic hearing loss. Genome Medicine. 2014;6(5):0-9. doi:10.1186/gm554.

indicate that 15% to 20% of childhood hearing loss can be attributed to cCMV infections.[1,4]Testing for cCMV must be performed before 3 weeks of age due to the abundance of CMV the environment.

SUMMARY

Recent compelling data in support of genetic diagnoses in newborns with congenital hearing loss or in DHH babies nonpenetrant at birth are well recognized for timely optimal developmental outcomes.[25,32] A comprehensive NBHS program including testing for pathogenetic variants and cCMV infection in addition to physiologic screening is technically feasible to implement. Initiatives such as those implemented in Australia, China, Taiwan, England, and Canada have demonstrated comprehensive NBHS is achievable and leads to improved outcomes for DHH individuals and their families.

FUTURE DIRECTIONS

A study conducted by Raymond and colleagues at Egleston Children's Hospital of Children's Healthcare of Atlanta analyzing genetic testing for congenital SNHL found that although genetics is the main cause, genetic testing or consultation was not uniformly ordered in the cohort.[47] Through early detection and intervention, delayed speech and language development are improved[48] but comprehensive NBHS must be incorporated into routine medical care.

Increasing access and affordability to GS has led to identification of novel human variants and better clinical management of individuals with hearing loss. Further research is needed to improve the knowledge of underlying pathology of these genetic variants. Through utilization of animal models or patient-derived cells, appropriate therapeutic and restorative approaches[49] are on the horizon, making it increasingly important to understand and identify the genetic causes of hearing loss. Currently more than 43 companies are focused on developing novel therapeutics for inner ear and central hearing disorders.[50] Comprehensive NBHS including physiologic testing, genetic testing, and cCMV testing can prevent unnecessary treatments such as antiviral drugs for cCMV infections[46] or aminoglycosides for individuals with a genetic predisposition for ototoxicity.[20,21] Newborn screening has long been driven by technology and can now embrace integration of genetic testing to provide life-altering treatments and management for individuals who are DHH.

CLINICS CARE POINTS

- A signficant number of children who pass NBHS have progressive losses or develop delayed onset of sensorineural hearing loss. Newborn screening needs to include genetic testing to identify newborns with genetic variants with risk to develop nonpenetrant hearing loss at birth.
- Testing for a limited number of genetic variants as part of newborn screening for all children can identify 50% of children expected to have delayed onset of hearing loss.
- Knowledge of mitochondrial genetic variants such as m.A1555G can be used in preventing hearing loss.
- Identification of cCMV can lead to early treatment that, in some cases, halts progression of hearing loss.

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DISCLOSURE

The authors have no disclosures to report.

REFERENCES

1. Thorpe RK, Smith RJH. Future directions for screening and treatment in congenital hearing loss. Precision Clin Med 2020;3(3):175–86.
2. Lindburg M, Ead B, Jeffe DB, et al. Hearing loss–related issues affecting quality of life in preschool children. Otolaryngol Head Neck Surg 2021;164(6):1322–9.
3. Krug E, Cieza A, Chadha S, et al. Childhood hearing loss strategies for prevention and care 2016. Available at: http://www.who.int/about/licensing/copyright_form/index.html. Accessed June 29, 2021.
4. Shearer AE, Shen J, Amr S, et al. A proposal for comprehensive newborn hearing screening to improve identification of deaf and hard-of-hearing children. Genet Med 2019;21(11):2614–30.
5. US Centers for Disease Control and Prevention. Summary of diagnostics among infants not passing hearing screening 2018. Available at: https://www.cdc.gov/ncbddd/hearingloss/2018-data/06-diagnostics.html.
6. Morton CC, Nance WE. Newborn hearing screening — A silent revolution. N Engl J Med 2006;354(20):2151–64.
7. Rudman J, Liu XZ. Genetics of hearing loss. Hearing J 2019;72(4):6–7.
8. Lieu JEC, Kenna M, Anne S, et al. Hearing loss in children: a review. JAMA 2020;324(21):2195–205.
9. Shearer AE, Shibata SB, Smith RJH. Genetic sensorineural hearing loss. In: Cummings otolaryngology - head and neck surgery vol. 150, 7th edition. Elsevier; 2021. p. 2279–92.
10. Inghamid NJ, Pearson SA, Vancollieid VE, et al. Mouse screen reveals multiple new genes underlying mouse and human hearing loss. PLoS Biol 2019;17(4):e3000194.

11. Shearer AE, Hildebrand MS, Smith RJ. Hereditary hearing loss and deafness overview. GeneReviews 1993;1–27.
12. Koffler T, Ushakov K, Avraham KB. Genetics of hearing loss: syndromic. Otolaryngol Clin North Am 2015;48(6):1041–61.
13. Wang Q, Xiang J, Sun J, et al. Nationwide population genetic screening improves outcomes of newborn screening for hearing loss in China. Genet Med 2019; 21(10):2231–8.
14. Azaiez H, Booth KT, Ephraim SS, et al. Genomic landscape and mutational signatures of deafness-associated genes. Am J Hum Genet 2018;103(4):484–97.
15. Hall WC, Smith SR, Sutter EJ, et al. Considering parental hearing status as a social determinant of deaf population health: insights from experiences of the "dinner table syndrome." PLoS One 2018;13(9):e0202169.
16. van Camp G, Smith R. Hereditary hearing loss - hereditary hearing loss homepage 2015. Available at: https://hereditaryhearingloss.org.
17. Chang KW. Genetics of hearing loss-nonsyndromic. Otolaryngol Clin North Am 2015;48(6):1063–72.
18. Sloan-Heggen CM, Bierer AO, Shearer AE, et al. Comprehensive genetic testing in the clinical evaluation of 1119 patients with hearing loss. Hum Genet 2016; 135(4):441–50.
19. Wang Q, Xue Y, Zhang Y, et al. Genetic basis of Y-linked hearing impairment. Am J Hum Genet 2013;92(2):301–6.
20. McDermott JH, Molina-Ramírez LP, Bruce IA, et al. Diagnosing and preventing hearing loss in the genomic age. Trends Hearing 2019;23:1–8.
21. McDermott JH, Mahood R, Stoddard D, et al. Pharmacogenetics to Avoid Loss of Hearing (PALOH) trial: a protocol for a prospective observational implementation trial. BMJ Open 2021;11(6):e044457.
22. Stark Z, Dolman L, Manolio TA, et al. Integrating genomics into healthcare: a global responsibility. Am J Hum Genet 2019;104(1):13–20.
23. Korver AMH, Smith RJH, van Camp G, et al. Congenital hearing loss. Nat Rev Dis Primers 2017;3:16094.
24. Boudewyns A, van den Ende J, Sommen M, et al. Role of targeted next generation sequencing in the etiological work-up of congenitally deaf children. Otol Neurotol 2018;39(6):732–8.
25. Boudewyns A, van den Ende J, Declau F, et al. Etiological work-up in referrals from neonatal hearing screening: 20 years of experience. Otology & neurotology 2020;41(9):1240–8.
26. Green GE, Scott DA, McDonald JM, et al. Performance of cochlear implant recipients with GJB2-related deafness. Am J Med Genet 2002;109(3):167–70.
27. Yan YJ, Li Y, Yang T, et al. The effect of GJB2 and SLC26A4 gene mutations on rehabilitative outcomes in pediatric cochlear implant patients. Eur Arch Otorhinolaryngol 2013;270(11):2865–70.
28. Shearer AE, Hansen MR. Auditory synaptopathy, auditory neuropathy, and cochlear implantation. Laryngoscope Invest Otolaryngol 2019;4(4):429–40.
29. Seligman KL, Shearer AE, Frees K, et al. Genetic causes of hearing loss in a large cohort of cochlear implant recipients. Otolaryngol Head Neck Surg 2021. https://doi.org/10.1177/01945998211021308. 019459982110213.
30. 2018 Summary of National CDC EHDI Data | Annual Data EHDI Program | CDC. Available at: https://www.cdc.gov/ncbddd/hearingloss/2018-data/01-data-summary.html. Accessed July 5, 2021.
31. Miller DT, Lee K, Chung WK, et al. ACMG SF v3.0 list for reporting of secondary findings in clinical exome and genome sequencing: a policy statement of the

American College of Medical Genetics and Genomics (ACMG). Genet Med 2021; 23(8):1381–90.
32. Dai P, Huang LH, Wang GJ, et al. Concurrent hearing and genetic screening of 180,469 neonates with follow-up in Beijing, China. Am J Hum Genet 2019; 105(4):803–12.
33. Wu CC, Tsai CH, Hung CC, et al. Newborn genetic screening for hearing impairment: a population-based longitudinal study. Genet Med 2017;19(1):6–12.
34. Minami SB, Mutai H, Nakano A, et al. GJB2-associated hearing loss undetected by hearing screening of newborns. Gene 2013;532(1):41–5.
35. Guo L, Xiang J, Sun L, et al. Concurrent hearing and genetic screening in a general newborn population. Hum Genet 2020;139(4):521–30.
36. Downie L, Halliday JL, Burt RA, et al. A protocol for whole-exome sequencing in newborns with congenital deafness: a prospective population-based cohort. BMJ Paediatr Open 2017;1(1):e000119.
37. Downie L, Halliday J, Lewis S, et al. Exome sequencing in newborns with congenital deafness as a model for genomic newborn screening: the Baby Beyond Hearing project. Genet Med 2020;22(5):937–44.
38. Downie L, Halliday J, Burt R, et al. Exome sequencing in infants with congenital hearing impairment: a population-based cohort study. Eur J Hum Genet 2020; 28(5):587–96.
39. Tutty E, Amor DJ, Halliday J, Lewis S, Martyn M, Goranitis I. Exome sequencing for isolated congenital hearing loss: a cost-effectiveness analysis. Laryngoscope 2021;131(7):E2371–7.
40. Downie L, Amor DJ, Halliday J, et al. Exome sequencing for isolated congenital hearing loss: a cost-effectiveness analysis. Laryngoscope 2020;131(7):E2371–7.
41. Khurana P, Cushing SL, Chakraborty PK, et al. Early hearing detection and intervention in Canada. Paediatr Child Health 2021;26(3):141–4.
42. Hearing loss risk factor screening. Newborn Screening Ontario. Available at: https://www.newbornscreening.on.ca/en/page/overview. Accessed June 24, 2021.
43. Pigeon BM, Gallagher LH, Dunn J. A World ' s first addition to Ontario ' s Infant Hearing Program. Canadian Audiologist; 2021;8(3):8–11.
44. Pfundt R, del Rosario M, Vissers LELM, et al. Detection of clinically relevant copy-number variants by exome sequencing in a large cohort of genetic disorders. Genet Med 2017;19(6):667–75.
45. Shearer AE, Kolbe DL, Azaiez H, et al. Copy number variants are a common cause of non-syndromic hearing loss. Genome Med 2014;6(5):37.
46. Peterson J, Nishimura C, Smith RJH. Genetic testing for congenital bilateral hearing loss in the context of targeted cytomegalovirus screening. Laryngoscope 2020;130(11):2714–8.
47. Raymond M, Walker E, Dave I, et al. Genetic testing for congenital non-syndromic sensorineural hearing loss. Int J Pediatr Otorhinolaryngol 2019;124:68–75.
48. Yoshinaga-Itano C, Sedey AL, Wiggin M, et al. Language outcomes improved through early hearing detection and earlier cochlear implantation. Otol Neurotol 2018;39(10):1256–63.
49. Nicolson T. Navigating hereditary hearing loss: pathology of the inner ear. Front Cell Neurosci 2021;15:1–7.
50. Schilder AGM, Su MP, Blackshaw H, et al. Hearing protection, restoration, and regeneration: an overview of emerging therapeutics for inner ear and central hearing disorders. Otol Neurotol 2019;40(5):559–70.