HHS Public Access

Author manuscript

Hum Genet. Author manuscript; available in PMC 2022 October 01.

Published in final edited form as:

Hum Genet. 2022 April ; 141(3-4): 311–314. doi:10.1007/s00439-021-02360-6.

Genetic hearing loss: the audiologist's perspective

Carmen C. Brewer[1], **Kelly A. King**[1]

[1]National Institute on Deafness and Other Communication Disorders, National Institutes of Health, 10 Center Drive, 5C422, Bethesda, MD 20892, USA

Abstract

As knowledge regarding the genetic underpinnings of hearing loss has rapidly evolved, the role of the clinician in managing the patient has expanded beyond that of defining the characteristics of the auditory phenotype. The importance and impact of a genetic diagnosis has yet to be fully realized in routine clinical care. However, audiologists are uniquely situated to be front-line healthcare providers for persons of all ages with hereditary hearing loss. Here, we discuss why the combination of genotype and phenotype are necessary for the delivery of personalized and effective clinical care for individuals with genetic hearing loss.

Introduction

Understanding of hereditary hearing loss has evolved dramatically over the last century, with an accelerated pace of new discoveries in recent decades. From the identification of the first causative gene for hearing loss (*Cx*26; Kelsell et al. 1997) to our current knowledge of over 120 non-syndromic hearing loss genes, during this time, the practice of audiology has evolved to include knowledge of genetics and genetic causes of hearing loss.

Human hereditary hearing loss is complex and heterogeneous; it can affect any age group, can be influenced by environmental and genetic modifiers, and knowledge of a genetic etiology can drive management and patient outcomes. At least 50% of congenital or early-onset hearing loss has a genetic origin, of which approximately 30% of cases are associated with a recognized syndrome and the remaining 70% are considered non-syndromic. The majority of early-onset, non-syndromic hearing loss, 80%, is autosomal recessive (Van Camp et al. 1997). This means that most early-onset genetic forms of hearing loss occur in isolation and in the absence of an overt family history. In these cases, the audiologist is a likely entry point to medical care, and providers must have an awareness of the clues to look for and the knowledge for appropriate referral beyond the sound booth.

Pathogenic mutations (variants) of a single gene can cause varying degrees of hearing loss, can be associated with a recessive or dominant mode of inheritance, and can cause syndromic or non-syndromic deafness. A genetic diagnosis alone is insufficient to predict individual outcomes, and clinical phenotypic data in the absence of a known genetic cause can limit prognostic counseling and re/habilitation efforts. The following vignettes

Carmen C. Brewer, brewerc@nidcd.nih.gov.

Conflict of interest The authors declare that they have no conflict of interests.

are illustrative for why the combination of genotype and phenotype are often critical to personalized and effective clinical care, and the unique contribution the audiologist makes toward diagnosing and managing genetic forms of hearing loss.

Two sides of the coin

Universal newborn hearing screening has had a profound impact on the age of identification of hearing loss in infants, leading to earlier intervention, habilitation, and improved outcomes (e.g., Tomblin et al. 2015). Decisions for management of hearing loss in an infant or young child are typically made by the parents or caregivers in collaboration with the medical care team. These include the option to fit hearing aids or proceed with cochlear implantation, choice of the primary mode of communication (e.g., manual sign language, listening and spoken language), and educational setting (e.g., mainstream classrooms, school for the deaf). Additionally, because hearing loss can be part of a syndrome, consideration needs to be given to other comorbidities. In some cases, the syndromic features are present at birth, others manifest later, and some are nonobvious but life-threatening (e.g., Long QT).

Consider the following scenario: A child, born at 40-week gestational age following a healthy and uncomplicated pregnancy and delivery, does not pass their newborn hearing screening. Subsequent diagnostic testing at 1 month via auditory brainstem response thresholds reveals a severe sloping to profound sensorineural hearing loss (SNHL) bilaterally. Family history for hearing loss is negative and there are no features suggestive of a syndrome. In this case, and assuming anatomical anomalies and environmental causes such as cytomegalovirus can be ruled out, the pedigree and patient presentation suggest the hearing loss may be caused by autosomal recessive, pathogenic variants of a gene. Should genetic testing be conducted? How could the results drive management and outcomes?

Mutations in *GJB2* (DFNB1) encoding connexin 26 account for a significant percentage of prelingual non-syndromic hearing loss throughout the world, ranging from roughly 18% (Chan and Chang 2014) to as much as 50% in some populations (Kenneson et al. 2002). While the majority of *GJB2* hearing loss is severe-to-profound, the degree of hearing loss varies depending on the type of genetic mutation. Biallelic truncating mutations usually result in more severe hearing loss than bilallelic nontruncating mutations (Snoeckx et al. 2005). This highlights the utility of complete sequencing of the single protein coding exon of *GJB2* in cases of congenital or early-onset SNHL (Chan and Chang 2014). In this case, the identification of *GJB2* as the pathogenic cause of the hearing loss provides a confirmatory diagnosis of DFNB1, predicts favorable outcomes from cochlear implantation (Eshraghi et al. 2020) should this option be pursued, and allows the family to be counseled about the probability that they could have another child with hearing loss.

Consider, however, an alternative hereditary cause to this hearing loss in a child for whom genetic testing was not offered or pursued. Take the example of a 20-year-old who was born with the same severe-to-profound SNHL. The family, with no known etiology for the hearing loss, elected to pursue American Sign Language as the primary mode of communication. Developmental history beyond the hearing loss was largely unremarkable and, although the child was a late walker, they learned to ride a bike and became engaged

regularly in athletic activities. Beginning in the teenage years, however, they began to experience difficulty with night vision. Although they underwent numerous optometric examinations and were told their vision was fine, an astute clinician eventually ordered additional testing given the combination of vision complaints and SNHL. Vestibular assessment revealed bilateral vestibular areflexia, and ophthalmologic evaluation revealed bilateral retinal degeneration. Subsequent genetic testing identified homozygous mutations in the *MY07A* gene with an ultimate diagnosis of Usher syndrome type 1.

While *GJB2* is the most common cause of non-syndromic hereditary hearing loss, there are numerous other genetic causes of congenital hearing loss that can present in apparent isolation at birth. Usher syndrome type 1 is defined by the constellation of congenital severe-to-profound SNHL, progressive vision loss from retinitis pigmentosa, and vestibular areflexia (Friedman et al. 2011). The hearing loss associated with *GJB2* and Usher syndrome type 1 is clinically indistinguishable, and congenital vestibular hypofunction is rarely identified or tested for in young children who are unlikely to be overtly symptomatic. Finally, the onset of progressive loss of vision is typically pre-pubertal and, therefore, separated in onset by years from the hearing loss. Consider the impact that knowledge of progressive blindness in a deaf child might have for parents as they make decisions about, for example, communication mode. In this case, the patient's family may have opted for cochlear implantation when the hearing loss was identified had the Usher syndrome diagnosis been known at that time. Similarly, the patient, now as a young adult, questions whether they may have made different choices about career options and other life decisions based on this diagnosis. The arguments for genetic testing in this case are apparent.

Finally, consider the scenario in which this individual did receive a diagnosis of Usher syndrome type 1 early in life. What role does clinical surveillance offer in this scenario? Although a molecular genetic diagnosis predicts clinical outcomes, only clinical data can precisely determine function for a given individual. This is evident in numerous examples of hereditary hearing loss. For example, individuals with atypical phenotypes including preserved hearing and vestibular function with genetically confirmed Usher type 1 have been reported (Wafa et al. 2021). As we move toward routine precision genetic testing at the molecular level, the knowledge gained from this approach cannot supplant nor precisely predict clinical and functional outcomes of the individual.

Missing the forest for the trees

Genetic testing should not be limited to persons with congenital or prelingual hearing loss. As we learn more about genetic forms of hearing loss with complex etiologies, such as presbycusis, and the potential ramifications for intervention, genetic testing for late-onset hearing loss will likely become more common. And while suspicion for heritable syndromic association may decline as a patient ages, it is imperative that clinicians, including audiologists, remain vigilant to the idea of syndromic forms of hearing loss in adult populations who may have telling pediatric histories and for whom care may be dispersed amongst specialists.

Consider the following scenario: a 19-year-old presents with a bilateral, mild-to-profound SNHL. Historical audiograms show the hearing loss has been progressive, initially identified when they were 6 years old after not passing a school hearing screening. Coincident with progressive hearing loss were advancing neurological signs and symptoms, including increasing difficulty with gross and fine motor skills, reduced deep tendon reflexes, and declining intelligence, which in combination, led to a clinical diagnosis of Charcot Marie Tooth (CMT) disease. However, targeted genetic testing was negative for variants of the different genes associated with CMT.

Additional components of this patient's presentation were important in their eventual diagnosis, but not considered when genetic testing for CMT was recommended. They had experienced a severe, blistering sunburn at the age of three months, following indirect exposure to sunlight. Their first skin cancer, a basal cell carcinoma, was diagnosed at age 14, and a subsequent melanoma was identified later in the same year. In an attempt to identify a unifying diagnosis, the patient was eventually referred to a geneticist as a young adult. Whole exome sequencing revealed compound heterozygous missense mutations in a gene for xeroderma pigmentosum type D (XP-D), *ERCC2.* Xeroderma pigmentosum (XP) is a rare, autosomal recessive disorder of DNA repair characterized by photosensitivity and more than a 10,000-fold increased risk for UV-related skin cancers. There are seven subtypes of XP, two of which (XP-A and XP-D) are associated with neurological decline and progressive SNHL (Totonchy et al. 2013).

What was gained from the genetic diagnosis? Most important for this patient was the impact on direct clinical care and counseling regarding the imperative for sun protection. Unfortunately, these recommendations were delayed and, by the time they received a diagnosis, they had had over 40 skin cancers. Second, the genetic diagnosis facilitated accurate counseling regarding the patient's prognosis that included further neurologic decline and additional progression of the hearing loss (Totonchy et al. 2013). The patient presented with a typical clinical course for XP-D. However, they were managed by separate specialties, and the unifying diagnosis was delayed. As specialists in the management of hearing loss, audiologists need to consider the whole patient and remain vigilant regarding other signs and symptoms. Earlier genetic identification of XP-D and adherence to strict avoidance of UV exposures may have avoided many of the skin cancers this patient experienced.

Back to the future/evolving implications

Hearing is important for our ability to communicate and connect as a species across the lifespan. At the same time that we see a rising global burden of disease—the World Health Organization predicts that nearly 2.5 billion people, one in every four, will be living with some degree of hearing loss by 2050 (World Report on Hearing, 2021)—we are at an exciting moment in the evolution of our understanding of how our genetic makeup influences our capacity for hearing and how we might leverage that knowledge to improve lives. Genetic testing has become an important tool in the evaluation of children with hearing loss and we anticipate expanding use in adults with hearing loss in coming years. Advantages across the lifespan include early diagnosis, understanding of and prognostic

counseling based on the underlying pathophysiology, and reduced time to (Omichi et al. 2019) and guidance for the most appropriate intervention.

We are at the cusp of implementing a precision medicine approach for understanding and treating hereditary hearing loss. An emerging example includes data suggesting patients with mutations in certain genes expressed in the cochlea will have better CI outcomes than patients with mutations in genes expressed in spiral ganglion neurons (Eshraghi et al. 2020). This may explain some of the tremendous variability seen in cochlear implant outcomes. Another is the discovery that a mutation in *NLRP3* is associated with non-syndromic SNHL (DFNA34) that is responsive to treatment with an IL-1β blocker (anakinra). Unlike nonspecific treatments for SNHL (e.g., corticosteroids), this is currently one of the few precision interventions for genetic hearing loss, and the identification of this genetic pathway may pave the way for treating a variety of hearing loss pathologies (Nakanishi et al. 2017).

As we move toward the actualization of gene therapy for SNHL in humans, strategies will include correction of genetic mutations, preservation and prevention of loss of cells within the cochlea, and possibly hair cell regeneration (Chien et al. 2015). The combination of early phenotypic identification of hearing loss and access to a molecular genetic diagnosis will be essential to implementing these therapies within what is likely to be a critical window of time. Finally, the field of audiology has an important role to play in addressing the large knowledge gaps that exist in our understanding of the genetics of hearing loss in underrepresented minority populations. We know very little about hereditary hearing loss in many racial and ethnic communities, which almost certainly hold unique molecular and clinical characteristics. The success of future research, clinical trials, and the delivery of care to alleviate the burden of genetic hearing loss will fall short if these current inequities persist.

Acknowledgements

We extend our thanks to our colleagues Wade Chien, Julie Christensen, and Thomas B. Freidman for their review of this manuscript as well as their support and guidance.

Funding

Preparation of this manuscript was funded by the Division of Intramural Research at the National Institute on Deafness and Other Communication Disorders to CCB (Grant DC000064).

References

Chan DK, Chang KW (2014) GJB2-associated hearing loss: systematic review of worldwide prevalence, genotype, and auditory phenotype. Laryngoscope 124:E34–53. 10.1002/lary.24332 [PubMed: 23900770]

Chien WW, Monzack EL, McDougald DS, Cunningham LL (2015) Gene therapy for sensorineural hearing loss. Ear Hear 36:1–7. 10.1097/AUD/0000000000000088 [PubMed: 25166629]

Eshraghi AA, Polineni SP, Davies C, Shahal D, Mittal J, Al-Zaghal Z, Sinha R, Jindal U, Mittal R (2020) Genotype-phenotype correlation for predicting cochlear implant outcome: current challenges and opportunities. Front Genet 11:678. 10.3389/fgene.2020.00678 [PubMed: 32765579]

Friedman TB, Schultz JM, Ahmed ZM, Tsilou ET, Brewer CC (2011) Usher syndrome: hearing loss with vision loss. Adv Otorhinolaryngol 70:56–65. 10.1159/000322473 [PubMed: 21358186]

Kelsell DP, Dunlop J, Stevens HP, Lench NJ, Liang JN, Parry G, Mueller RF, Leigh IM (1997) Connexin 26 mutations in hereditary non-syndromic sensorineural deafness. Nature 387:80–83. 10.1038/387080a0 [PubMed: 9139825]

Kenneson A, Van Naarden BK, Boyle C (2002) GJB2 (connexin 26) variants and nonsyndromic sensorineural hearing loss: a HuGE review. Genet Med 4:258–274. 10.1097/00125817-200207000-00004 [PubMed: 12172392]

Nakanishi H, Kawashima Y, Kurima K, Chae JJ, Ross AM, Pinto-Patarroyo G, Patel SK, Muskett JA, Ratay JS, Chattaraj P, Park YH, Grevich S, Brewer CC, Hoa M, Kim HJ, Butman JA, Broderick L, Hoffman HM, Aksentijevich I, Kastner DL, Goldbach-Mansky R, Griffith AJ (2017) *NLRP3* mutation and cochlear auto-inflammation cause syndromic and nonsyndromic hearing loss DFNA34 responsive to anakinra therapy. Proc Natl Acad Sci USA 114:E7766–E7775. 10.1073/pnas.1702946114 [PubMed: 28847925]

Omichi R, Shibata SB, Morton CC, Smith RJH (2019) Gene therapy for hearing loss. Hum Mol Genet 281:R65–R79. 10.1093/hmg/ddz129

Snoeckx RL, Huygen PL, Feldmann D, Marlin S, Denoyelle F, Waligora J, Mueller-Malesinska M, Pollak A, Ploski R, Murgia A, Orzan E, Castorina P, Ambrosetti U, Nowakowska-Szyrwinska E, Bal J, Wiszniewski W, Janecke AR, Nekahm-Heis D, Seeman P, Bendova O, Kenna MA, Frangulov A, Rehm HL, Tekin M, Incesulu A, Dahl HH, du Sart D, Jenkins L, Lucas D, Bitner-Glindzicz M, Avraham KB, Brownstein Z, del Castillo I, Moreno F, Blin N, Pfister M, Sziklai I, Toth T, Kelley PM, Cohn ES, Van Maldergem L, Hilbert P, Roux AF, Mondain M, Hoefsloot LH, Cremers CW, Lopponen T, Lopponen H, Parving A, Gronskov K, Schrijver I, Roberson J, Gualandi F, Martini A, Lina-Granade G, Pallares-Ruiz N, Correia C, Fialho G, Cryns K, Hilgert N, Van de Heyning P, Nishimura CJ, Smith RJ, Van Camp G (2005) GJB2 mutations and degree of hearing loss: a multicenter study. Am J Hum Genet 77:945–957. 10.1086/497996 [PubMed: 16380907]

Tomblin JB, Harrison M, Ambrose SE, Walker EA, Oleson JJ, Moeller MP (2015) Language outcomes in young children with mild to severe hearing loss. Ear Hear 36 Suppl 1(01):76S–91S. 10.1097/AUD.0000000000000219 [PubMed: 26731161]

Totonchy MB, Tamura D, Pantell MS, Zalewski C, Bradford PT, Merchant SN, Nadol J, Khan SG, Schiffmann R, Pierson TM, Wiggs E, Griffith AJ, DiGiovanna JJ, Kraemer KH, Brewer CC (2013) Auditory analysis of xeroderma pigmentosum 1971–2012: hearing function, sun sensitivity and DNA repair predict neurological degeneration. Brain 136(Pt 1):194–208. 10.1093/brain/aws317 [PubMed: 23365097]

Van Camp G, Willems PJ, Smith RJ (1997) Nonsyndromic hearing impairment: unparalleled heterogeneity. Am J Hum Genet 60:758–764 [PubMed: 9106521]

Wafa TT, Faridi R, King KA, Zalewski C, Yousaf R, Schultz JM, Morell RJ, Muskett J, Turriff A, Tsilou E, Griffith AJ, Friedman TB, Zein WM, Brewer CC (2021) Vestibular phenotype-genotype correlation in a cohort of 90 patients with Usher syndrome. Clin Genet 99:226–235. 10.1111/cge.13868 [PubMed: 33089500]

World Health Organization (2021) World report on hearing. World Health Organization, Geneva (License: CC BY-NC-SA 3.0 IGO)