# Prelingual Siblings of Children With *GJB2* Hearing Loss

## *Issues to Consider*

Newborn hearing screening is currently being implemented in the United States and other countries, allowing early identification of and intervention for hearing loss in neonates. Also, genetic testing is clinically available for the *GJB2* gene, which codes for the connexin 26 protein, and the results have begun to explain the cause of a significant number of cases of hearing loss. However, the current limited knowledge about the natural history of *GJB2*-related hearing loss in the postnatal period, particularly as it relates to age at diagnosis of the hearing loss, raises important clinical and ethical questions that need to be addressed regarding the evaluation of *prelingual siblings* of children identified with *GJB2*-related hearing loss.

Approximately 50% of prelingual hearing loss has a genetic basis and approximately 70% of genetic hearing loss is nonsyndromic.[1] Remarkably, the recently identified gene *GJB2* accounts for a large proportion of nonsyndromic genetic hearing loss,[2] with hearing loss variants in *GJB2* accounting for up to 50% of autosomal recessive nonsyndromic hearing loss in many populations,[3] as well as for some cases of syndromic hearing loss.[4,5] This gene produces connexin 26, a gap junction protein that is abundantly expressed in the cochlea and is essential for hearing.[6,7] More than 100 hearing loss variants in *GJB2* have been identified so far (http://www.crg.es/deafness/), with a few variants, such as 35delG in white populations,[8,9] 167delT in the Ashkenazi Jewish population,[10] and 235delC in Asian populations,[11] accounting for the majority of *GJB2* alleles containing hearing loss–associated variants. Clinical genetic testing is available for *GJB2* (see www.genetests.org or www.geneclinics.org for listing of laboratory services), and genetic testing is recommended in the context of genetic counseling for individuals with apparent nonsyndromic hearing loss.[12]

Hearing loss–associated variants in each copy of *GJB2* produces an autosomal recessive nonsyndromic sensorineural hearing loss that can range from mild to profound.[3,13-15] To date, the majority of individuals exhibit a bilateral hearing loss, although there are a few case reports of unilateral loss.[3] There is evidence of genotype-phenotype correlation, with protein nontruncating variants producing a milder phenotype than protein truncating variants.[14,15] However, some variability in the audiology phenotype exists, mainly involving protein nontruncating variants,[14,15] making it difficult to offer prognostic information in some cases.

Our current state of knowledge of *GJB2*-related hearing loss comes predominantly from cross-sectional or retrospective studies of individuals with documented prelingual bilateral sensorineural hearing loss that were conducted before universal hearing screening of neonates was available.[2,3,14,16-18] Because of the timing and nature of these research designs, very little is known about the audiometric characteristics of *GJB2*-related hearing loss in the postnatal or infancy period. Studies performed in conjunction with recently implemented early hearing, detection, and intervention programs clearly demonstrate that *GJB2*-related hearing loss can be congenital.[19-22] However, it is also possible that variants in this gene may produce hearing loss that may not be detectable in the immediate postnatal period. Evidence for later detection of *GJB2*-related hearing loss comes from a published report involving 2 neonates who had documented normal hearing before 6 months of age—one by automated auditory brainstem response screening of newborns and one by sound-field audiometry at the age of 5 months—who were later identified as having severe or profound hearing loss, one at the age of 15 months and the other at the age of 9 months.[23] *GJB2* testing was subsequently performed on both children, and both were found to be homozygous for the 35delG mutation. These cases are noteworthy, but it is yet unknown whether they are truly exceptional, whether they represent errors in the original audiometric testing, or whether they in fact represent a nontrivial subset of individuals with biallelic *GJB2* variants who will pass newborn hearing screening and be diagnosed with hearing loss some time after birth. Only through empirical studies of infants whose hearing status at birth is documented through newborn hearing screening will clinicians be able to determine which infants or children who are later identified with hearing loss have a postnatal or progressive condition. In those cases, it will be possible to determine if *GJB2* variants lead to a postnatal or a progressive hearing loss. This information will ultimately play a critical role in determining the appropriate evaluation of prelingual siblings of a child with documented *GJB2*-related hearing loss.

In light of the paucity of empirical data on age of identification of *GJB2*-related hearing loss, siblings of a child with documented *GJB2*-related hearing loss who pass newborn hearing screening may be viewed as being at risk for hearing loss, necessitating appropriate at-risk evaluation. For these children, there currently are 2 assessment options: audiologic assessment to determine hearing status and *GJB2* testing to determine genetic status. Both of these options, which are not necessarily mutually exclusive, raise clinical or ethical issues.

One strategy is to perform audiologic assessments on *all* prelingual siblings of a child with *GJB2*-related hearing loss. If a hearing loss is diagnosed, *GJB2* testing could then be performed to confirm the role of this gene in the sibling's hearing loss. Although this strategy appears to be innocuous, there are several questions about an assessment strategy that is based primarily on the results of audiologic assessment. How often should a young sibling who may be at heightened risk for *GJB2*-related hearing loss undergo audiologic assessment? For how many years should this sibling receive audiology assessments (ie, at what age is it safe to presume that the child is not at risk for *GJB2*-related hearing loss)? This issue is even more vexing when very young siblings are involved, as audiology diagnostic assessments for children between about 3 months and at least 6 months of age must involve diagnostic automated auditory brainstem response testing, generally with sedation, which puts the infant at a potentially unnecessary risk. There are also cost considerations that accompany repeated audiologic assessment, as well as the potential of creating a situation in which parents experience prolonged uncertainty about their child's hearing status.

An alternative strategy is first to perform *GJB2* testing in the context of genetic counseling on prelingual siblings who pass newborn hearing screening, and then to perform audiologic assessment on those who are identified as being at genetic risk for hearing loss. Although this strategy does not answer the questions about how to implement audiologic assessment, it does have the attractive feature of reducing the number of siblings on whom audiologic assessment is performed.

The genetic testing strategy could be justified as presymptomatic genetic testing for a later-onset condition for which audiologic surveillance provides the opportunity for earliest possible intervention if the result is positive or for which audiologic surveillance can be stopped if the result is negative. Genetic testing that leads to early identification of hearing loss and early intervention would presumably have a tremendously positive impact on the development of language skills of prelingual siblings who are identified as being truly at risk for *GJB2*-related hearing loss. However, testing also would identify the carrier status of many siblings who truly are not at risk for *GJB2*-related hearing loss. In fact, the chance that a sibling will be found to be a carrier is between one half (if hearing status truly has not been determined) and two thirds (if the sibling truly has normal hearing). Therefore, carrier status is the most likely outcome of genetic testing, which raises ethical issues pertaining to genetic testing in children.

Guidelines established by the American Academy of Pediatrics, the American Society of Human Genetics, and the American College of Medical Genetics pertaining to appropriate uses of genetic testing have been published, with special consideration for the testing of minors.[24,25] According to these published guidelines, genetic testing is considered appropriate in children for diagnostic purposes, to refine prognosis if genotype-phenotype correlations are strong, for predicting later-onset conditions in presymptomatic at-risk children when surveillance is associated with effective treatment, and to allow a reduction in surveillance for later-onset conditions.

Testing healthy minors to determine carrier status for autosomal recessive conditions, eg, cystic fibrosis or *GJB2*-related hearing loss, generally is not recommended,[3,22,24,25] for reasons that include the fear that knowledge of a child's carrier status will alter family dynamics and child rearing, that there will be confusion about the difference between being an asymptomatic carrier and having a condition, that the information is not clinically relevant, and that the child ought to be able to make an autonomous decision as an adult to seek this information, which could have reproductive ramifications. Moreover, hearing loss per se is not considered a disease entity by members of the Deaf community.[26,27] Performing genetic testing on minors that produces information that most likely could relate only to their future reproductive decision making may be construed as a pejorative to the Deaf community, which views hearing loss or deafness to be a personal trait but not a medical condition. Because *GJB2* testing will incidentally reveal carrier status, there should be careful consideration about whether or how to include genetic testing as a primary evaluation option for prelingual siblings of a child with *GJB2*-related hearing loss.

A possible solution to resolving the conflicting outcomes of genetic testing of prelingual siblings is to perform presymptomatic genetic testing for *familial mutations* and to report either that the sibling has the *same GJB2* results as the child with *GJB2*-related hearing loss and hence is at heightened risk for hearing loss or that the sibling does not have the same genotype as the child with *GJB2*-related hearing loss and hence is not at heightened risk for hearing loss. This procedure would enable parents to ensure appropriate audiologic follow-up for hearing children who have an at-risk molecular test result, while allowing those children who are not at genotypic risk for hearing loss to engage in independent decision making about determining carrier status when they are older. There are 2 additional levels of complexity that need to be considered, however. First, it has been noted that significantly more individuals with apparently nonsyndromic hearing loss have only 1 identified pathogenic *GJB2* allele than is predicted by the carrier rate, even after complete *GJB2* sequencing and testing for the 2 reported deletions in *GJB6*,[28] making it impossible to distinguish carrier status from the possibility that the single identified pathogenic allele is contributing to the hearing loss in those individuals. Although present in a minority of cases, a *GJB2* heterozygous result occurs frequently enough that it may need to be considered an at-risk molecular result for a sibling. The second level of complexity involves results that are sometimes inconclusive because of limited information about the role of particular *GJB2* variants in hearing loss,[18] even if 2 such variants are identified in a child with hearing loss. Such gaps in our knowledge may argue against *GJB2* testing in prelingual siblings.

There is at least 1 precedent for tailoring molecular tests to accommodate conflicting agendas. The concept of exclusion testing was developed in the context of Huntington disease to offer prenatal testing of fetuses who are at 25% risk (ie, the pregnancy of an adult who is at 50% risk) of inheriting the gene responsible for Huntington disease without disclosing parental mutation status.[29] In this way, individuals who are at 50% risk could be shielded from learning their mutation status yet make reproductive decisions.

Given the history of sensitivity toward the multifaceted outcomes of genetic testing, it is reasonable to think carefully about whether *GJB2* testing could or should be tailored to facilitate appropriate audiologic surveillance and protect carrier status of prelingual siblings. In addition to medical and psychosocial issues, however, there are laboratory issues that also must be considered as we think about how or whether to tailor *GJB2* testing of prelingual siblings, including (1) how to reconcile current recommendations that promote full description of molecular test results[30] with a philosophy that promotes selective disclosure of results, and (2) the development of a protocol that all molecular laboratories performing *GJB2* testing would accept and use. The second issue is not trivial, because considerable variability in laboratory practices related to *GJB2* testing in the United States has been recently demonstrated.[31]

It will take many years before we have a truly informed picture of the natural history of *GJB2*-related hearing loss. However, we are currently faced with the reality of making decisions about the evaluation of prelingual siblings of a child with *GJB2*-related hearing loss. Therefore, it is imperative that we begin to recognize the clinical and ethical issues raised by audiologic assessment and genetic testing, to conduct research that will address questions related to these issues, and to formulate a reasoned set of recommendations regarding appropriate evaluation of these children.

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