

Universal Newborn and Infant Hearing Screening and Genetic Testing

Why is genetic testing for hearing loss an emerging public health issue?

The prevalence and availability of interventions makes identifying those individuals with hearing loss a public health issue. Universal newborn screening for hearing loss has been widely adopted since it is known that early identification and management of deafness is important for the development of language and social skills. Research has shown that children with hearing loss identified before six months of age and who have begun appropriate interventions immediately after diagnosis demonstrate superior language skills over those identified after six months of age.

As such, thirty-two states have enacted legislation, which provides universal newborn hearing screening (UNHS).

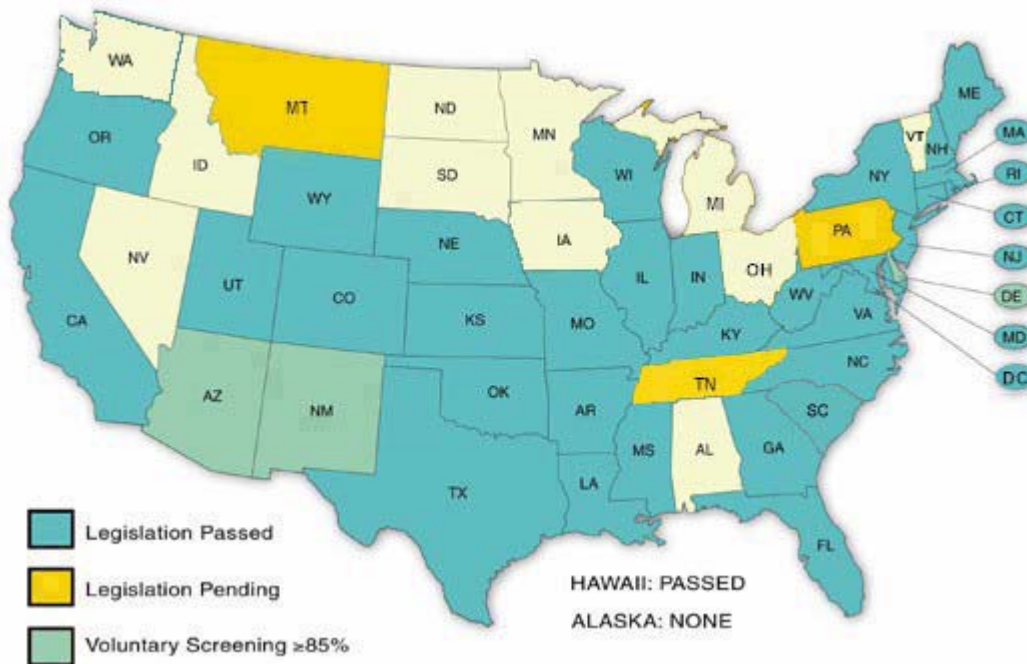


Figure 1. Legislative status for universal newborn and infant screening programs.

The American Speech-Language-Hearing Association has established minimum criteria for UNHS programs (http://www.asha.org/infant_hearing/overview.htm). The method of screening should include auditory brainstem response (ABR), otoacoustic emissions (OAE) or other objective physiological measures. [See definitions below].

Hearing loss can be acquired or inherited. Genetic findings have identified a change in a [gene](#) that accounts for a major form of inherited hearing loss.

This gene change involves the [protein](#), connexin 26 (Cx26). Therefore, Cx26 genetic testing is an emerging public health issue.

Some programs incorporate a screening protocol that may lead to genetic testing. The question is should genetic testing be a required component of all universal newborn and infant hearing screening programs?

Suggested reading: American Academy of Pediatrics Task Force on Newborn and Infant Hearing (1999) Newborn and Infant Hearing Loss: Detection and Intervention Policy Statement. *Pediatrics* 103:527-30 [www.aap.org/policy/re9846.html]

What is Hereditary Hearing Loss?

About one in 1000 infants has profound hearing loss, with at least half of these cases thought to be of genetic origin. Despite this number, genetic causes of hearing loss are frequently undiagnosed. Also, children who are the only deaf individuals in their families may have a genetic or inherited cause for their deafness.

There are many genes that contribute to hearing loss. These genes may be inherited in a variety of fashions. Hearing loss may be inherited in the following manners: [autosomal dominant](#), [autosomal recessive](#), [X-linked](#) or [mitochondrial](#). [Syndromes](#) may also be associated with hearing loss such as [Usher Syndrome](#), [Waardenburg Syndrome](#), and [Stickler Syndrome](#).

Infection in the mother during pregnancy or illness of the infant requiring care in a neonatal intensive care unit may result in isolated or sporadic cases of newborn hearing loss within families.

What is Cx26?

In half of newborns with severe-to-profound or profound [congenital](#) autosomal recessive non-syndromic hearing loss, mutations in a gene called GJB2 can be found. The gap junction gene called GJB2 [encodes](#) the protein connexin 26(Cx26). Many people simply refer to the gene as the “*connexin 26 gene*.” In two-thirds of persons with Cx26-related deafness, a single mutation is found called 35delG. The term 35delG means that at position 35 in the gene a change, here a [deletion](#) or del, has occurred. The Cx26 gene is located on [chromosome](#) 13. Connexins are expressed in many different tissues. Connexin 26 functions in the inner ear and is involved in the production of junctions that allow the transport of materials between cells.

Below is a summary of the gene changes currently known to be associated with connexin 26.

Percent of Patients	Gene Change
~66%	35delG of GJB2 (Cx26)
~30%-32%	Other GJB2 (Cx26) changes
~4%	Unknown

Table 1. Gene changes found in Cx26 related hearing loss

It is estimated that 1 in 31 individuals in the general population carry the 35delG gene change for Cx26, making it one of the most common causes of deafness.

This finding has raised a great deal of interest in the prospect of genetic testing for hearing loss. Genetic testing could facilitate establishing a cause for hearing loss in a significant number of deaf children, obviating a more extensive evaluation. It also offers the possibility of better and more accurate genetic counseling.

How is the Cx26 gene inherited?

The 35delG form of the Cx26 gene is [inherited](#) in an [autosomal recessive](#) fashion. There are other changes in the Cx26 gene, which are inherited in different patterns. The Cx26 gene can result in autosomal dominant deafness and in syndromic deafness.

With recessive inheritance, individuals who carry one gene responsible for this form of hearing loss are called carriers or [heterozygotes](#) and usually have no hearing loss. If an individual has two copies of the recessive gene change, they are said to be [homozygous](#) and are deaf or hard of hearing.

When two carriers (heterozygotes) have children, the risk is 1 in 4 or 25% their children will be deaf or hard of hearing: 25% their children will have no changed Cx26 genes and therefore, no hearing loss; and 50% their children will be carriers like themselves (again with no hearing loss).

What are the symptoms of hereditary hearing loss?

Individuals with connexin-26 related deafness are healthy and enjoy a normal life span. Those with Cx26 gene changes do not have visible differences of the external ear nor any related medical problems. This is known as non-syndromic hearing loss. To date, no clinical characterization of any inner ear differences have been reported. Affected infants and young children do not experience balance problems and learn to sit and walk at age-appropriate times.

Cx26 mutations can cause a range of hearing loss from mild to profound, however, usually the loss is severe or profound (see Table 2).

Degree of Hearing Loss	Threshold Difference from Norms (in decibel (dB))
Normal hearing	0-15
Slight/borderline	16-25
Mild	26-40
Moderate	41-55
Moderately Severe	56-70
Severe	71-90
Profound	Above 90

Table 2. Degrees of hearing loss

The range in which an individual's hearing thresholds are recorded determines the degree of hearing loss. A hearing threshold is the level, typically recorded in dB, at which a person responds consistently 50% of the time to a pure tone stimulus. Hearing is considered in the normal range if an individual's thresholds are recorded between 0-15 dB. The normal range of hearing represents the levels at which average young adults perceive a tone 50% of the time.

How is the Cx26 gene detected?

Children screened by universal newborn hearing screening (UNHS) programs with confirmed hearing loss might be referred for genetic testing. Before consideration of genetic testing, treatment should begin.

Indications for DNA testing for connexin-26 related deafness include the absence of any clinical findings from a medical history or physical examination and a family history consistent with autosomal recessive inheritance. Children who are the only deaf individuals in their families should also be tested.

DNA testing plays a prominent role in the diagnosis of GJB2 or Cx26 changes. Most Cx26 mutations can be detected. Individuals with Cx26 mutations may avoid medical testing associated with a diagnosis of hearing loss since a cause for the hearing loss has been determined. Failure to detect a Cx26 change does not exclude the diagnosis of a hereditary hearing loss since all mutations have yet to be identified. Many centers sequence the Cx26 gene.

How is hereditary hearing loss treated?

Once a diagnosis is known or confirmed by a complete assessment of auditory acuity using ABR emission testing and pure tone audiometry, fitting with appropriate hearing aids and determination if a special educational program is needed should be considered.

Follow-up care should include semiannual examination by a physician familiar with hereditary hearing loss and a repeated audiometry to confirm the stability of the hearing loss. Consideration should be given for cochlear implantation, although not all children with connexin 26 hearing loss are candidates for cochlear implants.

Types of screening and diagnostic hearing tests

ABR test

An ABR (auditory brainstem response) can be performed on a baby who is unable to have a regular behavioral audiological evaluation. A screening ABR uses an electrode attached to the infant's scalp to measure brain activity in response to "clicks" sounded to the baby's ear.

A diagnostic ABR test uses pure tones at a variety of frequencies, through earphones as well as through a bone conduction vibrator, to distinguish between conductive and sensorineural hearing loss. The ABR may determine if the hearing problem lies in the cochlea (coiled part of the inner ear) or in the part of the brain that first receives the sound information. This testing causes no discomfort and has no harmful effects.

OAE test

Otoacoustic emissions (OAE) testing uses a tiny insert placed in the baby's ear to project soft sounds. In a hearing baby, a microphone within the insert will record faint noises coming from the baby's ear in response to the auditory stimulation. The test is completed within a few minutes while the baby sleeps, and does not cause the baby any pain or discomfort.

Pure tone audiometry

This testing is seldom used with newborn screening programs. Pure tone audiometry involves the placement of earphones over the ears or use of a bone conduction vibrator on the mastoid or the

forehead to determine the lowest intensity at which an individual "hears" a pure tone, as a function of frequency or pitch. This is a behavioral test and is used with older children who can respond by raising their hand or dropping a toy in a bucket when a sound is heard.

Other issues to consider

Though Cx26 accounts for many cases of non-syndromic hearing loss, other causes must be considered. Although we know that at least 400 genes for hearing loss exist, not nearly these many have been identified. Their presence is inferred by the hundreds of syndromes with hearing loss as a feature.

Information and Support Resources

- [GeneClinics](#)
- [American Society for Deaf Children](#)
- [National Association of the Deaf](#)
- [NCBI Genes and Disease Webpage](#)
- Boys Town National Research Hospital: Center for Hearing Loss:
<http://www.boystown.org/Btnrh/Chlc/index.htm>
<http://www.boystown.org/btnrh/genetics/index.htm>
- [Finding Genes for Non-Syndromic Deafness](#)