Facts About Genetic Testing

What is a Genetic Test?

A genetic test determines the DNA sequence of a certain region of the human genome. This region could be a whole gene, a portion of a gene, or other areas thought to regulate genes. The test will look for certain changes in the sequence that are known to have consequences on the function of a gene. These tests can be used to 1) diagnose a disease or other trait, 2) determine if a person is a carrier of a mutation that could lead to disease in their children, and 3) predict if a disease or trait that is not yet detectable by other medical tests may occur in the future.

How are the Tests Performed?

Most genetic tests are performed on a DNA sample. Because every tissue in the body is made of cells that contain DNA, any tissue can be used as a source of DNA. However, blood is the most common source because it can easily be obtained in large quantities; typically 5-10 ml (1-2 teaspoons) are taken for a test. Some laboratories will allow cheek cells to be submitted for genetic testing. In this case, the cells are usually collected by rubbing the inside of the mouth with a small brush.

After the DNA is obtained from a blood or other tissue sample, a variety of different methods can be used to look for mutations in your genes. Which method is used often depends on the size of the gene and the types of mutations that are typically found in that gene. Sometimes the whole coding sequence of the gene is examined. This is similar to reading a page in a book to look for spelling errors in all of the words. Other times, methods are used that only look for the most common mutations. In this case, the test is similar to looking at a page only for a specific misspelled word and ignoring all of the other words. This latter approach is often taken if the gene’s role in disease is mostly due to only a small number of known mutations. Some laboratories may combine these methods by first screening for common mutations and then, in certain circumstances, examining the whole coding sequence of the gene.

Why Should I Have Genetic Testing?

Genetic testing can help identify the cause of the hearing loss and may help predict whether it will worsen. It can also help with treatment decisions because the successful use of hearing aids and/or cochlear implants may depend on the cause of the hearing loss. In addition, if a genetic test is positive it can reduce the need to perform the many other clinical tests that are used to find other causes of the hearing loss. Furthermore, if a genetic test for nonsyndromic hearing loss is positive, it can assure the family that no other problems associated with syndromic forms of hearing loss will develop. Testing can also help predict the likelihood that future children or other persons in the family will develop hearing loss.
WHO CAN HELP ME DECIDE IF I SHOULD HAVE A GENETIC TEST?

Often your primary care physician, pediatrician, or ear specialist (otolaryngologist or audiologist) can help you decide if having a genetic test is appropriate. However, the field of genetics is developing so quickly that it is often useful to go to a genetics specialist, such as a genetic counselor, clinical geneticist, or genetic testing lab to get the most up-to-date information about genetic testing for hearing loss.

WHERE DO I GO FOR GENETIC TESTING?

There are many places that offer genetic testing for hearing loss. Your doctor will assist you in finding a place. If your doctor is unfamiliar with available genetic tests for hearing loss, he or she can visit the GeneTests website (www.genetests.org) and search the Laboratory Directory for “deafness” or the gene name (e.g. “connexin 26”). Many of the locations that perform genetic testing have voluntarily registered at this site. If none of these sites are nearby, your doctor can often mail your blood sample to one of these sites.

HOW MUCH DOES A GENETIC TEST COST AND HOW LONG WILL IT TAKE TO GET RESULTS?

The cost and turn-around-time of a genetic test may vary depending on the lab and the methods used for testing. A typical range of cost might be $300-$2000 and a typical range of time to get the results might be 2-6 weeks. If the test only screens for common mutations or if the gene that is being tested is small (like connexin 26) the test may be less expensive and the results may be obtained more quickly. However, if the gene is large and the test examines the entire coding sequence of the gene, it may be more expensive and may take longer to perform. Insurance companies will often pay for genetic tests, but you should check with your company before your doctor orders the test.

CAN THE RESULTS OF GENETIC TESTS HARM ME?

Genetic information has been used in the past for discriminatory purposes; however, most states now have laws that prevent employers and insurance companies from discriminating against people on the basis of their genetic makeup. You can find out if such laws exist in your state by going to http://www.genome.gov/10001621.
**Connexin 26 Gene Testing**

**Could my hearing loss be caused by mutations in the connexin 26 gene?**

Mutations in the connexin 26 (Cx26) gene are the most common cause of hearing loss. Cx26 hearing loss is most often seen in a person with:

- Hearing loss that was found at birth or in early childhood
- Hearing loss that is mild, moderate, severe or profound
- Hearing loss without any other medical problems (nonsyndromic)
- Hearing loss with no identified cause

Although these are the most common characteristics of hearing loss due to a mutation in Cx26, there can be variations, even within a family. There have been several occasions when skin disorders have been found in people with deafness due to dominant Cx26 mutations. Furthermore, there have been instances when a child’s deafness was originally thought to be due to non-hereditary factors (e.g., an infection or exposure to antibiotics) and then the child was later found to have mutations in Cx26. In such cases, it is more likely that the child’s deafness was caused by the Cx26 mutations than by environmental agents. It should also be noted that many children with Cx26 mutations have no family history of hearing loss.

**Why should I have Cx26 testing?**

Cx26 testing can help identify the cause of the hearing loss as well as help predict the prognosis of the hearing loss (most Cx26 hearing loss does not worsen). It can also help with treatment decisions (most Cx26 hearing loss responds well to hearing aids and/or cochlear implants). In addition, identifying Cx26 mutations as the cause of a person’s hearing loss will reduce the need to perform other clinical tests. Furthermore, a positive test result can assure the family that no other problems associated with a syndromic form of hearing loss will develop. Testing can also help predict the likelihood that future children in the family will be born with hearing loss.

**How is the Cx26 gene test performed?**

To perform the Cx26 test, a DNA sample is obtained and your Cx26 gene sequence is compared to that of the regularly occurring sequence to look for changes. Some laboratories examine the entire sequence of the Cx26 gene, whereas other laboratories only search for common mutations, such as 35delG, the most common mutation in the Caucasian population. Some laboratories may combine these methods by first screening for a common mutation and then, in certain circumstances, sequencing the whole gene. It is recommended that your doctor choose a lab that will look at the whole coding sequence of the gene. If the lab does not sequence the whole gene, less common mutations could easily be missed.
HOW ARE THE RESULTS OF A Cx26 TEST INTERPRETED?

There are four possible outcomes of a Cx26 test:

1. **Two Cx26 mutations are found.** If two identical mutations (e.g., 35delG/35delG) or two different mutations (e.g., 35delG/167delT) are found, it can be assumed that the patient’s hearing loss is caused by the Cx26 mutations.

2. **No Cx26 mutations are detected.** If no mutations are found, one must first consider how the test was performed. Was the whole coding sequence of the gene analyzed or was the gene only screened for the most common mutation(s)? If the whole coding sequence was analyzed and no mutations were found, it is unlikely that the patient’s hearing loss was caused by Cx26 mutations.

3. **Only one Cx26 mutation is detected.** If only one mutation is detected, interpretation can be difficult. The most likely explanations are:

   A) The Cx26 mutation may be unrelated to the deafness. Many people (approximately 3%) have, or “carry”, single Cx26 mutations but are not hearing impaired. As such, it is possible for a person with hearing loss to carry a single Cx26 mutation but have hearing loss is due to another gene or a non-genetic cause. It should be noted that the correct name of this gene is GJB2 (gap junction beta 2). We use the protein name, connexin 26, because it is more common to the public.

   B) The test did not detect the second mutation. Even though examining the whole coding sequence of the gene will detect most mutations, there are other regions of the gene sequence and surrounding DNA that could contain a mutation. Unfortunately, these sequences are rarely analyzed unless a specific mutation is already known.

   C) The mutation may act as a dominant mutation, meaning that only one mutation is required to cause hearing loss. A list of the known dominant mutations for Cx26 can be found at http://www.crg.es/deafness

   D) There may be a mutation in another gene for a protein called connexin 30 that may work together with the Cx26 mutation to cause hearing loss. (Have your doctor check to see if the lab can test for the Cx30 deletion.)

4. **Cx26 mutations are detected but their significance is unknown.** Some changes in the Cx26 gene are not considered to affect the function of the gene. These changes are often called “polymorphisms”. Sometimes, a new mutation is found and it is not yet clear whether the change will cause hearing loss or not. Unfortunately, more studies would need to be done before a definite conclusion could be made.

A catalog of all Cx26 mutations can be found at the “Connexins and Deafness” website (http://www.crg.es/deafness). It should be noted that the correct name of this gene is GJB2 (gap junction beta 2). We use the protein name, connexin 26, because it is more common to the public.
SLC26A4 (PDS) GENE TESTING

COULD MY HEARING LOSS BE CAUSED BY MUTATIONS IN THE SLC26A4 GENE?

SLC26A4 hearing loss is most often seen in a person with:

- Temporal bone abnormalities (observed on a CT scan or MRI of the inner ear) including enlarged (dilated) vestibular aqueduct and/or Mondini malformation
- Hearing loss that was found at birth or in early childhood
- Hearing loss that is severe or profound
- Thyroid enlargement (goiter) that appears during childhood or early adulthood
- A positive perchlorate discharge test (for thyroid function)

Although these are the most common characteristics of hearing loss due to mutations in SLC26A4, there can be variations, even within a family. SLC26A4 mutations are usually thought to cause Pendred Syndrome, a genetic condition associated with hearing loss and goiter (thyroid enlargement). However, mutations in the SLC26A4 gene can sometimes cause hearing loss in people who do not have any thyroid problems. Also, some persons with SLC26A4 hearing loss do not have temporal bone abnormalities and some can have mild or moderate hearing loss.

HOW IS THE SLC26A4 GENE TEST PERFORMED?

To perform the SLC26A4 gene test, a DNA sample is obtained and your SLC26A4 sequence is compared to that of the regularly occurring gene sequence to look for changes. Some laboratories may examine the entire coding sequence of the gene, while other laboratories may only search for the common mutations. There are 3 common mutations (L236P, 1001+1G>A, T416P) that cause over half of the cases of hearing loss associated with this gene.

HOW ARE THE RESULTS OF A SLC26A4 GENE TEST INTERPRETED?

There are three possible outcomes of a SLC26A4 test:

1. **No SLC26A4 mutations are detected.** If no mutations are found, and the entire coding sequence was analyzed, it is unlikely that the hearing loss is caused by mutations in the SLC26A4 gene.

2. **Two SLC26A4 mutations are detected.** If two identical mutations or two different mutations are found, and these mutations have been previously found to cause hearing loss, it can be assumed that the hearing loss is caused by these mutations in the SLC26A4 gene.

3. **Only one SLC26A4 mutation is detected.** If only one mutation is detected, interpretation can be difficult. It is possible that the test did not detect the second mutation or that the SLC26A4 mutation found may be unrelated to the hearing loss.

A catalog of the reported SLC26A4 mutations can be found in the Deafness Gene Mutation Database at http://hearing.harvard.edu.
Mitochondrial Gene Testing

Could My Hearing Loss Be Caused by Mutations in a Mitochondrial Gene?

There are many forms of hearing loss that can be caused by mutations in mitochondrial genes. Some of the more common forms include:

- Isolated (nonsyndromic) sensorineural hearing loss
- Hearing loss that began after antibiotic treatment
- Hearing loss that is associated with neuromuscular disease
- Hearing loss that is associated with diabetes

There are two mitochondrial genes known to cause nonsyndromic hearing loss (12S rRNA and tRNAleu<sup>12S</sup>). There are several mitochondrial genes known to cause syndromic forms of hearing loss. For example, mutations in the tRNAleu<sup>12S</sup> and tRNAlys genes can both cause hearing loss associated with neuromuscular diseases such as MELAS and MERRF. Mutations in the tRNAleu<sup>12S</sup> gene can also be associated with diabetes. All forms of hearing loss due to mutations in mitochondrial genes are inherited only from the mother and not the father. See the booklet for a more detailed description of mitochondrial inheritance.

What’s Special About the A1555G Mutation?

There is a mutation called A1555G in the 12S rRNA gene that makes a person more likely to develop hearing loss following treatment with a particular type of antibiotic called aminoglycoside antibiotics (for example gentamicin, neomycin, amikacin, tobramycin). It should be noted that people can lose their hearing due to treatment with aminoglycoside antibiotics even if they do not have this mutation. Also, a person with this mutation can develop hearing loss even with no exposure to aminoglycoside antibiotics.

How are Mitochondrial Gene Tests Performed?

To perform the mitochondria gene tests, a DNA sample is obtained and your mitochondrial gene sequences are compared to those of the regularly occurring sequences to look for changes. The majority of hearing loss due to mutations in mitochondrial genes is caused by a small number of specific mutations. As a result, many labs that offer tests for mitochondrial genes, only screen for the specific mutations and typically do not sequence the whole genes.

A catalog of the mitochondrial gene mutations that have been reported to cause hearing loss can be found in the Deafness Gene Mutation Database at http://hearing.harvard.edu.
COCH GENE TESTING

COULD MY HEARING LOSS BE CAUSED BY MUTATIONS IN THE COCH GENE?

COCH hearing loss is most often seen in a person with:
- Isolated (non-syndromic) sensorineural hearing loss (initially worse at high frequencies)
- Hearing loss that begins between ages 15 and 65
- Hearing loss that progresses to anacusis (complete loss)
- Variable vestibular problems (e.g. dizziness, trouble with balance, etc.)
- A family history of dominantly inherited hearing loss

Although these are the most common characteristics of hearing loss due to a mutation in COCH, there can be variations, even within a family. Some individuals do not report vestibular problems and it is also possible that a family history may not be present. It should be noted that some people with COCH-associated hearing loss may initially be diagnosed with Menière’s disease.

HOW IS THE COCH GENE TEST PERFORMED?

To perform the COCH test, a DNA sample is obtained and your COCH gene sequence is compared to that of the regularly occurring sequence to look for changes. To date, all mutations in this gene have been found in one particular region of the gene (exons 4 and 5). As such, most testing for this gene involves sequencing only this particular region.

HOW ARE THE RESULTS OF A COCH GENE TEST INTERPRETED?

Because hearing loss due to mutations in the COCH gene is inherited in an autosomal dominant manner, only one mutation is required to cause the hearing loss. Therefore, if one mutation is found, and this mutation has been previously shown to cause hearing loss in other persons, it is highly likely that the mutation is the cause of the hearing loss.

If no COCH mutations are detected, it is still possible that a mutation could be present in regions of the gene that were not tested, such as in other exons or non-coding regions of the gene. In addition, there are other genes that may cause a similar form of hearing loss. Consequently, if no mutation is found in this gene, it is possible that a mutation may exist in another hearing loss gene.

A catalog of the reported COCH mutations can be found in the Deafness Gene Mutation Database at http://hearing.harvard.edu.
CONNXEXIN 30 GENE TESTING

COULD MY HEARING LOSS BE CAUSED BY MUTATIONS IN THE CONNEXIN 30 GENE?

Mutations in the connexin 30 (Cx30) gene are most often seen in a person with:

- Hearing loss that was found at birth or in early childhood
- Hearing loss that is severe or profound
- Hearing loss without any other medical problems (nonsyndromic)
- Hearing loss with no identified cause
- A single mutation in the connexin 26 (Cx26) gene

Most families with this form of hearing loss are missing a large section of the DNA that includes one copy of their Cx30 gene. Usually, these families actually have a single mutation in Cx26 as well as the deletion of one of their copies of Cx30. However, some families have also been found with two copies of the Cx30 deletion and no Cx26 mutations. It appears that this form of hearing loss usually requires two mutations, but they can be two Cx26 mutations, two Cx30 deletion mutations or one of each.

Though the Cx30 deletion is usually involved in the recessive hearing loss described above, there are other kinds of Cx30 mutations that have been found to cause a dominant form of hearing loss that starts later in life. Furthermore, other dominant mutations in this gene can cause a skin disease called Hidrotic Ectodermal Dysplasia.

HOW IS THE C30 GENE TEST PERFORMED?

The most common Cx30 test that is offered checks to see if the DNA sample has a deletion of one, or both, copies of the Cx30 gene. Some laboratories may also examine the entire coding sequence of the gene.

HOW ARE THE RESULTS OF A C30 TEST INTERPRETED?

There are three possible outcomes of a Cx30 test:

1. **Two Cx30 mutations are found.** If two mutations are found, it can be assumed that the patient’s hearing loss is caused by the Cx30 mutations.

2. **No Cx30 mutations are detected.** If no mutations are found, and the lab tested for the deletion and other mutations in the coding sequence, it is unlikely that the patient’s hearing loss was caused by Cx30.
3. *Only one Cx30 mutation is detected.* If one mutation is detected, and the patient also has a single Cx26 mutation, it can be assumed that the combination of two mutations is causing the hearing loss. If one mutation is found and no Cx26 mutations were detected (after analyzing the whole Cx26 coding sequence) interpretation can be difficult. The most likely explanations are:

A) The Cx30 deletion mutation may be unrelated to the deafness. It is possible for a person with hearing loss to carry a single Cx30 mutation when the real cause of the hearing loss is due to another gene or a non-genetic cause.

B) The test did not detect the second mutation. Even though the test for the deleted DNA and the examination of the coding sequence will detect most mutations, there are other regions of the Cx30 and Cx26 gene sequence and surrounding DNA that could contain a mutation. Unfortunately, these sequences are rarely analyzed unless a specific mutation is already known.

C) The mutation may act as a dominant mutation, meaning that only one mutation is required to cause hearing loss.

A catalog of all Cx30 mutations can be found at the “Connexins and Deafness” website (http://www.crg.es/deafness). It should be noted that the correct name of this gene is GJB6 (gap junction beta 6). We use the protein name, connexin 30, because it is more common to the public.
OTOF Gene Testing

Could my hearing loss be caused by mutations in the OTOF gene?

Mutations in the OTOF gene are most often seen in a person with:

- Hearing loss that is moderate to profound, from birth or early childhood
- Hearing loss with present otoacoustic emissions (OAEs)
- Hearing loss with absent or severely abnormal auditory brainstem responses (ABR) with a cochlear microphonic (CM)

Although these are the most common characteristics of hearing loss due to mutations in the OTOF gene, there can be variations, even within the same family. OTOF mutations are usually thought to cause auditory neuropathy, also called auditory dys-synchrony (AN/AD). AN/AD is a sensorineural hearing disorder characterized by an absent or severely abnormal ABR with preservation of cochlear outer hair cell function as measured by otoacoustic emission testing. Varying degrees of hearing loss are seen in patients with AN/AD but generally patients have poor speech reception and do not communicate well with hearing aids. In contrast, many patients do well with cochlear implants. Although the hallmark of this form of hearing loss is the initial presence of otoacoustic emissions with an abnormal ABR, these emissions often eventually disappear although the ABR will remain abnormal.

How is OTOF gene testing performed?

To perform the OTOF gene test, a DNA sample is obtained and the sequence of the gene is compared to that of the regularly occurring gene sequence to look for changes.
How are the results of an **OTOF** test interpreted?

There are three possible outcomes:

1. *No mutations are detected.* If no mutations are found, and the entire coding sequence was analyzed in a gene, it is unlikely that the hearing loss is caused by mutations in the **OTOF** gene.

2. *Two mutations are detected.* If two identical mutations or two different mutations are found, and these mutations have been previously found to cause hearing loss, it can be assumed that the hearing loss is caused by mutations in the **OTOF** gene.

3. *Only one mutation is detected.* If only one mutation is detected, interpretation can be difficult.
   
   A) It is possible that the test did not detect the second mutation. Even though examining the whole coding sequence of the gene will detect most mutations, there are other regions of the gene sequence and surrounding DNA that could contain a mutation. Unfortunately, these sequences are rarely analyzed unless a specific mutation is already known.

   B) The mutation that was found may be unrelated to the hearing loss.

4. *Mutations were detected but their significance is unknown.* Some changes in the **OTOF** gene are not considered to affect the function of the gene. These changes are often called “polymorphisms”. Sometimes, a new mutation is found and it is not yet clear whether the change will cause hearing loss or not. Unfortunately, more studies would need to be done before a definite conclusion could be made.
USHER GENETIC TESTING

COULD MY HEARING LOSS BE CAUSED BY MUTATIONS IN THE GENES THAT CAUSE USHER SYNDROME?

Usher Type I:
Hearing loss due to the MYO7A, USH1C, CDH23, PCDH15, and USH1G genes that cause Usher syndrome Type I is most often seen in a person with:
- Hearing loss that is severe-to-profound and present at birth
- Hearing loss associated with delayed walking or other evidence of vestibular (balance) problems.
- Hearing loss associated with retinitis pigmentosa (onset by first decade/pre-adolescence). Retinitis pigmentosa is an eye disease that causes night-blindness and a loss of peripheral vision through progressive degeneration of the retina.

Usher Type II:
Hearing loss due to the USH2A, GPR98, and DFNB31 genes that cause Usher syndrome Type II is most often seen in a person with:
- Hearing loss that is mild to severe and present at birth
- Normal vestibular (balance) system
- Hearing loss associated with retinitis pigmentosa (onset in adolescence)

Usher Type III:
Hearing loss due to the CLRN1 gene that causes Usher syndrome Type III is most often seen in a person with:
- Hearing loss that is mild to profound and progressive
- Hearing loss that may be present at birth or may occur after birth
- Hearing loss associated with variable impairment of the vestibular (balance) system
- Hearing loss associated with retinitis pigmentosa (onset in adulthood)

Although these are the most common characteristics of Usher syndrome due to mutations in these genes, there can be variations. Overlapping and atypical presentations have been described for all three types of Usher syndrome. For example some individuals with mutations in type I genes may have a milder presentation (moderate hearing loss and/or a normal vestibular system). In addition, certain genes (MYO7A, USH1C, CDH23, PCDH15, and DFNB31) can cause isolated hearing loss without developing retinitis pigmentosa. In addition, some mutations in USH2A can cause isolated retinitis pigmentosa without hearing loss.
How is Usher Syndrome Gene Testing Performed?

To perform this genetic testing, a DNA sample is obtained and the sequence of the gene(s) is compared to that of the regularly occurring gene sequence to look for changes. Some laboratories may examine the entire coding sequence of the gene, while other laboratories may only search for mutations that have been previously reported. Different laboratories may test a different number of Usher genes.

How are the Results of an Usher Syndrome Gene Test Interpreted?

There are four possible outcomes:

1. No mutations are detected. If no mutations are found, and the entire coding sequence was analyzed in a gene, it is unlikely that the hearing loss is caused by mutations in that specific gene. However, the patient may have Usher syndrome due to mutations in another gene that causes Usher syndrome. Not all genes for Usher syndrome have been identified.

2. Two mutations are detected. If two identical mutations or two different mutations in the same gene are found, and these mutations have been previously found to cause Usher syndrome, it can be assumed that the hearing loss is caused by these mutations.

3. Only one mutation is detected. If only one mutation is detected, interpretation can be difficult.
   A) It is possible that the test did not detect the second mutation. Even though examining the whole coding sequence of the gene will detect most mutations, there are other regions of the gene sequence and surrounding DNA that could contain a mutation. Unfortunately, these sequences are rarely analyzed unless a specific mutation is already known.
   B) The mutation that was found may be unrelated to the hearing loss.

4. Mutations were detected but their significance is unknown. Some changes in these genes are not considered to affect the function of the gene. These changes are often called “polymorphisms”. Sometimes, a new mutation is found and it is not yet clear whether the change will cause hearing loss or not. Unfortunately, more studies would need to be done before a definite conclusion could be made.