

# Understanding the Genetics of Deafness

A Guide for Patients and Families



Harvard Medical School  
Center For Hereditary Deafness



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## A Guide for Patients and Families

This Booklet was created by:

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**Heidi L. Rehm, Ph.D.**

Associate Director, Harvard Medical School Center for Hereditary Deafness  
Instructor of Pathology, Harvard Medical School  
Associate Molecular Geneticist, Harvard-Partners Center for Genetics and Genomics

**Robin E. Williamson**

Division of Medical Sciences, Harvard Medical School

**Margaret A. Kenna, M.D.**

Associate Professor of Otology and Laryngology, Harvard Medical School  
Director, Cochlear Implant Program, Children's Hospital Boston

**David P. Corey, Ph.D.**

Professor of Neurobiology, Harvard Medical School  
Co-Director, Harvard Medical School Center for Hereditary Deafness

**Bruce R. Korf, M.D., Ph.D.**

Chairman, Department of Genetics, University of Alabama at Birmingham

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For questions or comments, or to request additional copies of this booklet, please contact **Heidi Rehm** at:

**Harvard Medical School Center for Hereditary Deafness**

65 Landsdowne Street

Cambridge, MA 02139

Email: [hearing@hms.harvard.edu](mailto:hearing@hms.harvard.edu)

Website: <http://hearing.harvard.edu>



**Hearing** is a complex process, so it should be no surprise that the causes of hearing loss are also complex.

Hearing loss can occur because of damage to the ear, especially the inner ear. For example, infants may be born with hearing loss caused by a viral infection that was acquired during pregnancy. At other times the cause is genetic and therefore due to changes in the genes involved in the hearing process. Sometimes, hearing loss is due to a combination of genetic and environmental factors. There is, for example, a genetic change that makes some people more likely to develop hearing loss after taking certain antibiotic medications. Understanding the genetic causes of deafness has important benefits. This knowledge not only allows doctors to inform families about their chances of having children with hearing loss, but it can also influence the way a person's deafness is treated. Whether a person's hearing loss is going to worsen can sometimes be predicted if the specific cause is known. Also, deafness may be only one of a group of medical problems that a person may have. For example, some people with hearing loss also have problems that affect other parts of the body, such as the heart, kidneys, or eyes. Knowing the genetic cause in these cases allows a doctor to be aware that there might be problems in other systems as well.

It might seem reasonable to suspect a genetic cause of deafness only if the hearing loss runs in the family. But it is common for children to have genetic deafness even though neither one of their parents are affected. This deafness can also be passed on to future generations. Genetic tests can therefore be helpful even if there is only one person in the family with hearing loss.

The genetics of hearing loss can be complicated and difficult to understand. This booklet is designed to help explain the role of genetics in hearing loss, how genetic testing is done, what the results of genetic tests mean, and what options are available for treatment and counseling. If any of this information is unclear, please feel free to ask your physician or your child's physician questions, or request to speak with a genetic counselor or clinical geneticist.

## How is Hearing Loss Detected and Diagnosed?

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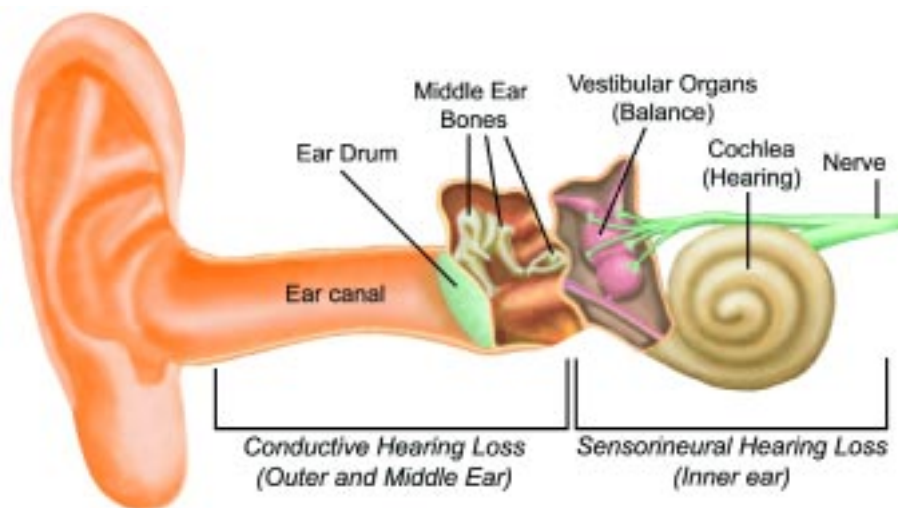
It is important to detect hearing loss as early as possible so that a child can develop appropriate communication and learning skills. For this reason, many states now give a simple, painless hearing test to all newborn babies to determine if they can hear sound. Without this newborn screening, hearing losses might not be noticed by parents, teachers or doctors until the child



begins to have difficulties speaking and learning—sometimes as late as age 2 or 3 years. Therefore, it is important to have this test done at a very early age. Babies who do not pass this screening test are referred to an **audiologist** for more in-depth testing.

An audiologist will first determine the severity and type of hearing loss. The severity of hearing loss is measured by observing how loud a sound needs to be for the child to hear it. This is often referred to as the **hearing threshold** level. The different types of hearing loss are classified according to what part of the hearing system is affected. Sound is picked up by the outer ear and then passes through the ear canal to the middle ear. Problems in these places cause **conductive hearing loss**. After passing through the middle ear, the sound then travels to a part of the inner ear called the cochlea, where it is changed to a signal that can be sent down the hearing nerve to the brain. Problems here cause **sensorineural hearing loss**.

### Anatomy of the Ear



Next, an effort is made to find the cause of the hearing loss. The pediatrician, family practitioner or audiologist involved in the care of the infant or child with a newly diagnosed hearing loss will often refer them to an otolaryngologist for further evaluation of the cause of the hearing loss. Some kinds of hearing loss occur when the hearing system is damaged by things like loud noise, head injury, medications, or infections. Sometimes, knowledge of these causes can help to treat the hearing loss or stop it from getting worse.

Another possibility is that the hearing loss is genetic. This means that it is carried down through a family. This is why recording a detailed family history is very important. There are two main forms of genetic deafness: **syndromic**,

in which there can be other medical problems in addition to the hearing loss, and **nonsyndromic**, where the only obvious medical problem is the loss of hearing. Although most hereditary hearing loss is nonsyndromic, there are also many syndromes that have deafness as a feature. A list of common deafness syndromes is given in the following table. Identification of these syndromes is particularly important in helping to predict whether other medical problems might occur. Deciding whether a hearing loss is syndromic or nonsyndromic is not always easy because some problems can be subtle or only detected by special tests. For example, a special eye exam is required to diagnose Usher syndrome and an **electrocardiogram** is needed to identify Jervell and Lange-Nielsen syndrome (see table). As a result, a doctor may ask for the help of other specialists such as a **cardiologist, ophthalmologist, or clinical geneticist**.

### Common Forms of Syndromic Deafness

Syndrome	Main features (besides deafness)
Alport	Kidney problems
Branchio-oto-renal	Neck cysts and kidney problems
Jervell and Lange-Nielsen	Heart problems
Neurofibromatosis type 2	Tumors of the hearing and balance nerve
Pendred	Thyroid enlargement
Stickler	Unusual facial features, eye problems, arthritis
Usher syndrome	Progressive blindness
Waardenburg syndrome	Skin pigment changes

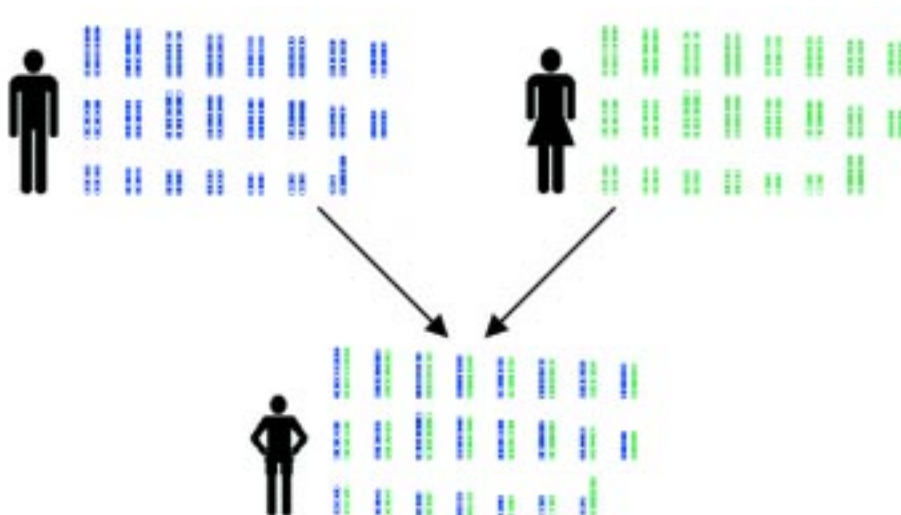
Although a family history can help find a genetic cause, the absence of a family history of deafness does not mean that the deafness is not genetic. In fact, genetic deafness may appear for the first time in a child whose parents are not deaf and may not have any family history of deafness. It is, therefore, important to combine information from physical exams, clinical tests, a family history, and genetic tests to identify the cause of hearing loss. This can help in the treatment and management of the deafness, and to predict the possibility of passing on the deafness to future generations.



## How is Hearing Loss Inherited?

It is estimated that about half of all childhood deafness is due to **hereditary** causes. These hereditary causes involve genes in the hearing process that are inherited or passed down in a family. All of the genes in our bodies are made of a chemical called DNA (deoxyribonucleic acid). DNA is a chemical made of four kinds of building blocks, or bases: adenine (A), cytosine (C), guanine (G), and thymidine (T). These bases can be strung together in many different combinations to create unique DNA sequences. Genes are made of these sequences and contain the instructions for life. A small part of a gene might have a DNA sequence that looks like this: ATTCTGATTTAAGCTA. In total, humans have about 100,000 different genes that are grouped into small structures called **chromosomes**. People have 23 pairs of chromosomes, including a pair of sex chromosomes. Each pair consists of one chromosome that is inherited from the mother and another chromosome that is inherited from the father. The sex chromosomes contain genes that determine the sex of a person. Girls inherit two X chromosomes, whereas boys receive one X chromosome and one Y chromosome. The following figure demonstrates how the chromosomes are passed down from a mother and father to a child.

### Chromosome Inheritance



Because people have two versions, or copies, of every chromosome, they therefore have two copies of every **gene**. The DNA sequences of these genes are more or less the same in everyone. However, sometimes there is a difference in one person's gene sequence as compared to the majority of the population. This DNA change is called an alteration, or **mutation**. Some mutations

may occur that do not interfere with the health of an individual. Other mutations disrupt the gene enough so it does not function correctly. Below is an example of a mutation in a gene associated with hearing. The base change from G to T is enough to alter the instructions contained in the DNA sequence.

... A G A T G A G C A ... Normal sequence = Working gene  
... A G A T T A G C A ... Mutated sequence = Non-working gene

Gene mutations can be **dominant** or **recessive**. If only one altered gene is needed for an individual to be affected, the mutation is considered dominant. For example, if a mother passes on a gene with a dominant mutation, the child will be affected even if the copy received from the father is unaltered. In other words, the altered copy from the mother was “stronger” than the unaltered copy from the father.

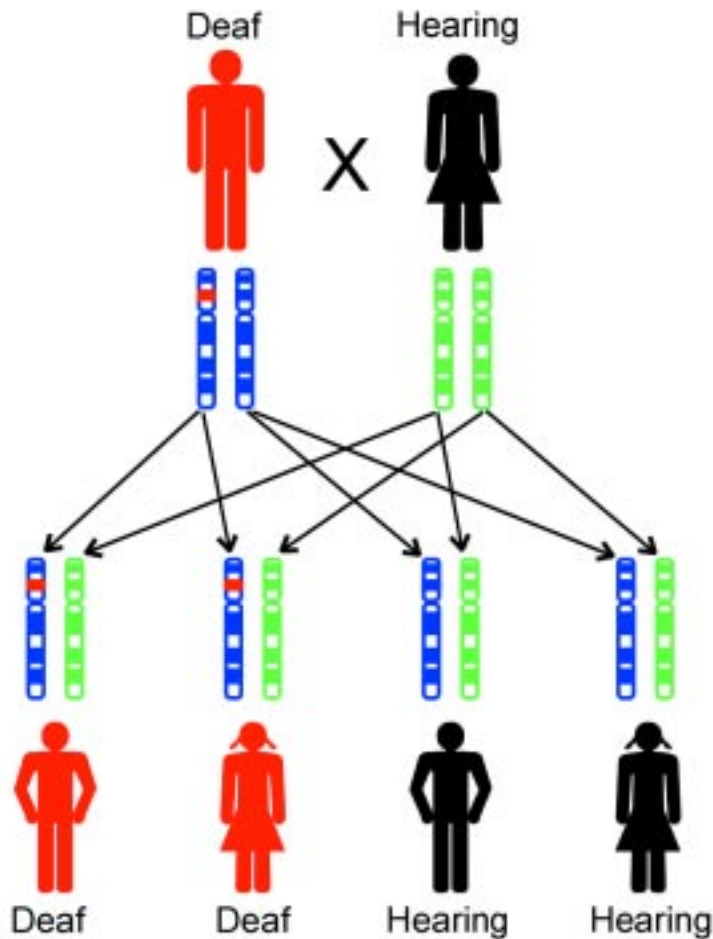
A mutation can also be recessive. In this case, the altered gene is not strong enough to have an effect if a person also has one unaltered gene. As a result, an individual must inherit two altered genes, one from each parent, in order to be affected. The term **carrier** is used to describe a person who has one unaltered gene and one gene with a recessive mutation. This person is not affected but can pass on that mutation to his or her children. Because the parents are carriers and therefore not deaf, this form of inheritance is common when there is no family history of deafness. Most cases of connexin 26 deafness are inherited in a recessive pattern.

An additional form of genetic inheritance, called X-linked inheritance, involves recessive mutations in genes on the X chromosome. Women have two X chromosomes, whereas men have one X chromosome and one Y chromosome. Therefore, a son only needs one copy of a recessive gene mutation on the X chromosome to be affected. This is because he does not have a second X chromosome to provide the unaltered version of the gene.

A special form of genetic inheritance observed with hearing loss is called mitochondrial inheritance. Mitochondria are small structures within cells involved in providing energy for the cell. Mitochondria have their own DNA which contains a unique set of genes, different from the cell's genes. If there is a mutation in one of these genes, the mutation can be passed through mitochondrial inheritance. An example of this form of inheritance is the A1555G mutation which makes people more likely to lose their hearing if they are treated with certain antibiotics. For more detailed explanations of these forms of inheritance, see the following four figures.



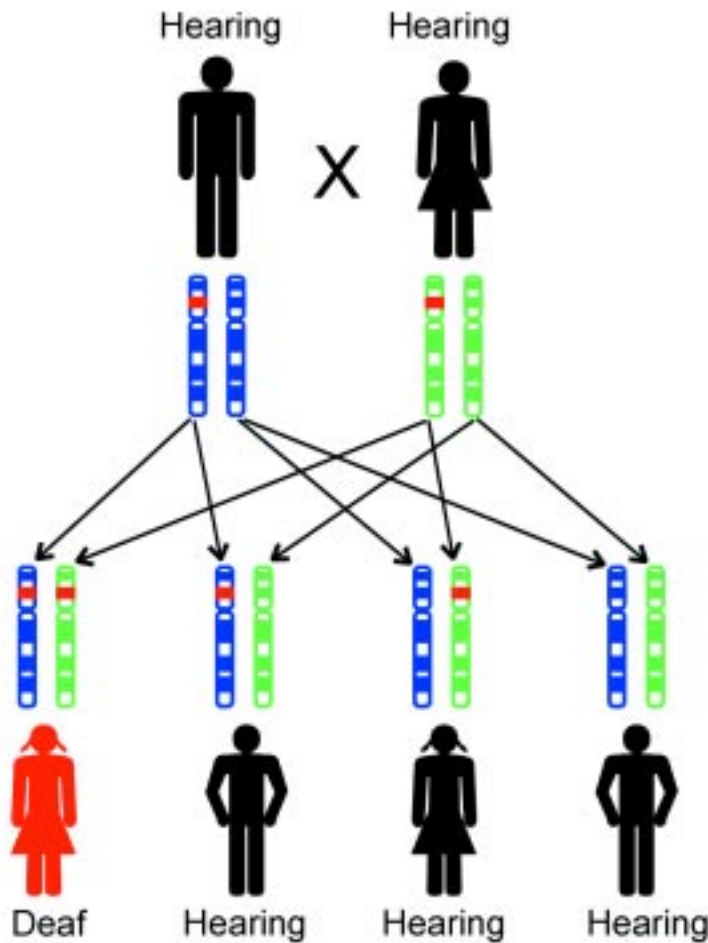
### Inheritance of a Dominant Mutation



Children receive one copy of each chromosome from their mother (shown in green) and one copy from their father (shown in blue). In this example, a red band is used to represent a dominant mutation in a gene on one copy of the father's chromosomes. Because the mother has two copies of the unaltered chromosomes, all of her children will receive an unaltered copy from her. In contrast, the children each have a 1 out of 2 (or 50%) chance of receiving the copy with the dominant mutation from their father. As shown in the figure, 50% of the children will inherit a chromosome with the dominant mutation. Remember that, in the case of dominant mutations, just one copy is needed for an individual to be affected. It follows, then, that in each pregnancy, there is a 50% chance that the child will be affected.



## Inheritance of a Recessive Mutation



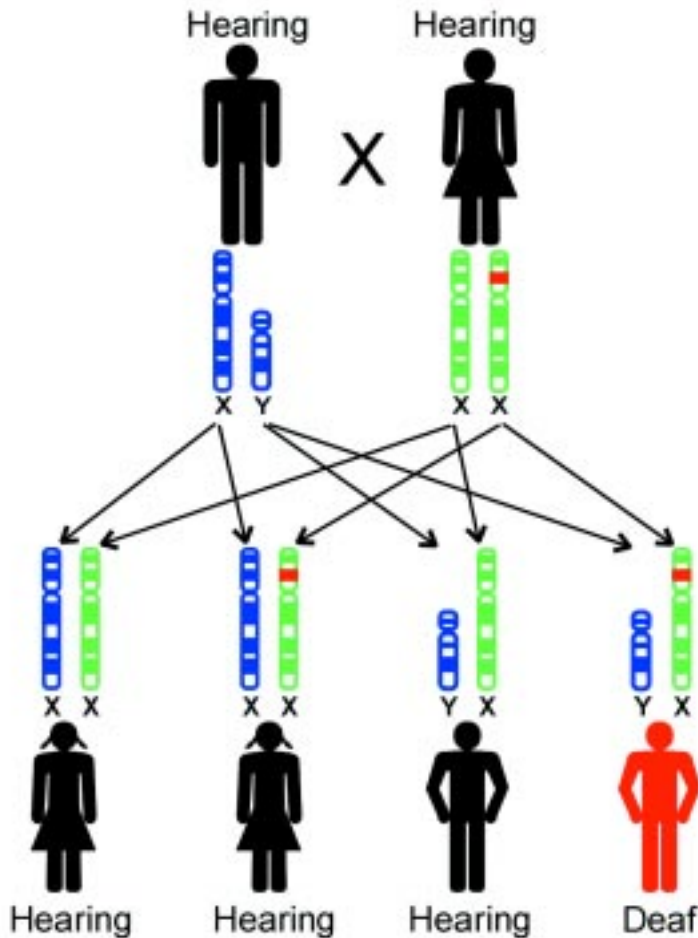
Children receive one copy of each chromosome from their mother (shown in green) and one copy from their father (shown in blue). In this example, a red band represents a recessive mutation in a gene on one copy of the father's chromosomes and a second red band represents a recessive mutation in the same gene on one copy of the mother's chromosomes. Each child has a 50% chance of receiving the copy with the recessive mutation from either parent. But, in the case of recessive mutations, both copies need to be altered for an individual to be affected. The chance of two events happening at the same time can be found by multiplying the chance of the two separate events together.

$$\begin{array}{rcl}
 \text{(chance of receiving mutation from father)} & & 1/2 \\
 \times \text{(chance of receiving mutation from mother)} & & \times 1/2 \\
 \hline
 = \text{(chance of receiving two mutations)} & & 1/4
 \end{array}$$

Therefore, in each pregnancy, there is a 25% chance that the child will inherit both mutations and, on average, 1 out of 4 children will be deaf.

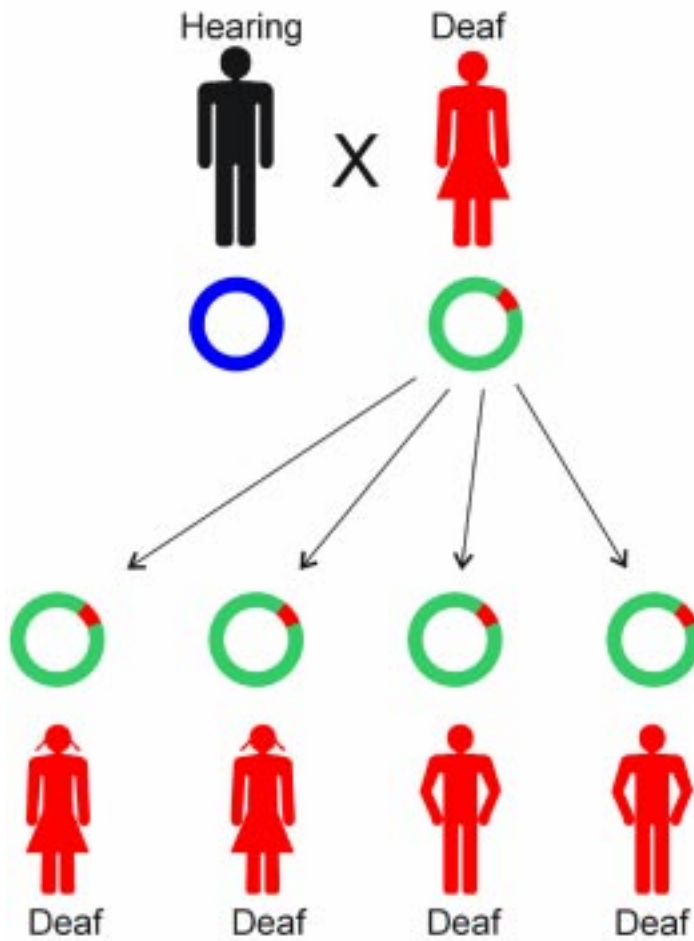


### Inheritance of an X-Linked Recessive Mutation



Children receive one sex chromosome from their mother (shown in green) and one sex chromosome from their father (shown in blue). Because women have two X chromosomes, all children inherit an X chromosome from their mother. On the other hand, males have one X chromosome and one Y chromosome. Therefore, children may receive an X chromosome from their father and become a girl, or receive a Y chromosome and become a boy. In this example, a red band is used to represent a recessive mutation of one of the mother's X chromosomes. As shown in the figure, even if the girls inherit an altered copy from their mother, they will still be unaffected because they will get an unaltered copy from their father. On the other hand, the boys receive a Y chromosome from their father so they do not have an unaltered copy of the X chromosome to block the effect of the mutation. Therefore, because sons have a 1 out of 2, or 50%, chance of inheriting the altered X chromosome from their mother, they have a 50% chance of being deaf.

## Inheritance of a Mitochondrial Mutation



During reproduction, only the egg from the mother, and not the sperm from the father, contributes mitochondria to the developing child. As a result, only females will pass on mitochondrial traits to their children. If a mutation occurs in one of the mother's mitochondrial genes, she will pass the mutation onto all of her children. In contrast, a male will not pass on a mitochondrial mutation to any of his children.



There are also cases in which a genetic mutation is seen for the first time in a person whose parents do not carry the mutation. This type of mutation is called a spontaneous mutation and is usually caused because of a DNA change in a gene in the parent's sperm or egg cells. This is one way that genetic inheritance of a trait can suddenly begin within a family when ancestors were not affected. In this case it would have been impossible to predict that the child would be affected, but the chance of future generations having deafness can be determined.

Although there are many forms of hearing loss that are caused by mutations in single genes, other types are believed to require mutations in two or more genes for a person to be affected. Also, mutations in some genes do not appear to cause hearing loss directly. Instead, they put a person at risk for deafness due to environmental factors, such as exposure to loud noise or antibiotics. The continued study of people with hearing loss is needed to understand these situations and the sometimes complex connections between genetics and hearing loss.

## What is Genetic Testing?

How are genetic mutations detected and how can we use the information learned from this analysis? Genetic testing is the process of comparing the sequence of a particular person's gene with that of the regularly occurring gene. The comparison may detect mutations that could make the gene stop working. It is important to keep in mind that genetic testing can only be performed if the gene that is altered in a given condition is known. Although the genes that contribute to deafness are being discovered at a rapid pace, there are many forms of hearing loss for which the responsible gene remains unknown. A person can only be tested for those genes that have already been discovered. Furthermore, some genes are very large and difficult to analyze. If such a gene is rarely involved in a disorder, it may not be practical to determine the sequence of a person's entire gene. However, as technology improves and more genes are discovered, many genetic tests will become widely available.

Mutations in the connexin 26 gene (on chromosome 13) are the most common genetic cause of deafness and are thought to be responsible for up to half of recessive nonsyndromic hearing loss. Consequently, the most common genetic test for deafness is the connexin 26 gene test. Luckily, the gene is very short, which makes the genetic test relatively easy. As a result, any child who is born with hearing loss, or who develops hearing loss after birth, is a candidate for

connexin 26 testing. This is especially true in cases where other obvious causes are not found.

Certain connexin 26 mutations are more common within specific populations. One mutation, called “35delG”, is often found in Caucasians, where it is estimated that as many as 2-3% of people have at least one altered copy of the gene. This mutation is called 35delG because the **G** at position **35** of the sequence is **deleted**. This mutation is shown below.

**35delG Mutation:** The G at position 35 is highlighted in blue.

```
...C T G G G G G G G T G T G A A C A A A C A C ... Hearing
...C T G G G G G V T G T G A A C A A A C A C ... Deaf
```

Another mutation, referred to as “167delT”, is common in the Ashkenazi Jewish population, with almost 1 out of 20 people having at least one altered copy. As before, the 167delT name means that the **T** at position **167** of the connexin 26 sequence has been **deleted**.

Usually, mutations in the connexin 26 gene are recessive, so that both copies of the connexin 26 gene must have mutations to cause deafness. People who have mutations in both copies of their gene can often be given accurate and straightforward genetic information. Sometimes, however, the results are more complicated. Some changes in gene sequences have never been seen before and are of unknown significance. Not all sequence changes in the connexin 26 gene cause hearing loss. Moreover, although both copies of the connexin 26 gene must usually be mutated for hearing loss to occur, some people with hearing loss have only one connexin 26 mutation. It may be that there is a change in the other copy of the gene that is difficult to identify and was therefore missed. Alternatively, the mutation may be dominant and one altered copy may be sufficient to cause hearing loss. Or there may be a mutation in another gene (e.g. connexin 30) that may work together with the single connexin 26 mutation to cause hearing loss. Also, it is possible that the deafness in such a person is not related to connexin 26 at all. The person may have another mutation in a different deafness gene that is causing the hearing loss. Finally, the deafness may be due to nongenetic causes entirely. These are reasons why interpretation of genetic test results is not always easy.

Many genes contribute to hereditary hearing loss and the list is growing quickly. As new genes are discovered, the number of genetic tests for hearing loss will also increase. Specific genetic tests currently available are described in the information cards included with this booklet.



## How is Genetic Testing Helpful?

Knowing the genetic cause of a person's hearing loss can lead to improved decisions about treatment and management. In some cases, genetic information can help predict whether the hearing loss will remain the same or whether it will worsen over time. Knowledge of the genetic cause is also useful in determining what kind of damage has happened to the hearing system to cause the deafness. This is important because how the inner ear is damaged may affect whether a cochlear implant, or other hearing device, may help a patient. In addition, because mutations in some genes cause syndromic hearing loss, genetic testing can help determine if problems besides hearing loss may be present or may develop in the future.

In addition to improved treatment choices, genetic information may help in other ways. Genetic testing can provide a deaf individual or the parents of a deaf child with the satisfaction of understanding the cause of the hearing loss. It can also be useful when making reproductive choices. If the genetic cause of a person's deafness is known, it is then possible to predict the likelihood that future children of that person will also have hearing loss. This may affect a couple's decision to have more children, or it may be used to help them prepare for the birth of a deaf child. In general, how people use genetic information will vary widely depending upon individual perspectives about hearing loss, religious beliefs, and other factors.

Regardless of how the genetic information is used it can be an overwhelming and stressful experience for people to learn that a mutation in their own genes is the cause of their child's deafness. It should be remembered, however, that genetic mutations are very common. All people carry gene mutations that might affect their health or physical characteristics. Mutations in some genes may cause medically important conditions, while others explain many of the normal differences between people. No person is responsible for the particular genes he or she possesses.

These benefits and drawbacks of genetic testing must be understood by anyone considering testing so that an informed decision about testing can be made. Genetic counselors are skilled in educating others about genetic testing and its many associated issues. You should feel free to contact a counselor or doctor if there is any information about genetic testing that is unclear, or if you would like to discuss your particular situation.

**Alexander Graham Bell Association for the Deaf and Hard of Hearing**

3417 Volta Place, N.W., Washington, DC 20007

Tel: 202-337-5220, TTY: 202-337-5221

■ [info@agbell.org](mailto:info@agbell.org)

● <http://www.agbell.org>

**American Society for Deaf Children**

P.O. Box 3355, Gettysburg, PA 17325

Tel (TTY/V): 717-334-7922

Fax: 717-334-8808

■ [ASDC1@aol.com](mailto:ASDC1@aol.com)

● <http://www.deafchildren.org>

**Boys Town National Research Hospital**

● <http://www.boystownhospital.org>

**Connexins and Deafness**

● <http://www.crg.es/deafness>

**Gallaudet University**

800 Florida Ave., NE, Washington, DC 20002-3695

Tel (TTY/V): 202-651-5000

● <http://www2.gallaudet.edu>

**GeneTests GeneClinics**

● <http://www.genetests.org>

**Harvard Medical School Center for Hereditary Deafness**

● <http://hearing.harvard.edu>

**Hereditary Hearing Loss Homepage**

● <http://dnalab-www.uia.ac.be/dnalab/hhh>

**National Association of the Deaf**

814 Thayer Ave., Silver Springs, MD 20910

Tel (V): 301-587-1788, (TTY): 301-587-1789

■ [NADinfo@nad.org](mailto:NADinfo@nad.org)

● <http://www.nad.org>

**National Center for Hearing Assessment and Management**

● <http://www.infanthearing.org>

**National Institute on Deafness and Other Communication Disorders**

31 Center Drive, MSC 2320, Bethesda, MD USA 20892-2320

Tel: 800-241-1044, TTY: 800-241-1055

■ [nidcdinfo@nidcd.nih.gov](mailto:nidcdinfo@nidcd.nih.gov)

● <http://www.nidcd.nih.gov>

**Self Help for Hard of Hearing People, Inc.**

7910 Woodmont Ave, Suite 1200, Bethesda, Maryland 20814

Tel: 301-657-2248, TTY: 301-657-2249

■ [National@shhh.org](mailto:National@shhh.org)

● <http://www.shhh.org>



# glossary

- Audiologist** ..... A person who specializes in evaluating people with hearing loss.
- Cardiologist** ..... A doctor who specializes in heart diseases.
- Carrier** ..... A person who has one unaltered version of a gene and one version with a recessive mutation. This person is not affected by the mutation.
- Chromosome** ..... A structure containing many genes arranged on a long strand of DNA. Each person has 23 pairs of chromosome, including a pair of sex chromosomes.
- Clinical geneticist** ..... A doctor who specializes in recognizing and treating patients with genetic diseases.
- Conductive hearing loss** ..... Hearing loss caused by problems in the outer or middle ear.
- DNA** ..... (deoxyribonucleic acid) The chemical that makes up genes. It is composed of adenine (A), cytosine (C), guanine (G), and thymidine (T).
- Dominant mutation** ..... A mutation in a gene that is strong enough to make a person affected even if the person also has a normal copy of the gene.
- Electrocardiogram** ..... (ECG or EKG) – An electrical measurement of heart function.
- Gene** ..... A unique sequence of DNA that serves as a specific set of instructions in the body.
- Hearing threshold** ..... The lowest level of sound that can be heard during a hearing test.
- Hereditary** ..... inherited; something that is passed from parent to child





- Mitochondria** ..... Small structures within cells that provide energy for the cell. Mitochondria have their own DNA, different from the cell's DNA.
- Mutation** ..... A change in a gene sequence that often disrupts the function of the gene.
- Nonsyndromic deafness** ..... Hearing loss that occurs in the absence of other medical problems.
- Ophthalmologist** ..... A doctor who specializes in studying eye diseases.
- Otolaryngologist (ENT/URL)** . . . A doctor who studies ear, nose and throat disorders.
- Recessive mutation** ..... A mutation in a gene that is not strong enough to make a person affected if the person also has a normal copy of the gene.
- Sensorineural hearing loss** . . . . Hearing loss caused by problems in the inner ear.
- Syndromic deafness** ..... Hearing loss that is associated with other medical problems.
- X-linked inheritance** ..... A special form of inheritance that involves mutations on the X-chromosome.







These cards contain information on clinically  
available genetic tests for hearing loss.



<http://hearing.harvard.edu>

For questions or comments, or to request additional copies of this booklet,  
please contact Heidi Rehm at:



Harvard Medical School  
Center For Hereditary Deafness

65 Landsdowne Street

Cambridge, MA 02139

E-mail: [hearing@hms.harvard.edu](mailto:hearing@hms.harvard.edu)

Website: <http://hearing.harvard.edu>

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# FACTS ABOUT GENETIC TESTING

## WHAT IS A GENETIC TEST?

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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?

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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?

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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?

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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?

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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](http://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?

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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?

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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?

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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?

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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?

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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?

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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?

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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?

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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?

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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?

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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  
OR
- Hearing loss that began after antibiotic treatment  
OR
- Hearing loss that is associated with neuromuscular disease  
OR
- Hearing loss that is associated with diabetes

There are two mitochondrial genes known to cause nonsyndromic hearing loss (*12S rRNA* and *tRNA<sup>ser</sup>(UCN)*). There are several mitochondrial genes known to cause syndromic forms of hearing loss. For example, mutations in the *tRNA<sup>Leu</sup>(UUR)* and *tRNA<sup>Lys</sup>* genes can both cause hearing loss associated with neuromuscular diseases such as MELAS and MERRF. Mutations in the *tRNA<sup>Leu</sup>(UUR)* 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?

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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?

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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?

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*COCH* hearing loss is most often seen in a person with:

- Isolated (nonsyndromic) 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?

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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?

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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 noncoding 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>.

# CONNEXIN 30 GENE TESTING

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

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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 Cx30 GENE TEST PERFORMED?

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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 Cx30 TEST INTERPRETED?

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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?

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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?

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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?

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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?

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### 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?

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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?

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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.