Understanding the Genetics of Deafness

A Guide for Patients and Families

Harvard Medical School
Center For Hereditary Deafness

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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.

hearing loss

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.

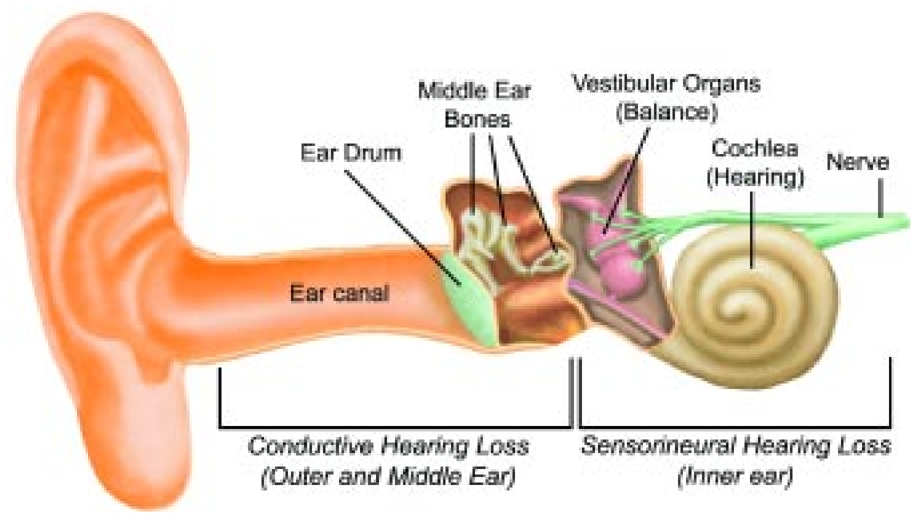
The genetics of hearing loss can be complicated and difficult to understand. This booklet is designed to help explain the role of genetics in hearing loss, how genetic testing is done, what the results of genetic tests mean, and what options are available for treatment and counseling. If any of this 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?

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

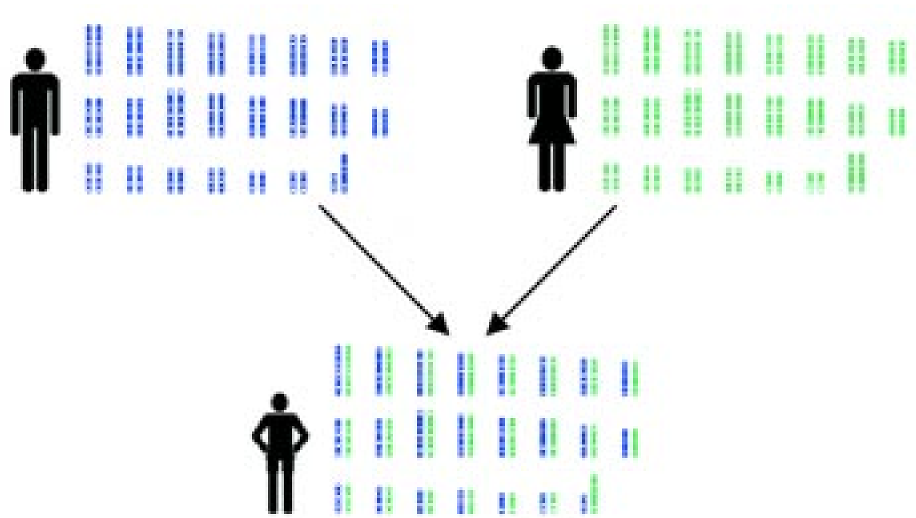
Syndrome	Main features (besides deafness)
Alport	Kidney problems
Branchio-oto-renal	Neck cysts and kidney problems
Jervell and Lange-Nielsen	Heart problems
Neurofibromatosis type 2	Tumors of the hearing and balance nerve
Pendred	Thyroid enlargement
Stickler	Unusual facial features, eye problems, arthritis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

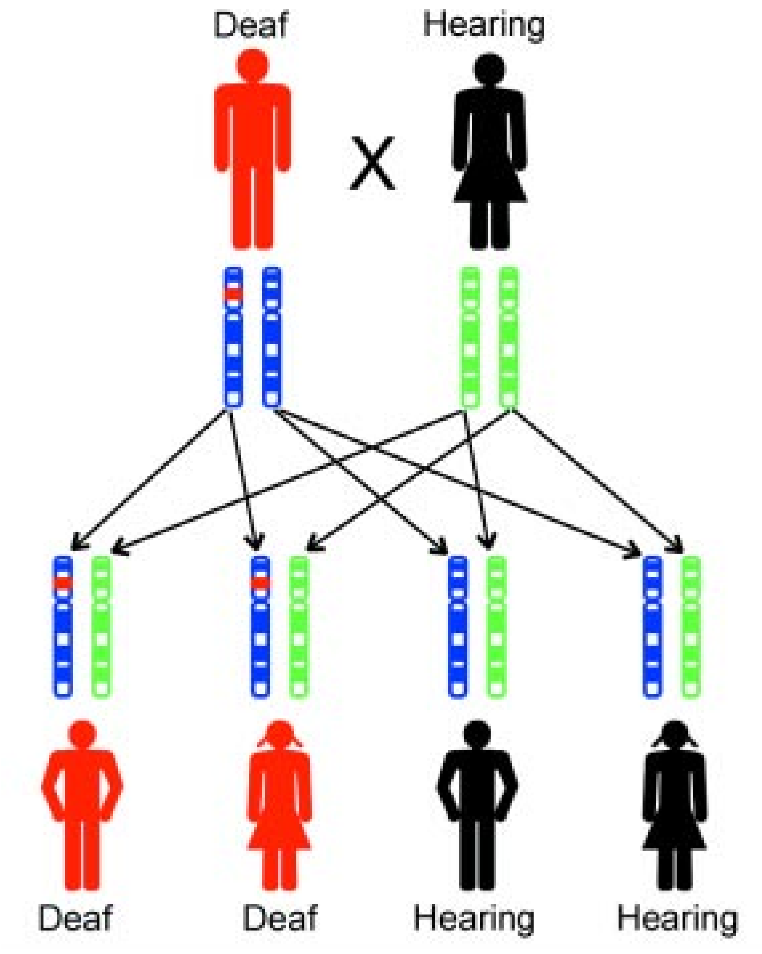
Gene mutations can be **dominant** or **recessive**. If only one altered gene is needed for an individual to be affected, the mutation is considered dominant. For example, if a mother passes on a gene with a dominant mutation, the child will be affected even if the copy received from the father is unaltered.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

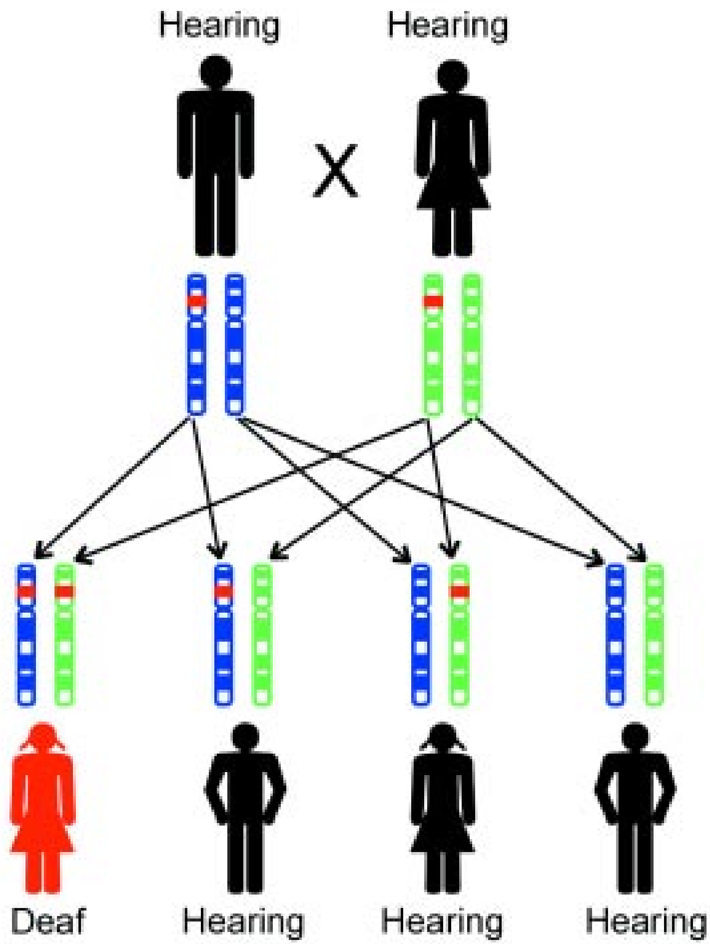
A special form of genetic inheritance observed with hearing loss is called mitochondrial inheritance. Mitochondria are small structures within cells involved in providing energy for the cell. Mitochondria have their own DNA which contains a unique set of genes, different from the cell's genes. If there 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

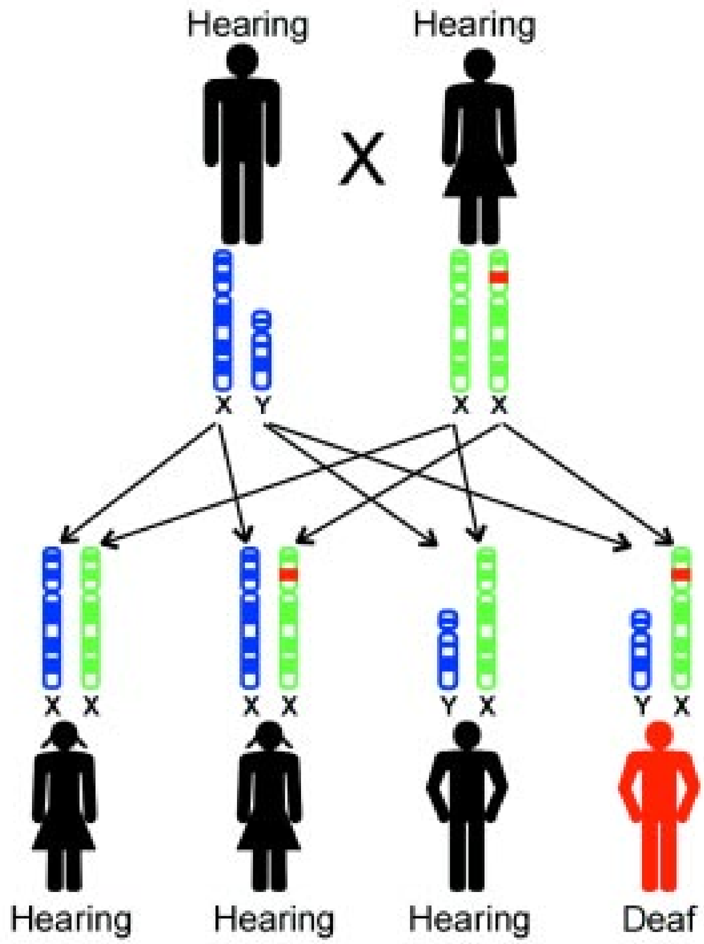


Children receive one copy of each chromosome from their mother (shown in green) and one copy from their father (shown in blue). In this example, a red band represents a recessive mutation in a gene on one copy of the father's chromosomes and a second red band represents a recessive mutation in the same 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.

	(chance of receiving mutation from father)	**1/2**
x	**(chance of receiving mutation from mother)**	**x 1/2**
=	**(chance of receiving two mutations)**	**1/4**

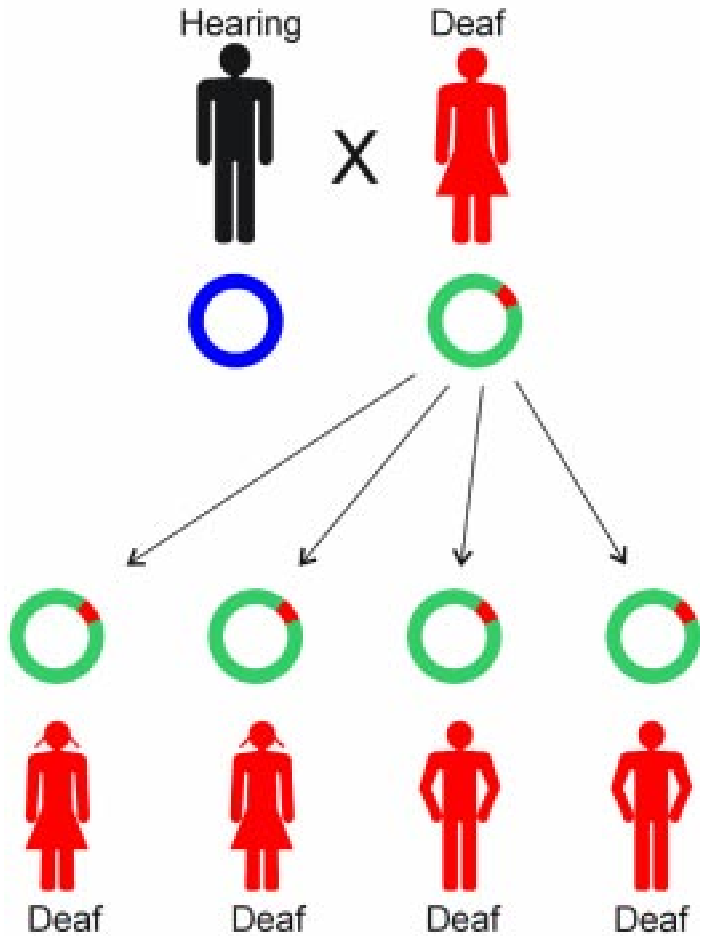
Therefore, in each pregnancy, there is a 25% chance that the child will inherit both mutations and, on average, 1 out of 4 children will be deaf.

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