

## Genes and Hearing Loss

One of the most common birth defects is hearing loss or deafness (congenital), which can affect as many as three of every 1,000 babies born. Inherited genetic defects play an important role in congenital hearing loss, contributing to about 60% of deafness occurring in infants. Although exact data is not available, it is likely that genetics plays an important role in hearing loss in the elderly. Inherited genetic defects are just one factor that can lead to hearing loss and deafness, both of which may occur at any stage of a person's lifespan. Other factors may include: medical problems, environmental exposure, trauma, and medications.

The most common and useful distinction in hearing impairment is syndromic versus non-syndromic.

**Non-syndromic** hearing impairment accounts for the vast majority of inherited hearing loss, approximately 70%. Autosomal-recessive inheritance is responsible for about 80% of cases of non-syndromic hearing impairment, while autosomal-dominant genes cause 20%, less than two percent of cases are caused by X-linked and mitochondrial genetic malfunctions.

**Syndromic** (sin-DRO-mik) means that the hearing impairment is associated with other clinical abnormalities. Among hereditary hearing impairments, 15 to 30% are syndromic. Over 400 syndromes are known to include hearing impairment and can be classified as: syndromes due to cytogenetic or chromosomal anomalies, syndromes transmitted in classical monogenic or Mendelian inheritance, or syndromes due to multi-factorial influences, and finally, syndromes due to a combination of genetic and environmental factors.

Variable expression of different aspects of syndromes is common. Some aspects may be expressed in a range from mild to severe or different combinations of associated symptoms may be expressed in different individuals carrying the same mutation within a single pedigree. An example of variable expressivity is seen in families transmitting autosomal dominant Waardenburg syndrome. Within the same family, some affected members may have dystopia canthorum (an unusually wide nasal bridge due to sideways displacement of the inner angles of the eyes), white forelock, heterochromia irides (two different-colored irises or two colors in the same iris), and hearing loss, while others with the same mutation may only have dystopia canthorum.

### HOW DO GENES WORK?

Genes are a road map for the synthesis of proteins, which are the building blocks for everything in the body: hair, eyes, ears, heart, lung, etc. Every child inherits half of its genes from one parent and half from the other parent. If the inherited genes are defective, a health disorder such as hearing loss or deafness can result. Hearing disorders are inherited in one of four ways:

**Autosomal Dominant Inheritance:** For autosomal dominant disorders, the transmission of a rare allele of a gene by a single heterozygous parent is sufficient to generate an affected child. A

heterozygous parent has two types of the same gene (in this case, one mutated and the other normal) and can produce two types of gametes (reproductive cells). One gamete will carry the mutant form of the gene of interest, and the other the normal form. Each of these gametes then has an equal chance of being used to form the offspring. Thus the chance that the offspring of a parent with an autosomal dominant gene will develop the disorder is 50 percent. Autosomal dominant traits usually affect males and females equally.

**Autosomal Recessive Inheritance:** An autosomal recessive trait is characterized by having parents who are heterozygous carriers for mutant forms of the gene in question but are not affected by the disorder. The problem gene that would cause the disorder is suppressed by the normal gene. These heterozygous parents (A/a) can each generate two types of gametes, one carrying the mutant copy of the gene (a) and the other having a normal copy of the gene (A). There are four possible combinations from each of the parents, A/a, A/A, a/A, and a/a. Only the offspring that inherits both mutant copies (a/a) will exhibit the trait. Overall, offspring of these two parents will face a 25 percent chance of inheriting the disorder.

**X-linked Inheritance:** A male offspring has an X chromosome and a Y chromosome, while a female has two copies of the X chromosome only. Each female inherits an X chromosome from her mother and her father. On the other hand, each male inherits an X chromosome from his mother and a Y chromosome from his father. In general, only one of the two X chromosomes carried by a female is active in any one cell while the other is rendered inactive. This is why when a female inherits a defective gene on one X chromosome, the normal gene on the other X chromosome can usually compensate. As males only have one copy of the X chromosome, any defective gene is more likely to manifest into a disorder.

**Mitochondrial Inheritance:** Mitochondria, small powerhouses within each cell, also contain their own DNA. Interestingly, the sperm does not have any mitochondria, and consequently, only the mitochondria in the egg from the mother can be passed from one generation to the next. This leads to an interesting inheritance pattern where only affected mothers (and not affected fathers as their sperms do not have mitochondria) can pass on a disease from one generation to the next. Sensitivity to aminoglycoside antibiotics can be inherited through a defect in mitochondrial DNA and is the most common cause of deafness in China!

In the last decade, advances in molecular biology and genetics have contributed substantially to the understanding of development, function, and pathology of the inner ear. Researchers have identified several of the various genes responsible for hereditary deafness or hearing loss, most notably the GJB2 gene mutation. As one of the most common genetic causes of hearing loss, GJB2-related hearing loss is considered a recessive genetic disorder because the mutations only cause deafness in individuals who inherit two copies of the mutated gene, one from each parent. A person with one mutated copy and one normal copy is a carrier but is not deaf. Screening tests for the GJB2 gene are available for at risk individuals to help them determine their risk of having a child with hearing problems.