Nonsyndromic hearing loss

Nonsyndromic hearing loss is a partial or total loss of hearing that is not associated with other signs and symptoms. In contrast, syndromic hearing loss occurs with signs and symptoms affecting other parts of the body.

Nonsyndromic hearing loss can be classified in several different ways. One common way is by the condition's pattern of inheritance: autosomal dominant (DFNA), autosomal recessive (DFNB), X-linked (DFNX), or mitochondrial (which does not have a special designation). Each of these types of hearing loss includes multiple subtypes. DFNA, DFNB, and DFNX subtypes are numbered in the order in which they were first described. For example, DFNA1 was the first type of autosomal dominant nonsyndromic hearing loss to be identified.

The characteristics of nonsyndromic hearing loss vary among the different types. Hearing loss can affect one ear (unilateral) or both ears (bilateral). Degrees of hearing loss range from mild (difficulty understanding soft speech) to profound (inability to hear even very loud noises). The term "deafness" is often used to describe severe-to-profound hearing loss. Hearing loss can be stable, or it may be progressive, becoming more severe as a person gets older. Particular types of nonsyndromic hearing loss show distinctive patterns of hearing loss. For example, the loss may be more pronounced at high, middle, or low tones.

Most forms of nonsyndromic hearing loss are described as sensorineural, which means they are associated with a permanent loss of hearing caused by damage to structures in the inner ear. The inner ear processes sound and sends the information to the brain in the form of electrical nerve impulses. Less commonly, nonsyndromic hearing loss is described as conductive, meaning it results from changes in the middle ear. The middle ear contains three tiny bones that help transfer sound from the eardrum to the inner ear. Some forms of nonsyndromic hearing loss, particularly a type called DFNX2, involve changes in both the inner ear and the middle ear. This combination is called mixed hearing loss.

Depending on the type, nonsyndromic hearing loss can become apparent at any time from infancy to old age. Hearing loss that is present before a child learns to speak is classified as prelingual or congenital. Hearing loss that occurs after the development of speech is classified as postlingual.

Frequency

Between 2 and 3 per 1,000 children in the United States are born with detectable hearing loss in one or both ears. The prevalence of hearing loss increases with age; the condition affects 1 in 8 people in the United States age 12 and older, or about 30 million people. By age 85, more than half of all people experience hearing loss.

Causes

The causes of nonsyndromic hearing loss are complex. Researchers have identified more than 90 genes that, when altered, are associated with nonsyndromic hearing loss. Many of these genes are involved in the development and function of the inner ear. Mutations in these genes contribute to hearing loss by interfering with critical steps in processing sound. Different mutations in the same gene can be associated with different types of hearing loss, and some genes are associated with both syndromic and nonsyndromic forms. In many affected families, the factors contributing to hearing loss have not been identified.

Most cases of nonsyndromic hearing loss are inherited in an autosomal recessive pattern. About half of all severe-to-profound autosomal recessive nonsyndromic hearing loss results from mutations in the *GJB2* gene; these cases are designated DFNB1. The *GJB2* gene provides instructions for making a protein called connexin 26, which is a member of the connexin protein family. Mutations in another connexin gene, *GJB6*, can also cause DFNB1. The *GJB6* gene provides instructions for making a protein called connexin 30. Connexin proteins form channels called gap junctions, which allow communication between neighboring cells, including cells in the inner ear. Mutations in the *GJB2* or *GJB6* gene alter their respective connexin proteins, which changes the structure of gap junctions and may affect the function or survival of cells that are needed for hearing.

The most common cause of moderate autosomal recessive nonsyndromic hearing loss is mutations in the *STRC* gene. These mutations cause a form of the condition known as DFNB16. Mutations in more than 60 other genes can also cause autosomal recessive nonsyndromic hearing loss. Many of these gene mutations have been found in one or a few families.

Nonsyndromic hearing loss can also be inherited in an autosomal dominant pattern. Mutations in at least 30 genes have been identified in people with autosomal dominant nonsyndromic hearing loss; mutations in some of these genes (including *GJB2* and *GJB6*) can also cause autosomal recessive forms of the condition. Although no single gene is associated with a majority of autosomal dominant nonsyndromic hearing loss cases, mutations in a few genes, such as *KCNQ4* and *TECTA*, are relatively common. Mutations in many of the other genes associated with autosomal dominant nonsyndromic hearing loss have been found in only one or a few families.

X-linked and mitochondrial forms of nonsyndromic hearing loss are rare. About half of all X-linked cases are caused by mutations in the *POU3F4* gene. This form of the condition is designated DFNX2. Mutations in at least three other genes have also been identified in people with X-linked nonsyndromic hearing loss.

Mitochondrial forms of hearing loss result from changes in mitochondrial DNA (mtDNA). Mitochondria are structures within cells that convert the energy from food into a form that cells can use. Although most DNA is packaged in chromosomes within the nucleus, mitochondria also have a small amount of their own DNA. Only a few mutations in

mtDNA have been associated with hearing loss, and their role in the condition is still being studied.

Mutations in some of the genes associated with nonsyndromic hearing loss can also cause syndromic forms of hearing loss, such as Usher syndrome (*CDH23* and *MYO7A*, among others), Pendred syndrome (*SLC26A4*), Wolfram syndrome (*WFS1*), and Stickler syndrome (*COL11A2*). It is often unclear how mutations in the same gene can cause isolated hearing loss in some individuals and hearing loss with additional signs and symptoms in others.

In addition to genetic changes, hearing loss can result from environmental factors or a combination of genetic risk and a person's environmental exposures. Environmental causes of hearing loss include certain medications, specific infections before or after birth, and exposure to loud noise over an extended period. Age is also a major risk factor for hearing loss. Age-related hearing loss (presbycusis) is thought to have both genetic and environmental influences.

Inheritance Pattern

As discussed above, nonsyndromic hearing loss has different patterns of inheritance. Between 75 and 80 percent of cases are inherited in an autosomal recessive pattern, which means both copies of the gene in each cell have mutations. Usually, each parent of an individual with autosomal recessive hearing loss carries one copy of the mutated gene but does not have hearing loss.

Another 20 to 25 percent of nonsyndromic hearing loss has an autosomal dominant pattern of inheritance, which means one copy of the altered gene in each cell is sufficient to cause the condition. Most people with autosomal dominant hearing loss inherit an altered copy of the gene from a parent who also has hearing loss.

Between 1 and 2 percent of cases have an X-linked pattern of inheritance. A condition is considered X-linked if the mutated gene that causes the disorder is located on the X chromosome, one of the two sex chromosomes in each cell. Males with X-linked nonsyndromic hearing loss tend to develop more severe hearing loss earlier in life than females who inherit a copy of the same gene mutation. A characteristic of X-linked inheritance is that fathers cannot pass X-linked traits to their sons.

Mitochondrial forms of the condition, which result from changes to mtDNA, account for less than 1 percent of all nonsyndromic hearing loss in the United States. These cases are inherited in a mitochondrial pattern, which is also known as maternal inheritance. This pattern of inheritance applies to genes contained in mtDNA. Because egg cells, but not sperm cells, contribute mitochondria to the developing embryo, children can only inherit disorders resulting from mtDNA mutations from their mother. These disorders can appear in every generation of a family and can affect both males and females, but fathers do not pass traits associated with changes in mtDNA to their children.

In some cases, hearing loss occurs in people with no history of the condition in their family. These cases are described as sporadic, and the cause of the hearing loss is often unknown. When hearing loss results from environmental factors, it is not inherited.

Other Names for This Condition

- isolated deafness
- nonsyndromic deafness
- nonsyndromic hearing impairment
- nonsyndromic hearing loss and deafness

Diagnosis & Management

Formal Diagnostic Criteria

- ACT Sheet: Congenital hearing loss >~30db
  https://www.ncbi.nlm.nih.gov/books/NBK55827/bin/Hearing_Loss.pdf

Genetic Testing Information

- What is genetic testing?
  /primer/testing/genetictesting
- Genetic Testing Registry: Deafness, X-linked
  https://www.ncbi.nlm.nih.gov/gtr/conditions/CN043651/
- Genetic Testing Registry: Hereditary hearing loss and deafness
  https://www.ncbi.nlm.nih.gov/gtr/conditions/C0236038/
- Genetic Testing Registry: Nonsyndromic hearing loss and deafness
  https://www.ncbi.nlm.nih.gov/gtr/conditions/CN043648/

Research Studies from ClinicalTrials.gov

- ClinicalTrials.gov
  https://clinicaltrials.gov/ct2/results?cond=%22nonsyndromic+deafness%22+OR+%22Hearing+Loss%22+OR+%22Deafness%22

Other Diagnosis and Management Resources

- Baby's First Test: Hearing Loss
  https://www.babysfirsttest.org/newborn-screening/conditions/hearing-loss
- GeneReview: Hereditary Hearing Loss and Deafness Overview
  https://www.ncbi.nlm.nih.gov/books/NBK1434
- MedlinePlus Encyclopedia: Age-related hearing loss
  https://medlineplus.gov/ency/article/001045.htm
- MedlinePlus Encyclopedia: Audiology
  https://medlineplus.gov/ency/article/003341.htm

- MedlinePlus Encyclopedia: Hearing loss
  https://medlineplus.gov/ency/article/003044.htm
- MedlinePlus Encyclopedia: Hearing or speech impairment - resources
  https://medlineplus.gov/ency/article/002152.htm

Additional Information & Resources

Health Information from MedlinePlus

- Encyclopedia: Age-related hearing loss
  https://medlineplus.gov/ency/article/001045.htm
- Encyclopedia: Audiology
  https://medlineplus.gov/ency/article/003341.htm
- Encyclopedia: Hearing loss
  https://medlineplus.gov/ency/article/003044.htm
- Encyclopedia: Hearing or speech impairment - resources
  https://medlineplus.gov/ency/article/002152.htm
- Health Topic: Hearing Disorders and Deafness
  https://medlineplus.gov/hearingdisordersanddeafness.html
- Health Topic: Hearing Problems in Children
  https://medlineplus.gov/hearingproblemsinchildren.html
- Health Topic: Newborn Screening
  https://medlineplus.gov/newbornscreening.html

Additional NIH Resources

- National Institute on Deafness and Other Communication Disorders
  https://www.nidcd.nih.gov/health/hearing-ear-infections-deafness

Educational Resources

- Boston Children's Hospital
  http://www.childrenshospital.org/conditions-and-treatments/conditions/h/hearing-loss
- Centers for Disease Control and Prevention: Hearing Loss in Children
  https://www.cdc.gov/ncbddd/hearingloss/
- Centre for Genetics Education (Australia)
  https://www.genetics.edu.au/publications-and-resources/facts-sheets/fact-sheet-63-deafness-and-hearing-loss
- Harvard Medical School Center for Hereditary Deafness
  https://hearing.harvard.edu/
- Hereditary Hearing Loss Homepage
  https://hereditaryhearingloss.org/

- Kennedy Krieger Institute
  https://www.kennedykrieger.org/patient-care/conditions/hearing-impairment
- KidsHealth from the Nemours Foundation
  https://kidshealth.org/en/kids/hearing-impairment.html
- Laurent Clerc National Deaf Education Center, Gallaudet University
  https://www3.gallaudet.edu/clerc-center.html
- MalaCards: autosomal dominant nonsyndromic deafness
  https://www.malacards.org/card/autosomal_dominant_nonsyndromic_deafness
- MalaCards: autosomal recessive nonsyndromic deafness
  https://www.malacards.org/card/autosomal_recessive_nonsyndromic_deafness
- MalaCards: x-linked nonsyndromic deafness
  https://www.malacards.org/card/x_linked_nonsyndromic_deafness
- March of Dimes: Hearing Impairment
  https://www.marchofdimes.org/baby/hearing-impairment.aspx
- Merck Manual Consumer Version
  https://www.merckmanuals.com/home/ear-nose-and-throat-disorders/hearing-loss-and-deafness/hearing-loss
- Orphanet: Non-syndromic genetic deafness
  https://www.orpha.net/consor/cgi-bin/OC_Exp.php?Lng=EN&Expert=87884
- The Connexin-Deafness Homepage
  http://davinci.crg.es/deafness/
- World Health Organization: Deafness and Hearing Loss
  https://www.who.int/en/news-room/fact-sheets/detail/deafness-and-hearing-loss

Patient Support and Advocacy Resources

- Contact a Family (UK)
  https://contact.org.uk/medical-information/conditions/d/deafness/
- Hearing Health Foundation
  https://hearinghealthfoundation.org/
- John Tracy Clinic
  https://www.jtc.org/
- My Baby's Hearing, Boys Town National Research Hospital
  https://www.babyhearing.org/
- National Association of the Deaf
  https://www.nad.org/

- National Center for Hearing Assessment and Management, Utah State University
  http://www.infanthearing.org/
- Resource List from the University of Kansas Medical Center
  http://www.kumc.edu/gec/support/hearing.html

Clinical Information from GeneReviews

- DFNA2 Nonsyndromic Hearing Loss
  https://www.ncbi.nlm.nih.gov/books/NBK1209
- DFNX1 Nonsyndromic Hearing Loss and Deafness
  https://www.ncbi.nlm.nih.gov/books/NBK57098
- Hereditary Hearing Loss and Deafness Overview
  https://www.ncbi.nlm.nih.gov/books/NBK1434
- Nonsyndromic Hearing Loss and Deafness, DFNA3
  https://www.ncbi.nlm.nih.gov/books/NBK1536
- Nonsyndromic Hearing Loss and Deafness, DFNB1
  https://www.ncbi.nlm.nih.gov/books/NBK1272
- Nonsyndromic Hearing Loss and Deafness, Mitochondrial
  https://www.ncbi.nlm.nih.gov/books/NBK1422
- OTOF-Related Deafness
  https://www.ncbi.nlm.nih.gov/books/NBK1251
- TBC1D24-Related Disorders
  https://www.ncbi.nlm.nih.gov/books/NBK274566
- WFS1-Related Disorders
  https://www.ncbi.nlm.nih.gov/books/NBK4144

Scientific Articles on PubMed

- PubMed
  https://www.ncbi.nlm.nih.gov/pubmed?term=%28%28Deafness%5BMAJR%5D%29+OR+%28hearing+loss%5BMAJR%5D%29%29+AND+%28%28nonsyndromic%5BTIAB%5D%29+OR+%28DFNA*%5BTI%5D%29+OR+%28DFNB*%5BTI%5D%29+OR+%28DFNX*%5BTI%5D%29%29+AND+english%5Bla%5D+AND+human%5Bmh%5D+AND+%22last+720+days%22%5Bdp%5D

Catalog of Genes and Diseases from OMIM

- DEAFNESS, AMINOGLYCOSIDE-INDUCED
  http://omim.org/entry/580000
- DEAFNESS, AUTOSOMAL DOMINANT 2A
  http://omim.org/entry/600101

- DEAFNESS, AUTOSOMAL DOMINANT 3A
  http://omim.org/entry/601544
- DEAFNESS, AUTOSOMAL DOMINANT 4A
  http://omim.org/entry/600652
- DEAFNESS, AUTOSOMAL DOMINANT 5
  http://omim.org/entry/600994
- DEAFNESS, AUTOSOMAL DOMINANT 6
  http://omim.org/entry/600965
- DEAFNESS, AUTOSOMAL DOMINANT 7
  http://omim.org/entry/601412
- DEAFNESS, AUTOSOMAL DOMINANT 9
  http://omim.org/entry/601369
- DEAFNESS, AUTOSOMAL DOMINANT 10
  http://omim.org/entry/601316
- DEAFNESS, AUTOSOMAL DOMINANT 11
  http://omim.org/entry/601317
- DEAFNESS, AUTOSOMAL DOMINANT 12
  http://omim.org/entry/601543
- DEAFNESS, AUTOSOMAL DOMINANT 12
  http://omim.org/entry/601543
- DEAFNESS, AUTOSOMAL DOMINANT 13
  http://omim.org/entry/601868
- DEAFNESS, AUTOSOMAL DOMINANT 15
  http://omim.org/entry/602459
- DEAFNESS, AUTOSOMAL DOMINANT 20
  http://omim.org/entry/604717
- DEAFNESS, AUTOSOMAL DOMINANT 22
  http://omim.org/entry/606346
- DEAFNESS, AUTOSOMAL DOMINANT 23
  http://omim.org/entry/605192
- DEAFNESS, AUTOSOMAL DOMINANT 36
  http://omim.org/entry/606705
- DEAFNESS, AUTOSOMAL DOMINANT 43
  http://omim.org/entry/608394
- DEAFNESS, AUTOSOMAL DOMINANT 48
  http://omim.org/entry/607841

- DEAFNESS, AUTOSOMAL DOMINANT 52
  http://omim.org/entry/607683
- DEAFNESS, AUTOSOMAL RECESSIVE
  http://omim.org/entry/607197
- DEAFNESS, AUTOSOMAL RECESSIVE 1A
  http://omim.org/entry/220290
- DEAFNESS, AUTOSOMAL RECESSIVE 2
  http://omim.org/entry/600060
- DEAFNESS, AUTOSOMAL RECESSIVE 3
  http://omim.org/entry/600316
- DEAFNESS, AUTOSOMAL RECESSIVE 7
  http://omim.org/entry/600974
- DEAFNESS, AUTOSOMAL RECESSIVE 9
  http://omim.org/entry/601071
- DEAFNESS, AUTOSOMAL RECESSIVE 12
  http://omim.org/entry/601386
- DEAFNESS, AUTOSOMAL RECESSIVE 13
  http://omim.org/entry/603098
- DEAFNESS, AUTOSOMAL RECESSIVE 16
  http://omim.org/entry/603720
- DEAFNESS, AUTOSOMAL RECESSIVE 17
  http://omim.org/entry/603010
- DEAFNESS, AUTOSOMAL RECESSIVE 18A
  http://omim.org/entry/602092
- DEAFNESS, AUTOSOMAL RECESSIVE 20
  http://omim.org/entry/604060
- DEAFNESS, AUTOSOMAL RECESSIVE 21
  http://omim.org/entry/603629
- DEAFNESS, AUTOSOMAL RECESSIVE 28
  http://omim.org/entry/609823
- DEAFNESS, AUTOSOMAL RECESSIVE 31
  http://omim.org/entry/607084
- DEAFNESS, AUTOSOMAL RECESSIVE 33
  http://omim.org/entry/607239
- DEAFNESS, AUTOSOMAL RECESSIVE 36, WITH OR WITHOUT VESTIBULAR INVOLVEMENT
  http://omim.org/entry/609006

- DEAFNESS, AUTOSOMAL RECESSIVE 37
  http://omim.org/entry/607821
- DEAFNESS, AUTOSOMAL RECESSIVE 67
  http://omim.org/entry/610265
- DEAFNESS, X-LINKED 1
  http://omim.org/entry/304500
- DEAFNESS, X-LINKED 2
  http://omim.org/entry/304400
- DEAFNESS, X-LINKED 3
  http://omim.org/entry/300030
- DEAFNESS, X-LINKED 4
  http://omim.org/entry/300066
- DEAFNESS, X-LINKED 5
  http://omim.org/entry/300614
- DEAFNESS, X-LINKED 6
  http://omim.org/entry/300914

Sources for This Summary

- Ding Y, Leng J, Fan F, Xia B, Xu P. The role of mitochondrial DNA mutations in hearing loss. Biochem Genet. 2013 Aug;51(7-8):588-602. doi: 10.1007/s10528-013-9589-6. Epub 2013 Apr 21. Review.
  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/23605717
- Duman D, Tekin M. Autosomal recessive nonsyndromic deafness genes: a review. Front Biosci (Landmark Ed). 2012 Jun 1;17:2213-36. Review.
  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/22652773
  Free article on PubMed Central: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3683827/
- Hildebrand MS, Morín M, Meyer NC, Mayo F, Modamio-Hoybjor S, Mencía A, Olavarrieta L, Morales-Angulo C, Nishimura CJ, Workman H, DeLuca AP, del Castillo I, Taylor KR, Tompkins B, Goodman CW, Schrauwen I, Wesemael MV, Lachlan K, Shearer AE, Braun TA, Huygen PL, Kremer H, Van Camp G, Moreno F, Casavant TL, Smith RJ, Moreno-Pelayo MA. DFNA8/12 caused by TECTA mutations is the most identified subtype of nonsyndromic autosomal dominant hearing loss. Hum Mutat. 2011 Jul;32(7):825-34. doi: 10.1002/humu.21512. Epub 2011 Jun 7.
  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/21520338
  Free article on PubMed Central: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3326665/
- Hilgert N, Smith RJ, Van Camp G. Function and expression pattern of nonsyndromic deafness genes. Curr Mol Med. 2009 Jun;9(5):546-64. Review.
  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/19601806
  Free article on PubMed Central: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2840995/
- Lin FR, Niparko JK, Ferrucci L. Hearing loss prevalence in the United States. Arch Intern Med. 2011 Nov 14;171(20):1851-2. doi: 10.1001/archinternmed.2011.506.
  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/22083573
  Free article on PubMed Central: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3564588/

- National Institute on Deafness and Other Communication Disorders: Quick Statistics https://www.nidcd.nih.gov/health/statistics/quick-statistics-hearing
- Shearer AE, Hildebrand MS, Sloan CM, Smith RJ. Deafness in the genomics era. Hear Res. 2011 Dec;282(1-2):1-9. doi: 10.1016/j.heares.2011.10.001. Epub 2011 Oct 8. Review.
  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/22016077
  Free article on PubMed Central: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3230685/
- Shearer AE, Hildebrand MS, Smith RJH. Hereditary Hearing Loss and Deafness Overview. 1999 Feb 14 [updated 2017 Jul 27]. In: Pagon RA, Adam MP, Ardinger HH, Wallace SE, Amemiya A, Bean LJH, Bird TD, Ledbetter N, Mefford HC, Smith RJH, Stephens K, editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2017. Available from http://www.ncbi.nlm.nih.gov/books/NBK1434/
  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/20301607
- Shearer AE, Smith RJ. Genetics: advances in genetic testing for deafness. Curr Opin Pediatr. 2012 Dec;24(6):679-86. doi: 10.1097/MOP.0b013e3283588f5e. Review.
  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/23042251
  Free article on PubMed Central: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3694178/
- Song MH, Lee KY, Choi JY, Bok J, Kim UK. Nonsyndromic X-linked hearing loss. Front Biosci (Elite Ed). 2012 Jan 1;4:924-33. Review.
  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/22201925

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