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Nonsyndromic Hearing Loss and Deafness, DFNA3 – RETIRED CHAPTER, FOR HISTORICAL REFERENCE ONLY

Richard JH Smith, MD[1] and Paul T Ranum, BA[2]

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Summary

NOTE: THIS PUBLICATION HAS BEEN RETIRED. THIS ARCHIVAL VERSION IS FOR HISTORICAL REFERENCE ONLY, AND THE INFORMATION MAY BE OUT OF DATE.

Clinical characteristics

Nonsyndromic hearing loss and deafness, DFNA3 is characterized by pre- or postlingual mild-to-profound progressive high-frequency sensorineural hearing impairment. Affected individuals have no other associated medical findings.

Diagnosis/testing

Diagnosis of DFNA3 depends on molecular genetic testing to identify a heterozygous pathogenic variant in *GJB2* (encoding connexin 26 [Cx26]) or *GJB6* (encoding connexin 30 [Cx30]).

Management

Treatment of manifestations: Early diagnosis, habilitation with hearing aids or cochlear implantation, and educational programming diminishes the likelihood of long-term speech or educational delay.

Surveillance: Semiannual examination by a physician who is familiar with hereditary hearing impairment; repeat audiometry to confirm stability of hearing loss

Agents/circumstances to avoid: Environmental exposures known to cause hearing loss, such as repeated loud noises.

Evaluation of relatives at risk: Once the *GJB2* or *GJB6* pathogenic variant has been identified in an affected family member, molecular genetic testing can be used to clarify the genetic status of at-risk relatives in infancy or early childhood so that appropriate early support and management can be provided.

Author Affiliations: 1 Professor of Internal Medicine, Division of Nephrology, Sterba Hearing Research Professor of Otolaryngology, Director, Molecular Otolaryngology and Renal Research Laboratories, University of Iowa, Iowa City, Iowa; Email: richard-smith@uiowa.edu. 2 Molecular Otolaryngology and Renal Research Laboratories, University of Iowa, Iowa City, Iowa; Email: paul-ranum@uiowa.edu.

Genetic counseling

DFNA3 is inherited in an autosomal dominant manner. Most individuals diagnosed as having DFNA3 have a deaf parent. Each child of an individual with DFNA3 has a 50% chance of inheriting the *GJB2* or *GJB6* pathogenic variant. Once the *GJB2* or *GJB6* pathogenic variant has been identified in a family member with DFNA3, prenatal testing for a pregnancy at increased risk and preimplantation genetic testing are possible.

Diagnosis

No formal diagnostic criteria have been published for DFNA3-related hearing loss.

Suggestive Findings

Nonsyndromic hearing loss and deafness, DFNA3 **should be suspected** in individuals with the following:

- Pre- or postlingual mild-to-profound progressive sensorineural hearing impairment [Denoyelle et al 2002]

  Note: (1) Hearing is measured in decibels (dB). The threshold or 0 dB mark for each frequency refers to the level at which normal young adults perceive a tone burst 50% of the time. Hearing is considered normal if an individual's thresholds are within 15 dB of normal thresholds. (2) Severity of hearing loss is graded as mild (26-40 dB), moderate (41-55 dB), moderately severe (56-70 dB), severe (71-90dB), or profound (>90dB). The frequency of hearing loss is designated as low (<500Hz), middle (501-2000Hz), or high (>2000Hz) (see Genetic Hearing Loss Overview).
- **No related systemic findings** identified by medical history and physical examination
- **A family history of nonsyndromic hearing loss** consistent with autosomal dominant inheritance

Establishing the Diagnosis

The diagnosis of DFNA3 **is established** in a proband by detection of a heterozygous pathogenic (or likely pathogenic) variant in *GJB2* (encoding connexin 26) or *GJB6* (encoding connexin 30) (see Table 1).

Note: (1) Per ACMG/AMP variant interpretation guidelines, the terms "pathogenic variant" and "likely pathogenic variant" are synonymous in a clinical setting, meaning that both are considered diagnostic and can be used for clinical decision making [Richards et al 2015]. Reference to "pathogenic variants" in this section is understood to include likely pathogenic variants. (2) Identification of a heterozygous *GJB2* or *GJB6* variant of uncertain significance does not establish or rule out the diagnosis.

Molecular genetic testing approaches in a person with hearing loss documented on audiogram can include a combination of **gene-targeted testing** (single-gene testing), multigene panels (including all genes implicated in nonsyndromic hearing loss), or **genomic testing** (e.g., exome or genome sequencing).

Gene-targeted testing requires the clinician to determine which gene(s) are likely involved based on phenotypic data, while comprehensive genomic testing does not. Because of the overlapping phenotypes of the many causes of hereditary hearing loss and deafness, most individuals with hereditary hearing loss and deafness are diagnosed by one of two approaches: a multigene panel of ALL genes implicated in nonsyndromic hearing loss and nonsyndromic mimics (recommended) or exome/genome sequencing (to consider).

Recommended Testing

A comprehensive deafness-specific multigene panel that includes all genes implicated in nonsyndromic hearing loss and nonsyndromic hearing-loss mimics (see Differential Diagnosis and Genetic Hearing Loss

Overview) is recommended as the initial test in the evaluation of hearing loss following an audiogram that has documented the hearing loss [Sloan-Heggen et al 2016] (Figure 1).

Note: (1) Genes included in available panels and the diagnostic sensitivity of the test used for each gene vary by laboratory and are likely to change over time [Shearer & Smith 2015]. (2) Some multigene panels may include genes not associated with the condition discussed in this *GeneReview*; thus, clinicians need to determine which multigene panel is most likely to identify the genetic cause of the condition while limiting identification of variants of uncertain significance and pathogenic variants in genes that do not explain the underlying phenotype. (3) Methods used in a panel may include sequence analysis, deletion/duplication analysis, and/or other non-sequencing-based tests. (4) All platforms used to identify deafness-causing genetic variants should include detection of copy number variants in the testing algorithm [Shearer et al 2014b].

For an introduction to multigene panels click here. More detailed information for clinicians ordering genetic tests can be found here.

Testing to Consider

Single-gene testing can be considered if a deafness-specific multigene panel is not available. However, performing sequence analysis of *GJB2* and *GJB6* alone is not cost effective unless it is limited to persons with severe-to-profound congenital nonsyndromic hearing loss. Offering single-gene testing of *GJB2* and *GJB6* reflexively to everyone with congenital hearing loss without regard to the degree of hearing loss is not evidence based and not cost effective [Jayawardena et al 2015, Shearer & Smith 2015].

Comprehensive genomic testing (i.e., exome sequencing and genome sequencing) *may be* considered; however, given the huge number of variants that will be identified by these sequencing strategies, even if a trio (i.e., parents and child) is studied, it is *extremely* unlikely that either strategy will identify a cause for hearing loss. With exome and genome sequencing, appropriate genetic counseling is mandatory before and after testing. For an introduction to comprehensive genomic testing click here. More detailed information for clinicians ordering genomic testing can be found here.

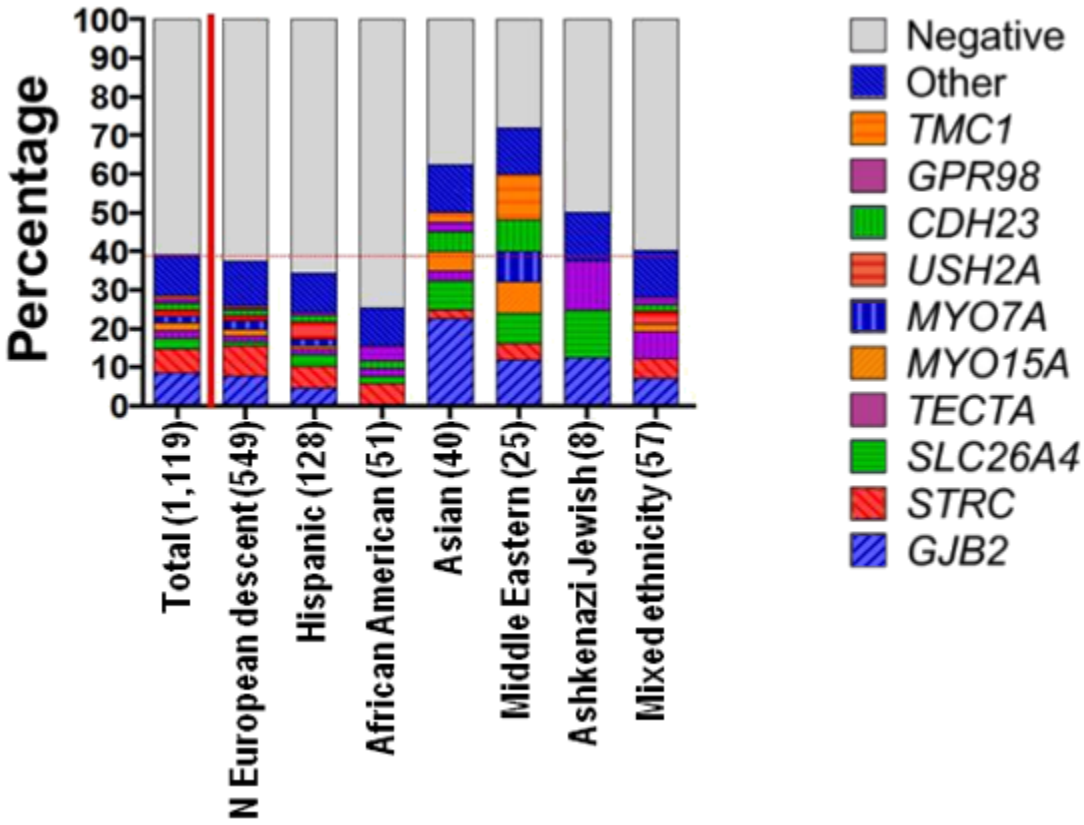

Figure 1. Genetic diagnostic rates in 1119 sequentially accrued persons with hearing loss. No person was excluded based on phenotype, inheritance, or previous testing. Testing resulted in identification of the underlying genetic cause for hearing loss in 440 individuals (39%). Pathogenic variants were found in 49 genes and included missense variants, large copy number changes, small insertions and deletions, nonsense variants, splice site alterations, and promoter variants. Note that the diagnostic rate for *GJB2*-related deafness varies based on ethnicity [Sloan-Heggen et al 2016].

Table 1. Molecular Genetic Testing Used in Nonsyndromic Hearing Loss and Deafness, DFNA3

Gene [1]	Proportion of DFNA3 Attributed to Pathogenic Variants in This Gene	Proportion of Pathogenic Variants [2] Detectable by This Method	
		Sequence analysis [3]	Gene-targeted deletion/ duplication analysis [4]
GJB2	>90%	100% [5]	See footnote 5.
GJB6	>10%	100%[6]	See footnote 5.

1. See Table A. Genes and Databases for chromosome locus and protein.
2. See Molecular Genetics for information on variants detected in this gene.
3. Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or pathogenic. Variants may include small intragenic deletions/insertions and missense, nonsense, and splice site variants; typically, exon or whole-gene deletions/duplications are not detected. For issues to consider in interpretation of sequence analysis results, click here.
4. Gene-targeted deletion/duplication analysis detects intragenic deletions or duplications. Methods used may include a range of techniques such as quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification (MLPA), and a gene-targeted microarray designed to detect single-exon deletions or duplications.
5. No data on detection rate of gene-targeted deletion/duplication analysis are available.

Clinical Characteristics

Clinical Description

Nonsyndromic hearing loss and deafness, DFNA3 is characterized by progressive mild-to-severe high-frequency sensorineural hearing impairment (Figure 2). *GJB2*-related DFNA3 is associated with prelingual and postlingual onset of hearing loss while *GJB6*-related DFNA3 is associated with prelingual hearing loss [Weegerink 2013].

DFNA3 audioprofiles (visual plots of hearing loss severity across a range of frequencies measured by pure tone audiometry) may vary significantly, even within a family. Note that when the hearing loss is postlingual, individuals with DFNA3 may pass the newborn hearing screen.

Tests of vestibular function and computed tomography of the temporal bones in persons with DFNA3 are normal [Denoyelle et al 2002].

Individuals with DFNA3 have no other associated medical findings.

Phenotype Correlations by Gene

GJB2. The twelve pathogenic missense variants of *GJB2* (Table 3) that cause deafness at the DFNA3 locus are associated with at least two different audioprofiles based on age of onset.

The majority of pathogenic variants cause progressive prelingual hearing loss (Figure 2):

- **p.Trp44Cys.** The audioprofile is characterized by a bilaterally symmetric sensorineural loss that varies from mild to profound, beginning with high-frequency hearing loss and progressing to loss at all frequencies.
- **p.Pro58Ala.** Hearing loss is progressive, ranging from mild to severe.
- **p.Arg75Gln and p.Arg75Trp.** Hearing loss is usually profound (average threshold for p.Arg75Gln is 105 dbHL).
- **p.Arg143Gln.** Progressive and profound high-frequency hearing loss is observed.
- **c.551G>A (p.Arg184Gln).** Audioprofiles are downsloping and consistent with severe-to-profound prelingual hearing loss [Janecke et al 2001, Löffler et al 2001, Tekin et al 2001, Denoyelle et al 2002, Feldmann et al 2005, Primignani et al 2007, Weegerink et al 2011].

In contrast, deafness related to the pathogenic variants resulting in the substitutions p.Thr55Asn, p.Asp179Asn, and p.Cys202Phe is postlingual:

- **c.164C>A (p.Thr55Asn).** Audioprofiles have a downsloping pattern and are consistent with a severe-to-profound postlingual hearing loss.
- **p.Asp179Asn.** Age of onset for hearing loss ranges from the first to the third decade. The audioprofile shows a mild-to-moderate hearing loss, particularly at high frequencies.
- **p.Cys202Phe.** Hearing loss is usually not detected until the second decade. Initially, the loss preferentially affects the high frequencies but progresses to affect the middle frequencies by middle age [Morlé et al 2000, Denoyelle et al 2002, Primignani et al 2003, Melchionda et al 2005].

Other:

- **p.Trp44Ser.** Audioprofiles are not available.
- **p.Asp46Asn.** Audioprofiles show intrafamilial variability with some individuals showing postlingual progressive hearing loss with onset in the first decade of life and some showing prelingual hearing loss.
- **p.Met163Leu.** A mild-to-moderate high-frequency hearing loss is observed; age of onset was not reported [Hamelmann et al 2001, Marziano et al 2003, Matos et al 2008, Bazazzadegan et al 2011].

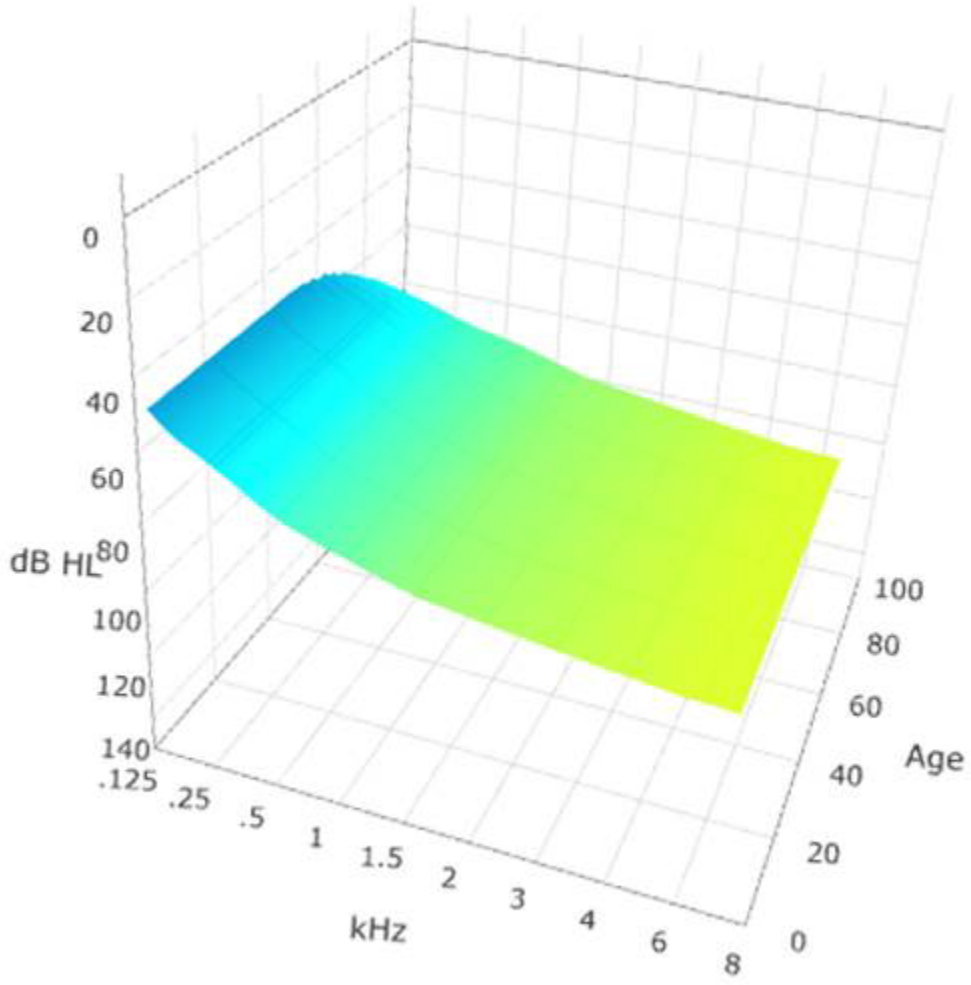

Figure 2. This audioprofile surface shows the anticipated progression of DFNA3 hearing loss with age. Note that the hearing loss is typically congenital and slowly becomes more severe with age [Taylor et al 2016].

***GJB6* (Table 4)**

- **p.Thr5Met.** The audioprofile of the one family reported [Grifa et al 1999] is characterized by middle- to high-frequency hearing loss. The degree of hearing loss is progressive and variable, ranging from mild to profound. The age of onset of hearing loss was not reported - and in the absence of linkage data, these results should be interpreted with caution [Friedman & Griffith 2003].
- **p.Ala40Val.** The audioprofile and age of onset were not included in the one reported individual [Yang et al 2007, Wang et al 2011].

Penetrance

GJB2 and *GJB6* pathogenic variants that cause DFNA3 are fully penetrant.

Nomenclature

The different gene loci for nonsyndromic deafness are designated DFN (for *deafn*ess).

Loci are named based on mode of inheritance:

- **DFNA.** Autosomal dominant
- **DFNB.** Autosomal recessive
- **DFN.** X-linked

The number following the above designations reflects the order of gene mapping and/or discovery.

Prevalence

The relative prevalence of DFNA3 as a cause of autosomal dominant nonsyndromic hearing loss is not known, but it is extremely rare [Sloan-Heggen et al 2016]: 14 pathogenic variants have been described worldwide. The majority of these pathogenic variants are described only in single families or simplex cases (i.e., a single occurrence in a family) [Denoyelle et al 2002, Hilgert et al 2009].

Prevalence for different pathogenic variants varies by population [Abe et al 2000, Hamelmann et al 2001, Löffler et al 2001, Liu et al 2002, Shearer et al 2014a, Xiao & Xie 2004].

Genetically Related (Allelic) Disorders

Table 2. Allelic Disorders

Gene	Phenotype [1]	MOI
GJB2	DFNB1	AR
	Palmoplantar keratoderma with deafness (OMIM 148350)	AD
	Keratitis-ichthyosis-deafness (KID) syndrome (OMIM 148210)	AD
	Hystrix-like ichthyosis-deafness (HID) syndrome (OMIM 602540)	AD
	Vohwinkel syndrome (OMIM 124500)	AD
	Bart-Pumphrey syndrome (OMIM 149200)	AD
GJB6	Hidrotic ectodermal dysplasia 2 (Clouston syndrome)	AD

AD= autosomal dominant; AR=autosomal recessive; MOI = mode of Inheritance
1. See hyperlinked *GeneReview* or OMIM phenotype entry for more information.

The following describes other phenotypes associated with mutation of *GJB2* and *GJB6*.

GJB2

DFNB1 is characterized by (generally) moderate-to-severe sensorineural impairment.

GJB2 is shared by an overlapping locus, DFNB1, which is associated with autosomal recessive nonsyndromic hearing loss. Variants in *GJB2* may cause either autosomal dominant DFNA3-associated or autosomal recessive DFNB1-associated nonsyndromic hearing loss and deafness. The mode of inheritance is ultimately determined by how the variant affects the expression and function of the connexin 26 protein.

Palmoplantar keratoderma with deafness is characterized by diffuse hyperkeratosis of the hands and feet [Richard et al 1998, Heathcote et al 2000, Feldmann et al 2005, de Zwart-Storm et al 2008].

Keratitis-ichthyosis-deafness (KID) and **hystrix-like ichthyosis-deafness (HID) syndromes** are associated with the same pathogenic variant (p.Asp50Asn) in the first extracellular domain of the *GJB2*-encoded protein connexin 26 [van Geel et al 2002].

- **Keratitis-ichthyosis-deafness (KID) syndrome** is an ectodermal dysplasia characterized by vascularizing keratitis, progressive erythrokeratoderma, and profound sensorineural hearing loss as well as scarring alopecia and predisposition to squamous cell carcinoma [Richard et al 2002, van Geel et al 2002, van Steensel et al 2002].
- **Hystrix-like ichthyosis-deafness (HID) syndrome** is a keratinizing disorder characterized by sensorineural hearing loss and hyperkeratosis of the skin. Shortly after birth, erythroderma develops, with spiky and cobblestone-like hyperkeratosis of the entire skin surface appearing by age one year. Severe palmoplantar keratoderma and scarring alopecia occur in some. HID syndrome is considered to differ from KID syndrome in: (1) the extent and time of occurrence of skin manifestations; (2) the severity of keratitis; and (3) electron microscopic features.

Vohwinkel syndrome is classified as a "mutilating" diffuse keratoderma because circumferential hyperkeratosis of the digits can lead to autoamputation (termed "pseudoainhum"). Mild-to-moderate sensorineural hearing loss is often associated with the disease.

Bart-Pumphrey syndrome is characterized by palmoplantar keratoderma, knuckle pads, leukonychia, and sensorineural hearing loss. The clinical features partially overlap with Vohwinkel syndrome and KID syndrome.

Other. With the *GJB2* pathogenic variants in which the epidermal disease and hearing loss cosegregate, the severity of the skin disease phenotype is highly variable, suggesting that other factors modify gene expression [Kelsell et al 2001, Feldmann et al 2005]. It is important to clinically assess each individual with autosomal dominant hearing loss for any syndromic features, which may be subtle or easily overlooked in affected relatives.

GJB6

Hidrotic ectodermal dysplasia 2 (Clouston syndrome) is characterized by hidrotic ectodermal dysplasia, alopecia, and palmoplantar hyperkeratosis [Smith et al 2002].

Differential Diagnosis

Other causes of postlingual, acquired forms of hearing loss need to be considered (see Genetic Hearing Loss Overview). Because the diagnosis of syndromic forms of hearing loss can be challenging, many multigene panels now include the more frequently diagnosed forms of autosomal dominant syndromic hearing loss [Sloan-Heggen et al 2016].

Autosomal dominant syndromic forms of hearing loss with:

- **Malformations of the head and neck.** Branchiootorenal (BOR) syndrome is characterized by malformations of the outer, middle, and inner ear associated with: conductive, sensorineural, or mixed hearing impairment; branchial fistulae and cysts; and renal malformations ranging from mild renal hypoplasia to bilateral renal agenesis [Chang et al 2004]. Pathogenic variants in *EYA1*, *SIX5*, or *SIX1* are causative.

- **Pigmentary anomalies.** Waardenburg syndrome type 1 (WS1) is characterized by congenital sensorineural hearing loss and pigmentary disturbances of the iris, hair, and skin, along with dystopia canthorum (lateral displacement of the inner canthi) [DeStefano et al 1998].

  Hearing loss occurs in approximately 57% and is congenital, sensorineural, typically non-progressive, and either unilateral or bilateral. Most commonly, hearing loss is bilateral and profound (>100 dB). The majority of individuals with WS1 have either a white forelock (45%) or graying of the scalp hair before age 30 years. Affected individuals may have complete heterochromia iridium, partial/segmental heterochromia, or hypoplastic or brilliant blue irides. The diagnosis is established by clinical findings.

Diagnostic criteria rely on the presence of sensorineural hearing loss, pigmentary changes, and calculation of the W index to identify dystopia canthorum. Pathogenic variants in *PAX3* are causative.

Management

Evaluations Following Initial Diagnosis

To establish the extent of involvement and needs in an individual diagnosed with nonsyndromic hearing loss, DFNA3, the following evaluations are recommended:

- Complete assessment of auditory acuity using age-appropriate tests including ABR testing, auditory steady-state response (ASSR) testing, and/or pure tone audiometry (See Genetic Hearing Loss Overview.)
- Consultation with a clinical geneticist and/or genetic counselor

Treatment of Manifestations

Early diagnosis, habilitation with hearing aids or cochlear implantation, and educational programming will diminish the likelihood of long-term speech or educational delay.

The following are indicated:

- Fitting with appropriate hearing aids
- Enrollment in an appropriate educational program for the hearing impaired
- Consideration of cochlear implantation, an effective habilitation option for persons with preserved residual hearing [Gantz et al 2016]
- Recognition that unlike with many clinical conditions, management and treatment of mild-to-profound deafness fall largely within the purview of the social welfare and educational systems rather than the medical care system [Smith et al 2005]

See Genetic Hearing Loss Overview for more detailed discussion of management issues.

Surveillance

The following are appropriate:

- Semiannual examination by a physician who is familiar with hereditary hearing impairment
- Repeat audiometry to confirm stability of hearing loss

Agents/Circumstances to Avoid

Individuals with hearing loss should avoid environmental exposures known to cause hearing loss. Most important is avoidance of repeated exposure to loud noises.

Evaluation of Relatives at Risk

If a *GJB2* or *GJB6* pathogenic variant has been identified in the proband, it is appropriate to clarify the genetic status of at-risk sibs shortly after birth so that appropriate early support and management can be provided to the child and family.

See Genetic Counseling for issues related to testing of at-risk relatives for genetic counseling purposes.

Therapies Under Investigation

Search ClinicalTrials.gov in the US and EU Clinical Trials Register in Europe for access to information on clinical studies for a wide range of diseases and conditions. Note: There may not be human trials for this condition.

Genetic Counseling

Genetic counseling is the process of providing individuals and families with information on the nature, mode(s) of inheritance, and implications of genetic disorders to help them make informed medical and personal decisions. The following section deals with genetic risk assessment and the use of family history and genetic testing to clarify genetic status for family members; it is not meant to address all personal, cultural, or ethical issues that may arise or to substitute for consultation with a genetics professional. —ED.

Mode of Inheritance

Nonsyndromic hearing loss and deafness, DFNA3 is inherited in an autosomal dominant manner.

Risk to Family Members

Parents of a proband

- Most individuals diagnosed as having DFNA3 have a deaf parent.
- The proportion of individuals with DFNA3 caused by a *de novo* *GJB2* or *GJB6* pathogenic variant is very small.
- Recommendations for the evaluation of parents of a proband with an apparent *de novo* pathogenic variant include (a) genetic testing to validate the *de novo* nature of the identified variant; (b) assessment of auditory acuity in the parents; and (c) medical history and physical examination to rule out other systemic findings in the family.
- If the pathogenic variant found in the proband cannot be detected in leukocyte DNA of either parent, possible explanations include a *de novo* pathogenic variant in the proband or germline mosaicism in a parent. While theoretically possible, germline mosaicism has not been reported.

Sibs of a proband

- The likelihood that a sib will have DFNA3 depends on the genetic status of the proband's parents: if one of the proband's parents has a *GJB2* or *GJB6* pathogenic variant, each sib has a 50% chance of inheriting the pathogenic variant.
- When the parents are clinically unaffected, the risk to the sibs of a proband appears to be low.
- If the *GJB2* or *GJB6* pathogenic variant found in the proband cannot be detected in the leukocyte DNA of either parent, the risk to sibs is presumed to be slightly greater than that of the general population (though still <1%) because of the theoretic possibility of parental germline mosaicism.

Offspring of a proband. Each child of an individual with DFNA3 has a 50% chance of inheriting the *GJB2* or *GJB6* pathogenic variant.

Other family members. The risk to other family members depends on the status of the proband's parents: if a parent is deaf, the parent's family members may also have DFNA3.

Related Genetic Counseling Issues

See Management, Evaluation of Relatives at Risk for information on evaluating at-risk relatives for the purpose of early diagnosis and treatment.

The following points are noteworthy:

- Communication with individuals who are members of the Deaf community and who sign requires the services of a skilled interpreter.
- Members of the Deaf community may view deafness as a distinguishing characteristic and not as a handicap, impairment, or medical condition requiring a "treatment" or "cure," or to be "prevented."
- Many deaf people are interested in obtaining information about the cause of their own deafness, including information on medical, educational, and social services, rather than information about prevention, reproduction, or family planning. It is, therefore, important to ascertain and address the questions and concerns of the family/individual.
- The use of certain terms is preferred: probability or chance vs risk; deaf and hard-of-hearing vs hearing impaired. Terms such as "abnormal" should be avoided.

Family planning

- The optimal time for determination of genetic status and discussion of the availability of prenatal/preimplantation genetic testing is before pregnancy.
- It is appropriate to offer genetic counseling (including discussion of the probability of deafness in offspring and reproductive options) to young adults who are deaf.

Considerations in families with an apparent *de novo* pathogenic variant. When neither parent of a proband with an autosomal dominant condition has the pathogenic variant identified in the proband or clinical evidence of the condition, the pathogenic variant is likely *de novo*. However, non-medical explanations including alternate paternity or maternity (e.g., with assisted reproduction) and undisclosed adoption could also be explored.

Prenatal Testing and Preimplantation Genetic Testing

Once the *GJB2* or *GJB6* pathogenic variant has been identified in a family member with DFNA3, prenatal and preimplantation genetic testing are possible.

Differences in perspective may exist among medical professionals and within families regarding the use of prenatal testing. While most centers would consider use of prenatal testing to be a personal decision, discussion of these issues may be helpful.

Resources

GeneReviews staff has selected the following disease-specific and/or umbrella support organizations and/or registries for the benefit of individuals with this disorder and their families. GeneReviews is not responsible for the information provided by other organizations. For information on selection criteria, click here.

- **Medical Home Portal**

  Hearing Loss and Deafness

- **MedlinePlus**

  Nonsyndromic hearing loss

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

  Phone: 866-337-5220 (toll-free); 202-337-5221 (TTY)

  Fax: 202-337-8314

  Email: info@agbell.org

  Listening and Spoken Language Knowledge Center

- **American Society for Deaf Children**

  Phone: 800-942-2732 (ASDC)

  Email: info@deafchildren.org

  www.deafchildren.org

- **BabyHearing.org**

  This site, developed with support from the National Institute on Deafness and Other Communication Disorders, provides information about newborn hearing screening and hearing loss.

  www.babyhearing.org

- **National Association of the Deaf**

  Phone: 301-587-1788 (Purple/ZVRS); 301-328-1443 (Sorenson); 301-338-6380 (Convo)

  Fax: 301-587-1791

  Email: nad.info@nad.org

  www.nad.org

Molecular Genetics

Information in the Molecular Genetics and OMIM tables may differ from that elsewhere in the GeneReview: tables may contain more recent information. —ED.

Table A. Nonsyndromic Hearing Loss and Deafness, DFNA3: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
GJB2		Gap junction beta-2 protein	Hereditary Hearing Loss Homepage (GJB2) CCHMC - Human Genetics Mutation Database (GJB2) The Connexin-deafness homepage (GJB2)	GJB2	GJB2
GJB6		Gap junction beta-6 protein	Hereditary Hearing Loss Homepage (GJB6) CCHMC - Human Genetics Mutation Database (GJB6) The Connexin-deafness homepage (GJB6)	GJB6	GJB6

Data are compiled from the following standard references: gene from HGNC; chromosome locus from OMIM; protein from UniProt. For a description of databases (Locus Specific, HGMD, ClinVar) to which links are provided, click here.

Table B. OMIM Entries for Nonsyndromic Hearing Loss and Deafness, DFNA3 (View All in OMIM)

121011	GAP JUNCTION PROTEIN, BETA-2; GJB2
601544	DEAFNESS, AUTOSOMAL DOMINANT 3A; DFNA3A
604418	GAP JUNCTION PROTEIN, BETA-6; GJB6
612643	DEAFNESS, AUTOSOMAL DOMINANT 3B; DFNA3B

GJB2

Gene structure. Most connexin genes have a common architecture, with the entire coding region contained in a single large exon separated from the 5'-untranslated region by an intron of variable size. The coding sequence of *GJB2* (exon 2) is 681 base pairs (including the stop codon) and is translated into a 226-amino acid protein, connexin 26 (Cx26). For a detailed summary of gene and protein information, see Table A, **Gene**.

Pathogenic variants. Twelve pathogenic variants in *GJB2* are known (see Table 3). The majority segregate in families; however, the p.Arg75Gln and p.Arg75Trp variants have also been identified as *de novo* variants in simplex cases (i.e., a single occurrence in a family). These two variants are implicated in both autosomal dominant nonsyndromic hearing loss and syndromic hearing loss associated with skin disorders (see Genetically Related Disorders) [Janecke et al 2001, Feldmann et al 2005].

Of note, although the pathogenicity of the p.Arg75Trp variant had been questioned as it was reported in one of 77 Egyptian controls whose hearing status was not reported [Richard et al 1998], subsequent case reports, animal models, and functional studies strongly argue for the pathogenicity of this variant [Janecke et al 2001, Kudo et al 2003, Maeda et al 2005, Maeda et al 2009, Mani et al 2009, Yum et al 2010, Weegerink et al 2011, Zhang et al 2011].

Table 3. Selected *GJB2* Variants

Variant Classification	DNA Nucleotide Change	Predicted Protein Change	Reference Sequences
Benign	c.101T>C	p.Met34Thr [1]	NM_004004.5 NP_003995.2
Pathogenic	c.132G>C	p.Trp44Cys	
	c.136G>A	p.Asp46Asn	
	c.164C>A	p.Thr55Asn	
	c.131G>C	p.Trp44Ser	
	c.172C>G	p.Pro58Ala	
	c.223C>T	p.Arg75Trp	
	c.224G>A	p.Arg75Gln	
	c.428G>A	p.Arg143Gln	
	c.487A>C	p.Met163Leu	
	c.535G>A	p.Asp179Asn	
	c.551G>A	p.Arg184Gln	
	c.605G>T	p.Cys202Phe	

Variants listed in the table have been provided by the authors. *GeneReviews* staff have not independently verified the classification of variants.
GeneReviews follows the standard naming conventions of the Human Genome Variation Society (varnomen.hgvs.org). See Quick Reference for an explanation of nomenclature.
1. Variant found in normal hearing persons and family with palmoplantar keratoderma

Normal gene product. Connexin 26 (Cx26) is a beta-2 gap junction protein. Gap junctions are highly specialized organelles consisting of clustered channels that permit direct intercellular exchange of ions and molecules through central aqueous pores. Postulated roles include: the rapid propagation of electrical signals and synchronization of activity in excitable tissues; and the exchange of metabolites and signal molecules in non-excitable tissues [Evans & Martin 2002].

Each connexin protein contains two extracellular (E1-E2), four transmembrane (M1-M4), and three cytoplasmic domains (N-terminus, C-terminus, and a cytoplasmic loop located between M2 and M3) [Maeda et al 2009]. Each extracellular domain contains three cysteine residues joined between the E1 and E2 loops by at least one disulfide bond [Kovacs et al 2007, Yeager & Harris 2007]. The presumed importance of these six cysteines can be inferred from Cx32 experiments in which any Cys pathogenic variant completely blocks the development of gap-junction conductances between *Xenopus* oocyte pairs. The third transmembrane domain (M3) is amphipathic and lines the putative wall of the intercellular channel [Kovacs et al 2007, Yeager & Harris 2007], which is created by oligomerization of six connexins to form a hexameric structure called a connexon. Two connexons, one from each cell, join in the extracellular gap to complete the cell-to-cell pathway. If the connexons contributed by each cell are of identical composition, the channel is homotypic; if each connexon is formed by a different composition of connexins, it is termed heterotypic. Most connexins are phosphoproteins and undergo post-transcriptional modifications [Moreno 2005, Locke et al 2006]. Cx26 forms functional combinations with itself, Cx30, Cx31, Cx32, Cx46, and Cx50 [Cottrell & Burt 2005, Liu et al 2009].

Abnormal gene product. Gap-junction channels are permeable to ions and small metabolites with relative molecular masses up to approximately 1.2 kd [Harris & Bevans 2001]. Differences in ionic selectivity and gating mechanisms among gap junctions reflect the existence of more than 20 different connexin isoforms in humans. The abnormal gene product in DFNA3 causes deafness via a dominant-negative mechanism of action.

GJB6

Gene structure. *GJB6* has three exons, of which only the third is coding. The translated protein, connexin 30 (Cx30), is 261 amino acids long. For a detailed summary of gene and protein information, see Table A, **Gene**.

Pathogenic variants. Two *GJB6* DFNA3-causing pathogenic variants are known: p.Thr5Met and p.Ala40Val [Grifa et al 1999, Yang et al 2007] (see Table 4).

Table 4. Selected *GJB6* Pathogenic Variants

DNA Nucleotide Change	Predicted Protein Change	Reference Sequences
c.14C>T	p.Thr5Met [1]	NM_001110219.2 NP_001103689.1
c.119C>T	p.Ala40Val	

Variants listed in the table have been provided by the authors. *GeneReviews* staff have not independently verified the classification of variants.
GeneReviews follows the standard naming conventions of the Human Genome Variation Society (varnomen.hgvs.org). See Quick Reference for an explanation of nomenclature.
1. See also Table 1 and Phenotype Correlations by Gene, ***GJB6***.

Normal gene product. Connexin 30 (Cx30) is a beta-6 gap junction protein. It shares an architecture that is common to all connexins (see *GJB2*, **Normal gene product**).

Abnormal gene product. Like the abnormal gene products of *GJB2*-related DFNA3, the p.Thr5Met and p.Ala40Val variants of *GJB6*-related DFNA3 act via a dominant-negative mechanism to inhibit activity of wild-type Cx30 gap junction channels.

Additionally, the p.Ala40Val variant exerts a trans-dominant-negative effect on Cx26, impairing gap junction formation in the cochlea.

In functional studies with a mouse model, the p.Thr5Met variant was shown to exert its pathogenic effect through diminished biochemical coupling between cochlear cells [Grifa et al 1999, Schütz et al 2010, Wang et al 2011].

Chapter Notes

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Author History

Paul T Ranum, BA (2014-present)

Daryl A Scott, MD, PhD; University of Iowa (1998-2001)

Abraham M Sheffield, MD; University of Iowa (2009-2014)

Val C Sheffield, MD, PhD; University of Iowa (1998-2001)

Richard JH Smith, MD (1998-present)

Guy Van Camp, PhD; University of Antwerp (1998-2016)

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