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DFNA2 Nonsyndromic Hearing Loss

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Summary

Clinical characteristics

DFNA2 nonsyndromic hearing loss is characterized by symmetric, predominantly high-frequency sensorineural hearing loss (SNHL) that is progressive across all frequencies. At younger ages, hearing loss tends to be mild in the low frequencies and moderate in the high frequencies; in older persons, the hearing loss is moderate in the low frequencies and severe to profound in the high frequencies. Although the hearing impairment is often detected during routine hearing assessment of a school-age child, it is likely that hearing is impaired from birth, especially at high frequencies. Most affected persons initially require hearing aids to assist with sound amplification between ages ten and 40 years. By age 70 years, all persons with DFNA2 nonsyndromic hearing loss have severe-to-profound hearing impairment.

Diagnosis/testing

The diagnosis of DFNA2 nonsyndromic hearing loss is established in an individual with a characteristic audioprofile, a family history consistent with autosomal dominant inheritance, and identification of a heterozygous pathogenic variant in *KCNQ4*.

Management

Treatment of manifestations: Hearing aids for those with mild-to-moderate hearing loss; consideration of cochlear implants when hearing loss is severe to profound; special assistance in school for hearing-impaired children and adolescents.

Surveillance: At least annual audiogram to follow progression of hearing loss.

Agents/circumstances to avoid: Avoiding exposure to loud noise may reduce the rate of progression of high-frequency SNHL.

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Evaluation of relatives at risk: Determining in infancy or early childhood whether a family member of the proband has inherited a pathogenic variant in *KCNQ4* allows for early support and management of the child and family.

Genetic counseling

DFNA2 nonsyndromic hearing loss is inherited in an autosomal dominant manner. Most individuals with DFNA2 nonsyndromic hearing loss have a parent with hearing loss; the proportion of individuals with a *de novo* *KCNQ4* pathogenic variant is unknown. Each child of an individual with DFNA2 nonsyndromic hearing loss has a 50% chance of inheriting the *KCNQ4* pathogenic variant. Once the *KCNQ4* pathogenic variant has been identified in a family member, prenatal testing for a pregnancy at increased risk and preimplantation genetic testing for DFNA2 nonsyndromic hearing loss are possible.

Diagnosis

Suggestive Findings

DFNA2 nonsyndromic hearing loss **should be considered** in an individual with the following clinical, imaging, and family history findings:

Clinical findings

- Symmetric, predominantly high-frequency sensorineural hearing loss (SNHL) that is progressive across all frequencies:
  - At younger ages, hearing loss tends to be mild in the low frequencies and moderate in the high frequencies.
  - In older persons, the hearing loss is moderate in the low frequencies and severe to profound in the high frequencies.
- Normal physical examination

Imaging findings. Temporal bone imaging (i.e., CT of the inner ears) is normal. Specifically, abnormalities such as dilatation of the vestibular aqueducts (also known as enlarged vestibular aqueducts) and Mondini dysplasia should not be present.

Family history of hearing loss is present and consistent with autosomal dominant inheritance.

Establishing the Diagnosis

The diagnosis of DFNA2 nonsyndromic hearing loss **is established** in a proband with the above characteristic audioprofile and identification of a heterozygous pathogenic variant in *KCNQ4* on molecular genetic testing (see Table 1).

Because the phenotype of DFNA2 nonsyndromic hearing loss is indistinguishable from many other inherited disorders with hearing loss, recommended molecular genetic testing approaches include use of a **multigene panel** or **comprehensive genomic testing**.

Note: Single-gene testing (sequence analysis of *KCNQ4,* followed by gene-targeted deletion/duplication analysis) is rarely useful and typically NOT recommended.

A multigene hearing loss and deafness panel that includes *KCNQ4* and other genes of interest (see Hereditary Hearing Loss and Deafness Overview) 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. Note: (1) The genes included in the panel and the diagnostic sensitivity of the testing

used for each gene vary by laboratory and are likely to change over time. (2) Some multigene panels may include genes not associated with the condition discussed in this *GeneReview*. (3) In some laboratories, panel options may include a custom laboratory-designed panel and/or custom phenotype-focused exome analysis that includes genes specified by the clinician. (4) Methods used in a panel may include sequence analysis, deletion/duplication analysis, and/or other non-sequencing-based tests. For this disorder, a multigene panel that also includes deletion/duplication analysis is recommended (see Table 1).

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

Comprehensive genomic testing (which does not require the clinician to determine which gene[s] are likely involved) is another good option. **Exome sequencing** is most commonly used; **genome sequencing** is also possible. **Exome array** (when clinically available) may be considered if exome sequencing is not diagnostic, particularly when evidence supports autosomal dominant inheritance.

For introduction to comprehensive genomic testing click here. More detailed information for clinicians ordering genomic testing can be found here.

Table 1. Molecular Genetic Testing Used in DFNA2 Nonsyndromic Hearing Loss

Gene [1]	Method	Proportion of Probands with a Pathogenic Variant [2] Detectable by Method
KCNQ4	Sequence analysis [3]	99% [4]
	Gene-targeted deletion/duplication analysis [5]	1% [6]

1. See Table A. Genes and Databases for chromosome locus and protein.
2. See Molecular Genetics for information on allelic 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. Sequence analysis detects pathogenic variants in *KCNQ4* in virtually all individuals with autosomal dominant nonsyndromic sensorineural hearing loss mapping to the DFNA2 locus.
5. 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.
6. Copy number variants (CNVs) can be detected in virtually any gene included in targeted sequencing panels for deafness. In sequential testing of 2,506 persons with hearing loss using OtoSCOPE, one CNV of *KCNQ4* was identified [Author, personal observation].

Clinical Characteristics

Clinical Description

All individuals with DFNA2 nonsyndromic hearing loss have symmetric, predominantly high-frequency hearing loss that is progressive across all frequencies. Initially, high frequencies are affected; later in life, hearing loss becomes severe to profound across all frequencies. A comprehensive review of the clinical presentation and prognosis of individuals diagnosed with DFNA2 nonsyndromic hearing loss has been provided by De Leenheer et al [2002a].

Onset of hearing loss is generally reported in early childhood or adolescence; however, it is likely that hearing is impaired from birth, especially at the high frequencies. The hearing loss is often detected during standard hearing assessment of a school-age child or less frequently during the evaluation of a child for delayed speech development.

In all affected individuals, the hearing loss is more severe at the high frequencies, resulting in a characteristic downsloping audioprofile with hearing thresholds between 50 and 90 dB at 500 Hz and between 90 and 120 dB at 2-4 kHz by age 50 years. A typical audiogram of an adolescent with DFNA2 nonsyndromic hearing loss is shown in Figure 1.

Whereas onset age varies within families, deterioration of annual thresholds for families with DFNA2 nonsyndromic hearing loss has been calculated at a relatively uniform ~1 dB/year [Coucke et al 1999, Talebizadeh et al 1999, Ensink et al 2000, Van Hauwe et al 2000, Akita et al 2001, De Leenheer et al 2002a, De Leenheer et al 2002b, Van Camp et al 2002]. Most persons with DFNA2 nonsyndromic hearing loss are first fitted with hearing aids to assist with sound amplification between ages ten and 40 years [De Leenheer et al 2002a]. By age 70 years, all persons with hearing loss attributed to a pathogenic variant in *KCNQ4* have severe-to-profound hearing loss.

Other findings

- **Vestibular function.** Thirty percent of individuals in two families with DFNA2 nonsyndromic hearing loss (Dutch families 1 and 4; Table 3) had increased vestibulo-ocular reflex activity [Marres et al 1997, De Leenheer et al 2002b]. Vestibular problems have not been observed in any other families with DFNA2 nonsyndromic hearing loss.
- **Speech recognition scores.** When measured in several Dutch families, speech recognition scores were relatively good given the pure-tone thresholds [De Leenheer et al 2002b, Van Camp et al 2002].

Genotype-Phenotype Correlations

The phenotype associated with heterozygous *KCNQ4* pathogenic missense variants is similar in all families: predominantly high-frequency sensorineural hearing loss (SNHL) that is detectable in childhood and progressive across all frequencies. At younger ages, hearing loss tends to be mild in the low frequencies and moderate in the high frequencies. In older persons, the hearing loss is moderate in the low frequencies and severe to profound in the high frequencies.

Although congenital onset of DFNA2 nonsyndromic hearing loss has been reported in one of the Dutch families with the p.Trp276Ser variant [De Leenheer et al 2002b, Van Camp et al 2002], it has not been reported in other families with this variant. The high-frequency hearing loss in this family was progressive without substantial loss of speech recognition during the first decades of life [De Leenheer et al 2002b].

The phenotype associated with heterozygous *KCNQ4* truncating variants differs from that associated with *KCNQ4* pathogenic missense variants. In two families, small frameshift deletions of *KCNQ4* (c.211_223del and c.211delC) are predicted to result in a profoundly truncated protein that either does not interact with normal protein translated from the normal allele or may not remain in cells as a result of nonsense-mediated decay. The hearing loss associated with this dosage effect is milder in low and mid-frequencies, more severe in high frequencies, and later in onset than the hearing loss seen with pathogenic missense variants [Coucke et al 1999, Akita et al 2001].

Penetrance

The penetrance is complete. All individuals with a heterozygous *KCNQ4* pathogenic variant exhibit the hearing loss phenotype; onset age and severity are variable.

Prevalence

In a study conducted between 2012 and 2014, the Molecular Otolaryngology and Renal Research Laboratories performed clinical diagnostic testing on a total of 1,119 individuals with hearing loss using the comprehensive genetic testing panel OtoSCOPE. It was determined that among the 440 individuals in whom hearing loss was

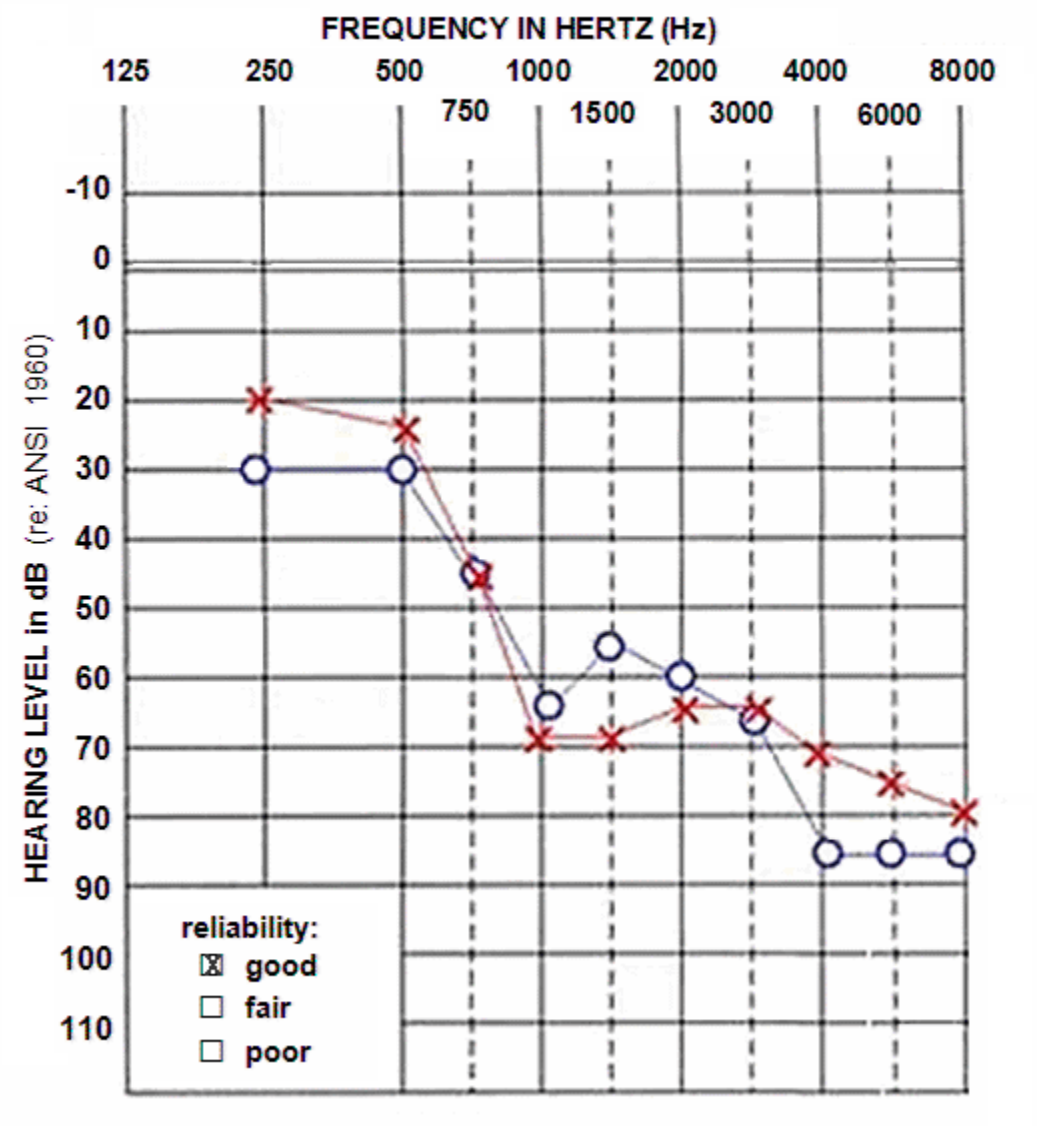

Figure 1. Audiogram from an individual age 12 years with DFNA2 hearing loss. Note that the loss is greater in the high frequencies at this age; with time, hearing at all frequencies progressively deteriorates.

hereditary, *KCNQ4* pathogenic variants accounted for 9.5% of autosomal dominant neurosensory hearing loss (ADNSHL) [Sloan-Heggen et al 2016].

Genetically Related (Allelic) Disorders

No phenotypes other than those discussed in this *GeneReview* are known to be associated with germline pathogenic variants in *KCNQ4*.

Differential Diagnosis

See Hereditary Hearing Loss and Deafness for complete differential diagnosis. Note: Table 4 has a complete listing of the genes and clinical manifestations of autosomal dominant nonsyndromic hearing impairment.

Management

Evaluations Following Initial Diagnosis

To establish the extent of hearing loss and needs in an individual diagnosed with DFNA2 nonsyndromic hearing loss, the evaluations summarized in this section (if not performed as part of the evaluation that led to the diagnosis) are recommended:

- Audiometry, including bone conduction testing
- Consultation with a clinical geneticist and/or genetic counselor

Treatment of Manifestations

See Hereditary Hearing Loss and Deafness Overview for complete discussion of treatment.

When hearing loss is mild to moderate, fitting of hearing aids to provide improved amplification is warranted.

When the hearing loss becomes severe to profound, cochlear implants (CIs) can be considered. In individuals with preserved or relatively good low-frequency hearing and severe-to-profound high-frequency loss, a hybrid (short) cochlear implant may be considered. Hybrid implants combine two proven technologies – acoustic amplification and implant technology – to provide electroacoustic hearing. The acoustic component, which is coupled to the cochlear implant sound processor, amplifies residual low-frequency hearing; the electrical component uses cochlear implant technology to provide electrostimulation for high-frequency hearing.

For school-age children or adolescents, special assistance for the hearing impaired may be warranted and, where available, should be offered.

Surveillance

Audiograms should be obtained on an annual basis to follow progression of hearing loss.

Agents/Circumstances to Avoid

The rate of progression of high-frequency hearing loss can be reduced by encouraging individuals with DFNA2 nonsyndromic hearing loss to avoid exposure to loud noise in the workplace and during recreation.

Evaluation of Relatives at Risk

Determining in infancy or early childhood whether a relative of a person with DFNA2 nonsyndromic hearing loss has inherited the *KCNQ4* pathogenic variant allows for early support and management of the child and the 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 clinical trials for this disorder.

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

DFNA2 nonsyndromic hearing loss is inherited in an autosomal dominant manner.

Risk to Family Members

Parents of a proband

- Most individuals diagnosed with DFNA2 nonsyndromic hearing loss have a deaf parent.
- A proband with DFNA2 nonsyndromic hearing loss may have deafness as the result of a *de novo KCNQ4* variant. The proportion of individuals with a *de novo KCNQ4* pathogenic variant is not known. Of six clinically diagnosed individuals reported in the sequential series by Sloan-Heggen et al [2016], five were verified to have autosomal dominant inheritance, whereas one represented a simplex case (i.e., a single occurrence in the family). Thus, it appears that in most instances *KCNQ4*-related hearing loss is inherited from an affected parent [Sloan-Heggen et al 2016].
- Recommendations for the evaluation of parents of a proband with an apparent *de novo* pathogenic variant include audiometry and molecular genetic testing.
- If the pathogenic variant found in the proband cannot be detected in the leukocyte DNA of either parent, possible explanations include a *de novo* pathogenic variant in the proband or germline mosaicism in a parent. Though theoretically possible, no instances of germline mosaicism have been reported.
- The family history of some individuals with DFNA2 nonsyndromic hearing loss may appear to be negative because of failure to diagnosis a parent with a milder phenotypic presentation, early death of the parent before the onset of hearing loss, or late onset of hearing loss in a parent. Therefore, an apparently negative family history cannot be confirmed until the appropriate clinical evaluation and molecular genetic testing have been performed on the parents of the proband.
- Note: If the parent is the individual in whom the pathogenic variant first occurred, the parent may have somatic mosaicism for the pathogenic variant and have mild hearing loss.

Sibs of a proband. The probability that the sibs of the proband will be deaf depends on the genetic status of the proband's parents:

- If a parent of the proband is deaf, each sib has a 50% chance of being deaf.
- If the *KCNQ4* pathogenic variant found in the proband cannot be detected in the leukocyte DNA of either parent, the probability that a sib will have DFNA2 nonsyndromic hearing loss is estimated to be 1% because of the theoretic possibility of parental germline mosaicism [Rahbari et al 2016].
- If the parents have not been tested for the *KNCQ4* pathogenic variant but are both hearing, the probability that a sib of the proband will be deaf appears to be low. (Note: Sibs of a proband with clinically unaffected parents are presumed to have an increased probability of having DFNA2 nonsyndromic hearing loss because of the theoretic possibility of parental germline mosaicism.)

Offspring of a proband. Each child of an individual with DFNA2 nonsyndromic hearing loss has a 50% chance of inheriting the pathogenic variant.

Other family members. The probability of deafness in other family members depends on the status of the proband's parents: if a parent is deaf, the parent's family members may also be deaf or develop deafness.

Related Genetic Counseling Issues

See Management, Evaluation of Relatives at Risk for information on evaluating relatives of a proband for the purpose of early diagnosis and management.

The following points are noteworthy:

- Communication with individuals who are members of the Deaf community and 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 important to ascertain and address the questions and concerns of the family/individual.
- The use of certain terms is preferred: probability or chance versus risk; deaf and hard-of-hearing versus hearing impaired. Terms such as "abnormal" should be avoided.

Considerations in families with an apparent *de novo* variant. When neither parent of a proband with DFNA2 nonsyndromic hearing loss has the pathogenic variant or clinical evidence of deafness, it is likely that the proband has a *de novo* variant. However, possible non-medical explanations could be explored including alternate paternity or maternity (i.e., with assisted reproduction) or undisclosed adoption.

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 that offspring will be deaf and reproductive options) to young adults who have DFNA2 nonsyndromic hearing loss.

Prenatal Testing and Preimplantation Genetic Testing

Once the *KCNQ4* pathogenic variant has been identified in a family member, prenatal testing for a pregnancy at increased risk and preimplantation genetic testing for DFNA2 nonsyndromic hearing loss 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

  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

  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. DFNA2 Nonsyndromic Hearing Loss: Genes and Databases

Locus Name	Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
DFNA2	*KCNQ4*	1p34.2	Potassium voltage-gated channel subfamily KQT member 4	KCNQ4 database Deafness Variation Database - KCNQ4	KCNQ4	KCNQ4

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 DFNA2 Nonsyndromic Hearing Loss (View All in OMIM)

600101	DEAFNESS, AUTOSOMAL DOMINANT 2A; DFNA2A
603537	POTASSIUM CHANNEL, VOLTAGE-GATED, KQT-LIKE SUBFAMILY, MEMBER 4; KCNQ4

Gene structure. *KCNQ4* has a transcript length of 2,335 base pairs. The transcript consists of 14 exons. For a detailed summary of gene and protein information, see Table A, **Gene**.

Variants of uncertain clinical significance. Two variants that result in synonymous amino acid changes are of uncertain clinical significance (see Table 2). These nucleotide variants were detected on a screen of 185 individuals with nonsyndromic hearing loss. These individuals were reported as having nonsyndromic hearing loss; no information regarding family history was provided. To date these variants remain of uncertain clinical

significance because to the authors' knowledge gene expression has not been tested (the hypothesis being that these variants disrupt exon-splice enhancers and interfere with normal gene splicing).

Table 2. *KCNQ4* Variants of Uncertain Clinical Significance Discussed in This *GeneReview*

DNA Nucleotide Change [1]	Predicted Protein Change [1]	Protein Domain	Population	Onset of Symptoms [2]	Reference
c.648C>T	p.Arg216= [3]	S4 transmembrane domain	Taiwanese	Childhood	Su et al [2007]
c.1503C>T	p.Thr501= [3]	Distal to S6 transmembrane domain			

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. Reference sequences for *KCNQ4*: NM_004700.2, NP_004691.2
2. Pathology was high-frequency hearing impairment and tissue-specific expression was in cochlear outer hair cells and brain for all pathogenic variants described in the table.
3. No effect on protein level is expected.

Pathogenic variants. Most *KCNQ4* pathogenic variants cluster in exons 5, 6, and 7, which encode highly conserved amino acid sequences that form the channel pore. The predominant pathogenic variants are missense variants that induce a dominant-negative effect. The variant p.Trp276Ser appears to be most common and has been identified in four unrelated families, including three of five Dutch families with DFNA2 nonsyndromic hearing loss and one Japanese family (see Table 3).

Table 3. *KCNQ4* Pathogenic Variants Discussed in This *GeneReview*

DNA Nucleotide Change (Alias [1])	Predicted Protein Change (Alias [1])	Protein Domain	Population	Onset of Symptoms [2]	Reference
c.211_223del13 (211del13)	p.Gln71ProfsTer64 (Q71fsTer134)	N-terminal cytoplasmic	Belgian	Adolescence	Coucke et al [1999]
c.211delC	p.Gln71SerfsTer68 (FS71)	N-terminal cytoplasmic	Japanese	Adolescence	Kamada et al [2006], Ishikawa et al [2014]
c.827G>C	p.Trp276Ser	P-loop	Dutch, Japanese	Childhood	Coucke et al [1999], Van Camp et al [2002], Topsakal et al [2005]
c.853G>T	p.Gly285Cys	P-loop	North American	Childhood	Coucke et al [1999]

Table 3. continued from previous page.

DNA Nucleotide Change (Alias [1])	Predicted Protein Change (Alias [1])	Protein Domain	Population	Onset of Symptoms [2]	Reference
c.853G>A	p.Gly285Ser	P-loop	Northern European, Han Chinese	Childhood	Kubisch et al [1999], Wang et al [2014]

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.
Reference sequences for *KCNQ4*: NM_004700.2, NP_004691.2
1. Variant designation that does not conform to current naming conventions
2. Pathology was high-frequency hearing impairment and tissue-specific expression was in cochlear outer hair cells and brain for all pathogenic variants described in the table.

Normal gene product. The protein encoded by *KCNQ4* is 695 amino acids in length and forms a potassium channel with six transmembrane domains and a P-loop region, which forms the channel pore. A highly conserved glycine-tyrosine-glycine (GYG) signature sequence within the P-loop comprises the selectivity filter that provides discrimination of potassium ions for selective transport [Kubisch et al 1999]. Pathogenic variants cluster in the channel pore region and some (i.e., p.Gly285Ser and p.Gly285Cys) directly affect the selectivity filter.

Abnormal gene product. Most *KCNQ4* pathogenic variants are missense alterations that cause hearing loss via a dominant-negative effect. The phenotype reflects the consequence of defective KCNQ4 protein in the inner ear. This protein assembles as a tetramer to form a potassium channel made of four subunits. In a person with one pathogenic missense variant, half of the total amount of encoded protein is defective and consequently only one of every 16 channels comprises four normal protein subunits [Kubisch et al 1999]. Over time the result is hypothesized to be progressive loss in potassium recycling in the inner ear. Because potassium ions are crucial for hair cell transduction, the inability to recycle these ions results in hearing loss. Most pathogenic variants affect amino acids located within or close to the channel pore. The presence of an abnormal protein subunit interferes with the assembly and/or function of the tetrameric channel protein in the inner ear.

Some *KCNQ4* pathogenic variants are deletions that result in haploinsufficiency. As a result, cells of the inner ear produce insufficient functional KCNQ4 protein and over time auditory function is compromised.

Evidence for locus heterogeneity. *GJB3* was suggested as a deafness-associated gene at the DFNA2 locus based on two different *GJB3* sequence variants identified in two small Chinese families [Xia et al 1998]. Individuals from both families had bilateral sensorineural hearing loss (SNHL) characterized by a gently downsloping audiogram from normal hearing thresholds below 1,000 Hz to moderate hearing loss in the high frequencies.

The evidence associating *GJB3* with hearing loss is neither substantial nor convincing:

- In both families, other individuals with normal hearing had the reported pathogenic variants in *GJB3*, a finding inconsistent with complete penetrance, which is observed in virtually all types of autosomal dominant SNHL.
- It is doubtful that *KCNQ4* pathogenic variants have been excluded in these two families, which were reported in 1998, as *KCNQ4* pathogenic variants were not implicated in autosomal dominant SNHL until 1999.
- No other families with autosomal dominant SNHL have been reported to segregate *GJB3* pathogenic variants.
- Specific pathogenic variants in *GJB3* cause erythrokeratodermia variabilis.

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Chapter Notes

Author Notes

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Deafness Variation Database. The Deafness Variation Database (DVD) collates data from major public databases to provide a single classification for each variant based on collected evidence; it is curated by experts in hereditary hearing loss with the goal of providing a single-source guide to variant interpretation focused on deafness.

Revision History

- 10 May 2018 (bp) Comprehensive update posted live
- 20 August 2015 (me) Comprehensive update posted live
- 20 June 2013 (me) Comprehensive update posted live
- 17 February 2011 (me) Comprehensive update posted live
- 4 April 2008 (me) Review posted live
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