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NLM Citation: Liu XZ, Yuan H, Mittal R, et al. DFNX1 Nonsyndromic Hearing Loss and Deafness – RETIRED CHAPTER, FOR HISTORICAL REFERENCE ONLY. 2011 Aug 4 [Updated 2018 Jul 19]. In: Adam MP, Feldman J, Mirzaa GM, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2024.
Bookshelf URL: https://www.ncbi.nlm.nih.gov/books/

DFNX1 Nonsyndromic Hearing Loss and Deafness – RETIRED CHAPTER, FOR HISTORICAL REFERENCE ONLY

Synonym: DFN2 Nonsyndromic Hearing Loss and Deafness

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Created: August 4, 2011; Updated: July 19, 2018.

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 THIS ARCHIVAL VERSION IS FOR HISTORICAL REFERENCE ONLY, AND THE INFORMATION MAY BE OUT OF DATE.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

DFNX1 nonsyndromic hearing loss and deafness is part of the spectrum of *PRPS1*-related disorders. Hearing loss in hemizygous males is bilateral, sensorineural, and moderate to profound; prelingual or postlingual in onset; and progressive or non-progressive. The audiogram shape is variable. Hearing in female carriers can be normal or abnormal.

Diagnosis/testing

Diagnosis relies on the presence of characteristic hearing loss in males and detection of a hemizygous *PRPS1* pathogenic variant.

Management

Treatment of manifestations: Routine management of sensorineural hearing loss. Cochlear implantation can improve auditory and oral communication skills in affected males.

Surveillance: Regular audiologic evaluation to assess hearing status and progression of hearing loss.

Evaluation of relatives at risk: Evaluate at-risk males at birth with detailed audiometry to assure early diagnosis and treatment of hearing loss.

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Genetic counseling

DFNX1 is inherited in an X-linked manner. The father of an affected male will not have the disorder nor will he be a carrier of the pathogenic variant. If the mother of an affected male has a pathogenic variant, the chance of transmitting it in each pregnancy is 50%. Males who inherit the variant will be affected; females who inherit the variant will be carriers and may have hearing loss. Carrier testing for at-risk female relatives, prenatal testing for a pregnancy at increased risk, and preimplantation genetic testing are possible if the *PRPS1* pathogenic variant in the family has been identified.

Diagnosis

Suggestive Findings

DFNX1 nonsyndromic hearing loss and deafness, part of the spectrum of *PRPS1*-related disorders, **should be considered** in a male proband with the following clinical, laboratory, and imaging findings and family history.

Clinical findings

- Sensorineural hearing loss is:
  - Bilateral moderate to profound;
  - Prelingual or postlingual in onset;
  - Progressive or non-progressive.
- Audiograms are usually flat across all frequencies. However, some individuals have severe hearing loss in the low frequencies and some have residual hearing in the high frequencies.
- Vestibular function is normal.

Imagining. Temporal bone imaging is normal.

Family history is consistent with X-linked inheritance. In heterozygous females hearing can be normal or abnormal.

Establishing the Diagnosis

Male proband. The diagnosis of DFNX1 **is established** in a male proband with sensorineural hearing loss and a hemizygous pathogenic variant in *PRPS1* identified by molecular genetic testing [Liu et al 2010, Kim et al 2016] (see Table 1).

Female carrier. The diagnosis of DFNX1 **is usually established** in a female carrier who may have normal hearing or sensorineural hearing loss and a heterozygous pathogenic variant in *PRPS1* identified by molecular genetic testing [Liu et al 2010] (see Table 1).

Molecular genetic testing. Because the phenotype of DFNX1 is indistinguishable from many other inherited disorders with hearing loss, recommended molecular genetic testing approaches include use of a multigene panel (see Option 1) or comprehensive genomic testing (see Option 2).

Note: Single-gene testing (sequence analysis of *PRPS1* followed by gene-targeted deletion/duplication analysis) is rarely useful and typically NOT recommended.

Option 1

A multigene panel that includes *PRPS1* 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*. Of note, given the rarity of DFNX1 nonsyndromic hearing loss and deafness some panels for hearing loss may not include this gene. (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 an introduction to multigene panels click here. More detailed information for clinicians ordering genetic tests can be found here.

Option 2

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.

For an 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 DFNX1

Gene [1]	Method	Proportion of Pathogenic Variants [2] Detectable by Method
PRPS1	Sequence analysis [3]	5/5 [4]
	Gene-targeted deletion/duplication analysis [5]	Unknown [6]

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. Sequencing of the seven exons of the coding region and the intron/exon boundaries of *PRPS1* in the five families reported to date with DFNX1 nonsyndromic hearing loss and deafness identified five different pathogenic missense variants [Liu et al 2010, Kim et al 2016]. To date no intragenic deletions or duplications have been observed.
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. No data on detection rate of gene-targeted deletion/duplication analysis are available.

Clinical Characteristics

Clinical Description

Hearing loss in individuals with DFNX1 nonsyndromic hearing loss and deafness can be prelingual or postlingual (in which onset ranges from 3 years to 20 years), progressive or non-progressive, and severe to profound [Liu et al 2010, Liu et al 2013, Kim et al 2016].

Synofzik et al [2014] concluded that the three *PRPS1*-related phenotypes (CMTX5, Arts syndrome, and DFNX1) constitute a continuum after observing all three phenotypes in one family with a loss-of-function pathogenic variant: a male with CMT and Arts syndrome and a heterozygous female with hearing loss due to skewing of X-chromosome inactivation. On detailed clinical and neurophysiologic examination manifestations of peripheral neuropathy that range from a subclinical axonal motor neuropathy to an axonal sensory-motor neuropathy were

found in males with *PRPS1*-related hearing loss [Robusto et al 2015]. In addition, optic atrophy and retinitis pigmentosa have been described in females heterozygous for a *PRPS1* pathogenic variant [Almoguera et al 2014].

Heterozygous females. Hearing in heterozygous females can be normal or abnormal. When hearing is abnormal, hearing loss can be either symmetric or asymmetric and ranges from mild to moderate [Liu et al 2013].

In the family described by Almoguera et al [2014], both the proband and her mother have peripheral neuropathy and ophthalmologic manifestations, whereas the phenotype of the affected sister is milder and confined to eye, with no hearing loss.

Genotype-Phenotype Correlations

The established *PRPS1*-related disorders are not distinct entities, but rather clusters on a phenotypic continuum as evidenced by overlap of the features of CMTX5 / Arts syndrome / DFNX1 both in affected individuals and within families. A wide and continuous spectrum of clinical manifestations has been associated with *PRPS1* missense variants (see Genetically Related Disorders). A relationship between the type (location) of PRS-I disruption and phenotype has been suggested, with the most severe phenotypes caused by variants predicted to affect allosteric and active sites and the milder phenotypes caused by variants predicted to disrupt the structure locally [de Brouwer et al 2010].

In females, who predictably have a less severe presentation, the ratio of X chromosome inactivation adds an additional variable in predicting clinical outcome [Synofzik et al 2014].

Prevalence

Prevalence has not been determined. Five families with DFNX1 have been reported [Liu et al 2010, Kim et al 2016].

Genetically Related (Allelic) Disorders

Other phenotypes associated with germline pathogenic variants in *PRPS1* are summarized in Table 2 and Table 3. Disorders included in Table 2 have overlapping phenotypic features with DFNX1 and should be considered in the differential diagnosis.

Table 2. Allelic Disorders to Consider in the Differential Diagnosis of DFNX1

Phenotype	Clinical Findings					
	In hemizygous males					In heterozygous females
	GA	PN	ID	SNHL	Other	
DFNX1 (DFN2)	–	–	–	+	None	Hearing could be normal or abnormal
CMTX5	–	+	–	+	Early-onset SNHL, optic neuropathy, progressive hypotonia, gait disturbances, loss of deep-tendon reflexes	No symptoms
Arts syndrome	–	+	+	+	Profound congenital SNHL, hypotonia, ataxia, optic atrophy, risk for infection	In some: isolated &/or milder signs

GA = gouty arthritis; ID = intellectual disability; PN = peripheral neuropathy; SNHL = sensorineural hearing loss

Table 3. Other Allelic Disorders (not in the Differential Diagnosis of DFNX1)

Phenotype		Clinical Findings					
		In hemizygous males					In heterozygous females
		GA	PN	ID	SNHL	Other	
PRS superactivity	Severe	+	–	+	+	Early-onset hyperuricemia, hyperuricosuria, hypotonia, ataxia	In some: ≥1 of these features
	Mild	+	–	–	–	Late-onset hyperuricemia, hyperuricosuria; no obvious neurologic findings	No heterozygous females have been described.

GA = gouty arthritis; ID = intellectual disability; PN = peripheral neuropathy; SNHL = sensorineural hearing loss

Differential Diagnosis

See Deafness and Hereditary Hearing Loss Overview for complete differential diagnosis of hereditary hearing loss.

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs of an individual diagnosed with DFNX1 nonsyndromic hearing loss and deafness, the evaluations summarized in this section (if not performed as part of the evaluation that led to the diagnosis) are recommended:

- Pure tone audiograms, auditory brain stem response testing
- Evaluation for peripheral neuropathy and ophthalmologic findings (optic atrophy and retinitis pigmentosa)
- Consultation with a clinical geneticist and/or genetic counselor

Treatment of Manifestations

Sensorineural hearing loss. Cochlear implantation in affected males can improve auditory and oral communication skills.

See Deafness and Hereditary Hearing Loss Overview.

Surveillance

Hearing loss in DFNX1 is prelingual or postlingual and progressive; regular audiologic evaluation is recommended to assess hearing status and progression of hearing loss.

Periodic reevaluation of clinical findings by a neurologist is indicated for males with clinical evidence of peripheral neuropathy.

Evaluation of Relatives at Risk

Determining in infancy whether at-risk male and female relatives of a person with DFNX1 nonsyndromic hearing loss and deafness have inherited the *PRPS1* pathogenic variant allows for early support and management of the child and the family.

Evaluations may include:

- Molecular genetic testing if the pathogenic *PRPS1* variant in the family is known.
- Audiometry if molecular genetic testing for the at-risk relative is not available.

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

DFNX1 nonsyndromic hearing loss and deafness is inherited in an X-linked manner.

Risk to Family Members

Parents of a male proband

- The father of an affected male will not have hearing loss nor will he be hemizygous for the *PRPS1* pathogenic variant.
- In a family with more than one affected individual, the mother of an affected male is an obligate heterozygote (carrier). Note: If a woman has more than one affected child and no other affected relatives and if the *PRPS1* pathogenic variant cannot be detected in her leukocyte DNA, she most likely has germline mosaicism. Although maternal germline mosaicism has not been reported to date, it remains a possibility.
- If a male is the only affected family member (i.e., a simplex case), the mother may be a heterozygote or the affected male may have a *de novo PRPS1* pathogenic variant, in which case the mother is not a heterozygote. The frequency of *de novo* pathogenic variants is not known.

Sibs of a male proband. The risk to sibs depends on the genetic status of the mother:

- If the mother of the proband has the *PRPS1* pathogenic variant, the chance of transmitting it in each pregnancy is 50%. Intrafamilial clinical variability has been reported.
  - Males who inherit the variant will have hearing loss; other features (e.g., mild peripheral neuropathy) may also be observed in hemizygous sibs [Gandía et al 2015, Robusto et al 2015].
  - Females who inherit the variant will be heterozygotes and may be unaffected, have nonsyndromic hearing loss, or have peripheral neuropathy and optic atrophy, as well as retinitis pigmentosa (RP) as the only manifestations [Almoguera et al 2014].
- If the proband represents a simplex case (i.e., a single occurrence in a family) and if the *PRPS1* pathogenic variant cannot be detected in the leukocyte DNA of the mother, the recurrence risk to sibs is low but greater than that of the general population because of the theoretic possibility of maternal germline mosaicism.

Offspring of a male proband. Males with DFNX1 transmit the *PRPS1* pathogenic variant to:

- All of their daughters, who will be heterozygotes and may be unaffected, have nonsyndromic hearing loss, or have peripheral neuropathy and optic atrophy and RP as the only manifestations [Almoguera et al 2014];
- None of their sons.

Other family members. A male proband's maternal aunts and maternal cousins may be heterozygous or hemizygous (depending on their sex) and have a range of clinical manifestations [Almoguera et al 2014, Gandía et al 2015, Robusto et al 2015].

Note: Molecular genetic testing may be able to identify the family member in whom a *de novo* pathogenic variant arose, information that could help determine genetic risk status of the extended family.

Heterozygote Detection

Molecular genetic testing of female relatives to determine their genetic status requires prior identification of the *PRPS1* pathogenic variant in the proband.

Note: Females who are heterozygotes for a *PRPS1* pathogenic variant may be unaffected, develop hearing loss (reported findings included either symmetric or asymmetric hearing loss that varied from mild to moderate in degree [Liu et al 2013]), or have peripheral neuropathy and optic atrophy, retinitis pigmentosa RP as the only manifestations [Almoguera et al 2014].

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 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, therefore, 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.

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 (or are carriers of) DFNX1 nonsyndromic hearing loss and deafness.

Prenatal Testing and Preimplantation Genetic Testing

Once the *PRPS1* pathogenic variant has been identified in an affected family member, prenatal testing for a pregnancy at increased risk and preimplantation genetic testing for DFNX1 nonsyndromic hearing loss and deafness are possible. Note: Prenatal genetic testing results cannot be used to reliably predict the phenotype as intrafamilial variability has been reported.

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
- **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
- **MedlinePlus**
  Nonsyndromic hearing loss
- **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. DFNX1 Nonsyndromic Hearing Loss and Deafness: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar

Table A. continued from previous page.

PRPS1	Xq22.3	Ribose-phosphate pyrophosphokinase 1	IPN Mutations, PRPS1 PRPS1 @ LOVD	PRPS1	PRPS1

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 DFNX1 Nonsyndromic Hearing Loss and Deafness (View All in OMIM)

304500	DEAFNESS, X-LINKED 1; DFNX1
311850	PHOSPHORIBOSYLPYROPHOSPHATE SYNTHETASE I; PRPS1

Gene structure. *PRPS1* spans approximately 23 kb with seven exons. See Table A, **Gene** for a detailed summary of gene and protein information.

Pathogenic variants. Five missense variants in *PRPS1* have been associated with *DFNX1* (see Table 4). These variants have been shown to result in reduced enzyme activity [Liu et al 2010, Kim et al 2016].

Table 4. Selected *PRPS1* Pathogenic Variants

DNA Nucleotide Change	Predicted Protein Change	Reference Sequences
c.193G>A	p.Asp65Asn	NM_002764.3 NP_002755.1
c. 244G>C	p.Ala82Pro	
c.259G>A	p.Ala87Thr	
c.869T>C	p.Ile290Thr	
c.916G>A	p.Gly306Arg	

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.

Normal gene product. *PRPS1* encodes a 318-amino acid protein, the PRS-I (ribose-phosphate pyrophosphokinase 1) enzyme. The active unit is a hexamer that consists of a trimer of homodimers. The enzyme catalyzes the phosphoribosylation of ribose 5-phosphate from adenosine triphosphate (ATP) to 5-phosphoribosyl-1-pyrophosphate, which is necessary for the *de novo* and salvage pathways of purine and pyrimidine biosynthesis. This enzyme is activated by inorganic Mg^{+2} but can be allosterically inhibited by adenosine diphosphate (ADP) and purines.

Phosphoribosylpyrophosphate synthetase (PRS) I enzyme activity can be analyzed in fibroblasts, lymphoblasts, and erythrocytes [Torres et al 1996, de Brouwer et al 2007, Kim et al 2007, Kim et al 2016] using high-performance liquid chromatography measurement of AMP; however, this assay is not currently part of routine care.

Abnormal gene product. Despite disease-associated variants resulting in loss of PRS-I enzyme activity, as evidenced by decreased enzyme activity in erythrocytes and cultured fibroblasts from males with DFNX1, all reported disease-associated variants are misssense changes [Liu et al 2010]. Pathogenic variants causing reduced enzyme activity either reduce stability of PRS-I or moderately affect interactions in the trimer interface. The lack of affected males in the family reported by Almoguera et al [2014] suggests that some causative variants are lethal in hemizygotes.

Interestingly, computer-assisted molecular modeling showed that pathogenic variants causing Arts syndrome and CMTX5 disturb the ATP binding site of PRS-I suggesting that these syndromes are caused by pathogenic variants predicted to affect allosteric and active sites (see Genotype-Phenotype Correlations).

Of note, pathogenic variants that result in PRS superactivity disturb either one or both allosteric sites involved in the inhibition of PRS-I enzyme activity by ADP or purine binding (see Genetically Related Disorders). Variants reported to be associate with superactivity have been reported from amino acid 52 to 192.

Chapter Notes

Revision History

- 8 June 2023 (ma) Chapter retired: covered in Phosphoribosylpyrophosphate Synthetase Deficiency
- 19 July 2018 (bp) Comprehensive update posted live
- 4 August 2011 (me) Review posted live
- 31 March 2011 (xzl) Original submission

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