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Deafness and Myopia Syndrome

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Summary

Clinical characteristics

Deafness and myopia (DFNMYP) syndrome is characterized by bilateral, congenital or prelingual deafness (sensorineural hearing loss or auditory neuropathy spectrum disorder) and high myopia (>-6 diopters). In individuals with a molecularly confirmed diagnosis reported to date, hearing loss was progressive and severity ranged from moderate to profound. Vestibular testing was normal. Myopia was diagnosed at infancy or early childhood.

Diagnosis/testing

The diagnosis is established in a proband by identification of biallelic pathogenic variants in *SLITRK6* on molecular genetic testing.

Management

Treatment of manifestations: For hearing loss: use of hearing habilitation devices including hearing aids and vibrotactile hearing tools; cochlear implantation may be considered in individuals with severe-to-profound sensorineural hearing loss and auditory neuropathy spectrum disorder; enrollment in appropriate early-intervention and educational programs for the hearing impaired. For myopia: routine correction of refractive error.

Surveillance: ENT and audiology evaluations at least yearly; regular speech and language evaluation to monitor language development; regular ophthalmology evaluations to monitor for potential complications from high myopia; yearly evaluations by a clinical geneticist familiar with hereditary forms of deafness.

Agents/circumstances to avoid: Known environmental factors for hearing loss (e.g., loud noises) and ototoxic medications.

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Evaluation of relatives at risk: If the *SLITRK6* pathogenic variants in the family are known, molecular genetic testing can be used to clarify the genetic status of at-risk sibs. If a molecular diagnosis has not been established, clinical audiology and ophthalmology evaluations should be considered for at-risk sibs.

Genetic counseling

DFNMYP syndrome is inherited in an autosomal recessive manner. At conception, each sib of an affected individual has a 25% chance of being affected, a 50% chance of being an asymptomatic carrier, and a 25% chance of being unaffected and not a carrier. Carrier testing for at-risk relatives and prenatal testing for a pregnancy at increased risk are possible if the *SLITRK6* pathogenic variants have been identified in an affected family member.

Diagnosis

Suggestive Findings

Deafness and myopia (DFNMYP) syndrome **should be suspected** in individuals with the following:

- Moderate-to-profound, bilateral, congenital or prelingual sensorineural hearing loss or auditory neuropathy spectrum disorder (sensorineural hearing loss originates from problems in the inner ear or the auditory nerve). Auditory neuropathy spectrum disorder is characterized by normal outer hair cell function (present otoacoustic emissions [OAE] and/or cochlear microphonic), suggesting that the hearing loss results from abnormal inner hair cells, synapses, or auditory nerve function that can be demonstrated with an absent or abnormal auditory brain stem response (ABR) test.
- High myopia (g>-6 diopters)
- Nondysmorphic facial appearance and normal temporal bone structure
- No neurologic, connective tissue, or other ocular manifestations

Establishing the Diagnosis

No formal clinical diagnostic criteria have been established for DFNMYP syndrome.

The diagnosis of DFNMYP **is established** in a proband with the above suggestive findings; identification of biallelic pathogenic variants in *SLITRK6* on molecular genetic testing (see Table 1) confirms the diagnosis.

Molecular genetic testing approaches can include **single-gene testing**, use of a **multigene panel**, and **more comprehensive genomic testing**:

- **Single-gene testing.** Sequence analysis of *SLITRK6* is performed first. Gene-targeted deletion/duplication analysis can be considered if only one or no pathogenic variant is found. However, to date, no large *SLITRK6* deletions or duplications have been reported.
- **A multigene panel** that includes *SLITRK6* and other genes of interest (see Differential Diagnosis) may be considered. 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*; thus, clinicians need to determine which multigene panel is most likely to identify the genetic cause of the condition at the most reasonable cost while limiting identification of variants of uncertain significance and pathogenic variants in genes that do not explain the underlying phenotype. (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.

- **More comprehensive genomic testing** (when available) including exome sequencing, mitochondrial sequencing, and genome sequencing may be considered. Such testing may provide or suggest a diagnosis not previously considered (e.g., mutation of a different gene or genes that results in a similar clinical presentation).

  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 Deafness and Myopia Syndrome

Gene [1]	Method	Proportion of Probands with Pathogenic Variants [2] Detectable by Method
SLITRK6	Sequence analysis [3]	4/4 [4]
	Gene-targeted deletion/duplication analysis [5]	None reported [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. Tekin et al [2013], Morlet et al [2014]
5. Gene-targeted deletion/duplication analysis detects intragenic deletions or duplications. Methods used may include 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. Tekin et al [2013]

Clinical Characteristics

Clinical Description

Deafness and myopia (DFNMYP) syndrome was described by Tekin et al [2013] in nine individuals with only deafness and myopia from three families, of Turkish, Greek, and Amish ancestry; all nine were found to be homozygous for *SLITRK6* pathogenic variants.

Sensorineural hearing loss (SNHL) was bilateral in all affected individuals, congenital in one and prelingual in 8/9. SNHL was progressive and required hearing aids in all. Severity of hearing loss ranged from moderate (2/9) to severe (5/9) to profound (2/9).

Sensorineural hearing loss progressed from moderate to profound by early adulthood in nine additional affected individuals from an endogamous Amish population [Morlet et al 2014]. An auditory neuropathy-spectrum disorder characterized by absent middle-ear muscle reflexes (MEMRs) and otoacoustic emissions (OAEs), large and prolonged cochlear microphonics (CMs), desynchronized auditory brain stem responses (ABRs), and progressive pure tone hearing loss was described [Morlet et al 2014].

Affected individuals had normal gross motor development. None had balance problems, vertigo, or dizziness. Vestibular testing and temporal bone CT were normal in one affected individual from each family.

Myopia was diagnosed in infancy or early childhood in seven individuals on whom data were available. Myopia was severe in all seven individuals (range: -6 to -11 diopters) and required corrective lenses. Although no details of myopia treatment or complications were available, none of the potential complications of high myopia was observed in any of the reported individuals at the time of reporting.

Life span does not appear to be altered in individuals with DFNMYP syndrome; however, the oldest individuals with a molecularly confirmed diagnosis are only in their late 30s.

Genotype-Phenotype Correlations

All reported individuals to date with DFNMYP syndrome have homozygous nonsense *SLITRK6* variants. No significant differences in clinical phenotype have been associated with specific genotypes.

Prevalence

Due to the rarity of the syndrome, no prevalence estimates have been established.

Genetically Related (Allelic) Disorders

No phenotypes other than those discussed in this *GeneReview* are known to be associated with pathogenic variants in *SLITRK6*.

Sporadic tumors (including papillary thyroid tumors) occurring as single tumors in the absence of any other findings of deafness and myopia syndrome may have somatic pathogenic variants in *SLITRK6* that are **not** present in the germline. In these circumstances predisposition to these tumors is not heritable [Heiliger et al 2012]. For more details, see Molecular Genetics, Cancer and Benign Tumors.

Differential Diagnosis

See Hereditary Deafness and Hearing Loss Overview.

Disorders with deafness and myopia to specifically consider include the following:

- **Stickler syndrome,** a clinically variable connective tissue disorder characterized by ocular, auditory, skeletal, and orofacial anomalies. Ocular findings typically include high myopia with cataracts and retinal detachment. Hearing loss is conductive and sensorineural. Severity of hearing loss is variable and may be progressive. Stickler syndrome, caused by mutation of *COL2A1*, *COL11A1*, or *COL11A2*, is inherited in an autosomal dominant manner; Stickler syndrome caused by mutation of *COL9A1*, *COL9A2*, or *COL9A3* is inherited in an autosomal recessive manner. Although myopia and sensorineural hearing loss are part of DFNMYP syndrome, individuals with DFNMYP syndrome do not manifest the skeletal and craniofacial findings traditionally seen in individuals with Stickler syndrome.
- **Donnai-Barrow syndrome (DBS),** a multiple congenital anomaly syndrome characterized by typical craniofacial features, ocular findings, sensorineural hearing loss, brain anomalies, intellectual disability, and congenital diaphragmatic hernia and/or omphalocele. High myopia is typically accompanied by retinal detachment, progressive vision loss, and iris coloboma. Hearing loss may be progressive and variable in severity. The constellation of craniofacial findings typically includes marked ocular hypertelorism, large anterior fontanelle, wide metopic suture, widow's peak in anterior hairline, depressed nasal bridge, short nose, and posteriorly rotated ears. DBS can be caused by mutation of *LRP2* and is inherited in an autosomal recessive manner. In contrast to individuals with DFNMYP syndrome, individuals with DBS have multiple congenital anomalies and craniofacial and neurologic findings in addition to myopia and hearing loss.

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with deafness and myopia (DFNMYP) syndrome, the following evaluations are recommended if they have not already been completed:

- Audiology evaluation for sensorineural hearing loss and auditory neuropathy spectrum disorder
- Ophthalmology evaluation for myopia and other ocular comorbidities
- Evaluation by early intervention/educational programs for the hearing impaired including baseline speech and language assessment in children
- Consultation with a clinical geneticist and/or genetic counselor

Treatment of Manifestations

Appropriate treatment includes the following:

- Implementation of hearing habilitation devices including hearing aids and vibrotactile hearing tools as needed
- Consideration of cochlear implantation (CI) in individuals with severe-to-profound sensorineural hearing loss and auditory neuropathy spectrum disorder. Although no CI has been reported among individuals with deafness and myopia syndrome, favorable outcome of CI has been reported in children with auditory neuropathy spectrum disorder [Breneman et al 2012].
- Enrollment in early intervention programs and educational programs for the hearing impaired to maximize long-term speech and language outcomes
- Routine correction of refractive error

Surveillance

The following are appropriate:

- ENT and audiology evaluations at least yearly
- Regular speech and language evaluation to monitor language development
- Regular ophthalmology evaluations to monitor for potential complications from high myopia including cataracts, glaucoma, and retinal detachment
- Yearly evaluations by a clinical geneticist familiar with hereditary forms of deafness

Agents/Circumstances to Avoid

Individuals with hearing loss should avoid the following:

- Known environmental factors for hearing loss (e.g., loud noises)
- Ototoxic medications

Evaluation of Relatives at Risk

It is appropriate to evaluate older and younger sibs of a proband in order to identify as early as possible those who would benefit from prompt treatment of hearing loss and myopia. Evaluations can include:

- Molecular genetic testing if the *SLITRK6* pathogenic variants in the family are known;
- Clinical audiology and ophthalmology evaluations if a molecular diagnosis has not been established.

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

Deafness and myopia (DFNMYP) syndrome is inherited in an autosomal recessive manner.

Risk to Family Members

Parents of a proband

- The parents of an affected child are obligate heterozygotes (i.e., carriers of one *SLITRK6* pathogenic variant).
- Although low myopia (<-3 diopters) of early and adult onset has been reported among some carrier parents, *SLITRK6* heterozygotes are not at risk of developing hearing loss or the high myopia characteristic of DFNMYP syndrome.

Sibs of a proband

- At conception, each sib of an affected individual has a 25% chance of being affected, a 50% chance of being an asymptomatic carrier, and a 25% chance of being unaffected and not a carrier.
- Heterozygotes (carriers) are generally asymptomatic and are not at risk of developing the disorder.

Offspring of a proband. The offspring of an individual with DFNMYP syndrome are obligate heterozygotes (carriers) for a pathogenic variant in *SLITRK6*.

Other family members. Each sib of the proband's parents is at a 50% risk of being a carrier of a *SLITRK6* pathogenic variant.

Carrier Detection

Carrier testing for at-risk relatives requires prior identification of the *SLITRK6* pathogenic variants in the family.

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.

Family planning

- The optimal time for determination of genetic risk, clarification of carrier status, and discussion of the availability of prenatal/preimplantation genetic testing is before pregnancy.
- It is appropriate to offer genetic counseling (including discussion of potential risks to offspring and reproductive options) to young adults who are affected, are carriers, or are at risk of being carriers.

DNA banking is the storage of DNA (typically extracted from white blood cells) for possible future use. Because it is likely that testing methodology and our understanding of genes, allelic variants, and diseases will improve in the future, consideration should be given to banking DNA of affected individuals.

Prenatal Testing and Preimplantation Genetic Testing

Once the *SLITRK6* pathogenic variants have been identified in an affected family member, prenatal testing for a pregnancy at increased risk 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.

- **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

- **National Institute on Deafness and Other Communication Disorders (NIDCD)**

  31 Center Drive

  MSC 2320

  Bethesda MD 20892-2320

  www.nidcd.nih.gov

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. Deafness and Myopia Syndrome: Genes and Databases

Gene	Chromosome Locus	Protein	HGMD	ClinVar
SLITRK6	13q31.1	SLIT and NTRK-like protein 6	SLITRK6	SLITRK6

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 Deafness and Myopia Syndrome (View All in OMIM)

221200	DEAFNESS AND MYOPIA; DFNMYP
609681	SLIT- AND NTRK-LIKE FAMILY, MEMBER 6; SLITRK6

Gene structure. *SLITRK6* contains two exons; exon 1 is noncoding. The full-length transcript spans 6.6 kb (6,562 bp) of genomic DNA. The cDNA NM_032229.2 comprises 4199 bp encoding 841 amino acids. For a detailed summary of gene and protein information, see Table A, **Gene**.

Pathogenic variants. Three *SLITRK6* pathogenic variants, all nonsense, have been described in DFNMYP syndrome. The c.1240C>T variant has been observed more than once among the Amish.

Table 2. *SLITRK6* Pathogenic Variants Discussed in This *GeneReview*

DNA Nucleotide Change	Predicted Protein Change	Reference Sequences
c.541C>T	p.Arg181Ter	NM_032229.2 NP_115605.2
c.890C>A	p.Ser297Ter	
c.1240C>T	p.Gln414Ter	

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. The *SLITRK* family of genes encodes six neuronal transmembrane proteins - mainly found in neural tissue - that modulate neurite outgrowth and synaptic development [Aruga 2003, Aruga & Mikoshiba 2003, Takahashi et al 2012].

SLITRK6 has an extracellular N-terminal domain that contains two leucine-rich domains highly homologous to SLIT domains; it also has a transmembrane domain and an intracellular C-terminus with two conserved tyrosine phosphorylation sites homologous to receptor sites from the NTRK-neurotrophin family. The expression of *SLITRK6* in the inner ear promotes innervation and survival of sensory neurons.

Unlike other members of the *SLITRK* family, which are broadly expressed in developing mouse brain, *SLITRK6* is differentially expressed in the auditory system during embryonic and postnatal life; expression is strongest in the inner ear, and modest in the thalamus and lateral geniculate nucleus [Beaubien & Cloutier 2009, Katayama et al 2009].

Abnormal gene product. The reported pathogenic variants (which impair cell surface expression and synapse-inducing activity of SLITRK6) did not trigger nonsense-mediated mRNA decay, produced truncated products, and are predicted to result in loss of function. However, the possibility of a toxic gain-of-function mechanism

from misdirection to the intracellular space from loss of an intracellular C-terminal domain cannot be excluded [Morlet et al 2014].

Cancer and Benign Tumors

Copy number changes were analyzed from human papillary thyroid cancerous tumors (PTC) using array CGH [Heiliger et al 2012]. *SLITRK6* deletions were detected in 16% of PTC samples compared to normal tissue. Deletions were not detected in PTC samples from a transgenic mouse model for thyroid neoplasia.

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Chapter Notes

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