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NLM Citation: Hildebrand MS, Avenarius MR, Smith RJH. *CATSPER*-Related Male Infertility – RETIRED CHAPTER, FOR HISTORICAL REFERENCE ONLY. 2009 Dec 3 [Updated 2017 Mar 23]. 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/

CATSPER-Related Male Infertility – RETIRED CHAPTER, FOR HISTORICAL REFERENCE ONLY

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Created: December 3, 2009; Updated: March 23, 2017.

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 THIS ARCHIVAL VERSION IS FOR HISTORICAL REFERENCE ONLY, AND THE INFORMATION MAY BE OUT OF DATE.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

CATSPER-related male infertility results from abnormalities in sperm and can be either *CATSPER*-related nonsyndromic male infertility (NSMI) or the deafness-infertility syndrome (DIS) when associated with non-progressive prelingual sensorineural hearing loss. Males with NSMI have infertility while females have no symptoms. Males with DIS have both infertility and hearing loss, while females have only hearing loss. Routine semen analysis typically identifies abnormalities in sperm number, morphology, and motility. Otologic examination and audiologic assessment can identify hearing loss.

Diagnosis/testing

The diagnosis of *CATSPER*-related NSMI is established in males by the identification of biallelic pathogenic variants in *CATSPER1*. The diagnosis of DIS is established in both males and females by the identification of biallelic contiguous-gene deletions at chromosome 15q15.3 that includes both *CATSPER2* and *STRC*.

Management

Treatment of manifestations: For infertile males with DIS or *CATSPER*-related NSMI, assisted reproductive technologies such as intracytoplasmic sperm injection are likely to be an effective fertility option. For males with DIS, treatment of hearing loss is best achieved by fitting hearing aids for amplification and special educational assistance for school-age children.

Agents/circumstances to avoid: For individuals with DIS, exposure to loud noise.

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Evaluation of relatives at risk: For sibs at risk for DIS, audiologic testing in infancy or early childhood to enable early management of hearing loss.

Genetic counseling

CATSPER-related NSMI and DIS are inherited in an autosomal recessive manner. When both parents are carriers for pathogenic variants, each child has a 25% chance of inheriting both pathogenic variants, a 50% chance of inheriting one pathogenic variant and being an asymptomatic carrier, and a 25% chance of inheriting neither pathogenic variant. Males who inherit two *CATSPER1* pathogenic variants will be infertile; females who inherit two *CATSPER1* pathogenic variants will have no signs/symptoms. Males who inherit two *CATSPER2-STRC* deletions will be infertile and deaf; females who inherit two *CATSPER2-STRC* deletions will be deaf. If the pathogenic variants have been identified in an affected family member, prenatal testing for at-risk pregnancies is possible through laboratories offering either prenatal testing for the gene of interest or custom testing.

GeneReview Scope

CATSPER-Related Male Infertility: Included Phenotypes [1]
• *CATSPER*-related nonsyndromic male infertility (NSMI) • Deafness-infertility syndrome (DIS)

For synonyms and outdated names, see Nomenclature.
1. For other genetic causes of these phenotypes see Differential Diagnosis.

Diagnosis

CATSPER-related male infertility results from abnormalities in sperm and can be either:

- Nonsyndromic (*CATSPER*-related nonsyndromic male infertility [NSMI]); or
- Associated with non-progressive prelingual sensorineural hearing loss (deafness-infertility syndrome [DIS]).

Suggestive Findings

CATSPER-related male infertility **should be suspected** in individuals with the following clinical features and semen analysis.

Clinical features

- Male factor infertility
- Hearing loss in either a male or female:
  - In DIS, prelingual hearing loss in the moderate-to-severe range across all frequencies (0.25 kHz – 8 kHz)
  - Normal vestibular function

Semen analysis. Routine semen analysis assesses sperm number, morphology, and motility and the function of the genital tract (semen volume and pH) [WHO 1999] (Table 1). Note: Although routine semen analysis effectively identifies azoospermia, changes in sperm morphology and motility can be missed unless the analysis includes measurement of sperm motility (e.g., path velocity, progressive velocity, and track speed).

- **NSMI.** While the pH of the semen was in the normal range, examination of all other parameters revealed non-motile sperm or sperm motility below the normal threshold, low sperm count, an increased number of abnormally structured spermatozoa, and reduced semen volume [Avenarius et al 2009].

- **DIS.** Semen analysis of males with DIS is normal for sperm count and semen volume, but sperm morphology and motility are abnormal.

Table 1. Semen Analysis

Test	CATSPER-Related Male Infertility		Normal [1]
	NSMI	DIS	
Ejaculate volume	0.4-1.0 mL	1-4 mL	1.5-5 mL
pH	7.5-8.0	Normal	>7.2
Sperm concentration	Normal	60-78 million/mL	>20 million/mL
Total sperm number (million/ejaculate)	10.4-12	>40	>40
Percent motility (% motile)	0%-50%	1%-5%	>50%
Forward progression (scale 0-4)	Normal	Normal	>2
Morphology (% normal)	20%-65%	9%-12%	>30%
Sperm agglutination (scale 0-3)	Normal	Normal	<2
Viscosity (scale 0-4)	Normal	Normal – 3+	<3

DIS = deafness-infertility syndrome; NSMI = nonsyndromic male infertility
1. Values from ASRM Practice Committee [Male Infertility Best Practice Policy Committee 2006]

Establishing the Diagnosis

Nonsyndromic Male Infertility (NSMI)

The diagnosis of *CATSPER*-related NSMI **is established** in males by identification of biallelic loss-of-function pathogenic (or likely pathogenic) variants in *CATSPER1* on molecular genetic testing (see Table 2).

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 *GeneReview* is understood to include any likely pathogenic variants. (2) Identification of biallelic *CATSPER1* variants of uncertain significance (or of one known *CATSPER1* pathogenic variant and one *CATSPER1* variant of uncertain significance) does not establish or rule out the diagnosis.

Single-gene testing. Sequence analysis of *CATSPER1* is performed first and followed by gene-targeted deletion/duplication analysis if only one or no pathogenic variant is found.

Alternate testing strategy for NSMI

- **A multigene panel** that includes *CATSPER1* and other genes of interest (see Differential Diagnosis) may also 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 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 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.

Deafness-Infertility Syndrome (DIS)

The diagnosis of *CATSPER*-related DIS **is established** in both males and females by the identification of biallelic contiguous-gene deletions at chromosome 15q15.3 that includes both *CATSPER2* and *STRC*.

Chromosomal microarray (CMA) using oligonucleotide or SNP arrays can detect a contiguous-gene deletion involving *CATSPER2* and *STRC* in a proband. The ability to size the deletion depends on the type of microarray used and the density of probes in the 15q15.3 region.

Table 2. Molecular Genetic Testing Used in *CATSPER*-Related Male Infertility

Gene [1] or Deletion [2]	Method	Proportion of Probands with Pathogenic Variants [3] Detectable by Method	
		NSMI	DIS
CATSPER1	Sequence analysis [4]	2/2 [5]	NA
	Gene-targeted deletion/ duplication analysis [6]	Unknown [7]	NA
Homozygous deletion at 15q15.3 including *CATSPER2* and *STRC*	CMA/array CGH [8]	NA	100% [9]
Unknown	NA	Unknown [10]	Unknown [10]

DIS = deafness-infertility syndrome; NA = not applicable; NSMI = nonsyndromic male infertility

1. See Table A. Genes and Databases for chromosome locus and protein.

2. See Molecular Genetics for details of the deletion and genes of interest included in the region.

3. See Molecular Genetics for information on variants detected in this gene.

4. Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or pathogenic. Variants may include missense, nonsense, and splice site variants and small intragenic deletions/insertions; typically, exon or whole-gene deletions/duplications are not detected. For issues to consider in interpretation of sequence analysis results, click here.

5. Two families with homozygous loss-of-function variants in *CATSPER1* have been reported [Avenarius et al 2009].

6. 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.

7. No data on detection rate of gene-targeted deletion/duplication analysis in individuals with NSMI are available.

8. Chromosomal microarray analysis (CMA) using oligonucleotide or SNP arrays or array comparative genomic hybridization (array CGH) using fluorescent probesThese approaches are in clinical use targeting the 15q15.3 region. Note: The 15q15.3 deletion may not have been detectable by older oligonucleotide or BAC platforms.

9. In all cases of *CATSPER2*-related DIS the entire *CATSPER1* gene, as well as *STRC,* has been deleted as part of a contiguous deletion (see Molecular Genetics). A case of brothers with a heterozygous *CATSPER2* deletion and an apparent NSMI phenotype has been reported; however, given the lack of a second pathogenic variant and no evidence of hearing loss, the cause of NSMI in this family was not clear [Jaiswal et al 2014].

10. The contribution of the other *CATSPER* gene family members (*CATSPER2*, *CATSPER3*, *CATSPER4*, *CATSPERB*, and *CATSPERG*) to NSMI is unknown [Lobley et al 2003, Liu et al 2007, Cai & Clapham 2008, Wang et al 2009, Hildebrand et al 2010].

Clinical Characteristics

Clinical Description

CATSPER-related male infertility includes *CATSPER*-related nonsyndromic male infertility (NSMI) and the deafness-infertility syndrome (DIS) [Nikpoor et al 2004, Clapham & Garbers 2005, Benoff et al 2007, Hildebrand et al 2010].

CATSPER-Related Nonsyndromic Male Infertility (NSMI)

CATSPER-related NSMI was reported in two unrelated Iranian families in 2009 [Avenarius et al 2009]. In both families, the affected infertile males were offspring of first-cousin marriages.

Females homozygous for the *CATSPER1* pathogenic variant and all heterozygous individuals within a family have normal fertility.

Deafness-Infertility Syndrome (DIS)

Infertility. All males homozygous for *CATSPER2-STRC* deletion are infertile. Semen analysis is typically abnormal. For example, in one affected male more than 88% of sperm were malformed (mainly thin heads, micro- and irregular acrosomes) and approximately 30% of sperm had short, coiled flagella [Zhang et al 2007]. Following liquidation fewer than 5% of sperm had full swimming capacity. Similar defects were observed in other affected males from the four families [Avidan et al 2003, Zhang et al 2007, Smith et al 2013].

Hearing loss. All affected males and females who are homozygous for the deletion of *CATSPER2-STRC* have hearing loss, although onset and severity of hearing loss may vary.

- Typically, the hearing loss in DIS is diagnosed in early childhood. It is non-progressive; vestibular function is normal.
- In all reported affected males, the degree of hearing loss is moderate to severe across all frequencies (0.25 kHz - 8 kHz). This auditory phenotype is comparable to that observed in persons with DFNB16 [Villamar et al 1999, Verpy et al 2001].

Note: Knijnenburg and colleagues reported a male of nonconsanguineous parentage with a complex phenotype that included intellectual disability, short stature, dysmorphic features, and hearing loss associated with a homozygous *CATSPER2-STRC* contiguous-gene deletion. Sperm motility could not be assessed in the proband, who was age ten years. The more severe phenotype in this individual may represent one end of a broader phenotypic spectrum associated with homozygous deletion of 15q15.3, or the intellectual disability and dysmorphic features may be unrelated or only partially related to the 15q15.3 deletion [Knijnenburg et al 2009].

Genotype-Phenotype Correlations

Since only two pathogenic loss-of-function variants for *CATSPER*-related NSMI in two unrelated families have been identified [Avenarius et al 2009], meaningful genotype-phenotype correlations are not possible.

Similarly, all families with DIS have homozygous deletions at 15q15.3 involving loss of *CATSPER2* and *STRC* [Avidan et al 2003, Zhang et al 2007, Knijnenburg et al 2009, Smith et al 2013, Gu et al 2015].

Historical Perspective

DIS was first identified by Avidan and colleagues in a French family segregating deafness, infertility, and congenital dyserythropoietic anemia type 1 (caused by pathogenic variants in *CDAN1*). The three affected males were homozygous for a p.Asn598Ser missense variant in *CDAN1* and were also homozygous for a contiguous-gene deletion that involved *CATSPER2* and *STRC* [Avidan et al 2003]. Four years later, three unrelated Iranian

families that segregated only deafness and infertility secondary to deletion of *CATSPER2* and *STRC* were identified [Zhang et al 2007]. Zhang and colleagues designated this new syndromic form of hearing loss deafness-infertility syndrome (DIS). None of these families share similar deletions.

Nomenclature

Deafness-infertility syndrome is also known as sensorineural deafness and male infertility.

CATSPER-related nonsyndromic male infertility is also referred to as autosomal recessive nonsyndromic male infertility.

Prevalence

The prevalence of *CATSPER*-related nonsyndromic male infertility (NSMI) is unknown; only two families have been reported.

The prevalence of deletions at 15q15.3 involving *CATSPER2* and *STRC* was examined in peripheral blood specimens from 5,152 individuals from the general population by array CGH [Hoppman et al 2013]. Of those, 57 individuals (2 of whom were sibs) were found to be heterozygous for similar deletions including *CATSPER2* and *STRC*, indicating that 1.09% of people in this sample were carriers. If this figure is representative of the general population, this would indicate that approximately one in 40,000 individuals is born with a homozygous deletion of this region, resulting in deafness and, in males, infertility [Hoppman et al 2013].

Genetically Related (Allelic) Disorders

CATSPER1. No phenotypes other than those discussed in this *GeneReview* are known to be caused by pathogenic variants in *CATSPER1*.

CATSPER2. No phenotypes other than those discussed in this *GeneReview* are known to be caused by mutation of *CATSPER2*. Note: Deletions or pathogenic variants involving only *CATSPER*2 have not been associated with nonsyndromic hearing loss.

STRC. Pathogenic variants in *STRC* (part of the *CATSPER2* contiguous-gene deletion and responsible for the deafness associated with the DIS phenotype) cause autosomal recessive nonsyndromic hearing loss at the DFNB16 locus [Verpy et al 2001].

Differential Diagnosis

Male infertility. In approximately half of the 15% of couples who cannot conceive, the cause is ascribed to male infertility as described by Mosher & Pratt [1990] and Templeton et al [1990]. Causes of male infertility other than pathogenic variants in *CATSPER* are numerous and include but are not limited to the following:

- Obstruction of the ejaculatory ducts (e.g., cystic fibrosis and congenital absence of the vas deferens)
- Abnormal sperm motility (See Primary Ciliary Dyskinesia.)
- Immunologic abnormalities (e.g., anti-sperm antibodies)
- Infection (e.g., mumps orchitis, epididymitis, urethritis)
- Vascular abnormalities (e.g., varicocele)
- Trauma
- Endocrine abnormalities including congenital adrenal hyperplasia (see 21-Hydroxylase-Deficient Congenital Adrenal Hyperplasia), isolated follicle-stimulating hormone deficiency (OMIM 229070), and hyperprolactinemia (OMIM 615555)
- Testicular tumor
- Exposure to toxic agents (e.g., radiation, chemotherapy agents, heat)

- Klinefelter syndrome (47,XXY)
- Balanced chromosome rearrangements
- Sertoli-cell-only syndrome

For review of these differential diagnoses refer to Y Chromosome Infertility: Differential Diagnosis.

Molecular genetic testing to attempt to identify the involved gene is appropriate. Pathogenic variants in a large number of genes cause male infertility (a partial list includes *CATSPER1*, *AKAP3*, *AKAP4*, *DNAH1*, *DNAH5*, *DNAH11*, *SPATA16*, *PRM1*, *PRM2*, *SYCP1*, and *SYCP3*); as asthenospermia (loss or reduction in spermatozoa motility) is caused by pathogenic variants in *CATSPER1* (NSMI) [Avenarius et al 2009] and *CATSPER2* (DIS) [Avidan et al 2003, Zhang et al 2007], the *CATSPER* family should be among the first genes tested.

See OMIM Phenotypic Series: Spermatogenic failure to view genes associated with this phenotype in OMIM.

Deafness. See Genetic Hearing Loss Overview.

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with *CATSPER*-related male infertility, the following evaluations are recommended (if not performed previously as part of the diagnostic evaluation):

- In males, pubertal age or older, semen analysis to assess sperm number, motility, and morphology
- In males and females with DIS, hearing evaluation including otologic examination and audiologic assessment (including measurement of bone conduction)
- Consultation with a clinical geneticist and/or genetic counselor

Treatment of Manifestations

Infertility. No available treatment can reverse the morphologic and/or motility defects observed in *CATSPER*-related asthenospermia or asthenoteratospermia (low motility with increased number of abnormal forms). For infertile males, one option is to bypass these morphologic and motility abnormalities using assisted reproductive technologies such as intracytoplasmic sperm injection (ICSI) [Smith et al 2013]. This approach has been used successfully in males with DIS [Zhang et al 2007].

Deafness. For males and females with DIS, treatment of hearing loss is best achieved by fitting hearing aids for amplification. For school-age children or adolescents, special educational assistance may also be warranted and, where possible, should be offered. (See Genetic Hearing Loss Overview and Related Genetic Counseling Issues for other issues pertinent to the care of deaf and hard-of-hearing persons.)

Prevention of Secondary Complications

Regardless of its etiology, uncorrected hearing loss has consistent sequelae. Auditory deprivation through age two years is associated with poor reading performance, poor communication skills, and poor speech production.

Educational intervention is insufficient to completely remediate these deficiencies. In contrast, early auditory intervention, whether through amplification, otologic surgery, or cochlear implantation, is effective [Smith et al 2005] (see Genetic Hearing Loss Overview).

Although decreased cognitive skills and performance in mathematics and reading are associated with deafness, examination of persons with hereditary hearing loss has shown that these deficiencies are not intrinsically linked to the cause of the deafness.

Thus, early identification and timely intervention are essential for optimal cognitive development in children with prelingual deafness.

Surveillance

Annual monitoring of hearing loss is not required in individuals with DIS because hearing loss is non-progressive.

Agents/Circumstances to Avoid

Individuals with DIS should avoid exposure to loud noise in the workplace or during recreation.

Evaluation of Relatives at Risk

It is appropriate to evaluate the sibs of a proband with DIS in infancy or early childhood in order to identify as early as possible those who would benefit from early support and management of hearing loss. Evaluations can include:

- Molecular genetic testing for the causative contiguous-gene deletion;
- Otologic examination and audiologic assessment.

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

CATSPER-related nonsyndromic male infertility (NSMI) and deafness-infertility syndrome (DIS) are inherited in an autosomal recessive manner.

CATSPER-Related NSMI – Risk to Family Members

Parents of a proband

- The parents of a male with *CATSPER*-related NSMI are typically obligate heterozygotes (i.e., carriers of a pathogenic variant in *CATSPER1*).
- Less likely, the mother may have two pathogenic variants and the father has one or, if the pregnancy was conceived using ICSI, the father may be infertile (as a result of having two *CATSPER1* pathogenic variants) and the mother has one.
- Women with two *CATSPER1* pathogenic variants and individuals who are heterozygous for *CATSPER1* pathogenic variants (carriers) are asymptomatic and are not at risk of developing the disorder.

Sibs of a proband

- When both parents are carriers:
  - At conception, each sib of an individual with *CATSPER*-related NSMI has a 25% chance of inheriting both pathogenic variants, a 50% chance of inheriting one pathogenic variant and being an asymptomatic carrier, and a 25% chance of inheriting neither pathogenic variant.
  - Males who inherit biallelic pathogenic variants will be infertile.
  - Females who inherit biallelic pathogenic variants will have no signs/symptoms.
- When one parent has two *CATSPER1* pathogenic variants and the other parent has one pathogenic variant:
  - Each sib has a 50% chance of inheriting biallelic pathogenic variants (one from each parent) and a 50% chance of inheriting one pathogenic variant.
  - Males who inherit biallelic pathogenic variants will be infertile.
  - Females who inherit biallelic pathogenic variants will have no signs/symptoms.
- Women with biallelic *CATSPER1* pathogenic variants and individuals who have a heterozygous *CATSPER1* pathogenic variant (carriers) are asymptomatic and are not at risk of developing the disorder.

Offspring of a proband. Assuming that the unaffected parent is not a carrier, the offspring of an individual with *CATSPER*-related NSMI are obligate heterozygotes (carriers) for a *CATSPER1* pathogenic variant.

Other family members of a proband. Each sib of the proband's parents has a 50% chance of being a carrier of the *CATSPER1* pathogenic variant.

Carrier detection. Carrier testing of at-risk family members is possible if biallelic *CATSPER1* pathogenic variants have been identified in an affected family member.

DIS – Risk to Family Members

Parents of a proband

- Typically, the parents of a male with DIS are obligate heterozygotes (i.e., carriers of a deletion that includes *CATSPER2-STRC*).
- Less likely, the mother may be deaf as a result of being homozygous for the deletion or, if the pregnancy was conceived using ICSI, the father may be deaf and infertile as a result of being homozygous for the deletion. In such cases, the other parent is heterozygous for the *CATSPER2-STRC* deletion.
- Heterozygotes (carriers) for the *CATSPER2-STRC* deletion are asymptomatic and are not at risk of developing the disorder.

Sibs of a proband

- When both parents are carriers:
  - At conception, each sib of an individual with DIS has a 25% chance of inheriting biallelic *CATSPER2-STRC* deletions, a 50% chance of inheriting one deletion and being an asymptomatic carrier, and a 25% chance of not inheriting a deletion, having normal hearing and fertility, and not being a carrier.
  - Males who inherit biallelic *CATSPER2-STRC* deletions will be infertile and deaf.
  - Females who inherit biallelic *CATSPER2-STRC* deletions will be deaf.
- When one parent has biallelic *CATSPER2-STRC* deletions and the other parent is heterozygous for a *CATSPER2-STRC* deletion:
  - Each sib has a 50% chance of inheriting biallelic deletions (1 from each parent) and a 50% chance of inheriting one deletion.
  - Males who inherit biallelic *CATSPER2-STRC* deletions will be infertile and deaf.

- Females who inherit biallelic *CATSPER2-STRC* deletions will be deaf.

Offspring of a proband. Assuming that the unaffected parent is not a carrier, the offspring of an individual with DIS are obligate heterozygotes (carriers) for the *CATSPER2-STRC* deletion. (Note: Pregnancies from males with DIS have been achieved using ICSI [Zhang et al 2007].)

Other family members of a proband. Each sib of the proband's parents has at least a 50% chance of being a carrier of the *CATSPER2-STRC* deletion.

Carrier detection. Carrier testing of at-risk family members is possible if biallelic *CATSPER2-STRC* deletions have been identified in an affected family member.

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 regarding hearing loss/deafness 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.
- 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 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 infertile or deaf.

DNA banking. Because it is likely that testing methodology and our understanding of genes, pathogenic mechanisms, and diseases will improve in the future, consideration should be given to banking DNA from probands in whom a molecular diagnosis has not been confirmed (i.e., the causative pathogenic mechanism is not known). For more information, see Huang et al [2022].

Prenatal Testing and Preimplantation Genetic Testing

Once the pathogenic variants have been identified in an affected family member, prenatal and preimplantation genetic testing for *CATSPER*-related male infertility 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.

- **InterNational Council on Infertility Information Dissemination, Inc. (INCIID)**
  Phone: 703-379-9178
  Fax: 703-379-1593
  Email: INCIIDinfo@inciid.org
  www.inciid.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
- **RESOLVE: The National Infertility Association**
  7918 Jones Branch Drive
  Suite 300
  McLean VA 22102
  Phone: 703-556-7172
  Fax: 703-506-3266
  Email: info@resolve.org
  www.resolve.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. CATSPER-Related Male Infertility: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
CATSPER1	11q13.1	Cation channel sperm-associated protein 1	CATSPER1 database	CATSPER1	CATSPER1
CATSPER2	15q15.3	Cation channel sperm-associated protein 2	CATSPER2 database	CATSPER2	CATSPER2
STRC	15q15	Stereocilin			STRC

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 CATSPER-Related Male Infertility (View All in OMIM)

606389	CATION CHANNEL, SPERM-ASSOCIATED, 1; CATSPER1
606440	STEREOCILIN; STRC
607249	CATION CHANNEL, SPERM-ASSOCIATED, 2; CATSPER2
611102	DEAFNESS-INFERTILITY SYNDROME; DIS

Table B. continued from previous page.

612997	SPERMATOGENIC FAILURE 7; SPGF7

Molecular Pathogenesis

NSMI. Despite the fact that a significant number of genes are implicated in NSMI [Matzuk & Lamb 2008], the genetic etiology often goes undiagnosed in the absence of more rigorous characterization of the sperm phenotype that includes measurement of sperm motility parameters such as path velocity, progressive velocity, and track speed. Pathogenic variants in *CATSPER1* cause an inherited form of NSMI.

DIS. DIS is a specific syndrome that results from homozygous *CATSPER2-STRC* deletion. *CATSPER1* and *CATSPER2* are members of the same gene family.

CATSPER1

Gene structure. *CATSPER1* has a transcript length of 2,634 base pairs (bp) with 12 exons (NM_053054.3). For a detailed summary of gene and protein information, see Table A, **Gene**.

Pathogenic variants. The pathogenic variants in Table 3 are the only two reported for *CATSPER1* to date [reviewed in Hildebrand et al 2010]. These frameshifts in exon 1, identified in two Iranian families, are predicted to result in premature stop codons and complete loss of CATSPER1 protein as a result of nonsense-mediated decay (NMD) or truncated proteins lacking all transmembrane domains and the channel pore.

Based on these data, loss-of-function variants of *CATSPER1* are predicted to result in NSMI, although no additional variants have been associated with disease [Avenarius et al 2009]. It is not known whether less disruptive gene alterations (e.g., missense variants) also lead to NSMI.

Table 3. Selected *CATSPER1* Pathogenic Variants Associated with NSMI

DNA Nucleotide Change (Alias [1])	Predicted Protein Change	Reference Sequences
c.539dupT [2]	p.His182ProfsTer8	NM_053054.3 NP_444282.3
c.944_948dupATGGC (948-949insATGGC) [2]	p.Asp317MetfsTer20	

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 designation that does not conform to current naming conventions
2. Avenarius et al [2009]

Normal gene product. CATSPER1 protein is a 780-amino acid calcium channel that most closely resembles a single six-transmembrane-spanning repeat of the voltage-dependent calcium channel four-repeat structure. CATSPER is vital to cAMP-mediated calcium influx, sperm motility, and fertilization [Ren et al 2001].

Abnormal gene product. Loss of CATSPER1 function is associated with disease. Sperm motility parameters are all markedly impaired in *CatSper1*$^{-/-}$ (knockout) mouse sperm as compared to wild-type sperm [Ren et al 2001].

CATSPER2

Gene structure. *CATSPER2* comprises 13 exons and has a transcript length of 1948 bp (NM_172095.1). For a detailed summary of gene and protein information, see Table A, **Gene**.

Pathogenic variants. See Table 4. In all cases of DIS (1 French and 3 Iranian) resulting from homozygous *CATSPER2-STRC* deletion, the entire *CATSPER2* gene is deleted [Avidan et al 2003, Zhang et al 2007, reviewed in Hildebrand et al 2010].

It is unclear whether nonsense or missense variants in *CATSPER2* would lead to a NSMI phenotype.

Table 4. Selected *CATSPER2/STRC* Pathogenic Variants Associated with DIS

Chromosome Rearrangement	Genes Deleted	Reference Sequences	
		CATSPER2 isoform 1	*STRC*
Del(15)(q15.1-q15.3) [1]	*CATSPER2* and *STRC*	NM_172095.1 NP_742093.1	NM_153700.2 NP_714544.1

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. Avidan et al [2003], Zhang et al [2007]

Normal gene product. CATSPER2 protein is 530 amino acids in length. It is one of several sperm-specific voltage-gated ion channels that have a Ca^{2+} ion-selective pore domain that is required for sperm cell motility and activated by progesterone signaling [Quill et al 2001, Qi et al 2007, Smith et al 2013].

Abnormal gene product. Reported pathogenic variants in *CATSPER2* are deletion of the entire gene as part of a contiguous-gene deletion syndrome [Avidan et al 2003]. The deletion is predicted to result in complete absence of CATSPER2 protein.

Deletion of *CATSPER2* is the cause of infertility in males with DIS based on murine data showing that independent loss of CATSPER2 protein in sperm leads to infertility in males [Ren et al 2001, Qi et al 2007, Avenarius et al 2009].

STRC

Gene structure. *STRC* is a 29-exon gene and has a transcript length of 5,515 bp (NM_153700.2). For a detailed summary of gene and protein information, see Table A, **Gene**.

Pathogenic variants. The only known pathogenic variants of *STRC* in individuals with DIS are contiguous deletions that also delete *CATSPER2* [Avidan et al 2003, Zhang et al 2007] (see Table 4). Other pathogenic variants in *STRC* as associated with nonsyndromic hearing loss (see Genetic Hearing Loss Overview.)

Normal gene product. STRC protein is 1775 amino acids in length (NP_714544.1). It is expressed in the stereocilia hair-bundle of outer hair cells, the inner ear cells that amplify the initial stimulation [Verpy et al 2008]. A deletion of the contiguous genes *CATSPER2* and *STRC* results in the DIS phenotype; intragenic variants in *STRC* result in autosomal recessive nonsyndromic hearing loss (ARNSHL) at the DFNB16 locus [Verpy et al 2001, Avidan et al 2003, Zhang et al 2007, Knijnenburg et al 2009].

Abnormal gene product. Reported pathogenic variants in *STRC* that cause DIS are homozygous deletions of the entire gene as part of contiguous-gene deletion that includes *CATSPER2*; deletion of *STRC* results in loss of its encoded protein, stereocilin.

Deletion of *STRC*, which encodes stereocilin, underlies the hearing loss in DIS. Pathogenic variants of only *STRC* result in ARNSHL at the DFNB16 locus [Verpy et al 2001]. This is supported by the generation of $Strc^{-/-}$ (knockout) mice that have a specific outer hair cell defect, while their inner hair cells appear unaffected [Verpy et al 2001]. Inactivation of *Strc* in mice leads to failure of the cochlear amplifier [Verpy et al 2008]. This murine

phenotype is in agreement with the moderate-to-severe hearing loss usually observed in individuals with DFNB16 or DIS.

Chapter Notes

Author Notes

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Acknowledgments

RJHS is the Sterba Hearing Research Professor, University of Iowa College of Medicine and is supported by NIH NIDCD grants RO1DC00354 and RO1 DC002842. MSH is supported by an Australian National Health and Medical Research (NHMRC) Overseas Biomedical Postdoctoral Training Fellowship.

Revision History

- 14 December 2023 (ma) Chapter retired: covered in *STRC*-Related Autosomal Recessive Hearing Loss
- 23 March 2017 (ma) Comprehensive update posted live
- 7 August 2014 (me) Comprehensive update posted live
- 9 August 2012 (me) Comprehensive update posted live
- 3 December 2009 (me) Review posted live
- 13 August 2009 (rjhs) Initial submission

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