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STRC-Related Autosomal Recessive Hearing Loss

Synonym: *STRC*-Related Sensorineural Hearing Loss

Shelby Redfield, MS, CGC[1] and A Eliot Shearer, MD, PhD[1,2]

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Summary

Clinical characteristics

STRC-related autosomal recessive hearing loss (*STRC*-HL) comprises both nonsyndromic sensorineural hearing loss and sensorineural hearing loss with decreased fertility in males who have biallelic contiguous gene deletions involving *STRC* and *CATSPER2*. The hearing loss is mild to moderate, congenital, bilateral, and symmetric. Mean pure tone hearing loss averages 40-50 decibels (dB) at the time of diagnosis; hearing loss is not severe to profound in children or young adults. Of note, while many newborns with *STRC*-HL will be identified by newborn hearing screening (NBHS), some newborns with *STRC*-HL will not because some screening methods may not detect milder hearing loss.

Males with biallelic contiguous gene deletions involving *STRC* and *CATSPER2* are at risk for *CATSPER2*-related male infertility due to morphologic sperm abnormalities that affect sperm motility. In contrast, females with contiguous gene deletions do not have related fertility issues.

Diagnosis/testing

The diagnosis of *STRC*-HL is established in a proband with suggestive findings who has ONE of the following identified by molecular genetic testing: (1) biallelic *STRC* pathogenic variants; (2) one *STRC* pathogenic variant and one contiguous gene deletion involving *STRC* and *CATSPER2*; or (3) biallelic contiguous gene deletions involving *STRC* and *CATSPER2*.

Management

Treatment of manifestations: Multidisciplinary supportive treatment for hearing loss that includes an otolaryngologist with expertise in the management of early childhood otologic disorders, an audiologist experienced in the assessment of hearing loss in children, a speech-language pathologist, a clinical geneticist, a genetic counselor, and a pediatrician is recommended. Hearing aids (i.e., sound amplification), customized by an

Author Affiliations: 1 Department of Otolaryngology & Communication Enhancement Boston Children's Hospital, Boston, Massachusetts; Email: shelby.redfield@childrens.harvard.edu; Email: eliot.shearer@childrens.harvard.edu. 2 Department of Otolaryngology Head and Neck Surgery, Harvard Medical School, Boston, Massachusetts; Email: eliot.shearer@childrens.harvard.edu.

audiologist to the degree and frequency of hearing loss, may be recommended for individuals who have mild-to-moderate hearing loss.

When males with biallelic contiguous gene deletions involving *STRC* and *CATSPER2* reach reproductive age, consultation with a reproductive specialist/endocrinologist for consideration of fertility-related evaluations is appropriate.

Surveillance: To monitor the degree of hearing loss, the individual's response to use of hearing aids, and development of speech and language, the following are recommended: (1) annual examination by an otolaryngologist familiar with genetic hearing loss to evaluate overall ear health; (2) repeat audiometry to identify any change in hearing, typically (a) every three months between birth and age two years, (b) every six months between ages two and five years, and (c) annually in children age five years and older if hearing is stable and there are no other otologic concerns; and (3) evaluation of speech/language/communication needs as recommended by a speech-language pathologist.

Agents/circumstances to avoid: Prolonged noise exposure exceeding 85 dB, including loud noise exposure from headphones and earbuds. Note that a headphone safety feature built into most smartphones can be set to limit the noise level.

Evaluation of relatives at risk: It is appropriate to clarify the genetic status of sibs of a proband with *STRC*-HL; early identification of infants and children with hearing loss allows appropriate support and management to be provided to the child and family.

Genetic counseling

STRC-HL is inherited in an autosomal recessive manner. The parents of an individual with *STRC*-HL are typically heterozygous for a genetic alteration involving *STRC* (i.e., a *STRC* pathogenic variant or a contiguous gene deletion involving *STRC* and *CATSPER2*). If both parents are known to be heterozygous for a genetic alteration involving *STRC*, each sib of the proband has at conception a 25% chance of having *STRC*-HL, a 50% chance of being a carrier and not having *STRC*-HL, and a 25% chance of not being a carrier and not having *STRC*-HL. Males with biallelic contiguous gene deletions involving *STRC* and *CATSPER2* are at risk of decreased fertility due to abnormal sperm motility; thus, when they reach reproductive age they may benefit from fertility counseling and discussion of assistive reproductive technology options. Once the genetic alterations involving *STRC* have been identified in a family member with *STRC*-HL, prenatal and preimplantation genetic testing are possible.

GeneReview Scope

***GeneReview* Scope: *STRC*-Related Autosomal Recessive Hearing Loss**

Phenotype	Genotype
Nonsyndromic sensorineural hearing loss [1]	Biallelic *STRC* pathogenic variants
	One *STRC* pathogenic variant & one contiguous gene deletion involving *STRC* & *CATSPER2*
Sensorineural hearing loss w/decreased fertility in males	Biallelic contiguous gene deletions involving *STRC* & *CATSPER2*

For synonyms and outdated names, see Nomenclature.
1. For other genetic causes of this phenotype, see Genetic Hearing Loss Overview.

Diagnosis

Suggestive Findings

The diagnosis of *STRC*-related autosomal recessive hearing loss (*STRC*-HL) should be considered in two scenarios: an abnormal newborn hearing screening (NBHS) result and a symptomatic individual with hearing loss.

Scenario 1: Abnormal Newborn Hearing Screening (NBHS) Result

Universal newborn hearing screening (NBHS) uses physiologic screening, either otoacoustic emissions (OAEs), which measure the response of the cochlea to auditory stimuli, or automated auditory brain stem response (AABR) testing, which measures physiologic response of the auditory nerve, brain stem, and brain to varying auditory stimuli. NBHS, required by law or rule in all 50 states in the United States, is performed on >98% of children in the US typically within days after birth (see www.cdc.gov). Note that NBHS, which is designed to detect moderate-to-profound hearing loss, may miss infants with mild hearing loss depending on the screening protocol used.

On receipt of an abnormal NBHS result, the following medical interventions will begin:

- First, diagnostic audiometric testing (typically an initial auditory brain stem response [ABR] test) is performed followed by a confirmatory ABR test, to establish the diagnosis of hearing loss. Note: Evoked otoacoustic emissions (EOAEs) are generally absent [Back et al 2019, Čada et al 2019, Simi et al 2021].
- After diagnostic testing, medical evaluation by an otolaryngologist (often the first point of contact for children with newly diagnosed hearing loss) is typically performed. This includes:
    - Prenatal and perinatal history (with risk factors for hearing loss including viral infection in utero, such as cytomegalovirus and rubella, prematurity, aminoglycoside exposure, hyperbilirubinemia)
    - Physical examination to identify:
        - Non-permanent causes (like otitis media, i.e., fluid in the middle ear)
        - Outer and middle ear abnormalities causing conductive hearing loss (which may include imaging studies of the middle/inner ear)

          Note: Imaging by computed tomography or magnetic resonance imaging shows no abnormalities of the brain and temporal bones for individuals with *STRC*-HL [Yokota et al 2019, Simi et al 2021].
        - Features related to an underlying syndrome associated with hearing loss
- Next steps may involve consideration of additional audiometric testing and/or genetic tests to establish the underlying diagnosis (see Establishing the Diagnosis).

Scenario 2: Symptomatic Individual

STRC-HL **should be suspected** in a proband with the following clinical findings and family history.

Clinical Findings

Congenital, generally non-progressive sensorineural hearing impairment that is mild to moderate as measured by ABR testing or pure tone audiometry. The audiograms of individuals with *STRC*-HL often have a gently downsloping configuration, with hearing typically less affected in the low frequencies compared with the high frequencies.

Hearing is measured in **decibels** (dB). The threshold or 0 dB mark for each frequency refers to the level at which young adults with normal hearing perceive a tone burst 50% of the time. Hearing is considered normal if an individual's thresholds are within ~10 dB of normal thresholds. Severity of hearing loss is graded as shown in Table 1.

Table 1. Severity of Hearing Loss in Decibels (dB)

Severity	Hearing Threshold in dB
Slight	12-25 dB
Mild	26-40 dB
Moderate	41-60 dB
Moderately severe	61-70 dB
Severe	71-90 dB
Profound	>90 dB

Based on Genetic Hearing Loss Overview.

No related systemic findings identified by medical history, physical examination, or imaging of the inner ear and temporal bones (if such imaging is performed).

Family History

Family history is consistent with autosomal recessive inheritance (e.g., affected sibs and/or parental consanguinity). Absence of a known family history does not preclude the diagnosis.

Establishing the Diagnosis

The diagnosis of *STRC*-HL **is established** in a proband with suggestive findings who has ONE of the following identified by molecular genetic testing (see Table 2):

- Biallelic *STRC* pathogenic (or likely pathogenic) variants

  OR

- One *STRC* pathogenic variant (or likely pathogenic variant) and one contiguous gene deletion involving *STRC* and *CATSPER2*

  OR

- Biallelic contiguous gene deletions involving *STRC* and *CATSPER2*

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 likely pathogenic variants. (2) Identification of biallelic *STRC* variants of uncertain significance (or of one known *STRC* pathogenic variant and one *STRC* variant of uncertain significance) does not establish or rule out the diagnosis.

Approaches to molecular genetic testing include use of a **hearing loss multigene panel that includes methods to detect copy number variants (CNVs)** or **comprehensive genomic testing**.

Note: Single-gene testing (sequence analysis of *STRC*, followed by gene-targeted deletion/duplication analysis) is NOT recommended.

- **A multigene hearing loss panel that includes methods to detect CNVs** and *STRC* and other genes of interest (see Differential Diagnosis) may be considered 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. This may be necessary given the high genomic complexity of the *STRC-CATSPER2* region, which includes pseudogenes with high homology due to segmental duplication.

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

- **Comprehensive genomic testing** does not require the clinician to determine which gene(s) is likely involved. **Exome sequencing** is most commonly used; **genome sequencing** is also possible. To date, a significant proportion of *STRC* pathogenic variants are deletions within the coding region which are variably detected by exome sequencing depending on the analysis tools used. Genome sequencing generally provides more sensitivity for detection of *STRC* deletions.

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

Table 2. Molecular Genetic Testing Used in *STRC*-Related Autosomal Recessive Hearing Loss

Gene [1]	Method	Proportion of Pathogenic Variants [2] Detectable by Method	Percent of Individuals w/*STRC*-HL in Whom Method(s) Establishes Molecular Diagnosis [3]
STRC	Sequence analysis [4]	~20% [5, 6]	~30% (biallelic *STRC* pathogenic variants)
	CNV analysis [7]	~80% [8]	~40% (biallelic contiguous gene deletions involving *STRC* & *CATSPER2*) [9]
	Both sequence & CNV analysis		~30% (compound heterozygosity for one *STRC* pathogenic variant & one contiguous gene deletion involving *STRC* & *CATSPER2*)

CNV = copy number variant; *STRC*-HL = *STRC*-related autosomal recessive hearing loss
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. Provided figures are estimates based on Shearer et al [2014], Han et al [2021], and Shubina-Oleinik et al [2021].
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. Provided figures are estimates based on Shearer et al [2014], Amr et al [2018], Han et al [2021], Nishio & Usami [2022], and data derived from the subscription-based professional view of Human Gene Mutation Database [Stenson et al 2020].
6. Supplementing standard next-generation sequencing (NGS) methods with long-range PCR-based sequencing or NGS assays increases the yield of pathogenic *STRC* sequencing variants by eliminating pseudogene contamination.
7. Most reported *STRC* deletions/duplications are large and detectable by chromosomal microarray analysis (CMA). CMA uses oligonucleotide or SNP arrays to detect genome-wide large deletions/duplications (including *STRC*) that cannot be detected by sequence analysis. The ability to determine the size of the deletion/duplication depends on the type of microarray used and the density of probes in the 15q15.3 region. CMA designs in current clinical use targets the 15q15.3 region. Smaller deletions/duplications involving single or multiple exons within the gene (which are less frequently seen than contiguous gene copy number abnormalities) are also detectable using quantitative PCR or multiplex ligation-dependent probe amplification (MLPA). MLPA is an effective method to also eliminate pseudogene contamination and is frequently used to evaluate *STRC* CNVs. Exome and genome sequencing with CNV detection may be able to detect deletions/duplications.
8. Provided figures are estimates based on Mandelker et al [2014], Shearer et al [2014], Han et al [2021], Nishio & Usami [2022].
9. Based on published reports to date, biallelic contiguous gene deletions involving *STRC* and *CATSPER2* are estimated to be the most prevalent genotype in individuals with *STRC*-HL [Nishio & Usami 2022].

Clinical Characteristics

Clinical Description

STRC-related autosomal recessive hearing loss (*STRC*-HL) comprises both nonsyndromic sensorineural hearing loss and sensorineural hearing loss with decreased fertility in males when associated with biallelic contiguous gene deletions involving *STRC* and *CATSPER2*.

STRC-Related Autosomal Recessive Hearing Loss

STRC-HL is characterized by congenital bilateral symmetric mild-to-moderate hearing loss. Although *STRC*-HL is congenital, some individuals with biallelic pathogenic *STRC* variants may pass their newborn hearing screening (NBHS) due to the variability of NBHS methods, some of which may not detect milder hearing loss.

Mean pure tone average at the time of the diagnosis of *STRC*-HL is approximately 40-50 decibels (dB). *STRC*-HL is generally not associated with hearing loss in the severe-to-profound range in children or young adults.

Rarely phenotypic variability has been noted in *STRC*-HL. In one study, about one in 39 individuals with *STRC*-HL had hearing loss in the moderate-to-severe range [Simi et al 2021].

A gradual progression of hearing loss, at a rate of 0.6 dB per year on average across frequencies, was documented in a cohort of individuals with *STRC*-HL, in which 18 of 31 individuals experienced progression over the study follow-up period (mean period of 6.1 years) (see Table 3). Hearing thresholds were in the moderate range of severity or better for more than 96% of this cohort at the end of the study period, with no individuals with hearing in the severe-to-profound range [Simi et al 2021].

Table 3. Progression of Hearing Loss in *STRC*-Related Autosomal Recessive Hearing Loss

Time Point	Pure Tone Hearing Average				
	Normal	Mild loss	Moderate loss	Moderate-to-severe loss	Severe-to-profound loss
Baseline	6%	39%	51%	3%	0%
Follow up [1]	3%	17%	77%	3%	0%

Simi et al [2021]
1. Mean period 6.1 years

With the degree of hearing loss and rate of progression documented by Simi et al [2021], as well as the underlying cochlear physiology of *STRC*-HL, in which cochlear inner hair cell function is preserved, it is expected that individuals with *STRC*-HL will continue to derive benefit from hearing aids and will not require alternative interventions such as cochlear implantation.

While *STRC*-HL is considered nonsyndromic, preliminary data suggest that affected individuals are at increased risk to develop recurrent benign paroxysmal positional vertigo (BPPV) [Frykholm et al 2018, Achard et al 2023a, Achard et al 2023b]. Although one study reported that 39% of 64 individuals developed BPPV at an median age of 13 years [Achard et al 2023a], these data need to be confirmed. The proposed mechanism includes possible physiologic differences in the vestibular system caused by aberrant attachment between hair cells in the crista ampullaris and the overlying cupula.

Decreased Male Fertility

Males with biallelic contiguous gene deletions involving *STRC* and *CATSPER2* are at risk for *CATSPER2*-related male infertility associated with morphologic sperm abnormalities that affect sperm motility.

Females with contiguous gene deletions involving *STRC* and *CATSPER2* have no related fertility issues.

Genotype-Phenotype Correlations

No genotype-phenotype correlations have been identified that distinguish between the hearing loss associated in persons with the following two genotypes:

- Biallelic intragenic *STRC* pathogenic variants (including whole-gene deletions without deletion of contiguous genes)
- Compound heterozygosity for one intragenic *STRC* pathogenic variant (including a whole-gene deletion without a contiguous gene deletion) and one *STRC* contiguous gene deletion

Males with biallelic contiguous gene deletions involving *STRC* and *CATSPER2* are at risk of decreased fertility due to abnormal sperm motility.

Nomenclature

Nonsyndromic hearing impairment may be referred to by the gene involved (e.g., *STRC*-related autosomal recessive hearing loss) or by the genetic locus (e.g., DFNB16).

Nonsyndromic deafness loci are designated DFN (for **D**ea**FN**ess) and further classified by mode of inheritance (DFN**A**: autosomal dominant; DFN**B**: autosomal recessive; DFN**X**: X-linked) and a number indicating the order of gene mapping and/or discovery. The term DFNB16 is used consistently in the literature to refer to *STRC*-HL but, as a term, does not encompass the decreased male fertility associated with biallelic contiguous gene deletions involving *STRC* and *CATSPER2*.

Prevalence

Prevalence of *STRC*-HL. *STRC*-HL, the second most common cause of hereditary sensorineural hearing loss after *GJB2*-related autosomal recessive nonsyndromic hearing loss, accounts for close to ~15% of all diagnoses of hereditary hearing loss and 30% of all diagnoses of mild-to-moderate sensorineural hearing loss [Shearer et al 2014, Sloan-Heggen et al 2016, Perry et al 2023].

In a large meta-analysis, the overall prevalence of *STRC*-HL in individuals who did not have *GJB2*-related autosomal recessive nonsyndromic hearing loss was 4.08%, and the proportion of *STRC* pathogenic variants in the mild-to-moderate hearing loss group was 14.36% [Han et al 2021]. A study analyzing a large cohort of Japanese individuals with hearing loss found the prevalence of *STRC*-HL to be 4.27% in individuals with mild-to-moderate hearing loss [Nishio & Usami 2022].

Carrier frequency for *STRC* pathogenic variants or *STRC-CATSPER2* contiguous gene deletions. One study that analyzed exome data alongside phenotypic information from a large, ethnically and racially diverse cohort of normal-hearing children estimated the carrier frequency to be 1.8% [Shubina-Oleinik et al 2021]. In another meta-analysis of individuals with normal hearing the estimated carrier frequency was 1.36% [Han et al 2021].

Based on published data to date, an estimated 27,000 individuals in the United States have biallelic *STRC* pathogenic genetic alterations.

Genetically Related (Allelic) Disorders

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

Differential Diagnosis

Autosomal recessive nonsyndromic hearing loss (AR NSHL). As of this writing, more than 75 genes have been associated with AR NSHL. Biallelic genetic alterations involving *STRC* are the most common cause of mild-to-moderate sensorineural hearing loss and the second most common cause of autosomal recessive hearing loss overall [Sloan-Heggen et al 2016]. See Genetic Hearing Loss Overview.

Table 4 lists selected genes of interest in the differential diagnosis of *STRC*-related autosomal recessive hearing loss; for a current, comprehensive list of all identified autosomal recessive nonsyndromic hearing loss genes, see Hereditary Hearing Loss Homepage.

Table 4. Selected Genes of Interest in the Differential Diagnosis of Nonsyndromic Mild-to-Moderate *STRC*-Related Autosomal Recessive Hearing Loss

Gene(s)	Disorder	MOI	Comment
GJB2	*GJB2*-related AR NSHL	AR	• Most common genetic cause of congenital severe-to-profound non-progressive sensorineural HL in many world populations • Some *GJB2* pathogenic variants are assoc w/mild-to-moderate HL.

Table 4. continued from previous page.

Gene(s)	Disorder	MOI	Comment
ADGRV1 *USH2A* *WHRN*	Usher syndrome type II	AR	• Usher syndrome overall (i.e., Usher syndrome types I, II, & III) is the most common type of AR syndromic HL & is a nonsyndromic HL mimic (HL is congenital w/later onset of retinitis pigmentosa in adolescence or early adulthood). • Usher syndrome type II is assoc w/congenital, bilateral sensorineural HL that is mild to moderate in the low frequencies & severe to profound in the high frequencies.
OTOA	Nonsyndromic hearing loss (OMIM 607039)	AR	• May be assoc w/mid-frequency HL in moderate range (but is often severe to profound) • Gene deletions are common causative variants.
OTOG *OTOGL*	Nonsyndromic hearing loss (OMIM 614944)	AR	• Non-progressive moderate HL • Occasional vestibular hypofunction

AD = autosomal dominant; AR = autosomal recessive; NSHL = nonsyndromic hearing loss; HL = hearing loss; MOI = mode of inheritance; XL = X-linked

Decreased fertility. See OMIM Phenotypic Series: Spermatogenic failure for genes associated with male infertility.

Management

Evaluations Following Initial Diagnosis

To establish the extent of involvement and needs of an individual diagnosed with *STRC*-related autosomal recessive hearing loss (*STRC*-HL), the following evaluations are recommended:

- Complete assessment of auditory acuity using age-appropriate tests such as auditory brain stem response (ABR) testing, auditory steady-state response (ASSR) testing, and pure tone audiometry
- Evaluation by an otolaryngologist to assess ear health (e.g., middle ear status, cerumen management), dizziness and vertigo (which could be an indication of benign paroxysmal positional vertigo [BPPV]), medical appropriateness of amplification/hearing aids, need for hearing support in a school setting, and overall well-being
- Evaluation by a speech-language pathologist for assessment of communication needs (through early intervention, in a school setting, or privately)
- Complete ophthalmologic examination to assess visual acuity. Although *STRC*-HL is not associated with ophthalmologic findings, ophthalmologic examination is performed because children with hearing loss rely heavily on their vision; thus, it is imperative that reduced vision of whatever cause be promptly identified and addressed.
- Consultation with a medical geneticist, certified genetic counselor, or certified advanced genetic nurse to inform affected individuals and their families about the nature, mode of inheritance, and implications of *STRC*-HL in order to facilitate medical and personal decision making. Counseling on risk for decreased fertility in males with biallelic contiguous gene deletions involving *STRC* and *CATSPER2* should also be shared, when appropriate.
- Assess need for family support and resources including community or online resources such as Parent to Parent and social work involvement for parental support.

Treatment of Manifestations

Multidisciplinary supportive treatment. Multidisciplinary supportive treatment for hearing loss that includes an otolaryngologist with expertise in the management of early childhood otologic disorders, an audiologist

experienced in the assessment of hearing loss in children, a speech-language pathologist, a clinical geneticist, a genetic counselor, and a pediatrician is recommended.

Hearing aids (i.e., sound amplification), customized by an audiologist to the degree and frequency of hearing loss, are often recommended in individuals with mild-to-moderate hearing loss.

See Genetic Hearing Loss Overview for discussion of other management issues.

Decreased male fertility. Males with biallelic contiguous gene deletions involving *STRC* and *CATSPER2* are at risk for abnormal sperm motility. When reproductive age is reached, consultation with a reproductive specialist/endocrinologist for consideration of fertility-related evaluations is appropriate.

Surveillance

To monitor the degree of hearing loss, the individual's response to use of hearing aids, and development of speech and language, the following evaluations are recommended:

- Annual examination by an otolaryngologist familiar with genetic hearing loss to assure that no other reversible factors may be contributing to hearing loss, such as otitis media or cerumen impaction. This visit also ensures health of the ears in the presence of hearing aids.
- Repeat audiometry to identify any change in hearing. In general, audiologic evaluation is recommended every three months between birth and age two years and every six months between the ages of two and five years. Hearing tests can occur annually for children age five years and older if hearing is stable and there are no additional otologic concerns. Audiologic scheduling and follow up will be determined by the individual's managing audiologist.
- Evaluation of speech and language and/or communication as recommended by a speech-language pathologist

Agents/Circumstances to Avoid

Noise exposure is a well-recognized environmental cause of hearing loss. Since this risk can be minimized by avoidance, persons with documented hearing loss should be counseled appropriately and repeated overexposure to loud noises should be avoided. There is no established "safe" noise level; however, the United States Occupational Safety and Health Administration (OSHA) and National Institute for Occupational Safety and Health (NIOSH) have identified a permissible noise exposure limit of 85 decibels (dB) over an eight-hour work day.

One of the primary sources of loud noise exposure in our environment is sound from headphones and earbuds. An 85-dB limit on earbuds and headphones may provide a reasonable way to reduce loud noise exposure. The headphone safety feature built into most smartphones can be set to limit noise level.

Headphone/earbud safety features can be found in the phone settings menu:

- In iPhones, under Settings > Sounds & Haptics > Headphone Safety
- In Android phones, under Settings > Sounds & Vibrations > Volume > Media Volume Limit

Also see these general resources on noise reduction:

- 6 Simple Ways To Check If Your Headphones Are Too Loud
- How Do I Prevent Hearing Loss from Loud Noise?

Evaluation of Relatives at Risk

It is appropriate to clarify the genetic status of sibs of a proband with *STRC*-HL if:

- A newborn sib has an abnormal result on universal newborn hearing screening (NBHS);
- A newborn sib has a normal result on NBHS (as NBHS may miss newborns with milder hearing loss); or
- A sib did not undergo NBHS and/or NBHS results are unknown.

Early identification of infants and children with hearing loss allows appropriate support and management to be provided to the child and family.

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

Therapies Under Investigation

Using a mouse model with a targeted deletion of *STRC* and a resulting 60-dB sensorineural hearing loss, Shubina-Oleinik et al [2021] used a dual adeno-associated viral vector approach to deliver a full-length copy of *STRC* to the outer hair cells of the cochlea that restored – in 50% of mice – auditory function by a significant margin. Although this study indicates *STRC* may be a promising target for gene therapy, to date there are no human clinical trials for this disorder.

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

STRC-related autosomal recessive hearing loss (*STRC*-HL) is inherited in an autosomal recessive manner.

Risk to Family Members

Parents of a proband

- The parents of an individual with *STRC*-HL are presumed to be heterozygous for a genetic alteration involving *STRC* (i.e., an *STRC* pathogenic variant or a contiguous gene deletion involving *STRC* and *CATSPER2*).
- Molecular genetic testing capable of detecting the genetic alterations identified in the proband is recommended for the parents to confirm that both parents are heterozygous for a genetic alteration involving *STRC* and to allow reliable recurrence assessment.
- If a genetic alteration is detected in only one parent and parental identity testing has confirmed biological maternity and paternity, it is possible that one of the genetic alterations identified in the proband occurred as a *de novo* event in the proband or as a postzygotic *de novo* event in a mosaic parent [Jónsson et al 2017]. Preliminary data suggest that a significant proportion *STRC* copy number alterations are *de novo* [Klimara et al 2022].

  If the proband appears to have homozygous genetic alterations (i.e., the same two genetic alterations), additional possibilities to consider include:

- A single- or multiexon deletion in the proband that was not detected by sequence analysis and that resulted in the artifactual appearance of homozygosity;
- Uniparental isodisomy for the parental chromosome with the genetic alteration that resulted in homozygosity for the pathogenic variant in the proband.

- Individuals who are heterozygous for a genetic alteration involving *STRC* do not have an increased chance of *STRC*-HL.

Sibs of a proband

- If both parents are known to be heterozygous for a genetic alteration involving *STRC*, each sib of the proband has at conception a 25% chance of having *STRC*-HL, a 50% chance of being a carrier and not having *STRC*-HL, and a 25% chance of not being a carrier and not having *STRC*-HL.
- *STRC*-HL is typically congenital and in the mild-to-moderate range of severity with minimal or no progression for both probands and sibs, regardless of the familial genetic alterations. There can be slight differences in clinical presentations between sibs.
- Individuals who are heterozygous for a genetic alteration involving *STRC* do not have an increased chance of *STRC*-HL.

Offspring of a proband. Unless the proband's reproductive partner also has *STRC*-HL or is a carrier of a genetic alteration involving *STRC*, offspring will be obligate heterozygotes (i.e., carriers of a genetic alteration involving *STRC*).

Other family members. Each sib of the proband's parents has a 50% chance of being a carrier of a genetic alteration involving *STRC*.

Carrier detection. Carrier testing for relatives requires prior identification of the genetic alterations involving *STRC* 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.

Other. See Related Genetic Counseling Issues in Genetic Hearing Loss Overview for review of communication, terminology, and family-centered counseling considerations.

Family planning

- The optimal time for determination of genetic status and discussion of the availability of prenatal/preimplantation genetic testing is before pregnancy.
- It is appropriate to offer genetic counseling (including discussion of the probability of deafness in offspring and reproductive options) to young adults who are deaf.
- Males with biallelic contiguous gene deletions involving *STRC* and *CATSPER2* are at risk of decreased fertility due to abnormal sperm motility; thus, when they reach reproductive age they may benefit from fertility counseling and discussion of assistive reproductive technology options.

Prenatal Testing and Preimplantation Genetic Testing

Once the genetic alterations involving *STRC* have been identified in a family member with *STRC*-HL, prenatal and preimplantation genetic testing are possible.

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

Resources

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

- **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
- **American Speech-Language-Hearing Association (ASHA)**
  Phone: 800-638-8255; 301-296-5650 (TTY)
  Fax: 301-296-8580
  www.asha.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.
  babyhearing.org
- **Hands & Voices**
  www.handsandvoices.org
- **Medical Home Portal**
  Hearing Loss and Deafness
- **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
  nad.org
- **Newborn Screening in Your State**

Health Resources & Services Administration
www.newbornscreening.hrsa.gov/your-state

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. STRC-Related Autosomal Recessive Hearing Loss: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
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 STRC-Related Autosomal Recessive Hearing Loss (View All in OMIM)

603720	DEAFNESS, AUTOSOMAL RECESSIVE 16; DFNB16
606440	STEREOCILIN; STRC
607249	CATION CHANNEL, SPERM-ASSOCIATED, 2; CATSPER2
611102	DEAFNESS-INFERTILITY SYNDROME; DIS

Molecular Pathogenesis

The delicate molecular machinery of the cochlea that permits hearing in humans involves hundreds of genes. *STRC* encodes stereocilin, an extracellular structural protein that is expressed on outer hair cells (OHCs) in the organ of Corti of the cochlea. Stereocilin connects adjacent stereocilia and links hair cell bundles to the tectorial membrane, enabling sound dampening, amplification of soft sounds, and frequency tuning. For proper auditory function, a physical connection must be maintained between these bundles of stereocilia and the overlying tectorial membrane. The OHCs and tectorial membrane (which work to detect pitch, discriminate frequency, and dampen sound) are nonfunctioning in *STRC*-HL and result in loss of proper auditory function. Because the inner hair cells (IHCs) (which are responsible for the mechanotransduction of sound) are still viable, loss of stereocilin function does not lead to severe-to-profound hearing loss.

Mechanism of disease causation. Loss of function

***STRC*-specific laboratory technical considerations.** *STRC* is part of a large tandem duplication that gave rise to a pseudogene (*STRCP1*) that shares 98.9% overall homology with *STRC* and more than 99% sequence homology with the coding region of *STRC* [Francey et al 2012]. As such, accurate gene sequencing and detection of single nucleotide variants present a diagnostic challenge. Sensitivity for variant detection is improved with long-range PCR and genome sequencing techniques. Given these challenges, some clinical molecular diagnostic laboratories do not offer direct sequencing of *STRC*.

In addition, the *STRC* locus lies within a tandem duplication with a predisposition for nonallelic homologous recombination and is therefore associated with a high frequency of 15q15.3 contiguous gene deletions involving *CATSPER2*, necessitating accurate methods for detection of copy number variants (CNVs). Methods such as multiplex ligation-dependent amplification (MLPA), array comparative genomic hybridization (CGH), or single-nucleotide polymorphism (SNP) arrays should be considered by clinical molecular diagnostic laboratories

testing for *STRC*-HL. CNV analysis methods as part of exome or genome sequencing may also be used. Genome sequencing has been shown to be sensitive for detection of deletions involving 15q15.3 [Abbasi et al 2022].

Chapter Notes

Author Notes

Translational Hearing Genomics Lab

A Eliot Shearer, MD, PhD (eliot.shearer@childrens.harvard.edu), is actively involved in clinical research regarding individuals with *STRC*-related autosomal recessive hearing loss (*STRC*-HL). He would be happy to communicate with persons who have any questions regarding diagnosis of *STRC*-HL or other considerations.

Dr Shearer is also interested in hearing from clinicians treating families affected by hereditary hearing loss in whom no causative variant has been identified through molecular genetic testing of the genes known to be involved in this group of disorders.

Contact Dr Shearer to inquire about review of *STRC* variants of uncertain significance.

Revision History

- 14 December 2023 (bp) Review posted live
- 7 July 2023 (aes) Original submission

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