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SLC26A2-Related Atelosteogenesis

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Summary

Clinical characteristics

Clinical features of *SLC26A2*-related atelosteogenesis include rhizomelic limb shortening with normal-sized skull, hitchhiker thumbs, small chest, protuberant abdomen, cleft palate, and distinctive facial features (midface retrusion, depressed nasal bridge, epicanthus, micrognathia). Other typical findings are ulnar deviation of the fingers, gap between the first and second toes, and clubfoot. *SLC26A2*-related atelosteogenesis is usually lethal at birth or shortly thereafter due to pulmonary hypoplasia and tracheobronchomalacia. However, it exists in a continuous phenotypic spectrum with *SLC26A2*-related diastrophic dysplasia, and long-term survivors have been reported.

Diagnosis/testing

The diagnosis of *SLC26A2*-related atelosteogenesis is established in a proband with characteristic clinical, radiologic, and histopathologic features and biallelic pathogenic variants in *SLC26A2* identified by molecular genetic testing.

Management

Treatment of manifestations: There is no specific treatment currently available, and the aim of therapy (supportive versus palliative) will depend on clinical status and respiratory prognosis of the individual patient.

Genetic counseling

SLC26A2-related atelosteogenesis is inherited in an autosomal recessive manner. If both parents are known to be heterozygous for an *SLC26A2* pathogenic variant, each sib of a proband with *SLC26A2*-related atelosteogenesis has at conception 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 and preimplantation genetic testing for a pregnancy at increased risk are possible if both pathogenic variants in the

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family are known. Ultrasound examination early in pregnancy is a reasonable complement or alternative to molecular genetic prenatal testing.

Diagnosis

Suggestive Findings

SLC26A2-related atelosteogenesis is usually lethal at birth or shortly thereafter because of pulmonary hypoplasia and tracheobronchomalacia. *SLC26A2*-related atelosteogenesis **should be suspected** when the following are present.

Clinical features

- Rhizomelic limb shortening with normal-sized skull
- Hitchhiker thumbs
- Small chest
- Protuberant abdomen
- Cleft palate
- Distinctive facial features (midface retrusion, depressed nasal bridge, epicanthus, micrognathia)

Other usual findings are ulnar deviation of the fingers, gap between the first and second toes, and clubfoot.

Radiographic findings

- Normal-sized skull with disproportionately short skeleton
- Platyspondyly, hypodysplastic vertebrae, and cervical kyphosis. Ossification of the upper thoracic vertebrae and coronal clefts of the lumbar and lower thoracic vertebrae may be incomplete.
- Hypoplastic ilia with flat acetabulum. The pubic bones are often unossified.
- Shortened long bones with metaphyseal flaring. The distal humerus is sometimes bifid or V-shaped, sometimes pointed and hypoplastic; the femur is distally rounded; the radius and tibia are typically bowed.
- Note: (1) A distally pointed, triangular humerus had led Slaney et al [1999] to the suggestion of a new condition, but this finding is a typical feature of *SLC26A2*-related achondrogenesis bordering on *SLC26A2*-related atelosteogenesis [Unger et al 2001]. (2) The first individuals with de la Chapelle dysplasia described by de la Chapelle et al [1972] and Whitley et al [1986] showed a triangular remnant of ulna and fibula. Those individuals were subsequently classified as having *SLC26A2*-related atelosteogenesis [Bonafé et al 2008].
- Characteristic hand findings of sulfate transporter-related dysplasia:
  - Hitchhiker thumb with ulnar deviation of the fingers (characteristic of *SLC26A2*-related diastrophic dysplasia [*SLC26A2*-DTD])
  - Gap between the first and second toe (characteristic of *SLC26A2*-related achondrogenesis [when the phalanges are identifiable on x-ray] and *SLC26A2*-DTD)
  - Hypoplasia of the first metacarpal bone (also present in *SLC26A2*-related achondrogenesis and *SLC26A2*-DTD)

Histopathology (important when radiologic material is not available or is of poor quality)

- Paucity of sulfated proteoglycans in cartilage matrix [Superti-Furga et al 1996a, Rossi et al 1997] similar to that seen *SLC26A2*-DTD and *SLC26A2*-related achondrogenesis
- Abnormal extracellular matrix with threads of fibrillar material between cystic acellular areas and areas of normal cellularity
- Some chondrocytes appear surrounded by lamellar material forming concentric rings that are in some cases indistinguishable from the collagen rings typical of *SLC26A2*-related achondrogenesis.

- The growth plate shows disruption of column formation and hypertrophic zones with irregular invasion of the metaphyseal capillaries and fibrosis.
- These cartilage matrix abnormalities are present in long bones as well as in tracheal, laryngeal, and peribronchial cartilage, whereas intramembranous ossification shows no abnormalities.

Establishing the Diagnosis

The diagnosis of *SLC26A2*-related atelosteogenesis **is established** in a proband with suggestive findings and biallelic pathogenic (or likely pathogenic) variants in *SLC26A2* identified by molecular genetic testing (see Table 1).

Note: (1) Per ACMG/AMP variant interpretation guidelines, the terms "pathogenic variants" and "likely pathogenic variants" are synonymous in a clinical setting, meaning that both are considered diagnostic and both can be used for clinical decision making [Richards et al 2015]. Reference to "pathogenic variants" in this section is understood to include any likely pathogenic variants. (2) Identification of biallelic *SLC26A2* variants of uncertain significance (or of one known *SLC26A2* pathogenic variant and one *SLC26A2* variant of uncertain significance) does not establish or rule out the diagnosis.

Molecular genetic testing approaches can include a combination of **gene-targeted testing** (single-gene testing, multigene panel) and **comprehensive genomic testing** (exome sequencing, genome sequencing) depending on the phenotype.

Gene-targeted testing requires that the clinician determine which gene(s) are likely involved, whereas genomic testing does not. Individuals with the distinctive clinical and radiographic findings described in Suggestive Findings are likely to be diagnosed using gene-targeted testing (see Option 1), whereas those with a phenotype indistinguishable from many other inherited disorders with perinatal-lethal skeletal dysplasia are more likely to be diagnosed using genomic testing (see Option 2).

Option 1

When the phenotypic and radiographic findings suggest the diagnosis of *SLC26A2*-related atelosteogenesis, molecular genetic testing approaches can include **single-gene testing** or use of a **multigene panel**:

- **Single-gene testing.** Sequence analysis of *SLC26A2* is performed first to detect small intragenic deletions/insertions and missense, nonsense, and splice site variants. Note: Depending on the sequencing method used, single-exon, multiexon, or whole-gene deletions/duplications may not be detected. If no variant is detected by the sequencing method used, the next step is to perform gene-targeted deletion/duplication analysis to detect exon and whole-gene deletions or duplications. Note: To date such variants have not been identified as a cause of *SLC26A2*-related atelosteogenesis.
- **A skeletal dysplasia multigene panel** that includes *SLC26A2* and other genes of interest (see Differential Diagnosis) can 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. (4) Methods used in a panel may include sequence analysis, deletion/duplication analysis, and/or other non-sequencing-based tests.

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

Option 2

When the phenotype is indistinguishable from many other inherited disorders characterized by perinatal-lethal skeletal dysplasia, **comprehensive genomic testing**, which does not require the clinician to determine which gene is likely involved, may be pursued. **Exome sequencing** is most commonly used; **genome sequencing** is also possible.

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 *SLC26A2*-Related Atelosteogenesis

Gene [1]	Method	Proportion of Pathogenic Variants [2] Detectable by Method
SLC26A2	Sequence analysis [3]	>90% [4]
	Gene-targeted deletion/duplication analysis [5]	None reported

1. See Table A. Genes and Databases for chromosome locus and protein.
2. See Molecular Genetics for information on variants detected in this gene.
3. Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or pathogenic. Variants may include small intragenic deletions/insertions and missense, nonsense, and splice site variants; typically, exon or whole-gene deletions/duplications are not detected. For issues to consider in interpretation of sequence analysis results, click here.
4. Rossi & Superti-Furga [2001] and data derived from the subscription-based professional view of Human Gene Mutation Database [Stenson et al 2020]
5. Gene-targeted deletion/duplication analysis detects intragenic deletions or duplications. Methods used may include a range of techniques such as quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification (MLPA), and a gene-targeted microarray designed to detect single-exon deletions or duplications.

Clinical Characteristics

Clinical Description

To date, only a handful of individuals with *SLC26A2*-related atelosteogenesis have been reported [Rossi & Superti-Furga 2001]. The following description of the phenotypic features associated with this condition is based on these reports.

The diagnosis of *SLC26A2*-related atelosteogenesis should be made only if specific *SLC26A2* pathogenic variants that are associated with SLC26A2-related atelosteogenesis (see Genotype-Phenotype Correlations) have been identified, and/or the clinical and radiographic severity lies somewhere between *SLC26A2*-related achondrogenesis and *SLC26A2*-related diastrophic dysplasia (*SLC26A2*-DTD) (see Genetically Related Disorders). It follows, then, that the diagnosis of *SLC26A2*-related atelosteogenesis will only apply to a fetus/individual with severe prenatal-onset short stature. Almost all individuals will have club feet (adducted feet) and many will have lung hypoplasia (consequences of the generalized skeletal alterations). The dysmorphic facial features are very consistent and cleft palate is frequent.

SLC26A2-related atelosteogenesis is usually lethal in the neonatal period because of lung hypoplasia, tracheobronchomalacia, and laryngeal malformations. Pregnancy complication of polyhydramnios may occur.

Newborns with *SLC26A2*-related atelosteogenesis present with short limbs, adducted feet with wide space between the hallux and the second toe, hitchhiker thumb, cleft palate, and facial dysmorphism. *SLC26A2*-related atelosteogenesis is clinically very similar to *SLC26A2*-DTD [Rossi et al 1996b].

Skeletal features. Disproportion between the short skeleton and normal-sized skull is immediately evident; the limb shortening is mainly rhizomelic; the gap between the toes, ulnar deviation of the fingers, and adducted

thumbs are typical of sulfate transporter-related dysplasias [Newbury-Ecob 1998, Superti-Furga et al 2001]. The neck is short, the thorax narrow, and the abdomen protuberant.

Craniofacial features. Cleft palate is a constant feature, whereas the degree of facial dysmorphism is variable. Midface retrusion is usually present, together with a flat nasal bridge and micrognathia. Epicanthal folds, widely spaced eyes, and low-set ears can also be present.

Other. Spinal scoliosis and dislocation of the elbows are reported [Newbury-Ecob 1998].

Genotype-Phenotype Correlations

Genotype-phenotype correlations indicate that the amount of residual activity of the sulfate transporter modulates the phenotype [Rossi et al 1997] in a spectrum from lethal *SLC26A2*-related achondrogenesis to mild *SLC26A2*-related multiple epiphyseal dysplasia (*SLC26A2*-MED).

- Homozygosity or compound heterozygosity for pathogenic variants predicting stop codons or structural variants in transmembrane domains of the sulfate transporter are associated with the more severe phenotype of *SLC26A2*-related achondrogenesis.
- The combination of a severe pathogenic variant (predicting stop codons or structural variants in transmembrane domains) with a pathogenic variant located in extracellular loops, in the cytoplasmic tail of the protein, or in the regulatory 5'-flanking region of the gene results in the less severe phenotypes, i.e., *SLC26A2*-related atelosteogenesis and *SLC26A2*-DTD [Hästbacka et al 1996, Superti-Furga et al 1996b, Rossi et al 1997, Karniski 2001, Rossi & Superti-Furga 2001, Karniski 2004].

The pathogenic variant p.Arg279Trp, the most common *SLC26A2* variant outside Finland (45% of alleles), results in a mild *SLC26A2*-MED phenotype when homozygous and mostly the *SLC26A2*-DTD phenotype when in the compound heterozygous state.

The pathogenic variant p.Arg178Ter is the second-most common variant (9% of alleles) and is associated with a more severe *SLC26A2*-DTD phenotype or even the perinatal-lethal *SLC26A2*-related atelosteogenesis phenotype, particularly when combined in *trans* with the p.Arg279Trp variant. It has also been found in some individuals with more severe *SLC26A2*-MED and *SLC26A2*-related achondrogenesis, making it one of two pathogenic variants identified in all four *SLC26A2*-related dysplasias.

Pathogenic variants p.Cys653Ser and c.-26+2T>C are the third-most common variants (8% of alleles for each).

- c.-26+2T>C is sometimes referred to as the "Finnish" variant because it is much more frequent in Finland than in the remainder of the world population. It produces low levels of correctly spliced mRNA and results in *SLC26A2*-DTD when homozygous.
- Together with p.Arg178Ter, c.-26+2T>C is the only pathogenic variant that has been identified in all four *SLC26A2*-related dysplasias, in compound heterozygosity with mild (*SLC26A2*-MED and *SLC26A2*-DTD) or severe (*SLC26A2*-related atelosteogenesis and *SLC26A2*-related achondrogenesis) alleles [Dwyer et al 2010; Bonafe, unpublished results].
- The pathogenic variant p.Cys653Ser results in *SLC26A2*-MED when homozygous and in *SLC26A2*-MED or *SLC26A2*-DTD when compounded with other pathogenic variants. It is not found in *SLC26A2*-related atelosteogenesis or *SLC26A2*-related achondrogenesis.

Another pathogenic variant specific to the Finnish population is p.Thr512Lys, which results in *SLC26A2*-related atelosteogenesis (de la Chapelle dysplasia) when homozygous and in *SLC26A2*-DTD when in compound heterozygosity with a milder allele [Bonafé et al 2008].

Most other pathogenic variants are rare.

The same pathogenic variants found in some individuals who have the *SLC26A2*-related atelosteogenesis phenotype can also be found in individuals with a milder phenotype (*SLC26A2*-MED and *SLC26A2*-DTD) if the second allele is a relatively mild variant. Indeed, pathogenic missense variants located outside the transmembrane domain of the sulfate transporter are often associated with a residual activity that can "rescue" the effect of a null allele [Rossi & Superti-Furga 2001].

Nomenclature

The name "atelosteogenesis" was coined by Maroteaux et al [1982] for a different condition.

Sillence et al [1987] created the term "atelosteogenesis type 2" for a group of fetuses or stillborns who had all previously been diagnosed as having "severe diastrophic dysplasia." The reason was an apparent hypoplasia of the distal humerus and variable fibular hypoplasia (but not aplasia) that was slightly reminiscent of atelosteogenesis type 1 (AO1). The redefinition of this severe DTD variant as atelosteogenesis type 2 was unfortunate because it suggested a relationship with AO1 and at the same time denied the relationship with diastrophic dysplasia. Later biochemical and molecular studies brought this entity back to its origin – that is, in the diastrophic dysplasia-achondrogenesis group in which *SLC26A2*-related atelosteogenesis is considered to be a severe form of *SLC26A2*-DTD, and in which lethality distinguishes *SLC26A2*-related atelosteogenesis from *SLC26A2*-DTD.

De la Chapelle et al [1972] described two sibs with a novel condition very similar to *SLC26A2*-related atelosteogenesis, with very hypoplastic ulna and fibula; one additional sib and one more person with this condition (de la Chapelle dysplasia) were reported by Whitley et al [1986]. The histopathologic similarities with *SLC26A2*-related achondrogenesis suggested a relationship with the sulfate transporter-related dysplasias. The identity of de la Chapelle dysplasia with *SLC26A2*-related atelosteogenesis was subsequently confirmed by molecular testing, which revealed pathogenic variants in *SLC26A2* [Bonafé et al 2008].

SLC26A2-related atelosteogenesis may also be referred to as **McAlister dysplasia**.

SLC26A2-related atelosteogenesis is classified in the sulfation disorders group in the 2023 revision of the Nosology of Genetic Skeletal Disorders [Unger et al 2023].

Prevalence

No data on the prevalence of *SLC26A2*-related atelosteogenesis are available. Among the sulfate transporter-related dysplasias, *SLC26A2*-related atelosteogenesis is the rarest phenotype.

Genetically Related (Allelic) Disorders

Three other phenotypes (all with an autosomal recessive mode of inheritance) – *SLC26A2*-related achondrogenesis, *SLC26A2*-related diastrophic dysplasia (*SLC26A2*-DTD), and *SLC26A2*-related multiple epiphyseal dysplasia (*SLC26A2*-MED) – are associated with pathogenic variants in *SLC26A2*. *SLC26A2*-related achondrogenesis and *SLC26A2*-DTD have phenotypic overlap with *SLC26A2*-related atelosteogenesis and should be considered in the differential diagnosis (see Table 2).

Table 2. *SLC26A2* Allelic Disorders in the Differential Diagnosis of *SLC26A2*-Related Atelosteogenesis

Allelic Disorder	Comment	Differentiating Features
SLC26A2-related achondrogenesis	• Characterized by severe hypoplasia/dysplasia of spine, rib cage, & extremities, w/relatively preserved cranium • Among most severe skeletal disorders in humans; invariably lethal in perinatal period.	• The radiologic differentiation of *SLC26A2*-related atelosteogenesis from *SLC26A2*-related achondrogenesis is based on more severe underossification of skeleton & extreme limb shortening seen in *SLC26A2*-related achondrogenesis. • Histopathology is similar in *SLC26A2*-related atelosteogenesis & *SLC26A2*-related achondrogenesis.
SLC26A2-related diastrophic dysplasia (*SLC26A2*-DTD)	*SLC26A2*-DTD, a skeletal dysplasia, is characterized by short stature, joint contractures, cleft palate, & characteristic clinical signs incl "hitchhiker" thumb, & cystic swelling of external ears.	• *SLC26A2*-related atelosteogenesis, rather than *SLC26A2*-DTD, must be considered when distinct hypoplasia of ≥1 long bones (humerus, ulna, radius, or fibula) &/or pulmonary hypoplasia is present. • Histopathology is very similar in *SLC26A2*-DTD & *SLC26A2*-related atelosteogenesis, but cartilage growth plate shows fewer disorganized hypertrophic & proliferative zones & columnar zones in *SLC26A2*-DTD.

***SLC26A2*-related multiple epiphyseal dysplasia** is characterized by joint pain (usually the hips and knees); malformations of the hands, feet, and knees; and scoliosis. Approximately 50% of individuals have an abnormal finding at birth, e.g., clubfoot, cleft palate, or cystic ear swelling. Median height in adulthood is in the tenth centile.

Differential Diagnosis

SLC26A2-related achondrogenesis and *SLC26A2*-related diastrophic dysplasia have phenotypic overlap with *SLC26A2*-related atelosteogenesis (and should be considered in the differential diagnosis (see Table 2).

The differentiation of *SLC26A2*-related atelosteogenesis from other subtypes of atelosteogenesis ("incomplete bone formation"), and even from other lethal skeletal dysplasias, should be based on clinical examination as well as radiographic imaging.

Table 3. Genes of Interest in the Differential Diagnosis of *SLC26A2*-Related Atelosteogenesis

Gene(s)	Differential Disorder	MOI	Differentiating Clinical & Radiographic Features
FLNB	*FLNB*-related AO1 (*FLNB*-AOI) (See *FLNB* Disorders.)	AD	• Hitchhiker thumb & gap between toes are not present in *FLNB*-AO1 & cleft palate is rare. • *FLNB*-AO1 shows better development of long bones & better ossification of spine & pelvis. • Absence of fibula may suggest *FLNB*-AO1; dysplasia of fibula is more typical of *SLC26A2*-related atelosteogenesis. • Humerus may be completely absent in *FLNB*-AO1.
Multiple genes [1] incl: *DYNC2H1* *IFT80* *TTC21B*	Lethal short-rib polydactyly syndromes (w/o polydactyly) (OMIM 613091, 611263, 613819)	AR	• Thoracic hypoplasia is more significant. • There may be trident pelvis.
FGFR3	Thanatophoric dysplasia (TD)	AD	• Typical "telephone receiver" femur is visible on x-ray in TD. • Cloverleaf skull is common in TD type II.

AD = autosomal dominant; AO1 = atelosteogenesis type 1; AR = autosomal recessive; MOI = mode of inheritance
1. See OMIM Short-Rib Thoracic Dysplasia Phenotypic Series for genes associated with this phenotype in OMIM.

Management

There is no specific treatment available. Decisions regarding supportive therapy versus palliative treatment depend on the degree of respiratory compromise at birth.

Evaluations Following Initial Diagnosis

To establish the extent of disease in an individual diagnosed with *SLC26A2*-related atelosteogenesis, the evaluations summarized in Table 5 (if not performed as part of the evaluation that led to the diagnosis) are recommended.

Table 4. Recommended Evaluations Following Initial Diagnosis in Individuals with *SLC26A2*-Related Atelosteogenesis

System/Concern	Evaluation	Comment
Musculoskeletal	Complete skeletal survey in viable newborn	
Pulmonary	Eval of respiratory status in viable newborn	
Genetic counseling	By genetics professionals [1]	To inform affected persons & their families re nature, MOI, & implications of *SLC26A2*-related atelosteogenesis to facilitate medical & personal decision making

MOI = mode of inheritance

1. Medical geneticist, certified genetic counselor, or certified advanced genetic nurse

Treatment of Manifestations

For long-term survivors, care should include surgical repair of cleft palate.

Utility of surgery for club feet is unclear as this is quite complicated and the results limited.

Physiotherapy is useful for retaining range of motion.

Evaluation of Relatives at Risk

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

SLC26A2-related atelosteogenesis 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., presumed to be carriers of one *SLC26A2* pathogenic variant based on family history).
- Molecular genetic testing is recommended for the parents of a proband to confirm that both parents are heterozygous for an *SLC26A2* pathogenic variant and to allow reliable recurrence risk assessment. (Although a *de novo* pathogenic variant has not been reported in *SLC26A2*-related atelosteogenesis to date, *de novo* variants are known occur at a low but appreciable rate in autosomal recessive disorders [Jónsson et al 2017].)
- Heterozygotes (carriers) are asymptomatic and have normal stature. No evidence suggests that carriers are at increased risk of developing degenerative joint disease.

Sibs of a proband

- If both parents are known to be heterozygous for an *SLC26A2* pathogenic variant, each sib of an affected individual has at conception 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 asymptomatic and have normal stature. No evidence suggests that carriers are at increased risk of developing degenerative joint disease.

Offspring of a proband. *SLC26A2*-related atelosteogenesis is usually perinatal lethal; affected individuals do not reproduce.

Other family members. Each sib of the proband's parents is at a 50% risk of being a carrier of an *SLC26A2* pathogenic variant.

Carrier Detection

At-risk relatives. Carrier testing for at-risk relatives requires prior identification of the *SLC26A2* pathogenic variants in the family.

Reproductive partners of known carriers. Sequence analysis of *SLC26A2*. Caution should be used when interpreting the phenotypic outcome of various pathogenic variant combinations.

Related Genetic Counseling Issues

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 carriers or are at risk of being carriers.

Prenatal Testing and Preimplantation Genetic Testing

High-risk pregnancies

- **Molecular genetic testing.** Once the *SLC26A2* pathogenic variants have been identified in an affected family member, prenatal and preimplantation genetic testing are possible.
- **Ultrasound examination.** Transvaginal ultrasound examination early in pregnancy is a reasonable alternative to molecular prenatal testing because the testing is not invasive. However, the diagnosis can be made with confidence only at weeks 14-15, and reliability is highly operator dependent.

Low-risk pregnancies

- If one parent is known to be heterozygous for an *SLC26A2* pathogenic variant and the other parent does not have an *SLC26A2* pathogenic variant, routine prenatal care is recommended.
- **Routine ultrasound examination.** Routine prenatal ultrasound examination may identify very short fetal limbs ± polyhydramnios ± small thorax, raising the possibility of *SLC26A2*-related atelosteogenesis in a fetus not known to be at risk. Subtle findings on ultrasound examination may be recognizable in the first trimester, but in low-risk pregnancies, the diagnosis of skeletal dysplasia is usually not made until the second trimester.
- **Molecular genetic testing.** DNA extracted from cells obtained by amniocentesis can theoretically be analyzed to try to make a molecular diagnosis prenatally. However, the differential diagnosis in such a setting is very broad (see Differential Diagnosis).

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.

- **National Library of Medicine Genetics Home Reference**
  Atelosteogenesis, type 2
- **Compassionate Friends**
  Supporting Family After a Child Dies
  Phone: 877-969-0010
  compassionatefriends.org
- **Helping After Neonatal Death (HAND)**
  PO Box 341
  Los Gatos CA 95031
  Phone: 888-908-HAND (4263)
  www.handonline.org
- **UCLA International Skeletal Dysplasia Registry (ISDR)**
  Phone: 310-825-8998
  International Skeletal Dysplasia Registry

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. Atelosteogenesis Type 2: Genes and Databases

Gene	Chromosome Locus	Protein	HGMD	ClinVar
SLC26A2	5q32	Sulfate transporter	SLC26A2	SLC26A2

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 Atelosteogenesis Type 2 (View All in OMIM)

256050	ATELOSTEOGENESIS, TYPE II; AO2
606718	SOLUTE CARRIER FAMILY 26 (SULFATE TRANSPORTER), MEMBER 2; SLC26A2

Molecular Pathogenesis

SLC26A2 encodes a sulfate transporter protein [Hästbacka et al 1994]. This protein transports sulfate into chondrocytes to maintain adequate sulfation of proteoglycans. The sulfate transporter protein belongs to the family of sulfate permeases. *SLC26A2* is expressed in developing cartilage in human fetuses but also in a wide variety of other tissues [Haila et al 2001].

Impaired activity of the sulfate transporter in chondrocytes and fibroblasts results in the synthesis of proteoglycans, which are either not sulfated or insufficiently sulfated [Rossi et al 1998, Satoh et al 1998], most probably because of intracellular sulfate depletion [Rossi et al 1996a]. Undersulfation of proteoglycans affects the composition of the extracellular matrix and leads to impairment of proteoglycan deposition, which is necessary for proper enchondral bone formation [Corsi et al 2001, Forlino et al 2005].

Loss of SLC26A2 sulfate transporter activity is associated with several skeletal disorders (see Genetically Related Disorders) [Rossi & Superti-Furga 2001].

Mechanism of disease causation. Loss of function. The predicted residual activity of the sulfate transporter correlates with phenotypic severity [Rossi et al 1997, Cai et al 1998, Rossi & Superti-Furga 2001, Karniski 2004, Maeda et al 2006].

Table 5. Notable *SLC26A2* Pathogenic Variants

Reference Sequences	DNA Nucleotide Change	Predicted Protein Change	Comment [Reference]
NM_000112.4	c.-26+2T>C (IVS1+2T>C [1])	--	Founder variant in Finnish population [2]
NM_000112.4 NP_000103.2	c.532C>T	p.Arg178Ter	Common pathogenic variant [2]
	c.835C>T	p.Arg279Trp	Most common pathogenic variant outside of Finland [2]
	c.1535C>A	p.Thr512Lys	Second-most common pathogenic variant in the Finnish population [Bonafé et al 2008]

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. See Genotype-Phenotype Correlations for severity.

Chapter Notes

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Revision History

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