



SLC26A2-Related Multiple Epiphyseal Dysplasia

Synonym: *SLC26A2*-Related Recessive MED (*SLC26A2*-rMED)

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Summary

Clinical characteristics

SLC26A2-related multiple epiphyseal dysplasia (*SLC26A2*-MED) is characterized by joint pain (usually in the hips or knees); malformations of hands, feet, and knees; and scoliosis. Approximately 50% of affected individuals have an abnormal finding at birth, including clubfoot, clinodactyly, or (rarely) cystic ear swelling. Onset of articular pain is variable but usually occurs in late childhood. Stature is usually within the normal range prior to puberty; in adulthood, stature is only slightly diminished and ranges from 150 to 180 cm. Functional disability is mild.

Diagnosis/testing

Diagnosis of *SLC26A2*-MED is based on detection of biallelic variants in *SLC26A2* by molecular genetic testing in an individual with compatible clinical and radiographic findings.

Management

Treatment of manifestations: Physiotherapy for muscular strengthening and maintaining mobility; cautious use of analgesic medications such as nonsteroidal anti-inflammatory drugs; orthopedic surgery (joint replacement) as indicated; career counseling.

Prevention of secondary complications: Intensive physiotherapy may help in delaying joint contractures and maintaining mobility.

Surveillance: Radiographs as indicated.

Agents/circumstances to avoid: Sports involving joint overload.

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Genetic counseling

SLC26A2-MED is inherited in an autosomal recessive manner. 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. Once the *SLC26A2* pathogenic variants have been identified in an affected family member, carrier testing for at-risk relatives and prenatal/preimplantation genetic testing are possible.

Diagnosis

Suggestive Findings

SLC26A2-related multiple epiphyseal dysplasia (*SLC26A2*-MED) **should be suspected** in individuals with the following clinical and radiographic features.

Clinical features

- Joint pain (usually in the hips and knees). Onset of pain is variable, but usually occurs in late childhood. Some individuals have no pain.
- Deformity of hands, feet, and knees
- Scoliosis

Radiographic features

- Flat epiphyses with early arthritis (degenerative and painful changes in the articular cartilage of the hip joint)
- Mild brachydactyly
- Double-layered patella (i.e., presence of a separate anterior and posterior ossification layer) (see Figure 1). Observed in approximately 60% of individuals on lateral knee radiographs, the presence of a double-layered patella is a quite specific, although not highly sensitive, sign of *SLC26A2*-MED [Mäkitie et al 2003]. This finding appears to be age related and may disappear in adults.

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 *SLC26A2*-MED is **established** in a proband with the characteristic clinical and radiographic features described in 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 of the disorder.

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.



Figure 1. Double-layered patella

Ballhausen et al [2003]; reprinted with permission from the BMJ Publishing Group

Gene-targeted testing requires that the clinician determine which gene(s) are likely involved, whereas genomic testing does not. Individuals with the distinctive 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 skeletal dysplasias are more likely to be diagnosed using genomic testing (see Option 2).

Option 1

Single-gene testing. Sequence analysis of *SLC26A2* detects small intragenic deletions/insertions and missense, nonsense, and splice site variants. Typically, if only one or 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; however, to date such variants have not been identified as a cause of this disorder.

A multigene panel that includes *SLC26A2* and other genes of interest (see Differential Diagnosis) is most likely to identify the genetic cause of the condition while limiting identification of variants of uncertain significance and pathogenic variants in genes that do not explain the underlying phenotype. Note: (1) The genes included in the panel and the diagnostic sensitivity of the testing used for each gene vary by laboratory and are likely to change over time. (2) Some multigene panels may include genes not associated with the condition discussed in this *GeneReview*. (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 other skeletal dysplasias, **comprehensive genomic testing**, which does not require the clinician to determine which gene is likely involved, is the best option. **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 Multiple Epiphyseal Dysplasia

Gene ¹	Method	Proportion of Pathogenic Variants ² Detectable by Method
<i>SLC26A2</i>	Sequence analysis ³	100% ^{4, 5}
	Gene-targeted deletion/duplication analysis ⁶	None reported ⁷

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. The four most common *SLC26A2* pathogenic variants (p.Arg279Trp, c.-26+2T>C, p.Arg178Ter, and p.Cys653Ser) account for approximately 70% of disease alleles in all *SLC26A2*-related dysplasias. Targeted analysis of these four variants identified at least one pathogenic variant in nearly 100% of individuals with *SLC26A2*-MED (80% of individuals with *SLC26A2*-MED have two of the most common pathogenic variants, and another 16% have one common pathogenic variant in compound heterozygosity with another pathogenic variant).

5. Rossi & Superti-Furga [2001]

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. Data derived from the subscription-based professional view of Human Gene Mutation Database [Stenson et al 2020]

Clinical Characteristics

Clinical Description

SLC26A2-related multiple epiphyseal dysplasia (*SLC26A2*-MED) is characterized by early-onset joint pain, malformations of hands, feet, and knees, and scoliosis. Approximately 50% of affected individuals have an abnormal finding at birth, including clubfoot, clinodactyly, cleft palate, or (rarely) cystic ear swelling. However, only half of those with findings at birth are suspected of having a skeletal dysplasia.

Skeletal manifestations. Chronic joint pain most often occurs in the hips, knees, wrists, and fingers. The onset of joint pain is variable; adolescents are usually symptomatic in multiple joints, and joint pain increases after physical exercise.

Waddling gait, hand/foot deformities (mild brachydactyly, clinodactyly, clubfoot, broadening of the space between the first and second toes), and mild scoliosis are also reported. Brachydactyly is evident after puberty in most individuals. Habitus is unremarkable in most affected individuals, except for genu valgum in some.

Stature is usually within the normal range prior to puberty. In adulthood, stature is only slightly diminished, with the median height shifting from the 50th to the tenth centile; range of adult height is 150-180 cm. Approximately one third of affected adults have proportionately short stature that is two standard deviations below the mean for age.

Craniofacial features. Facies are typically normal. Cleft palate may be present. Cystic ear swelling rarely occurs.

Progression. Functional disability is mild or absent in childhood and adolescence [Ballhausen et al 2003]; joint involvement progresses slightly in young adults, but hip and knee surgery is usually not needed. Bowing of the extremities is not observed.

Genotype-Phenotype Correlations

Genotype-phenotype correlations indicate that the amount of residual activity of the sulfate transporter modulates the phenotype in this spectrum of disorders, which extends from lethal [achondrogenesis type 1B](#) (ACG1B) to mild *SLC26A2*-MED. Homozygosity or compound heterozygosity for pathogenic variants predicting stop codons or structural pathogenic variants in transmembrane domains of the sulfate transporter are associated with ACG1B, while pathogenic variants located in extracellular loops, in the cytoplasmic tail of the protein, or in the regulatory 5'-flanking region of the gene result in less severe phenotypes [Superti-Furga et al 1996, Karniski 2001, Maeda et al 2006].

The pathogenic variant p.Arg279Trp is the most common *SLC26A2* variant found outside of Finland (45% of alleles); it results in the mild *SLC26A2*-MED phenotype when homozygous and mostly in [diastrophic dysplasia](#) (DTD) and [atelosteogenesis type 2](#) (AO2) phenotypes when found in the compound heterozygous state [Barbosa et al 2011].

Pathogenic variant p.Arg178Ter is the second most common variant (9% of alleles) and is associated with a more severe DTD phenotype or even the perinatal-lethal AO2 phenotype, particularly when combined in *trans* with the p.Arg279Trp variant.

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

Pathogenic variant p.Cys653Ser results in *SLC26A2*-MED when homozygous and in *SLC26A2*-MED or DTD when present in *trans* with other pathogenic variants [Czarny-Ratajczak et al 2010].

Pathogenic variant 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 DTD when homozygous. It is the only variant that has been identified in all four *SLC26A2*-related dysplasias, in compound heterozygosity with mild (*SLC26A2*-MED and DTD) or severe (AO2 and ACG1B) alleles [Dwyer et al 2010].

The same pathogenic variants found in the ACG1B phenotype can also be found in the milder phenotypes (AO2 and DTD) if the second allele is a relatively mild variant. Indeed, missense variants located outside of the transmembrane domain of the sulfate transporter are often associated with residual activity that can "rescue" the effect of a null allele [Rossi & Superti-Furga 2001].

Nomenclature

Multiple epiphyseal dysplasia (MED) is a disorder with clinical and genetic heterogeneity. In the past, the disorder was clinically subdivided into the milder Ribbing type, with flattened epiphysis and normal or near-normal stature; the more severe Fairbank type, with round, small epiphyses and short stature; and the unclassified types [International Working Group on Constitutional Diseases of Bone 1998].

The genetic dissection of this heterogeneous group of conditions in recent years has provided a molecular-pathogenic classification of the different subtypes according to the gene involved:

- *SLC26A2*-related multiple epiphyseal dysplasia (*SLC26A2*-MED) is classified in the sulfation disorders group of the 2023 revised Nosology of Genetic Skeletal Disorders [Unger et al 2023]. It accounts for approximately 25% of cases of MED.
- *SLC26A2*-MED was originally referred to as recessive MED (rMED), and this term continues to be used regularly in the medical literature. However, in order to avoid confusion with the autosomal recessive *CANT1*-related phenotype that is also described as multiple epiphyseal dysplasia (MED) and to move toward dyadic naming, rMED caused by *SLC26A2* pathogenic variants is now designated "multiple epiphyseal dysplasia, *SLC26A2*-related" in the 2023 revised nosology [Unger et al 2023].

- The other subtypes of MED are classified in the pseudoachondroplasia and the multiple epiphyseal dysplasias group in the 2023 revised nosology [Unger et al 2023]. The most frequent form of MED is caused by autosomal dominant pathogenic variants in *COMP* (~50% of cases). The remaining 20%-25% of cases are split between *MATN3*, *COL9A1*, *COL9A2*, and *COL9A3*.
- Some individuals with MED do not have pathogenic variants in a known gene [Zankl et al 2007, Unger et al 2008]; in these individuals, MED remains unclassified.

Prevalence

Exact data about the prevalence of MED and its subtypes are not available. Based on the number of individuals seen in growth clinics, rheumatology clinics, and genetics clinics, and compared to conditions whose incidences are more precisely known (e.g., [achondroplasia](#), [osteogenesis imperfecta](#)), it seems reasonable to estimate an overall prevalence of 1:20,000 [Unger et al 2008]. This prevalence is probably an underestimation, as simplex cases (i.e., a single occurrence in a family) may remain undiagnosed. *SLC26A2*-MED is one of the most frequent forms of MED, accounting for almost 25% of all individuals diagnosed with MED [Jackson et al 2012].

Genetically Related (Allelic) Disorders

SLC26A2-related multiple epiphyseal dysplasia (*SLC26A2*-MED) is the mildest phenotype in the spectrum of *SLC26A2*-related autosomal recessive skeletal disorders (see Table 2).

Table 2. *SLC26A2* Skeletal Disorder Spectrum

Disorder	Comment
Achondrogenesis type 1B	<ul style="list-style-type: none"> • Extremely short limbs w/short fingers & toes; hypoplasia of the thorax; & protuberant abdomen • Hydropic fetal appearance caused by the abundance of soft tissue relative to the short skeleton • Death occurs prenatally or shortly after birth
Atelosteogenesis type 2	<ul style="list-style-type: none"> • Commonly lethal in perinatal period • Presents around birth or before • Chondrodysplasia w/clinical & histologic characteristics resembling those of DTD but more pronounced
Diastrophic dysplasia (DTD)	<ul style="list-style-type: none"> • Short limb type of dwarfism assoc w/clubfeet & other joint restrictions incl "hitchhiker thumbs" • Progressive scoliosis in childhood
<i>SLC26A2</i> -related multiple epiphyseal dysplasia	Topic of this <i>GeneReview</i>

Differential Diagnosis

SLC26A2-related multiple epiphyseal dysplasia (*SLC26A2*-MED) needs to be distinguished from the more common autosomal dominant forms of multiple epiphyseal dysplasia (MED). Clinical and radiographic differences between the genetically distinct forms of these skeletal dysplasias may allow clinicians to distinguish between them (see Table 3).

Note: In contrast to autosomal dominant MED, prepubertal children with *SLC26A2*-MED usually do not have short stature.

Table 3. Autosomal Dominant Multiple Epiphyseal Dysplasia *

Gene	Clinical Features
<i>COL9A1</i>	<i>COL9A1</i> -, <i>COL9A2</i> -, & <i>COL9A3</i> -MED appear to have more severe knee involvement but relative sparing of the hips, resulting in a milder course than MED assoc w/ <i>COMP</i> or <i>SLC26A2</i> pathogenic variants.
<i>COL9A2</i>	
<i>COL9A3</i>	
<i>COMP</i>	<i>COMP</i> -MED is usually assoc w/significant involvement at the capital femoral epiphyses & irregular acetabula. ¹
<i>MATN3</i>	<i>MATN3</i> -MED appears to be the mildest form of MED identified to date & is assoc w/a high degree of intrafamilial variability.

* See [Multiple Epiphyseal Dysplasia, Autosomal Dominant](#).

MED = multiple epiphyseal dysplasia

1. Pathogenic variants in *COMP* are also associated with the more severe disorder [pseudoachondroplasia](#).

CANT1-related MED. Homozygous *CANT1* missense variants were reported in four individuals from two families with radiographic phenotypes described as compatible with MED [Balasubramanian et al 2017]. No further individuals have yet been described; thus, given the paucity of available data, no clear clinical and radiographic delineation can be made.

Unclassified MED. Some individuals with MED do not have pathogenic variants in a known gene [Zankl et al 2007, Unger et al 2008]; in these individuals, MED remains unclassified.

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease in an individual diagnosed with *SLC26A2*-related multiple epiphyseal dysplasia (*SLC26A2*-MED), the following evaluations (if not performed as part of the evaluation that led to the diagnosis) are recommended:

- Height measurement
- Elicitation of pain history
- Radiographs of the entire spine (AP and lateral), pelvis (AP), and knees (AP and lateral), to determine the extent and severity of joint involvement
- 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 *SLC26A2*-MED to facilitate medical and personal decision making

Treatment of Manifestations

Symptomatic individuals should be seen by a physical therapist and an orthopedist to assess the possibility of treatment (physiotherapy for muscular strengthening and maintaining mobility, cautious use of analgesic medications such as nonsteroidal anti-inflammatory drugs) and the optimal time for surgery (joint replacement), if indicated.

Intensive physiotherapy may delay joint contractures and help maintain mobility.

Psychosocial support addressing issues of chronic pain and career counseling is warranted.

Surveillance

Radiographic surveillance by an orthopedist is appropriate.

Agents/Circumstances to Avoid

Sports involving joint overload are to be avoided.

Evaluation of Relatives at Risk

Predictive testing of at-risk sibs is not indicated because no preventive measures or therapeutic interventions to reduce morbidity are available.

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

Pregnancy Management

Women affected by *SLC26A2*-MED may suffer from chronic joint pain that may increase during pregnancy as a result of maternal weight gain. Appropriate pain management should be offered, and physical therapy should be intensified.

See [MotherToBaby](#) for further information on medication use during pregnancy.

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 multiple epiphyseal dysplasia (*SLC26A2*-MED) is inherited in an autosomal recessive manner.

Risk to Family Members

Parents of a proband

- The parents of an affected individual are presumed to be heterozygous for an *SLC26A2* pathogenic variant.
- Molecular genetic testing is recommended for the parents of the proband to confirm that both parents are heterozygous for an *SLC26A2* pathogenic variant and to allow reliable recurrence risk assessment.
- If a pathogenic variant is detected in only one parent and parental identity testing has confirmed biological maternity and paternity, it is possible that one of the pathogenic variants 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]. If the proband appears to have homozygous pathogenic variants (i.e., the same two pathogenic variants), 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 pathogenic variant that resulted in homozygosity for the pathogenic variant in the proband.

- Heterozygotes (carriers) are asymptomatic and have normal stature. No evidence that carriers are at increased risk of developing degenerative joint disease has been presented.

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 that carriers are at increased risk of developing degenerative joint disease has been presented.

Offspring of a proband. Unless an affected individual's reproductive partner also has *SLC26A2*-MED or is a carrier, offspring will be obligate heterozygotes (carriers) for a pathogenic variant in *SLC26A2*.

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

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

Related Genetic Counseling Issues

Family planning

- The optimal time for determination of genetic risk and discussion of availability of prenatal/preimplantation genetic testing is before pregnancy.
- It is appropriate to offer genetic counseling (including discussion of potential risks to offspring and reproductive options) to young adults who are affected, are carriers, or are at risk of being carriers.
- Carrier testing for reproductive partners of known carriers should be considered.
- A *SLC26A2* founder variant has been identified in individuals of Finnish heritage (see Table 4 and [Resources for Genetics Professionals — Genetic Disorders Associated with Founder Variants Common in the Finnish Population](#)).

Prenatal Testing and Preimplantation Genetic Testing

Once the *SLC26A2* pathogenic variants have been identified in an affected family member, prenatal and preimplantation genetic testing are possible.

Differences in perspective may exist among medical professionals and in 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](#).

- **MedlinePlus**
[Multiple epiphyseal dysplasia](#)
- **Human Growth Foundation**
www.hgfound.org

- **Little People of America**
Phone: 888-LPA-2001; 714-368-3689
Fax: 707-721-1896
Email: info@lpaonline.org
lpaonline.org
- **MAGIC Foundation**
Phone: 800-362-4423
Email: contactus@magicfoundation.org
www.magicfoundation.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. SLC26A2-Related Multiple Epiphyseal Dysplasia: 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 SLC26A2-Related Multiple Epiphyseal Dysplasia ([View All in OMIM](#))

226900	EPIPHYSEAL DYSPLASIA, MULTIPLE, 4; EDM4
606718	SOLUTE CARRIER FAMILY 26 (SULFATE TRANSPORTER), MEMBER 2; SLC26A2

Molecular Pathogenesis

SLC26A2 pathogenic variants are responsible for the family of chondrodysplasias including [achondrogenesis type 1B](#) (ACG1B), [atelosteogenesis type 2](#) (AO2), [diastrophic dysplasia](#) (DTD), and *SLC26A2*-related multiple epiphyseal dysplasia (*SLC26A2*-MED). Impaired activity of the sulfate transporter in chondrocytes and fibroblasts results in the synthesis of proteoglycans that are not sulfated or are insufficiently sulfated [Rossi et al 1998, Satoh et al 1998], most likely because of intracellular sulfate depletion [Rossi et al 1996, Gualeni et al 2010]. Undersulfation of proteoglycans affects the composition of the extracellular matrix and leads to impairment of proteoglycan deposition, which is necessary for proper endochondral bone formation [Corsi et al 2001, Forlino et al 2005, Dawson 2011]. The clinical severity can be correlated with the residual activities of the sulfate transporter resulting from different pathogenic variants [Rossi et al 1996, Rossi et al 1997, Corsi et al 2001, Rossi & Superti-Furga 2001, Rossi et al 2003, Karniski 2004, Maeda et al 2006].

In a *Xenopus* oocyte model, the p.Arg178Ter pathogenic variant was shown to abolish sulfate transporter activity, and the p.Val341del pathogenic variant showed detectable but very low activity (17% of the wild type) of the sulfate transporter [Karniski 2001]. The same variants associated in some individuals with the ACG1B phenotype can be found in individuals with a milder phenotype (AO2 and DTD) if the second allele is a relatively mild variant. Indeed, missense variants located outside the transmembrane domain of the sulfate transporter are often associated with residual activity that can "rescue" the effect of a null allele. Other

conclusions from the *Xenopus* study are at odds with consistent clinical observations, the discrepancy probably being the result of temperature and cellular processing differences between *Xenopus* oocytes and humans (20 °C vs 37 °C) [Superti-Furga et al 1996, Rossi & Superti-Furga 2001, Superti-Furga 2001, Superti-Furga 2002]. Similar studies conducted in mammalian cells [Karniski 2004] have produced results that are much more consistent with clinical genotype-phenotype correlations. These studies have essentially confirmed predictions that ACG1B-causing variants are associated with no residual transport activity, while the milder phenotypes result from either different combinations of "null" variants with other alleles that allow for some residual activity or from two variants with residual activity. Original observations were: (1) intracellular retention of the sulfate transporter protein with the variant p.Gly678Val; and (2) abnormal molecular weight of the sulfate transporter with p.Gln454Pro, possibly indicating protease sensitivity or aberrant glycosylation.

Mechanism of disease causation. Loss of function

Table 4. Notable *SLC26A2* Pathogenic Variants

Reference Sequences	DNA Nucleotide Change (Alias ¹)	Predicted Protein Change (Alias ¹)	Comment [Reference]
NM_000112.3	c.-26+2T>C	--	Founder variant in Finland; only variant that has been identified in all 4 <i>SLC26A2</i> -related dysplasias, in compound heterozygosity w/mild (<i>SLC26A2</i> -MED & DTD) or severe (AO2 & ACG1B) alleles [Dwyer et al 2010]
NM_000112.3 NP_000103.2	c.532C>T (559C>T)	p.Arg178Ter	Second most common variant (9% of alleles); assoc w/ more severe DTD phenotype or perinatal-lethal AO2, esp when combined in trans w/variant p.Arg279Trp
	c.835C>T (c.862C>T)	p.Arg279Trp	Most common variant found outside of Finland (45% of alleles); mild <i>SLC26A2</i> -MED when homozygous & mostly DTD & AO2 when found in compound heterozygous state [Barbosa et al 2011]
	c.1020_1022delTGT (1045-1047delGTT)	p.Val341del	See Molecular Pathogenesis.
	c.1361A>C (1388A>C)	p.Gln454Pro	
	c.1957T>A (1984T>A)	p.Cys653Ser	Third most common variant (8% of alleles); <i>SLC26A2</i> -MED when homozygous & <i>SLC26A2</i> -MED or DTD when present in <i>trans</i> w/other pathogenic variants [Czarny-Ratajczak et al 2010]
	c.2033G>T (2060G>T)	p.Gly678Val	See Molecular Pathogenesis.

ACG1B = achondrogenesis type 1B; AO2 = atelosteogenesis type 2; DTD = diastrophic dysplasia; MED = multiple epiphyseal dysplasia
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

Chapter Notes

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References

Literature Cited

- Balasubramanian K, Li B, Krakow D, Nevarez L, Ho PJ, Ainsworth JA, Nickerson DA, Bamshad MJ, Immken L, Lachman RS, Cohn DH. MED resulting from recessively inherited mutations in the gene encoding calcium-activated nucleotidase CANT1. *Am J Med Genet A*. 2017;173:2415–21. PubMed PMID: 28742282.
- Ballhausen D, Bonafé L, Terhal P, Unger SL, Bellus G, Classen M, Hamel BC, Spranger J, Zabel B, Cohn DH, Cole WG, Hecht JT, Superti-Furga A. Recessive multiple epiphyseal dysplasia (rMED): phenotype delineation in eighteen homozygotes for DTDST mutation R279W. *J Med Genet*. 2003;40:65–71. PubMed PMID: 12525546.
- Barbosa M, Sousa AB, Medeira A, Lourenço T, Saraiva J, Pinto-Basto J, Soares G, Fortuna AM, Superti-Furga A, Mittaz L, Reis-Lima M, Bonafé L. Clinical and molecular characterization of Diastrophic Dysplasia in the Portuguese population. *Clin Genet*. 2011;80:550–7. PubMed PMID: 21155763.
- Corsi A, Riminucci M, Fisher LW, Bianco P. Achondrogenesis type IB: agenesis of cartilage interterritorial matrix as the link between gene defect and pathological skeletal phenotype. *Arch Pathol Lab Med*. 2001;125:1375–8. PubMed PMID: 11570921.
- Czarny-Ratajczak M, Bieganski T, Rogala P, Glowacki M, Trzeciak T, Kozłowski K. New intermediate phenotype between MED and DD caused by compound heterozygous mutations in the DTDST gene. *Am J Med Genet A*. 2010;152A:3036–42. PubMed PMID: 21077204.
- Dawson PA. Sulfate in fetal development. *Semin Cell Dev Biol*. 2011;22:653–9. PubMed PMID: 21419855.
- Dwyer E, Hyland J, Modaff P, Pauli RM. Genotype-phenotype correlation in DTDST dysplasias: Atelosteogenesis type II and diastrophic dysplasia variant in one family. *Am J Med Genet A*. 2010;152A:3043–50. PubMed PMID: 21077202.
- Forlino A, Piazza R, Tiveron C, Della Torre S, Tatangelo L, Bonafé L, Gualeni B, Romano A, Pecora F, Superti-Furga A, Cetta G, Rossi A. A diastrophic dysplasia sulfate transporter (SLC26A2) mutant mouse: morphological and biochemical characterization of the resulting chondrodysplasia phenotype. *Hum Mol Genet*. 2005;14:859–71. PubMed PMID: 15703192.

- Gualeni B, Facchini M, De Leonardis F, Tenni R, Cetta G, Viola M, Passi A, Superti-Furga A, Forlino A, Rossi A. Defective proteoglycan sulfation of the growth plate zones causes reduced chondrocyte proliferation via an altered Indian hedgehog signalling. *Matrix Biol.* 2010;29:453–60. PubMed PMID: 20470884.
- International Working Group on Constitutional Diseases of Bone. International nomenclature and classification of the osteochondrodysplasias, 1997. *Am J Med Genet.* 1998;79:376–82. PubMed PMID: 9779805.
- Jackson GC, Mittaz-Crettol L, Taylor JA, Mortier GR, Spranger J, Zabel B, Le Merrer M, Cormier-Daire V, Hall CM, Offiah A, Wright MJ, Savarirayan R, Nishimura G, Ramsden SC, Elles R, Bonafé L, Superti-Furga A, Unger S, Zankl A, Briggs MD. Pseudoachondroplasia and multiple epiphyseal dysplasia: a 7-year comprehensive analysis of the known disease genes identify novel and recurrent mutations and provides an accurate assessment of their relative contribution. *Hum Mutat.* 2012;33:144–57. PubMed PMID: 21922596.
- Jónsson H, Sulem P, Kehr B, Kristmundsdottir S, Zink F, Hjartarson E, Hardarson MT, Hjorleifsson KE, Eggertsson HP, Gudjonsson SA, Ward LD, Arnadottir GA, Helgason EA, Helgason H, Gylfason A, Jonasdottir A, Jonasdottir A, Rafnar T, Frigge M, Stacey SN, Th Magnusson O, Thorsteinsdottir U, Masson G, Kong A, Halldorsson BV, Helgason A, Gudbjartsson DF, Stefansson K. Parental influence on human germline de novo mutations in 1,548 trios from Iceland. *Nature.* 2017;549:519–22. PubMed PMID: 28959963.
- Karniski LP. Functional expression and cellular distribution of diastrophic dysplasia sulfate transporter (DTDST) gene mutations in HEK cells. *Hum Mol Genet.* 2004;13:2165–71. PubMed PMID: 15294877.
- Karniski LP. Mutations in the diastrophic dysplasia sulfate transporter (DTDST) gene: correlation between sulfate transport activity and chondrodysplasia phenotype. *Hum Mol Genet.* 2001;10:1485–90. PubMed PMID: 11448940.
- Maeda K, Miyamoto Y, Sawai H, Karniski LP, Nakashima E, Nishimura G, Ikegawa S. A compound heterozygote harboring novel and recurrent DTDST mutations with intermediate phenotype between atelosteogenesis type II and diastrophic dysplasia. *Am J Med Genet A.* 2006;140:1143–7. PubMed PMID: 16642506.
- Mäkitie O, Savarirayan R, Bonafé L, Robertson S, Susic M, Superti-Furga A, Cole WG. Autosomal recessive multiple epiphyseal dysplasia with homozygosity for C653S in the DTDST gene: double-layer patella as a reliable sign. *Am J Med Genet.* 2003;122A:187–92. PubMed PMID: 12966518.
- Richards S, Aziz N, Bale S, Bick D, Das S, Gastier-Foster J, Grody WW, Hegde M, Lyon E, Spector E, Voelkerding K, Rehm HL, et al. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. *Genet Med.* 2015;17:405–24. PubMed PMID: 25741868.
- Rossi A, Bonaventure J, Delezoide AL, Cetta G, Superti-Furga A. Undersulfation of proteoglycans synthesized by chondrocytes from a patient with achondrogenesis type 1B homozygous for an L483P substitution in the diastrophic dysplasia sulfate transporter. *J Biol Chem.* 1996;271:18456–64. PubMed PMID: 8702490.
- Rossi A, Bonaventure J, Delezoide AL, Superti-Furga A, Cetta G. Undersulfation of cartilage proteoglycans ex vivo and increased contribution of amino acid sulfur to sulfation in vitro in McAlister dysplasia/atelosteogenesis type 2. *Eur J Biochem.* 1997;248:741–7. PubMed PMID: 9342225.
- Rossi A, Cetta G, Piazza R, Bonaventure J, Steinmann B, Supereti-Furga A. In vitro proteoglycan sulfation derived from sulfhydryl compounds in sulfate transporter chondrodysplasias. *Pediatr Pathol Mol Med.* 2003;22:311–21. PubMed PMID: 14692227.
- Rossi A, Kaitila I, Wilcox WR, Rimoin DL, Steinmann B, Cetta G, Superti-Furga A. Proteoglycan sulfation in cartilage and cell cultures from patients with sulfate transporter chondrodysplasias: relationship to clinical severity and indications on the role of intracellular sulfate production. *Matrix Biol.* 1998;17:361–9. PubMed PMID: 9822202.

- Rossi A, Superti-Furga A. Mutations in the diastrophic dysplasia sulfate transporter (DTDST) gene (SLC26A2): 22 novel mutations, mutation review, associated skeletal phenotypes, and diagnostic relevance. *Hum Mutat.* 2001;17:159–71. PubMed PMID: 11241838.
- Satoh H, Susaki M, Shukunami C, Iyama K, Negoro T, Hiraki Y. Functional analysis of diastrophic dysplasia sulfate transporter. Its involvement in growth regulation of chondrocytes mediated by sulfated proteoglycans. *J Biol Chem.* 1998;273:12307–15. PubMed PMID: 9575183.
- Stenson PD, Mort M, Ball EV, Chapman M, Evans K, Azevedo L, Hayden M, Heywood S, Millar DS, Phillips AD, Cooper DN. The Human Gene Mutation Database (HGMD®): optimizing its use in a clinical diagnostic or research setting. *Hum Genet.* 2020;139:1197–207. PubMed PMID: 32596782.
- Superti-Furga A. Defects in sulfate metabolism and skeletal dysplasias. In: Scriver CR, Beaudet AL, Sly WS, Valle D, Vogelstein B, Childs B, eds. *The Metabolic and Molecular Bases of Inherited Disease*. 8 ed. New York, NY: McGraw-Hill; 2001:5189-201.
- Superti-Furga A. Skeletal dysplasias related to defects in sulfate metabolism. In: Royce P, Steinmann B, eds. *Connective Tissue and Its Heritable Disorders*. 2 ed. New York, NY: Wiley-Liss, Inc; 2002:939-60.
- Superti-Furga A, Rossi A, Steinmann B, Gitzelmann R. A chondrodysplasia family produced by mutations in the diastrophic dysplasia sulfate transporter gene: genotype/phenotype correlations. *Am J Med Genet.* 1996;63:144–7. PubMed PMID: 8723100.
- Unger S, Bonafé L, Superti-Furga A. Multiple epiphyseal dysplasia: clinical and radiographic features, differential diagnosis and molecular basis. *Best Pract Res Clin Rheumatol.* 2008;22:19–32. PubMed PMID: 18328978.
- Unger S, Ferreira CR, Mortier GR, Ali H, Bertola DR, Calder A, Cohn DH, Cormier-Daire V, Girisha KM, Hall C, Krakow D, Makitie O, Mundlos S, Nishimura G, Robertson SP, Savarirayan R, Sillence D, Simon M, Sutton VR, Warman ML, Superti-Furga A. Nosology of genetic skeletal disorders: 2023 revision. *Am J Med Genet A.* 2023. Epub ahead of print.
- Zankl A, Jackson GC, Crettol LM, Taylor J, Elles R, Mortier GR, Spranger J, Zabel B, Unger S, Merrer ML, Cormier-Daire V, Hall CM, Wright MJ, Bonafé L, Superti-Furga A, Briggs MD. Preselection of cases through expert clinical and radiographic review significantly increases mutation detection rate in multiple epiphyseal dysplasia. *Eur J Hum Genet.* 2007;15:150–4. PubMed PMID: 17133256.

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