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Achondrogenesis Type 1B

[*ACG1B*]

Luisa Bonafé, MD, PhD
Assistant Professor
Head, Division of Molecular Pediatrics
Centre Hospitalier Universitaire Vaudois
University of Lausanne, Switzerland
luisa.bonafe@chuv.ch

Diana Ballhausen, MD
Division of Molecular Pediatrics
Centre Hospitalier Universitaire Vaudois
University of Lausanne, Switzerland
Diana.Ballhausen@chuv.ch

Andrea Superti-Furga, MD
Professor of Pediatrics
Chair, Department of Pediatrics, University of Freiburg
Director, Centre for Pediatrics and Adolescent Medicine
Freiburg University Hospital, Germany
asuperti@uniklinik-freiburg.de

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Summary

Disease characteristics. Clinical features of achondrogenesis type 1B (ACG1B) include extremely short limbs with short fingers and toes, hypoplasia of the thorax, protuberant abdomen, and hydropic fetal appearance caused by the abundance of soft tissue relative to the short skeleton. The face is flat, the neck is short, and the soft tissue of the neck may be thickened. Death occurs prenatally or shortly after birth.

Diagnosis/testing. The diagnosis of ACG1B rests upon a combination of clinical, radiologic, and histopathologic features. *SLC26A2(DTDST*) is the only gene known to be associated with AO2. The diagnosis can be confirmed by molecular genetic testing of *SLC26A2*, which is clinically available. Sulfate incorporation assay in cultured skin fibroblasts (or chondrocytes) is possible in rare cases in which molecular genetic testing fails to identify *SLC26A2* mutations.

Management. *Treatment of manifestations:* palliative care for liveborn neonates.

Genetic counseling. ACG1B is inherited in an autosomal recessive manner. At conception, each sib of a proband with ACG1B has a 25% chance of being affected, a 50% chance of being an asymptomatic carrier, and a 25% chance of being unaffected and not a carrier. Once an at-risk sib is known to be unaffected, the risk of his/her being a carrier is 2/3. Prenatal diagnosis for pregnancies at 25% risk is possible. Both disease-causing alleles of an affected family member must be identified and carrier status confirmed in the parents before prenatal molecular genetic testing of an at-risk pregnancy can be performed. Ultrasound examination early in pregnancy is a reasonable complement or alternative to molecular prenatal diagnosis.

Diagnosis

Clinical Diagnosis

Achondrogenesis type 1B (ACG1B) is a perinatal lethal disorder with death occurring prenatally or shortly after birth. The diagnosis is usually established with the following:

Clinical features

- Extremely short limbs with short fingers and toes
- Hypoplasia of the thorax
- Protuberant abdomen
- Hydropic fetal appearance caused by the abundance of soft tissue relative to the short skeleton
- Flat face
- Short neck
- Thickened soft tissue of the neck

Radiographic findings. Even though the degree of ossification generally depends on gestational age, variability can be observed between radiographs taken at similar gestational ages; thus, no single feature should be considered obligatory.

- Disproportion between the nearly normal-sized skull and very short body length. The skull may have a normal appearance or be mildly abnormal (reduced ossification for age; lateral or superior extension of the orbits; micrognathia).
- Total lack of ossification of the vertebral bodies or only rudimentary calcification of the center. The vertebral lateral pedicles are usually ossified.
- Short and slightly thin (but usually not fractured) ribs
- Iliac bone ossification limited to the upper part, giving a crescent-shaped, "paraglider-like" appearance on x-ray. The ischium is usually not ossified.
- Shortening of the tubular bones such that no major axis can be recognized. Metaphyseal spurring gives the appearance of a "thorn apple" or (for hematologic experts) "acanthocyte." The phalanges are poorly ossified and therefore are only rarely identified on x-ray.
- Only mildly abnormal clavicles (somewhat shortened but normally shaped and ossified) and scapulae (small with irregular contours) [Superti-Furga 1996]

Testing

Histopathologic testing. In ACG1B, the histology of the cartilage shows a rarified cartilage matrix partially replaced by a larger number of cells. After hematoxylin-eosin staining, the matrix appears non-homogeneous with coarse collagen fibers. The fibers are denser around the chondrocytes, where they can form "collagen rings." After staining with cationic dyes (toluidine blue, alcian blue), which bind to the abundant polyanionic sulfated proteoglycans, normal cartilage matrix appears as a homogeneous deep blue or violet; in ACG1B, cartilage staining with these dyes is much less intense because of the defective sulfation of the proteoglycans.

Biochemical testing. The incorporation of sulfate into macromolecules can be studied in cultured chondrocytes and/or skin fibroblasts through double labeling with ^{3}H-glycine

and ^{35}S-sodium sulfate. After incubation with these compounds and purification, the electrophoretic analysis of medium proteoglycans reveals a lack of sulfate incorporation [Superti-Furga 1994], which can be observed even in total macromolecules. The determination of sulfate uptake is possible but cumbersome and is not used for diagnostic purposes [Superti-Furga, Hastbacka, Wilcox et al 1996].

Molecular Genetic Testing

GeneReviews designates a molecular genetic test as clinically available only if the test is listed in the GeneTests Laboratory Directory *by either a US CLIA-licensed laboratory or a non-US clinical laboratory. GeneTests does not verify laboratory-submitted information or warrant any aspect of a laboratory's licensure or performance. Clinicians must communicate directly with the laboratories to verify information.*—ED.

Molecular Genetic Testing—Gene. *SLC26A2(DTDST*) is the only gene currently known to be associated with ACG1B.

Clinical uses

- Confirmatory diagnostic testing
- Carrier testing
- Prenatal diagnosis

Clinical testing. In individuals with radiologic and histologic features compatible with the diagnosis of sulfate transporter-related dysplasias, mutations in the *SLC26A2* gene can be found in more than 90% of alleles [Rossi & Superti-Furga 2001]. Very rarely, in individuals with typical clinical, radiologic, and histologic features of *SLC26A2* dysplasia, *SLC26A2* molecular testing detects no mutation or only a single heterozygous pathogenic mutation; in these cases, the mutations may be present in the 5' region of the gene, which is currently not entirely covered by clinically available testing.

- **Targeted mutation analysis.** Testing for the five most common *SLC26A2* mutations (p.R279W, VS1+2T>C ("Finnish"), delV340, p.R178X, and p.C653S) is available on a clinical basis. Recurrent mutations commonly associated with ACG1B are p.R178X and delV340, which are respectively the third- and the fourth-most common pathogenic alleles of the *SLC26A2* gene in the general population.
- **Sequence analysis.** Sequence analysis of the whole *SLC26A2* coding region is available on a clinical basis. Sequence analysis may detect rare "private" mutations in individuals in whom mutation analysis detects none or only one of the common alleles.

Table 1 summarizes molecular genetic testing for this disorder.

Table 1. Molecular Genetic Testing Used in Achondrogenesis Type 1B

Testing Method	Mutations Detected	Mutation Detection Rate	Test Availability
Targeted mutation analysis	Panel of five *SLC26A2* mutations [1]	~65%	Clinical Testing
Sequence analysis	Private and common *SLC26A2* mutations	>90%	

1. p.R279W, IVS1+2T>C, delV340, p.R178X, p.C653S

Interpretation of test results. For issues to consider in interpretation of sequence analysis results, click here.

Testing Strategy for a Proband

Clinical and radiologic features can strongly suggest the diagnosis of achondrogenesis, but it is often difficult to distinguish between the three different forms of achondrogenesis, ACG1A, ACG1B, and ACG2 (see Differential Diagnosis). The histologic and biochemical testing of cartilage tissue provide additional important information.

is the preferred diagnostic test in probands with a clinical, radiologic, and/or histopathologic diagnosis of ACG1B. It allows precise diagnosis in the great majority of cases.

- Targeted mutation analysis for the five most common mutations is carried out at first, as it is likely to identify one or both alleles in a significant percentage of probands (one allele in one-third of cases and both alleles in about one-fourth of cases).
- Sequence analysis of the whole coding region is carried out when neither or only one allele has been identified by targeted mutation analysis. Parental DNA analysis for the mutations found in the proband is recommended as most probands are compound heterozygous.

Sulfate incorporation assay in cultured skin fibroblasts (or chondrocytes) is possible in the rare instances in which the diagnosis of ACG1B is strongly suspected, but molecular genetic testing fails to detect *SLC26A2* mutations.

Genetically Related (Allelic) Disorders

Three other phenotypes (all with an autosomal recessive mode of inheritance) are associated with mutations in *SLC26A2(DTDST)*:

- **Atelosteogenesis type 2 (AO2)** is a neonatally lethal chondrodysplasia with clinical and histologic characteristics that resemble those of diastrophic dysplasia [Hastbacka et al 1996].
- **Diastrophic dysplasia (DTD)** is a skeletal dysplasia characterized by short stature, joint contractures, cleft palate, and characteristic clinical signs such as the "hitchhiker" thumb and cystic swelling of external ears. The first mutations in the *SLC26A2* gene were found in individuals with DTD [Hastbacka et al 1994].
- **Recessive multiple epiphyseal dysplasia (EDM4)** is characterized by joint pain (usually in the hips and knees), deformities of the hands, feet, and knees, and scoliosis. About 50% of affected individuals have an abnormal finding at birth, e.g., clubfoot, cleft palate, or cystic ear swelling. Median height in adulthood is at the tenth centile [Superti-Furga, Rossi et al 1996; Superti-Furga et al 1999; Superti-Furga et al 2001].

Clinical Description

Natural History

Achondrogenesis type 1B (ACG1B), one of the most severe chondrodysplasias, is a perinatal lethal disorder with death occurring prenatally or shortly after birth. The mechanism of the prenatal death is unknown. In the viable newborn, death is secondary to respiratory failure and occurs shortly after birth.

Fetuses with ACG1B often present in breech position. Pregnancy complications as a result of polyhydramnios may occur.

Clinical features of ACG1B include extremely shortened limbs, inturning of the feet and toes (talipes equino varus), and brachydactyly (short stubby fingers and toes). The thorax is narrow and the abdomen protuberant. Frequently, umbilical or inguinal herniae are present.

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 that extends from lethal ACG1B to mild recessive multiple epiphyseal dysplasia (EDM4). Homozygosity or compound heterozygosity for mutations predicting stop codons or structural mutations in transmembrane domains of the sulfate transporter are associated with ACG1B, while mutations 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, Rossi et al 1996; Karniski 2001].

Mutation p.R279W is the most common mutation of the *SLC26A2* gene outside Finland; it results in the mild EDM4 phenotype when homozygous and mostly in the diastrophic dysplasia (DTD) phenotype when in the compound heterozygous state.

Mutation IVS1+2T>C, the second-most common mutation, is very frequent in Finland ("Finnish" mutation). It produces low levels of correctly spliced mRNA and results in DTD when homozygous.

Mutation p.C653S is the third-most common mutation, with a frequency among DTDST pathogenic alleles very close to that of mutation IVS1+2T>C in non-Finnish populations. It results in EDM4/rMED when homozygous and in EDM4/rMED or DTD when compounded with other mutations.

Mutations 1045-1047delGTT (V340del) and 558C>T (p.R178X) are associated with the severe phenotypes ACG1B and AO2.

The same mutations found in the ACG1B phenotype can also be found in the milder phenotypes (AO2 and DTD) if the second allele is a relatively mild mutation. Indeed, missense mutations 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 term achondrogenesis (Greek for "not producing cartilage") was given by the pathologist Marco Fraccaro in 1952 to the condition observed in a stillborn with severe micromelia and marked histologic changes in cartilage. In 1939, Hans Grebe attributed the same name to the condition observed in two sisters with markedly short limbs and digits but normal trunk; this condition, although superficially similar to Fraccaro's achondrogenesis, became later known as Grebe chondrodysplasia or Grebe syndrome.

Subsequently, the name achondrogenesis was used to characterize the most severe forms of human chondrodysplasia, invariably lethal before or shortly after birth. In the 1970s, the heterogeneity of achondrogenesis was recognized. Using a combination of radiologic and histologic criteria, achondrogenesis type I (also called Fraccaro-Houston-Harris type) and type II (called Langer-Saldino type) were distinguished.

In the 1980s, a new classification of achondrogenesis (types I to IV) based on radiologic criteria was proposed; the classification did not prove helpful and was later abandoned.

In the late 1980s it was shown that achondrogenesis type II was caused by mutations in the gene encoding collagen II.

Borochowitz et al (1988) provided convincing histologic criteria for the further subdivision of achondrogenesis type I into IA and IB which are still very useful for the differential diagnosis.

- ACG1A corresponds to the former eponym Houston-Harris type

- ACG1B corresponds to the Fraccaro type. The confirmation of ACG1B as a separate entity came with the demonstration of sulfate transporter mutations in this histologic type.
- ACG2 corresponds to the Langer-Saldino type.

ACG1B is currently classified in the "sulfation disorders group" in the revised Nosology and Classification of Genetic Disorders of Bone [Superti-Furga & Unger 2006].

Prevalence

No data on the prevalence of ACG1B are available.

Differential Diagnosis

For current information on availability of genetic testing for disorders included in this section, see GeneTests Laboratory Directory. —ED.

Achondrogenesis type 1B (ACG1B) should be distinguished from other lethal chondrodysplasias. As this is a large group of disorders, differentiation may be problematic.

Making the correct diagnosis in fetuses with severe short-limbed chondrodysplasia by clinical and ultrasonographic findings alone is difficult. It is therefore important to obtain good radiographs, tissue for DNA extraction, skin biopsy for fibroblast culture, and bone and cartilage tissues for histology and biochemistry. The combination of radiologic and histologic findings gives a provisional diagnosis, which can then be confirmed by selected biochemical and/or molecular genetic investigations [Unger et al 2001].

Achondrogenesis is subtyped according to radiologic and histopathologic characteristics [Borochowitz et al 1988, Superti-Furga et al 2001]:

- Achondrogenesis type 1A (ACG1A; Houston-Harris type)
- ACG1B (Fraccaro type)
- Achondrogenesis type 2 (ACG2; Langer-Saldino type)

Within the achondrogenesis group, clinical and radiologic distinction between ACG1A, ACG1B, and ACG2 is not always possible. The presence of rib fractures and the absence of ossification of vertebral pedicles may suggest ACG1A. The hands and fingers are markedly shortened in ACG1B and less so in ACG1A; they can be almost normal in ACG2. ACG2 shows more severe underossification of the vertebral bodies compared to ACG1B, in addition to quite typical configuration of the iliac bones with concave medial and inferior borders, and nonossification of the ischial and pubic bones.

Histology of the cartilage is very useful in distinguishing the three different forms of achondrogenesis:

- **ACG1A.** The cartilage matrix is normal and inclusions are present in the chondrocytes.
- **ACG1B.** The matrix is clearly abnormal (presence of "demasked," coarse collagen fibers, sometimes giving a wavy, spongelike appearance) and has abnormal staining properties because of the reduced proteoglycans.
- **ACG2.** The cartilage is hypervascular and hypercellular with reduced matrix and vacuoles ("Swiss cheese-like"), but has roughly normal staining properties.

Features observed on histologic examination after staining with cationic dyes distinguish ACG1B from ACG1A, in which the matrix appears close to normal and chondrocytes show intracytoplasmic inclusions, and from ACG2, in which the matrix is rarified and vacuolated but stains normally and there are no "collagen rings." ACG2 also has inclusions.

Other osteochondrodysplasias that are often in the differential diagnosis of ACG1B:

- Osteogenesis imperfecta types 2 and 3. Typical signs are soft undermineralized skull and blue sclerae; the bones are bowed but not as short as in achondrogenesis. Multiple fractures are present.
- Thanatophoric dysplasia. The limbs are longer than in ACG and the thorax is narrow but elongated. In thanatophoric dysplasia type II, cloverleaf skull is common.
- Short rib-polydactyly syndromes. Polydactyly is usually present; when absent, the short rib-polydactyly syndromes may be confused with thanatophoric dysplasia.
- Roberts syndrome. Severe limb shortening with only mildly affected axial skeleton may suggest Roberts syndrome. In Roberts syndrome standard cytogenetic preparations stained with Giemsa or C-banding techniques show in most chromosomes during metaphase the characteristic chromosomal abnormality of premature centromere separation (PCS) and separation of the heterochromatic regions [also called heterochromatin repulsion (HR)]f. Mutations in the *ESCO2* gene are causative.
- Fibrochondrogenesis. Distinguishing radiographic features of fibrochondrogenesis are marked metaphyseal flaring of the long bones and clefts of the vertebral bodies.

Management

Evaluations at Initial Diagnosis to Establish the Extent of Disease

- Complete skeletal survey
- Respiratory status

Treatment of Manifestations

- Palliative care for the viable newborn

Testing 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 for access to information on clinical studies for a wide range of diseases and conditions.

Genetic Counseling

Genetic counseling is the process of providing individuals and families with information on the nature, 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. This section is not meant to address all personal, cultural, or ethical issues that individuals may face or to substitute for consultation with a genetics professional. To find a genetics or prenatal diagnosis clinic, see the GeneTests Clinic Directory.

Mode of Inheritance

Achondrogenesis type 1B (ACG1B) is inherited in an autosomal recessive manner.

Risk to Family Members

Parents of a proband

- The parents of an affected child are obligate heterozygotes and therefore carry a single copy of a disease-causing mutation in the *SLC26A2* gene.
- Heterozygous 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

- At conception, each sib of a proband with ACG1B has a 25% chance of being affected, a 50% chance of being an asymptomatic carrier, and a 25% chance of being unaffected and not a carrier.
- Once an at-risk sib is known to be unaffected, the risk of his/her being a carrier is 2/3.
- To date, *de novo* mutations in the proband and germline mosaicism in the parents have not been reported.

Offspring of a proband. ACG1B is a perinatally lethal condition; affected individuals do not reproduce.

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

Carrier Detection

- Carrier testing is available on a clinical basis once the mutation(s) has/have been identified in the proband.
- Carrier detection in reproductive partners of a heterozygous individual is available on a clinical basis. The partners can be screened for the five most common pathogenic alleles: p.R279W, IVS1+2T>C, delV340, p.R178X, and p.C653S. When these five alleles are excluded, the risk of carrying a *SLC26A2* mutation is reduced from the general population risk of 1:100 to about 1:300.

Related Genetic Counseling Issues

Family planning. The optimal time for determination of genetic risk, clarification of carrier status, and discussion of availability of prenatal testing is before pregnancy.

DNA banking. DNA banking is the storage of DNA (typically extracted from white blood cells) for possible future use. Because it is likely that testing methodology and our understanding of genes, mutations, and diseases will improve in the future, consideration should be given to banking DNA of affected individuals. DNA banking is particularly relevant in situations in which the sensitivity of currently available testing is less than 100%. See DNA Banking for a list of laboratories offering this service.

Prenatal Testing

High-risk pregnancies

- **Molecular genetic testing.** Prenatal diagnosis for pregnancies at 25% risk is possible by analysis of DNA extracted from fetal cells obtained by chorionic villus sampling

(CVS) at about ten to 12 weeks' gestation or by amniocentesis usually performed at about 15-18 weeks' gestation. Both disease-causing alleles of an affected family member must be identified before prenatal testing can be performed.

Note: Gestational age is expressed as menstrual weeks calculated either from the first day of the last normal menstrual period or by ultrasound measurements.

- **Ultrasound examination.** Transvaginal ultrasound examination early in pregnancy is a reasonable alternative to molecular prenatal diagnosis because the testing is not invasive. However, the diagnosis can be made with confidence only at week 14-15, and reliability is highly operator dependent.
- **Biochemical testing.** There are no data on prenatal functional biochemical testing (sulfate incorporation test on chorionic villus or fibroblasts).

Low-risk pregnancies

- **Routine ultrasound examination.** Routine prenatal ultrasound examination may identify very short fetal limbs ± polyhydramnios ± small thorax and raise the possibility of achondrogenesis in a fetus not known to be at risk. Subtle ultrasound findings may be recognizable in the first trimester, but in low-risk pregnancies the diagnosis of a skeletal dysplasia is usually not made until the second trimester.
- **Molecular genetic testing.** DNA extracted from cells obtained by amniocentesis can be theoretically analyzed to try to make a molecular diagnosis prenatally. However, the differential diagnosis in such a setting is very broad (see Differential Diagnosis).

Preimplantation genetic diagnosis (PGD) may be available for families in which the disease-causing mutations have been identified in an affected family member. For laboratories offering PGD, see Testing.

Molecular Genetics

Information in the Molecular Genetics tables is current as of initial posting or most recent update. —ED.

Table A. Molecular Genetics of Achondrogenesis Type 1B

Gene Symbol	Chromosomal Locus	Protein Name
SLC26A2	5q32-q33.1	Sulfate transporter

Data are compiled from the following standard references: Gene symbol from HUGO; chromosomal locus, locus name, critical region, complementation group from OMIM; protein name from Swiss-Prot.

Table B. OMIM Entries for Achondrogenesis Type 1B

600972	ACHONDROGENESIS, TYPE IB; ACG1B
606718	SOLUTE CARRIER FAMILY 26 (SULFATE TRANSPORTER), MEMBER 2; SLC26A2

Table C. Genomic Databases for Achondrogenesis Type 1B

Gene Symbol	Entrez Gene	HGMD
SLC26A2	1836 (MIM No. 606718)	SLC26A2

For a description of the genomic databases listed, click here.

Molecular Genetic Pathogenesis

Mutations in the *SLC26A2* gene [Dawson & Markovich 2005] are responsible for the family of chondrodysplasias including ACG1B, AO2, DTD, and EMD4 [Hastbacka et al 1996;

Superti-Furga, Hastbacka, Rossi et al 1996; Superti-Furga et al 1999]. 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, Bonaventure et al 1996; Rossi et al 1998; Satoh et al 1998], most likely because of intracellular sulfate depletion [Rossi, Bonaventure et al 1996]. 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]. A correlation exists between the mutation, the predicted residual activity of the sulfate transporter, and the severity of the phenotype [Cai et al 1998, Rossi & Superti-Furga 2001, Karniski 2004, Maeda et al 2006].

Normal allelic variants: The coding sequence of the *SLC26A2* gene (GenBank accession number U14528) is organized in two exons separated by an intron of approximately 1.8 kb, and encodes a protein of 739 amino acids that is predicted to have 12 transmembrane domains and a carboxy-terminal, cytoplasmic, moderately hydrophobic domain [Hastbacka et al 1994]. A further untranslated exon is located 5' relative to the two coding exons; it has probable regulatory functions, as the mutation IVS1+2T>C (the "Finnish" allele) located in this region, was shown to lead to reduced mRNA transcription [Hastbacka et al 1999]. The p.T689S allele has been frequently observed at the heterozygous or homozygous state in several controls of different ethnicities and is very likely to be a polymorphism [Cai et al 1998, Rossi & Superti-Furga 2001]. Evidence suggests that p.R492W is a rare polymorphism, found in seven out of 200 Finnish controls and in five out of 150 non-Finnish controls [authors, unpublished data]. This allele was erroneously considered pathogenic in previous reports [Rossi et al 2001].

Pathologic allelic variants: Five pathogenic alleles of the *SLC26A2* gene appear to be recurrent: p.R279W, IVS1+2T>C, delV340, p.R178X, and p.C653S. Together they represent approximately two-thirds of the pathogenic mutations in *SLC26A2*.

Of the five, delV340 and p.R178X are most commonly associated with the ACG1B phenotype. In compound heterozygotes, the phenotype associated with each pathogenic allele depends on the combination with the second mutation. Distinct phenotypes known to be allelic to ACG1B are atelosteogenesis type 2 (AO2), diastrophic dysplasia (DTD), and recessive multiple epiphyseal dysplasia (rMED). (For more information, see Genomic Databases table above.)

Normal gene product: The diastrophic dysplasia sulfate transporter gene *SLC26A2* encodes a transmembrane protein that transports sulfate into chondrocytes to maintain adequate sulfation of proteoglycans. The sulfate transporter protein belongs to the family of sulfate permeases. The overall structure with 12 membrane-spanning domains is shared with two other human anion exchangers: PDS (OMIM 274600), a chloride-iodide transporter involved in Pendred syndrome, and CLD, which is responsible for congenital chloride diarrhea. The function of the carboxy-terminal hydrophobic domain of *SLC26A2* is not yet known. *SLC26A2* is expressed in developing cartilage in human fetuses but also in a wide variety of other tissues [Haila et al 2000, Haila et al 2001]. The size of the predominant mRNA species is larger than 8 kb, indicating the existence of significant untranslated sequences [Hastbacka et al 1999].

Abnormal gene product: Most of the *SLC26A2* mutations either predict a truncated polypeptide chain or affect amino acids that are located in transmembrane domains or are conserved in man, mouse, and rat. Individuals homozygous for the "Finnish" mutation IVS1+2T>C have reduced levels of mRNA with intact coding sequence [Rossi, van der Harten et al 1996]. Thus, the mutation presumably interferes with splicing and/or further mRNA processing and transport [Hastbacka et al 1996, Hastbacka et al 1999].

The p.R278X and delV340 mutations were shown to abolish sulfate transporter activity in a *Xenopus* oocyte model [Karniski 2001], and in a HEK-293 cell culture model [Karniski 2004], respectively.

Resources

GeneReviews provides information about selected national organizations and resources for the benefit of the reader. GeneReviews is not responsible for information provided by other organizations. Information that appears in the Resources section of a GeneReview is current as of initial posting or most recent update of the GeneReview. Search GeneTests*for this disorder and select* Resources *for the most up-to-date Resources information.*—ED.

National Library of Medicine Genetics Home Reference
Achondrogenesis

Compassionate Friends
PO Box 3696
Oak Brook IL 60522-3696
Phone: 877-969-0010; 630-990-0010
Fax: 630-990-0246
Email: nationaloffice@compassionatefriends.org
www.compassionatefriends.org

Helping After Neonatal Death (HAND)
A non-profit California-based group that lists support groups
www.handonline.org/resources/groups/index.html

European Skeletal Dysplasia Network
c/o European Projects Office
North West Genetics Knowledge Park (Nowgen)
The Nowgen Centre 29 Grafton Street
Manchester M13 9WU
Phone: (+44) 161 276 3202
Fax: (+44) 161 276 4058
Email: info@esdn.org
www.esdn.org

International Skeletal Dysplasia Registry
Medical Genetics Institute
8635 West Third St. Suite 665
Los Angeles CA 90048
Phone: 800-CEDARS-1 (800-233-2771)
Fax: 310-423-0462
www.csmc.edu

References

Medical Genetic Searches: A specialized PubMed search designed for clinicians that is located on the PubMed Clinical Queries page. PubMed

Published Statements and Policies Regarding Genetic Testing

No specific guidelines regarding genetic testing for this disorder have been developed.

Literature Cited

Borochowitz Z, Lachman R, Adomian GE, Spear G, Jones K, Rimoin DL. Achondrogenesis type I: delineation of further heterogeneity and identification of two distinct subgroups. J Pediatr. 1988;112:23–31. [PubMed: 3275766]

Cai G, Nakayama M, Hiraki Y, Ozono K. Mutational analysis of the DTDST gene in a fetus with achondrogenesis type 1B. Am J Med Genet. 1998;78:58–60. [PubMed: 9637425]

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: 11570921]

Dawson PA, Markovich D. Pathogenetics of the human SLC26 transporters. Curr Med Chem. 2005;12:385–96. [PubMed: 15720248]

Forlino A, Piazza R, Tiveron C, Della Torre S, Tatangelo L, Bonafe 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: 15703192]

Haila S, Hastbacka J, Bohling T, Karjalainen-Lindsberg ML, Kere J, Saarialho-Kere U. SLC26A2 (diastrophic dysplasia sulfate transporter) is expressed in developing and mature cartilage but also in other tissues and cell types. J Histochem Cytochem. 2001;49:973–82. [PubMed: 11457925]

Haila S, Saarialho-Kere U, Bohling T, Hastbacka J, Kere J. DTDST is expressed in developing fetal cartilage but also in a wide variety of other tissues and cell types. Am J Hum Genet. 2000;67:A371.

Hastbacka J, de la Chapelle A, Mahtani MM, Clines G, Reeve-Daly MP, Daly M, Hamilton BA, Kusumi K, Trivedi B, Weaver A, et al. The diastrophic dysplasia gene encodes a novel sulfate transporter: positional cloning by fine-structure linkage disequilibrium mapping. Cell. 1994;78:1073–87. [PubMed: 7923357]

Hastbacka J, Kerrebrock A, Mokkala K, Clines G, Lovett M, Kaitila I, de la Chapelle A, Lander ES. Identification of the Finnish founder mutation for diastrophic dysplasia (DTD). Eur J Hum Genet. 1999;7:664–70. [PubMed: 10482955]

Hastbacka J, Superti-Furga A, Wilcox WR, Rimoin DL, Cohn DH, Lander ES. Atelosteogenesis type II is caused by mutations in the diastrophic dysplasia sulfate-transporter gene (DTDST): evidence for a phenotypic series involving three chondrodysplasias. Am J Hum Genet. 1996;58:255–62. [PubMed: 8571951]

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: 11448940]

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: 15294877]

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: 16642506]

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: 8702490]

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: 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: 11241838]

Rossi A, van der Harten HJ, Beemer FA, Kleijer WJ, Gitzelmann R, Steinmann B, Superti-Furga A. Phenotypic and genotypic overlap between atelosteogenesis type 2 and diastrophic dysplasia. Hum Genet. 1996;98:657–61. [PubMed: 8931695]

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: 9575183]

Superti-Furga A. A defect in the metabolic activation of sulfate in a patient with achondrogenesis type IB. Am J Hum Genet. 1994;55:1137–45. [PubMed: 7977372]

Superti-Furga A. Achondrogenesis type 1B. J Med Genet. 1996;33:957–61. [PubMed: 8950678]

Superti-Furga A, Bonafe L, Rimoin DL. Molecular-pathogenetic classification of genetic disorders of the skeleton. Am J Med Genet. 2001;106:282–93. [PubMed: 11891680]

Superti-Furga A, Hastbacka J, Rossi A, van der Harten JJ, Wilcox WR, Cohn DH, Rimoin DL, Steinmann B, Lander ES, Gitzelmann R. A family of chondrodysplasias caused by mutations in the diastrophic dysplasia sulfate transporter gene and associated with impaired sulfation of proteoglycans. Ann N Y Acad Sci. 1996;785:195–201. [PubMed: 8702127]

Superti-Furga A, Hastbacka J, Wilcox WR, Cohn DH, van der Harten HJ, Rossi A, Blau N, Rimoin DL, Steinmann B, Lander ES, Gitzelmann R. Achondrogenesis type IB is caused by mutations in the diastrophic dysplasia sulphate transporter gene. Nat Genet. 1996;12:100–2. [PubMed: 8528239]

Superti-Furga A, Neumann L, Riebel T, Eich G, Steinmann B, Spranger J, Kunze J. Recessively inherited multiple epiphyseal dysplasia with normal stature, club foot, and double layered patella caused by a DTDST mutation. J Med Genet. 1999;36:621–4. [PubMed: 10465113]

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: 8723100]

Superti-Furga A, Unger S. Nosology and classification of genetic skeletal disorders: 2006 revision. Am J Med Genet A. 2006;143A:1–18. [PubMed: 17120245]

Unger S, Le Merrer M, Meinecke P, Chitayat D, Rossi A, Superti-Furga A. New dysplasia or achondrogenesis type 1B? The importance of histology and molecular biology in delineating skeletal dysplasias. Pediatr Radiol. 2001;31:893–4. [PubMed: 11727031]

Chapter Notes

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