GENEReviews

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Diastrophic Dysplasia

[*Diastrophic Dwarfism*]

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Summary

Disease characteristics. Diastrophic dysplasia (DTD) is characterized by limb shortening, normal-sized skull, hitchhiker thumbs, spinal deformities (scoliosis, exaggerated lumbar lordosis, cervical kyphosis), and contractures of the large joints with deformities and early-onset osteoarthritis. Other typical findings are ulnar deviation of the fingers, gap between the first and second toes, and clubfoot. On occasion the disease can be lethal at birth, but most affected individuals survive the neonatal period and develop physical limitations with normal intelligence.

Diagnosis/testing. The diagnosis of DTD rests upon a combination of clinical, radiologic, and histopathologic features. The diagnosis is confirmed by molecular genetic testing of *SLC26A2 (DTDST*), the only gene known to be associated with DTD. Biochemical studies of fibroblasts and/or chondrocytes are available, especially in the rare instances in which molecular genetic testing fails to identify *SLC26A2* mutations.

Management. *Treatment of manifestations:* in children, physiotherapy and casting to maintain joint positioning and mobility as much as possible; surgical correction of clubfoot when ambulation becomes impossible; cervical spine surgery restricted to individuals with clinical or neurophysiologic evidence of spinal cord impingement; surgical correction of scoliosis in those at risk for rapid increase in curvature; total arthroplasty of hips and knees in relatively young adults to decrease pain and increase mobility. *Surveillance:* annual monitoring of spinal curvature and joint contractures. *Agents/circumstances to avoid:* obesity, which places an excessive load on the large, weight-bearing joints. *Other:* Undertake orthopedic surgery with caution as deformities tend to recur.

Genetic counseling. DTD is inherited in an autosomal recessive manner. At conception, each sib of a proband with DTD 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. The unaffected sibs of a proband have a 2/3 chance of being heterozygotes. Prenatal diagnosis for pregnancies

at increased risk is possible if both disease-causing alleles of an affected family member have been identified. Ultrasound examination early in pregnancy is a reasonable complement or alternative to prenatal diagnosis by molecular genetic testing.

Diagnosis

Clinical Diagnosis

Diastrophic dysplasia (DTD) encompasses a range of disease that varies from severe (atelosteogenesis type 2) to mild [formerly called "diastrophic variant," recessive multiple epiphyseal dysplasia (rMED, EDM4)].

Clinical features [Superti-Furga 2001, Superti-Furga 2002]

- Limb shortening
- Normal-sized skull
- Slight trunk shortening
- Hitchhiker thumbs (Figure1)
- Small chest
- Protuberant abdomen
- Contractures of large joints
- Dislocation of the radius
- Cleft palate (in approximately one-third of individuals)
- Cystic ear swelling in the neonatal period (in approximately two-thirds of infants with classic findings)
- Other usual findings: ulnar deviation of the fingers, gap between the first and second toes, clubfoot, and flat hemangiomas of the forehead

Radiographic findings

- The skull appears of normal size with disproportionate short skeleton.
- Cervical kyphosis is seen in most newborns and children with DTD.
- Ossification of the upper thoracic vertebrae may be incomplete with broadening of cervical spinal canal ("cobra-like" appearance).
- Coronal clefts may be present in the lumbar and lower thoracic vertebrae.
- Narrowing of the interpedicular distance from L1 to L5 is a constant finding.
- The more cephalad ribs are short and the chest can be bell-shaped.
- The sternum may present duplication of the ossification centers.
- The ilia are hypoplastic with flat acetabula.
- The long bones appear moderately shortened with some metaphyseal flaring.
- The distal humerus is sometimes bifid or V-shaped, sometimes pointed and hypoplastic.
- The femur is distally rounded.
- The patella may appear fragmented or multilayered.

- Radius and tibia may be bowed.
- Proximal radial dislocation may be present at birth.
- Hands may exhibit typical features (Figure2):
  - Hitchhiker thumb with ulnar deviation of the fingers
  - Shortness of the first metacarpal
  - Delta-shaped proximal and middle phalanges
  - In some severe cases, ossification of two to three carpal bones in the newborn, simulating advanced skeletal age

Testing

Histologic and biochemical testing provide important information.

Histopathologic testing. The histopathology of cartilage is similar to that seen in atelosteogenesis type 2 (AO2) and achondrogenesis type 1B (ACG1B), as it reflects the paucity of sulfated proteoglycans in cartilage matrix. It shows an 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; in some cases, these are indistinguishable from the collagen rings typical of ACG1B. 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 bone shows no ossification abnormalities [Superti-Furga 2001, Superti-Furga 2002].

Biochemical testing. The incorporation of sulfate into macromolecules can be studied in cultured chondrocytes and/or skin fibroblasts through double labeling with 3H-glycine and 35S-sodium sulfate. After incubation with these compounds and purification, the electrophoretic analysis of medium proteoglycans reveals a lack of sulfate incorporation, which can be observed even in total macromolecules.

Note: (1) The determination of sulfate uptake is cumbersome and not used for diagnostic purposes. (2) The sulfate incorporation assay in cultured skin fibroblasts (or chondrocytes) is recommended only in the rare instance in which the diagnosis of DTD is strongly suspected but molecular genetic testing fails to detect *SLC26A2* mutations [Rossi et al 1996; Superti-Furga, Hastbacka et al 1996; Rossi et al 1997; Rossi et al 1998; Rossi et al 2003].

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* is the only gene currently known to be associated with diastrophic dysplasia (DTD) [Hastbacka et al 1994; Superti-Furga, Hastbacka et al 1996; Rossi & Superti-Furga 2001; Superti-Furga 2001; Superti-Furga 2002].

Clinical testing

- **Targeted mutation analysis.** The five most common *SLC26A2* mutations (p.Arg279Trp, IVS1+2T>C, p.Val340del, p.Arg178X, and p.Cys653Ser) account for approximately 65% of disease alleles.
- **Sequence analysis.** Sequence analysis of the *SLC26A2* coding region may detect rare mutations in individuals for whom targeted mutation analysis detects none or only one of the more common alleles. Mutations in *SLC26A2* are found in more than 90% of alleles in individuals with radiologic and histologic features compatible with the diagnosis of DTD [Rossi & Superti-Furga 2001].

Table 1 summarizes molecular genetic testing for this disorder.

Table 1. Molecular Genetic Testing Used in Diastrophic Dysplasia

Test Method	Mutations Detected	Mutation Detection Frequency [1]	Test Availability
Targeted mutation analysis	Panel of five *SLC26A2* mutations [2]	~65%	Clinical Testing
Sequence analysis	*SLC26A2* sequence variants	>90%	

1. % of disease alleles detected in individuals with typical clinical, radiologic, and histologic features of DTD
2. IVS1+2T>C, p.Arg178X, p.Arg279Trp, p.Val340del, p.Cys653Ser. Mutation panel may vary by laboratory.

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

Testing Strategy

To confirm the diagnosis in a proband

- Clinical and radiologic features can strongly suggest the diagnosis of DTD.
- Molecular genetic testing, the diagnostic test of choice in probands with clinical and radiologic findings compatible with DTD, allows for precise diagnosis in the great majority of cases.
  - Targeted mutation analysis for the five most common mutations is likely to identify one or both alleles in a significant proportion of probands (one allele in 1/3 of cases and both alleles in 1/4 of cases).
  - Sequence analysis of the entire coding region is performed when only one or neither allele has been identified by targeted mutation analysis. Parental DNA analysis for the mutations found in the proband is recommended as most cases are compound heterozygous.
- Histologic and biochemical tests provide confirmatory information but are usually not required to establish the clinical diagnosis. Note: These tests are particularly helpful in aborted fetuses, when the radiographic material is of poor quality.
- The sulfate incorporation assay in cultured skin fibroblasts (or chondrocytes) is possible in the rare cases in which the diagnosis of DTD is strongly suspected but mutation analysis fails to detect *SLC26A2* mutations.

Carrier testing for at-risk relatives requires prior identification of the disease-causing mutations in the family. Note: Carriers are heterozygotes for an autosomal recessive disorder and are not at risk of developing the disorder.

Prenatal diagnosis for at-risk pregnancies requires prior identification of the disease-causing mutations in the family.

Genetically Related (Allelic) Disorders

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

- **Achondrogenesis type 1B (ACG1B),** among the most severe skeletal disorders in humans, is characterized by severe hypodysplasia of the spine, rib cage, and extremities, with a relatively preserved cranium. ACG1B is invariably lethal in the perinatal period.
- **Atelosteogenesis type 2 (AO2)** is a neonatally lethal chondrodysplasia with clinical and histologic characteristics that resemble those of DTD but are more pronounced.
- **Recessive multiple epiphyseal dysplasia (rMED, EDM4)** is characterized by joint pain (usually in the hips and knees), deformities of the hands, feet, and knees, and scoliosis. About 50% of 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.

Clinical Description

Natural History

Neonates with diastrophic dysplasia (DTD) may experience respiratory insufficiency because of the small rib cage and tracheal instability and collapsibility. Mechanical ventilation is required in a significant proportion of infants. Mortality in the first months of life is increased, mainly because of respiratory complications such as pneumonia, sometimes aspiration pneumonia.

From the newborn period throughout life, the disorder appears to involve the skeleton as well as the tendons, ligaments, and joint capsules, which are tighter and shorter than normal, causing restricted joint mobility. Growth of the tendons and joint capsules may be impaired; a recent report indicated a high prevalence of congenital aplasia of menisci and cruciate ligaments within the knee joints [Peltonen et al 2003]. Pretibial dimples may be present, possibly a consequence of reduced intrauterine movement.

Joint contractures and spine deformity tend to worsen with age. Painful degenerative arthrosis of the hip is common in young adults. Anterior tilting of the pelvis may occur as a consequence and contribute to exaggerate the lumbar lordosis. The spine frequently develops excessive lumbar lordosis, thoracolumbar kyphosis, and scoliosis. In anteroposterior radiographs of the lumbar spine, a decrease of the vertebral interpedicular distance is almost invariably observed; however, related neurologic symptoms are only rarely observed [Remes et al 2004].

The knee may be unstable in childhood, but flexion contractures develop with progressive valgus deformity and lateral positioning of the patella. The development and position of the patella may determine whether contraction of the quadriceps muscle results in extension of the knee or paradoxical flexion of the knee. If paradoxical flexion occurs, severe difficulty with walking results [Remes et al 2004].

Because of foot deformities and shortened tendons, many adults with DTD are unable to place their heels on the ground. Thus, they stand solely on their metatarsals and toes. Typically, the adult with classic DTD stands on his toes because of severe clubfoot and has marked lumbar lordosis and thoracic kyphoscoliosis; this appearance originally prompted use of the term "diastrophic" (twisted).

Brachydactyly, ulnar deviation, phalangeal synostosis, and ankylosis of the fingers with significant disability may be observed. Phalangeal synostosis, usually between proximal and middle phalanges, develops in those fingers that have an abnormal phalangeal patterning at

birth, including so-called delta-shaped phalanges that usually lack a proper joint space. Often, newborns with DTD lack phalangeal flexion creases (Figure1), a sign of marked reduction of joint motion already present at early developmental stages. The thumb may be placed more proximally than usual and may also be hypotonic and thus weak (probably because of ligamentous dysplasia). As a consequence, some individuals may have difficulty opposing the thumb and the index finger to accomplish a pincer grasp. In older children and adults, ulnar deviation of the second finger frequently occurs together with radial deviation of the fifth finger (clinodactyly), giving a characteristic "brackets" appearance.

The facial appearance of children and young adults with DTD is remarkably different from the "standard" chondrodysplasia face with a depressed nasal bridge and anteverted nares. The forehead is high and broad; the palpebral fissures are relatively small and may be downslanting; the nose is not shortened or stubby as in other chondrodysplasias but rather long and thin because of hypoplastic alae nasi; the nares are not anteverted; the facial tissues are tight; the mouth is small, and the mandible normally developed.

Adult stature ranged between 100 and 140 cm in an early review of Americans and Europeans with DTD. A 1982 study reported a mean adult height of 118 cm [Horton et al 1982], while a study of Finnish individuals with DTD (who are genetically homogeneous at the *SLC26A2* locus) revealed a mean adult height of 136 cm for males and 129 cm for females [Makitie & Kaitila 1997]. The discrepancy in mean height between the older studies and the recent Finnish study may be the result of mutation heterogeneity or may reflect bias of ascertainment of more severely affected individuals in the older studies. It must be noted that the usefulness of such growth curves in predicting adult height is limited by the occurrence of many different allelic combinations [Superti-Furga 2001; Superti-Furga 2002]

In addition to the skeletal abnormalities, a mild degree of muscular hypoplasia of the thighs and legs is common.

Neurologic complications may occur, particularly in the cervical region. Cervical kyphosis is seen in lateral radiographs in most newborns; in most cases, it lessens over the first three to five years of life but in some cases, severe cervical kyphosis may lead to spinal cord compression, either spontaneously or during the procedure of endotracheal intubation, which requires hyperextension of the neck. A newborn with DTD and severe cervical kyphosis died immediately after birth of respiratory insufficiency; autopsy revealed neuronal degeneration and gliosis of the cervical spinal cord that had developed before birth.

Newer MRI findings have confirmed that in DTD, the foramen magnum is of normal size but the cervical spinal canal is narrowed. Individual cervical vertebral bodies (usually C3 to C5) may be hypoplastic, but the frequently observed kyphosis is not explained by changes of the vertebral bodies and may thus be the consequence of abnormal intervertebral disks. The rate of spontaneous correction of cervical kyphosis is rather high.

Cervical spina bifida occulta has been frequently reported in individuals with DTD.

Hearing loss is unusual in individuals with DTD, and vision defects are seldom observed, although a tendency towards myopia has been reported.

Mental development and intelligence are usually normal; numerous individuals affected by DTD attain high academic and social recognition or success in the arts.

MRI studies have shown a peculiar signal anomaly of intervertebral disks, suggesting a reduced water content. This anomaly may be the consequence of reduced proteoglycan sulfation.

Genotype-Phenotype Correlations

Genotype-phenotype correlations indicate that the amount of residual activity of the sulfate transporter modulates the phenotype in a spectrum that goes from lethal ACG1B to mild autosomal recessive MED (rMED, EDM4).

Homozygosity or compound heterozygosity for mutations predicting stop codons or structural mutations in transmembrane domains of the sulfate transporter are associated with the more severe phenotype of ACG1B.

The combination of a severe mutation (predicting stop codons, structural mutations in transmembrane domains, or loss of function) with a mutation located in extracellular loops, in the cytoplasmic tail of the protein, or in the regulatory 5'-flanking region of the gene results in less severe phenotypes, i.e., AO2 and DTD [Maeda et al 2006].

Mutation p.Arg279Trp is the most common mutation of the *SLC26A2* gene outside Finland, and is a mild mutation resulting in the MED phenotype when homozygous and mostly in the DTD phenotype when compounded.

In individuals with AO2, the p.Arg279Trp mutation is combined with a severe, structural mutation (e.g., p.Arg178X, p.Cys418del, p.Asn425Asp) whereas in individuals with DTD, the p.Arg279Trp mutation is combined with a mutation predicting some residual activity, such as IVS1+2T>C or p.Val340del. Therefore, the same mutations associated in some individuals with the AO2 phenotype can be found in individuals with the DTD phenotype if the second allele is a relatively mild mutation, or in individuals with the ACG1B phenotype if the second mutation is a structural, severe one. The combination of p.Arg279Trp and p.Arg178X has been reported in individuals with clinical diagnoses of DTD as well as AO2. However, the radiologic features in such individuals are consistent with severe DTD; the diagnosis of AO2 should be reserved for cases characterized by perinatal lethality.

Mutation IVS1+2T>C, the second most common mutation, is common in Finland (and is thus called the "Finnish" mutation). It produces low levels of correctly spliced mRNA and results in DTD when homozygous. More recently identified, p.Cys653Ser is the third most common mutation; it has been found in several individuals with milder DTD or rMED/EDM4.

Mutations 1045-1047delGTT (p.Val340del) and 558C>T (p.Arg178X) are associated with the severe phenotypes ACG1B and AO2.

Penetrance

For pathogenic mutations in the *SLC26A2* gene, penetrance is complete.

Nomenclature

Diastrophic dysplasia (DTD) was recognized as a distinct entity by Lamy and Maroteaux in 1960. At that time, they described a disorder that "resembled achondroplasia in the newborn period but had a quite distinct evolution." The name was chosen to indicate the "twisted" appearance of the spine and limbs in severely affected individuals. The clinical and radiographic features of diastrophic dysplasia are so characteristic that no other name has been associated with the condition.

The existence of clinical variability was recognized early; instances of "severe" or "lethal" DTD are now classified as atelosteogenesis type 2 (AO2), while milder cases, once termed "diastrophic variant," are now classified as recessive multiple epiphyseal dysplasia (rMED, EDM4).

DTD is classified in the "sulfation disorder" group of the current Nosology and Classification of Genetic Skeletal Disorders [Superti-Furga & Unger 2007].

Prevalence

No reliable data exist regarding the prevalence of DTD. In the experience of several genetic and metabolic centers that can compare its incidence with that of other genetic diseases, DTD disorders are generally believed to be in the range of approximately 1:100,000.

Differential Diagnosis

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

Diastrophic dysplasia (DTD) is part of a disease spectrum. At the severe end, it borders a condition defined as atelosteogenesis type 2 that is commonly lethal in the perinatal period. Affected individuals present around birth or before. At the mild end, DTD can present as what was formerly called "diastrophic variant" and borders recessive multiple epiphyseal dysplasia; this differential diagnosis is usually considered in toddlers or school-age children.

Premature carpal ossification and digital malformations can be seen in newborns and infants with otopalatodigital syndrome (caused by mutations in *FLNA*; see Otopalatodigital Spectrum Disorders), in the Larsen syndrome/atelosteogenesis 1 spectrum (filamin B mutations), and in Desbuquois dysplasia.

Contractures and mesomelic limb shortening reminiscent of diastrophic dysplasia can be seen in omodysplasia. Congenital contractures with mild skeletal anomalies can be seen in various forms of congenital arthrogryposis.

Differential diagnosis in the prenatal period must include skeletal dysplasias as well as other conditions with reduced length and/or contractures. Even the demonstration of a hitchhiker thumb deformity is not pathognomic.

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease in an individual diagnosed with diastrophic dysplasia (DTD), the following evaluations are recommended:

- Cervical films
- Complete skeletal survey
- Orthopedic referral
- Physical therapy consultation

Treatment of Manifestations

In children, the principle is to maintain joint positioning and mobility as much as possible by physical means (physiotherapy and casting, e.g., for clubfeet); however, tightness of joint capsules and ligaments in diastrophic dysplasia makes correction by casting or other physical means difficult.

Surgical correction of clubfoot is indicated when the foot deformity makes ambulation impossible; however, surgery needs to be undertaken with caution as deformities tend to recur. Simple tenotomy does not suffice, and more extensive plasty of tarsal bones may be needed.

The rate of spontaneous correction of cervical kyphosis is rather high, and cervical spine surgery in infancy may be restricted to individuals with clinical or neurophysiologic evidence of spinal cord impingement.

Indications for surgical correction of scoliosis have not been established nor have criteria to define a successful surgical outcome [Matsuyama et al 1999, Remes et al 2001]. It should be noted that surgical series are inevitably biased toward more severely affected individuals. Although surgery before puberty may be helpful for those who have developed severe spinal deformity with respiratory compromise or neurologic signs, surgical correction of scoliosis is best postponed until after puberty in the majority of individuals with diastrophic dysplasia. The key issue seems to be the early identification of those individuals at risk for rapid increase in scoliotic curvature.

Total arthroplasty of hips and knees decreased pain and increased mobility in a group of adult Finnish individuals with premature degenerative arthrosis [Helenius, Remes, Lohman et al 2003; Helenius, Remes, Tallroth et al 2003]. The authors concluded that arthroplasty is indicated in "relatively young adults" with DTD.

Surveillance

Annual monitoring of spinal curvature and joint contractures is appropriate.

Agents/Circumstances to Avoid

Obesity places an excessive load on the large weight-bearing joints and thus should be avoided.

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. Note: There may not be clinical trials for this disorder.

Other

Genetics clinics, staffed by genetics professionals, provide information for individuals and families regarding the natural history, treatment, mode of inheritance, and genetic risks to other family members as well as information about available consumer-oriented resources. See the GeneTests Clinic Directory.

Support groups have been established for individuals and families to provide information, support, and contact with other affected individuals. The Resources section may include disease-specific and/or umbrella support organizations.

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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

Diastrophic dysplasia (DTD) 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 thus carry a single copy of a disease-causing mutation in the *SLC26A2* gene.
- Heterozygotes (carriers) are usually asymptomatic and have normal stature. There is no evidence that are at increased risk for degenerative joint disease.
- To date, neither *de novo* mutations nor germline mosaicism in parents has been reported.

Sibs of a proband

- At conception, each sib of a proband with DTD 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.

Offspring of a proband. The offspring of an individual with diastrophic dysplasia are obligate heterozygotes (carriers) for a disease-causing mutation.

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

Carrier Detection

- Carrier testing for at-risk family members is available on a clinical basis once the mutations have been identified in the family.
- Carrier detection in reproductive partners of a heterozygous individual is available on a clinical basis. The reproductive partners can be screened for the five most common pathogenic alleles: p.Arg279Trp, IVS1+2T>C, p.Val340del, p.Arg178X, and p.Cys653Ser. The risk of carrying a *SLC26A2* mutation is reduced from the general risk of 1:100 to about 1:300 when these five alleles are excluded.

Related Genetic Counseling Issues

It is appropriate to offer genetic counseling (including discussion of potential risks to offspring and reproductive options) to young adults who are affected.

Family planning. Determination of genetic risk, clarification of carrier status, and discussion of availability of prenatal testing are best done before pregnancy whenever possible.

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. DNA banking is particularly relevant in situations in which the sensitivity of currently available testing is less than 100%. For laboratories offering DNA banking, see DNA Banking. 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.
- **Ultrasound examination.** Transvaginal ultrasound examination early in pregnancy is a reasonable alternative to molecular prenatal diagnosis because ultrasound examination is not invasive [Tongsong et al 2002, Severi et al 2003, Wax et al 2003]. However, the diagnosis can be made with confidence only at week 14-15, and reliability is highly operator-dependent. See also Note: Low-Risk Pregnancies.
- **Biochemical testing.** No data on prenatal functional biochemical tests (sulfate incorporation test on chorionic villus or fibroblasts) are available.

Low-Risk Pregnancies

- **Routine ultrasound examination.** Routine prenatal ultrasound examination may identify short fetal limbs and/or polyhydramnios and/or small thorax and raise the possibility of DTD in a fetus not known to be at risk. The finding of radially deviated thumbs ("hitchhiker thumbs") is suggestive, although never pathognomonic, of DTD. 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.

  Note: While several reports of "successful" early ultrasonographic identification of DTD have been published, the literature is heavily biased toward positive cases [Tongsong et al 2002, Severi et al 2003, Wax et al 2003]. In the authors' experience, only a minority of fetuses with DTD in low-risk pregnancies are identified correctly by ultrasound examination, most cases being diagnosed as unspecific skeletal dysplasia or some other skeletal condition. Therefore, a good clinical and pathologic examination is important
- **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 Note and Differential Diagnosis).

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

Molecular Genetics

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

Table A. Molecular Genetics of Diastrophic Dysplasia

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 Diastrophic Dysplasia

222600	DIASTROPHIC DYSPLASIA
606718	SOLUTE CARRIER FAMILY 26 (SULFATE TRANSPORTER), MEMBER 2; SLC26A2

Table C. Genomic Databases for Diastrophic Dysplasia

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 are responsible for the family of chondrodysplasias including ACG1B, AO2, DTD, and rMED/EDM4. Impaired activity of the sulfate transporter in chondrocytes and fibroblasts results in the synthesis of proteoglycans that are not sulfated or are insufficiently sulfated [Satoh et al 1998, Rossi et al 1998], most probably because of intracellular sulfate depletion [Rossi et al 1996]. Undersulfation of proteoglycans affects the composition of the extracellular matrix and leads to impaired proteoglycan deposition, which is necessary for proper enchondral bone formation [Corsi et al 2001, Forlino et al 2005]. The predicted severity of the mutations can be correlated with the residual activities of the sulfate transporter and the severity of the phenotypes [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.Arg178X mutation was shown to abolish sulfate transporter activity, and the p.Val340del mutation showed detectable but very low activity (17% of the wild type) of sulfate transporter [Karniski 2001]. The same mutations 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 mutation. Indeed, missense mutations 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 the human (20° C vs. 37° C) [Superti-Furga, Rossi 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 achondrogenesis 1B mutations are associated with no residual transport activity, while the milder phenotypes result from either different combinations of "null" mutations with others that allow for some residual activity or from two mutations with residual activity. Original observations were: (1) intracellular retention of the sulfate transporter protein with mutation p.Gly678Val and (2) abnormal molecular weight of sulfate transporter with mutation p.Gln454Pro, possibly indicating protease sensitivity or aberrant glycosylation.

Normal allelic variants: The coding sequence of the *SLC26A2* gene is organized in two exons separated by an intron of approximately 1.8 kb. A further untranslated exon is located 5' relative to the two coding exons; it has probable regulatory functions. The p.Thr689Ser allele has been

frequently observed in the heterozygous or homozygous state in several controls of different ethnicities, and it is very likely to be a polymorphism.

There is evidence that p.Arg492Trp is a rare polymorphism found in seven of 200 Finnish controls and in five non-Finnish controls [Authors, unpublished data]. This allele was erroneously considered pathogenic in previous reports [Rossi & Superti-Furga 2001].

Pathologic allelic variants: Five pathogenic alleles of the *SLC26A2* gene appear to be recurrent: p.Arg279Trp, IVS1+2T>C, p.Val340del, p.Arg178X, p.Cys653Ser. The mutation IVS1+2T>C (the "Finnish" allele), located 5' relative to the two coding exons, leads to reduced mRNA transcription. These five alleles represent approximately 2/3 of the pathogenic mutations in the *SLC26A2* gene. The phenotype associated with each pathogenic allele depends, in compound heterozygotes, on the combination with the second mutation. Distinct phenotypes known to be allelic to DTD are ACG1B, AO2, and recessive EDM4.

Normal gene product: The protein consists of 739 amino acids and is predicted to have 12 transmembrane domains and a carboxy-terminal, cytoplasmic, moderately hydrophobic domain. This transmembrane protein transports sulfate into chondrocytes to maintain adequate sulfation of proteoglycans. The sulfate transporter protein belongs to the family of anion exchangers known as SLC26 [Mount & Romero 2004], which to date comprises ten members, including PDS (MIM #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. The *SLC26A2* gene is expressed in developing cartilage in human fetuses but also in a wide variety of other tissues. The size of the predominant mRNA species is greater than 8 kb, indicating that there are significant untranslated sequences.

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 +2>C have reduced levels of mRNA with intact coding sequence. Thus, the mutation presumably interferes with splicing and/or further mRNA processing and transport.

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
Diastrophic dysplasia

AboutFace International
123 Edward Street Suite 1003
Toronto M5G 1E2
Canada
Phone: 800-665-FACE (800-665-3223)
Fax: 416-597-8494
Email: info@aboutfaceinternational.org
www.aboutfaceinternational.org

American Cleft Palate-Craniofacial Association
Cleft Palate Foundation
1504 East Franklin Street Suite 102
Chapel Hill NC 27514-2820
Phone: 800-242-5338; 919-933-9044
Fax: 919-933-9604
Email: info@cleftline.org
www.cleftline.org

Human Growth Foundation
997 Glen Cove Avenue Suite 5
Glen Head NY 11545
Phone: 800-451-6434
Fax: 516-671-4055
Email: hgf1@hgfound.org
www.hgfound.org

Little People of America (LPA)
5289 NE Elam Young Parkway Suite F-100
Hillsboro OR 97124
Phone: 888-LPA-2001 (888-572-2001); 503-846-1562
Fax: 503-846-1590
Email: info@lpaonline.org
www.lpaonline.org

The MAGIC Foundation
6645 West North Avenue
Oak Park IL 60302
Phone: 800-362-4423; 708-383-0808
Fax: 708-383-0899
Email: info@magicfoundation.org
www.magicfoundation.org

European Skeletal Dysplasia Network
North West Genetics Knowledge Park (Nowgen)
The Nowgen Centre 29 Grafton Street
Manchester M13 9WU
United Kingdom
Phone: 0161 276 3202
Fax: 0161 276 4058
Email: info@esdn.org
www.esdn.org

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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.

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Chapter Notes

Revision History

- 12 June 2007 (me) Update posted to live Web site
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- 17 February 2004 (asf) Original submission

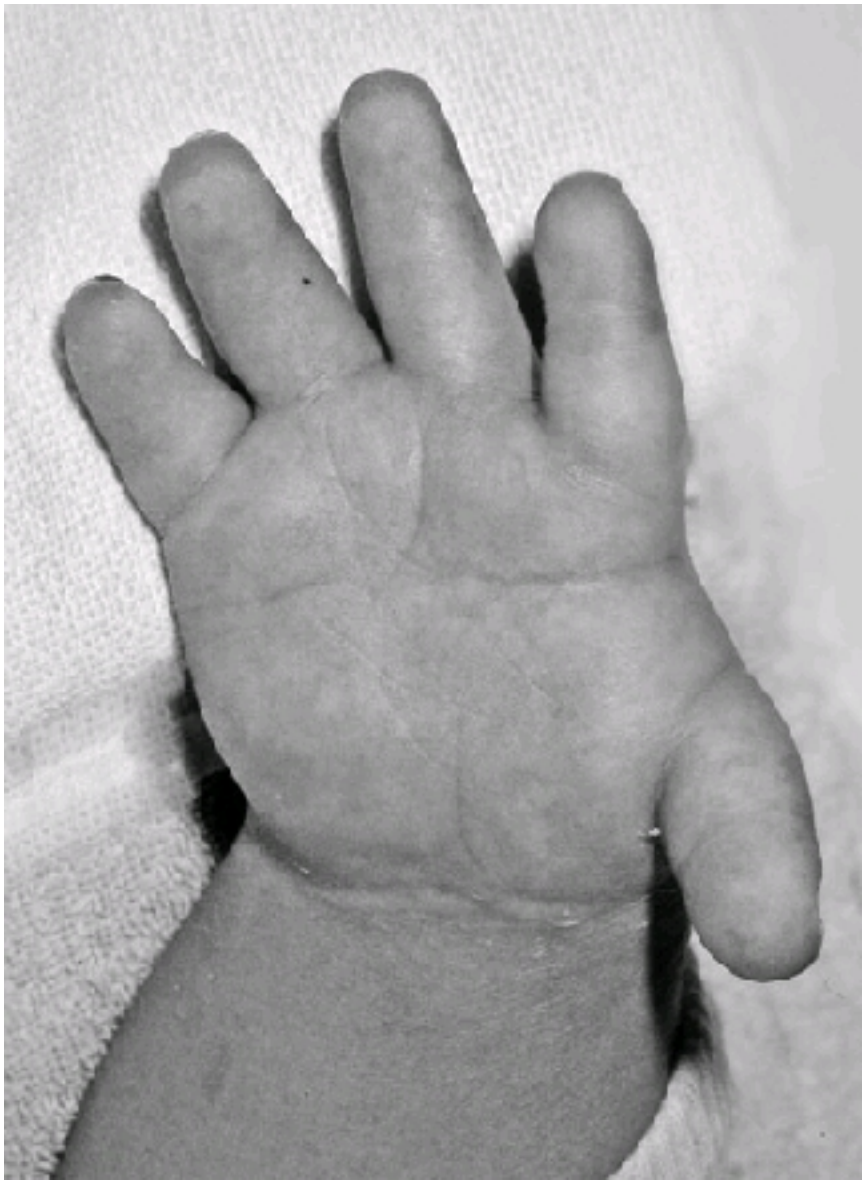

Figure 1. Hand of a newborn with diastrophic dysplasia, showing brachydactyly (short fingers), absence of flexion creases of the fingers, and proximally placed, abducted "hitchhiker thumb." The thumb deformity results in difficulty with thumb opposition, affecting activities such as writing or opening a screw cap.

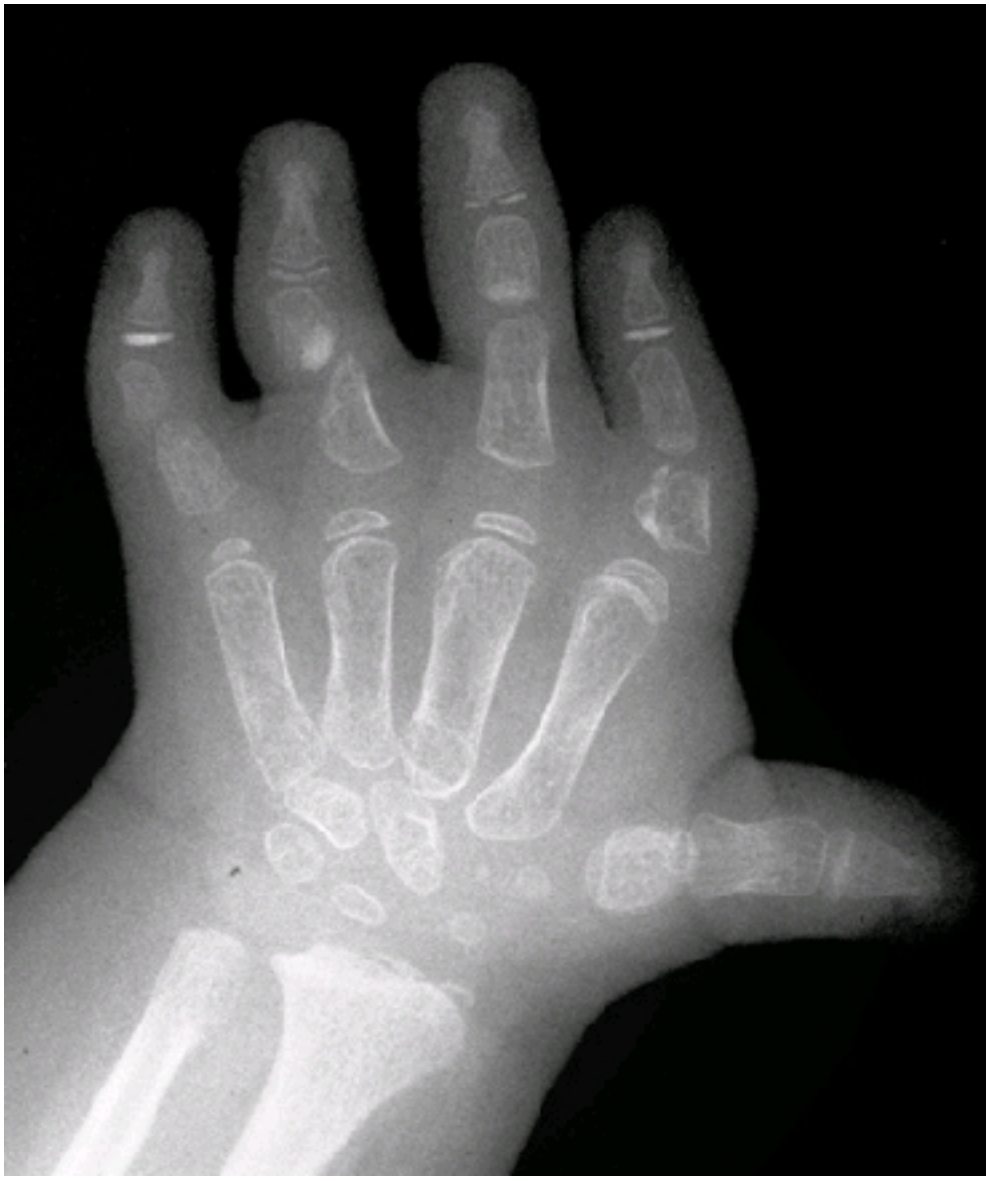

Figure 2. Radiograph of the hand of a three-year-old child with diastrophic dysplasia. The phalanges are short; some show a "delta"-shape deformity. Ossification of the carpal bones is advanced for age, a phenomenon known as "pseudo-acceleration" of the bone age, because the advanced bone age is not related to hormonal processes, but rather is caused by the biochemical abnormality intrinsic to diastrophic dysplasia.