GENEReviews

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Thanatophoric Dysplasia

[*Includes: Thanatophoric Dysplasia Type I, Thanatophoric Dysplasia Type II*]

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Summary

Disease characteristics. Thanatophoric dysplasia (referred to as TD in this entry) is a neonatal lethal short-limb dwarfism syndrome. TD is divided into type I, characterized by micromelia with bowed femurs and, uncommonly, the presence of cloverleaf skull deformity (kleeblattschaedel) of varying severity; and type II, characterized by micromelia with straight femurs and uniform presence of moderate-to-severe cloverleaf skull deformity. Other features common to the two subtypes of TD include short ribs, narrow thorax, macrocephaly, distinctive facial features, brachydactyly, hypotonia, and redundant skin folds along the limbs. Most affected infants die of respiratory insufficiency shortly after birth. Rare long-term survivors have been reported.

Diagnosis/testing. Diagnosis of TD is based on clinical examination and/or prenatal ultrasound examination and radiologic studies. Characteristic histopathology is also present. *FGFR3* is the only gene associated with TD. Up to 99% of mutations causing TD type I and more than 99% of mutations causing TD type II can be identified through molecular genetic testing of *FGFR3*. Confirmatory molecular genetic testing of *FGFR3* is available on a clinical basis.

Management. Treatment of prenatally diagnosed TD is designed to avoid potential pregnancy complications such as prematurity, polyhydramnios, malpresentation, and cephalopelvic disproportion caused by macrocephaly from hydrocephalus or a flexed and rigid neck. Management concerns are limited to the parents' desire for extreme life support measures and provision-of-comfort care for the newborn. Newborns require respiratory support (with tracheostomy and ventilation) to survive. Other treatment measures may include: medication to control seizures, shunt placement for hydrocephaly, suboccipital decompression for relief of craniocervical junction constriction, and hearing aids. Surveillance for long-term survivors includes neurologic, orthopedic and audiologic evaluations, CT for craniocervical constriction, and EEG for seizure activity.

Genetic counseling. TD is inherited in an autosomal dominant manner; the majority of probands have a *de novo* mutation in *FGFR3*. Risk of recurrence is not significantly increased over that of the general population. Germline mosaicism in healthy parents, although not previously reported, remains a theoretical possibility. Prenatal diagnosis is clinically available.

Diagnosis

Clinical Diagnosis

Thanatophoric dysplasia (TD) is one of the short-limb dwarfism conditions suspected when significantly shortened long bones and a narrow thorax are detected prenatally or neonatally, especially when perinatal death occurs.

Prenatal ultrasound examination [Sawai et al 1999, De Biasio et al 2000, Chen et al 2001, Ferreira et al 2004, De Biasio et al 2005]:

- **First trimester**
  - Shortening of the long bones, possibly visible as early as 12-14 weeks' gestation
  - Increased nuchal translucency (two case reports) and reverse flow in the ductus venosus (one case report), possibly the result of the narrow thorax compressing vascular flow
- **Second/third trimester**
  - Growth deficiency with limb length below fifth centile recognizable by 20 weeks' gestation
  - Well-ossified spine and skull
  - Platyspondyly
  - Ventriculomegaly
  - Narrow chest cavity with short ribs
  - Polyhydramnios
  - Bowed femurs (TD type I)
  - Cloverleaf skull (kleeblattschaedel) (often in TD type II; occasionally in TD type I) and/or relative macrocephaly

Note: Although identification of a lethal skeletal dysplasia in the second trimester is often straightforward, establishing the specific diagnosis can be difficult [Sawai et al 1999, Parilla et al 2003]. Ultrasound examination or review of the ultrasound films by an OB/geneticist may be most helpful in making a specific diagnosis prenatally. A 3-D ultrasound examination may also aid in visualizing facial features and other soft tissue findings of TD [Chen et al 2001].

Postnatal physical examination [Tavormina et al 1995, Lemyre et al 1999, Passos-Bueno et al 1999, Sawai et al 1999, De Biasio et al 2000]:

- Macrocephaly
- Large anterior fontanel
- Frontal bossing, flat facies with low nasal bridge, proptotic eyes
- Marked shortening of the limbs (micromelia)
- Trident hand with brachydactyly
- Redundant skin folds
- Narrow bell-shaped thorax with short ribs and protuberant abdomen
- Relatively normal trunk length

- Generalized hypotonia
- Bowed femurs (TD type I)
- Cloverleaf skull (always in TD type II; sometimes in TD type I)

Radiographs/other imaging studies [Wilcox et al 1998, Lemyre et al 1999]:

- Rhizomelic shortening of the long bones
- Irregular metaphyses of the long bones
- Platyspondyly
- Small foramen magnum with brain stem compression
- CNS abnormalities including temporal lobe malformations, hydrocephaly, brain stem hypoplasia, neuronal migration abnormalities
- Bowed femurs (TD type I)
- Cloverleaf skull (always in TD type II; sometimes in TD type I)

Other reported findings include cardiac defects (patent ductus arteriosis and atrial septal defect) and renal abnormalities.

Testing

Histopathology [Tavormina et al 1995, Wilcox et al 1998, Lemyre et al 1999]:

- Disorganized chondrocyte columns
- Poor cellular proliferation
- Lateral overgrowth of the metaphyseal bone
- Mesenchymal cells extending inward forming a fibrous band at the periphery of the physeal bone
- Increased vascularity of the resting cartilage

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. *FGFR3* is the only gene known to cause TD type I and TD type II. A single *FGFR3* mutation (K650E) has been identified in all individuals with TD type II [Rousseau, el Ghouzzi et al 1996; Gorlin 1997; Bellus et al 2000].

Molecular genetic testing: Clinical uses

- Diagnostic confirmation when TD is suspected based on findings of pre- or postnatal examination
- Prenatal diagnosis for families with a previous child with confirmed TD who opt for molecular genetic testing (even though recurrence risk is not significantly elevated and ultrasound examination can detect TD early in pregnancy)

Molecular genetic testing: Clinical methods

- **Targeted mutation analysis** of *FGFR3* using a panel of the three most common mutations
- **Sequence analysis** of select regions of *FGFR3* previously reported to contain mutations; for TD type I, *FGFR3* exons 7, 10, 15, and 19; for TD type II, *FGFR3* exon 15.

Table 1 summarizes molecular genetic testing for this disorder.

Table 1. Molecular Genetic Testing Used in Thanatophoric Dysplasia

Test Method	Mutations Detected	Mutation Detection Rate [1]		Test Availability
		TD Type I	TD Type II	
Targeted mutation analysis	Three most common mutations [2]	~90%	NA	Clinical Testing
	K650E	NA	>99%	
Sequence analysis	*FGFR3* sequence alteration	99%	>99%	

NA = Not applicable

1. Sensitivities determined through a survey of US labs listed in GeneTests
2. R248C, Y373C, and S249C

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

Testing Strategy for a Proband

- If TD type II is suspected on the basis of straight femurs and cloverleaf skull, targeted testing for the K650E mutation may be an appropriate first step in diagnostic testing.
- Otherwise, sequencing or a full mutation panel is recommended.

Genetically Related (Allelic) Disorders

FGFR3 mutations have been identified in several disorders with highly variable phenotypes:

- **Achondroplasia**. The causative *FGFR3* mutations G380R and G375C have been identified in nearly 100% of individuals [Camera et al 2001]. Camera et al (2001) reported an individual with the common TD type I mutation R248C and a clinical phenotype of achondroplasia. Although mosaicism remains a possible explanation for the mild phenotype, no mosaicism was identified in either buccal mucosal cells or blood.
- **Hypochondroplasia**. Although *FGFR3* mutations are identifiable in about 80% of individuals with hypochondroplasia, several families are not linked to the *FGFR3* gene; therefore, genetic heterogeneity is likely [Rousseau, Bonaventure et al 1996; Camera et al 2001].
- **SADDAN** (**s**evere **a**chondroplasia with **d**evelopmental **d**elay and **a**canthosis **n**igricans) is caused by *FGFR3* mutation K650M [Bellus et al 1999, Tavormina et al 1999].
- **Crouzon syndrome with acanthosis nigricans** (see *FGFR*-Related Craniosynostosis Syndromes) is caused by *FGFR3* mutation A391E.
- **Nonsyndromic coronal synostosis** (Muenke syndrome) (see also *FGFR*-Related Craniosynostosis Syndromes), characterized by a P250R mutation in *FGFR3* [Passos-Bueno et al 1999, McIntosh et al 2000]

- **Platyspondylic lethal skeletal dysplasia, San Diego type (PLSD-SD).** Although PLSD-SD has been described as a distinct clinical entity, much phenotypic overlap exists with TD. Both disorders feature short, bowed long bones, platyspondyly, and short ribs. In PLSD-SD, metaphyseal flaring and chondrocyte abnormalities can be less severe [Brodie et al 1999]. An important histologic difference is the consistent presence in the chondrocytes in PLSD-SD of dilated loops/inclusion bodies in the endoplasmic reticulum, which are not typical in TD. All individuals with platyspondylic lethal skeletal dysplasia, San Diego type (PLSD-SD) studied by Brodie et al (1999) had *FGFR3* mutations previously reported in association with TD type I.
- **LADD syndrome** (**L**acrimo-**a**uriculo-**d**ento-**d**igital syndrome, Levy Hollister syndrome). *FGFR3* mutation D513N has been reported in one family with this syndrome [Rohmann et al 2006].

Clinical Description

Natural History

Thanatophoric dysplasia type I and thanatophoric dysplasia type II are diagnosed prenatally or in the immediate newborn period. Both subtypes are considered lethal skeletal dysplasias; most affected individuals die of respiratory insufficiency in the first hours or days of life. Respiratory insufficiency may be secondary to a small chest cavity and lung hypoplasia, compression of the brain stem by the small foramen magnum, or a combination of both [Baker et al 1997].

Long-term survivors. The clinical findings of two individuals (a male aged 4.75 years and a female aged 3.7 years at last follow-up) were summarized by MacDonald et al (1989). Both had birth length and weight below the third percentile. Head circumference was at the 97th percentile. In both, growth plateaued after ten months of age.

- The male required ventilatory support at birth and tracheostomy at age three months. Other clinical findings include micromelia, redundant skin folds, hydrocephalus diagnosed at two months, seizure activity at three months, a small foramen magnum with compression of the brain stem diagnosed at 15 months, and little developmental progress after 20 months. Platyspondyly, bowed tubular bones, and splayed ribs were noted radiographically. Head CT showed abnormal differentiation of the white and grey matter of the brain.
- The female required ventilatory support beginning at two months of age. A small foramen magnum with brain stem compression was diagnosed at two months and hydrocephaly was diagnosed at four months. Bilateral hearing loss and progressive lack of ossification of the caudal spine were noted at 3.7 years. She had two words and knew some sign language.

A nine-year-old male with the common TD type I mutation R248C was reported [Baker et al 1997]. Birth weight was at the 50th percentile (normal growth charts); birth length was more than four SD below the mean (achondroplasia growth charts). He required tracheostomy and ventilatory support. At age three years, he demonstrated stable ventriculomegaly, craniosynostosis, and little limb growth. By age eight years, he had seizures, bilateral hearing loss, kyphosis, and both joint hypermobility and joint contractures. At nine years of age, the limbs had grown little and radiologic findings were similar to those expected in TD. Extensive acanthosis nigricans was present. He was severely developmentally delayed and had no language. Final height was estimated to be 80-90 cm (32-35 in). The affected individual is alive at age 17 years; status is unchanged [Pauli, personal communication].

Mosaicism. A 47-year-old female mosaic for the common TD type I mutation R248C had asymmetrical limb length, bilateral congenital hip dislocation, focal areas of bone bowing, an "S"-shaped humerus, extensive acanthosis nigricans, redundant skin folds along the length of the limbs, and flexion deformities of the knees and elbows [Hyland et al 2003]. She had delayed developmental milestones as a child. Academic achievements were below those of healthy siblings, but she is able to read and write and is employed as a factory worker. Her only pregnancy ended with the stillbirth at 30 weeks' gestation of a male with a short-limb skeletal dysplasia and pulmonary hypoplasia.

Genotype-Phenotype Correlations

[Wilcox et al 1998, Brodie et al 1999, Camera et al 2001]

TD type I and TD type II do not share common mutations.

No strong genotype-phenotype correlation for *FGFR3* mutations causing TD exists. Variability in the TD phenotype has been described and, with the exception of the proposed mutation-dependent differences in severity of endochondral disturbance in the long bones [Bellus et al 2000], is not mutation specific.

Other clinical disorders do rarely involve *FGFR3* mutations previously identified in individuals with TD. See Allelic Disorders.

Penetrance

The penetrance of mutations in the *FGFR3* gene is 100%.

Anticipation

Anticipation is not observed.

Nomenclature

Thanatophoric dysplasia was originally described as thanatophoric dwarfism, a term no longer in use.

Although considered to be one of the platyspondylic lethal skeletal dysplasias, the term PLSD used with a specific subtype (San Diego, Luton, or Torrance) would be considered a separate clinical entity from TD type I and TD type II. The PLSDs are sometimes referred to as "TD variants" because of their clinical similarity.

Prevalence

Thanatophoric dysplasia occurs in approximately 1/20,000 to 1/50,000 births [Wilcox et al 1998, Sawai et al 1999, Baitner et al 2000, Chen et al 2001].

Differential Diagnosis

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

Disorders to consider in the differential diagnosis [Passos-Bueno et al 1999, De Biasio et al 2000, Lee et al 2002, Neumann et al 2003]:

- **Homozygous achondroplasia** has a similar clinical presentation and should be a part of the differential diagnosis when both parents have achondroplasia.

- **Achondrogenesis including achondrogenesis type IA, type IB, and type II, Schneckenbecken dysplasia.** 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. The vertebral bodies show no or minimal ossification. The ribs are short. The iliac bones are ossified only in their upper part, giving a crescent-shaped, "paraglider-like" appearance on X-ray. The ischium is usually not ossified. The tubular bones are shortened such that no major axis can be recognized; metaphyseal spurring gives the appearance of a "thorn apple." The phalanges are poorly ossified and therefore only rarely identified in x-rays. Death occurs prenatally or shortly after birth. The final diagnosis should be based on molecular genetic testing of the *SLC26A2(DTDST*) gene. The presence of rib fractures and the absence of ossification of vertebral pedicles may suggest ACG1A. ACG2 shows more severe underossification of the vertebral bodies than ACG1B, in addition to quite typical configuration of the iliac bones with concave medial and inferior borders, and non-ossification of the ischial and pubic bones. The gene defect in ACG1A is not known; ACG2 is caused by *COL2A1* mutations.
- **SADDAN (severe achondroplasia with developmental delay and acanthosis nigricans)** (see Achondroplasia). SADDAN is a rare disorder characterized by extremely short stature, severe tibial bowing, profound developmental delay, and acanthosis nigricans. Unlike individuals with TD, those with SADDAN dysplasia survive past infancy. The three unrelated individuals with this phenotype who have been observed to date have had obstructive apnea, but have not required prolonged mechanical ventilation. An *FGFR3* K650M mutation has been identified in all three individuals.
- **Osteogenesis imperfecta type II (OI type II).** Osteogenesis imperfecta (OI) is characterized by fractures with minimal or absent trauma. Clinically, OI was classified into four types, with the type that is most reminiscent of TD being OI type II (the perinatal lethal form). This disorder is characterized by extremely short stature, dark blue sclerae, severe limb deformity, multiple fractures of ribs, minimal calvarial mineralization, platyspondyly, and marked compression of long bones. Biochemical testing (i.e., analysis of the structure and quantity of type I collagen synthesized in vitro by cultured dermal fibroblasts) detects abnormalities in 98% of individuals with OI type II. The majority of individuals with OI type II have mutations in either *COL1A1* or *COL1A2*, the two genes encoding type I collagen. Osteogenesis imperfecta type II is inherited in an autosomal dominant manner.
- **Short rib-polydactyly syndromes.** The short rib-polydactyly syndromes are short-limb dwarfisms with narrow thorax. They are currently classified into four subtypes that may or may not be proven to be distinct clinical entities. Findings distinguishing these disorders from TD include polydactyly and/or syndactyly of the hands or feet. Type I (Saldino-Noonan type) features cardiac defects. Type II (Majewski type) may have cleft lip, cleft palate, ambiguous genitalia, and renal abnormalities. Inheritance is autosomal recessive.
- **Campomelic dysplasia (CD).** Campomelic dysplasia is a prenatal-onset, usually lethal skeletal dysplasia with narrow thorax. Individuals with CD have bowed tibiae, skin dimples, and hypoplastic scapulae. Many individuals with CD have 11 pairs of ribs. The tubular bones are poorly developed and show immature ossification. Up to 75% of chromosomal (i.e., 46,XY) males with CD have phenotypic sex reversal or ambiguous genitalia. Campomelic dysplasia is caused by new, autosomal dominant

mutations in *SOX9* or chromosomal rearrangements upstream or downstream of the *SOX9* gene on chromosome 17.

- **Rhizomelic chondrodysplasia punctata (RCDP).** RCDP is a disorder of peroxisome biogenesis. Type 1 (RCDP1), the classic type, is characterized by proximal shortening of the humerus and to a lesser degree the femur (rhizomelia), punctate calcifications in cartilage with epiphyseal and metaphyseal abnormalities (chondrodysplasia punctata), coronal clefts of the vertebral bodies, and cataracts that are usually present at birth or appear in the first few months of life. Later, severe mental deficiency and postnatal growth retardation are evident. The majority of affected individuals do not survive the first decade of life. The diagnosis of RCDP1 is confirmed by the demonstration of deficiency of red blood cell plasmalogens, increased plasma concentration of phytanic acid, and deficiencies in plasmalogen biosynthesis and phytanic acid oxidation in cultured skin fibroblasts. The disorder is caused by a *PEX7* receptor defect. A common mutation is responsible in the majority. Inheritance is autosomal recessive.
- **Asphyxiating thoracic dystrophy (Jeune thoracic dystrophy)** This is another chondrodysplasia marked by a narrow thorax. Short stature and short limbs are noted in infancy, but survivors may only manifest mild to moderate short stature. Survivors commonly develop renal insufficiency and can develop liver disease. A gene for this disorder has not been identified, but a locus has been mapped to 15q13. Inheritance is autosomal recessive.
- **Platyspondylic lethal skeletal dysplasia — San Diego type, Torrance type, and Luton type.** These short limb dwarfism syndromes are clinically very similar to TD and have often been referred to as "TD variants." The Luton type is considered to be a mild form of the Torrance type [Nishimura et al 2004]. PLSD, Torrance type is characterized by shortened long bones with ragged metaphyses, radial bowing, and wafer-like vertebrae. All subtypes can be distinguished from TD histologically by the consistent presence of dilated loops of endoplasmic reticulum in the chondroctyes. *FGFR3* mutations have been identified in PLSD, San Diego type, but not in Torrance or Luton types [Brodie et al 1999, Neumann et al 2003]. Nishimura et al (2004) identified *COL2A1* mutations in two individuals with PLSD, Torrance type.
- **Dyssegmental dysplasia, Silverman-Handmaker type (DDSH).** DDSH is a lethal disorder characterized by narrow thorax, short neck, short stature, bowed limbs, and irregular ossification of the vertebral bodies. Encephalocele and cleft palate are common. DDSH is caused by mutations in the heparan sulfate proteoglycan (HSPG) gene [Arikawa et al 2001]. Inheritance is autosomal recessive.

Management

Evaluations at Initial Diagnosis to Establish the Extent of Disease

In the newborn:

- Assessment of respiratory status via respiratory rate and skin color
- Assessment of the presence of hydrocephaly or other CNS abnormalities by CT or MRI

Treatment of Manifestations

When thanatophoric dysplasia has been diagnosed prenatally, potential pregnancy complications include prematurity, polyhydramnios, malpresentation, and cephalopelvic

disproportion caused by macrocephaly from hydrocephalus or a flexed and rigid neck. Cephalocentesis and cesarean section may be considered to avoid maternal complications.

Management concerns are limited to the parents' desire for extreme life support measures and provision-of-comfort care for the newborn.

Newborns require respiratory support (with tracheostomy and ventilation) to survive [Baker et al 1997].

Other measures:

- Medication to control seizures as in the general population
- Shunt placement when hydrocephaly is identified
- Suboccipital decompression for relief of craniocervical junction constriction
- Hearing aids when hearing loss is identified

Surveillance

- Asssessment of neurologic status by physical examination
- Orthopedic evaluation upon the development of joint contractures or joint hypermobility [Baker et al 1997, Wilcox et al 1998]
- Audiology assessment
- CT for craniocervical constriction
- EEG for seizure activity

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

Thanatophoric dysplasia (TD) is inherited in an autosomal dominant manner; the majority of probands have a *de novo* mutation.

Risk to Family Members

Parents of a proband

- TD is almost always caused by a *de novo* mutation in *FGFR3*.
- Parents of probands are not affected.

- Somatic mosaicism that included the germline mutation in *FGFR3* (R248C) has been reported in an affected individual [Hyland et al 2003]; this individual's only offspring had a lethal skeletal dysplasia. Current diagnostic techniques will not detect mosaicism for *FGFR3* mutations causing TD.
- An advanced paternal age effect has been reported [Lemyre et al 1999].

Sibs of a proband

- The risk to the sibs of the proband depends upon the genetic status of the proband's parents.
- Because TD generally occurs as the result of a *de novo* mutation, the risk to the sibs of a proband is small.
- Although no instances of germline mosaicism in an individual without signs of TD have been reported in the literature, it remains a theoretical possibility.

Offspring of a proband

- Individuals with TD do not reproduce.
- Somatic and germline mosaicism for a mutation in *FGFR3* (R248C) has been reported in an affected individual [Hyland et al 2003]; this individual's only offspring had a lethal skeletal dysplasia.

Other family members of a proband. Extended family members of the proband are not at increased risk.

Related Genetic Counseling Issues

Family planning. The optimal time for determination of genetic risk and discussion of the 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. Prenatal diagnosis for pregnancies at increased risk as a result of parental mosaicism is possible by analysis of DNA extracted from fetal cells obtained by amniocentesis usually performed at about 15-18 weeks' gestation or chorionic villus sampling (CVS) at about 10-12 weeks' gestation. The disease-causing allele in the family should 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.

Low-risk pregnancies. Routine prenatal ultrasound examination may identify skeletal findings (such as cloverleaf skull, very short extremities, and a small thorax) that raise the possible diagnosis of TD in a fetus not known to be at risk. Once a lethal skeletal dysplasia is identified prenatally, it is often difficult to pinpoint a specific diagnosis. Consideration of molecular genetic testing for *FGFR3* mutations in these situations is appropriate.

Preimplantation genetic diagnosis (PGD) may be available for families in which the disease-causing mutation has been identified in an affected family member in a research or clinical laboratory. 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 Thanatophoric Dysplasia

Gene Symbol	Chromosomal Locus	Protein Name
FGFR3	4p16.3	Fibroblast growth factor receptor 3

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 Thanatophoric Dysplasia

134934	FIBROBLAST GROWTH FACTOR RECEPTOR 3; FGFR3
187600	THANATOPHORIC DYSPLASIA; TD
187601	THANATOPHORIC DYSPLASIA WITH KLEEBLATTSCHAEDEL

Table C. Genomic Databases for Thanatophoric Dysplasia

Gene Symbol	Entrez Gene	HGMD
FGFR3	2261 (MIM No. 134934)	FGFR3

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

Normal allelic variants: *FGFR3* is 19 exons in length with transcription initiation located in exon 2 [Perez-Castro et al 1997]. According to the NCBI SNP database (www.ncbi.nlm.nih.gov/SNP), multiple single nucleotide polymorphisms are reported in the coding and non-coding sequence of *FGFR3*.

Pathologic allelic variants:

- **TD type I.** *FGFR3* mutations responsible for the TD type I phenotype can be divided into two categories:
  - **Missense mutations** [Rousseau, el Ghouzzi et al 1996; Passos-Bueno et al 1999]. Most of these mutations create new, unpaired cysteine residues in the protein. The two common mutations (noted by **) probably account for 60-80% of TD type I:

    R248C**
    Y373C**
    S249C
    G370C

    S371C

    K650M
  - **Stop codon mutations** [Rousseau et al 1995; Rousseau, el Ghouzzi et al 1996]. These mutations cause a read-through of the native stop codon, adding a highly hydrophobic alpha helix-containing domain to the C terminus of

the protein. Stop codon mutations represent 10% or more of TD type I mutations:

X807L
X807G
X807R

X807C

X807W

- **TD type II.** A single *FGFR3* mutation (K650E) has been identified in all cases of TD type II [Rousseau, el Ghouzzi et al 1996; Gorlin 1997; Bellus et al 2000]. The lysine residue at position 650 plays a role in stabilizing the activation loop of the tyrosine kinase domain in an inactive state. Mutations of this residue destabilize the loop, allowing ligand-independent activation of the TK domain, likely without the need for receptor dimerization at the cell surface [Bellus et al 2000]. Other mutations at this position give rise to different phenotypes: K650M has been identified in TDI and K650Q is seen in SADDAN.

Normal gene product: *FGFR3* encodes one of four known fibroblast growth factor receptors (FGFRs) [Tavormina et al 1995]. All FGFRs share considerable amino acid homology [Gorlin 1997] and the genomic organization is nearly identical to that seen in mice [Perez-Castro et al 1997]. FGFRs are proteoglycans that function as tyrosine kinases upon binding of a ligand — usually one of more than 20 fibroblast growth factors (FGFs) plus proteoglycans containing heparan sulfate [McIntosh et al 2000, Torley et al 2002, Lievens & Liboi 2003]. Once a ligand binds, the FGFRs form homo- or heterodimers and undergo phosphorylation of the tyrosine residues in the tyrosine kinase domain. This is followed by a conformational change that frees intracellular binding sites. Intracellular proteins bind and initiate a signal cascade that usually influences protein activation or gene expression [Cohen 2002, Torley et al 2002]. Multiple pathways have been implicated, including ras/MAPK/ERK, P13/Akt, PLC-γ and STAT1 [Cohen 2002, Torley et al 2002]. After activation, the complex is internalized for signal downregulation. This is accomplished via one of two pathways [Lievens et al 2006]: ubiquitination and degradation of the activated FGFR or feedback from the end targets (namely ERK) through the docking protein FRS2α.

FGFR3 consists of an extracellular signal peptide, three immunoglobulin-like domains (IgI, IgII, and IgIII) with an acid box between IgI and IgII, a transmembrane domain, and a split intracellular tyrosine kinase (TK) domain [Gorlin 1997, Hyland et al 2003]. Ligand binding occurs between IgII and IgIII [McIntosh et al 2000]. The normal function of *FGFR3* is to serve as a negative regulator of bone growth during ossification [Legeai-Mallet et al 1998, Cohen 2002]. Mice with knockout mutations of *FGFR3* are overgrown with elongated vertebrae and long femurs and tails. The growth plates of the long bones are expanded [McIntosh et al 2000, Cohen 2002]. Alternative splicing of exons 8 and 9 has been documented [Perez-Castro et al 1997], with such diversity conferring the capacity for differential expression and binding of multiple ligands [Gorlin 1997, Perez-Castro et al 1997, Cohen 2002]. Three reported isoforms of FGFR3 include the native protein, an intermediate intracellular membrane-associated glycoprotein, and a mature glycoprotein [Lievens & Loboi 2003].

FGFR3 is expressed in a spatial- and temporal-specific pattern during embryogenesis [McIntosh et al 2000]. The highest levels of expression occur in cartilage and the central nervous system [Cohen 2002]. FGFR3 is also expressed in the dermis and epidermis [McIntosh et al 2000, Torley et al 2002].

The FGFR3 signaling pathway is activated in several cancers, including bladder and cervical cancer and multiple myeloma. Meyer et al (2004) have identified FGFR3 in complex with Pyk2, a focal adhesion kinase known to regulate apoptosis in multiple myeloma cells and to activate Stat5B. FGFR3 phosphorylates Pyk2 and activates a signaling pathway without recruitment of proteins from the Src family (which are normally recruited by Pyk2 in the absence of FGFR3). Hyperactivated FGFR3 (i.e. mutations similar to those causing TD) causes hyperphosphorylation of Pyk2. FGFR3 may also sequester Pyk2 from Shp2, which normally functions to decrease Pyk2 phosphorylation and downregulate Pyk2 signaling. Both FGFR3 and Pyk2 may work in concert to maximally activate Stat5B [Meyer et al 2004].

Abnormal gene product: Mutations in *FGFR3* are gain-of-function mutations that produce a constitutively active protein capable of initiating intracellular signal pathways in the absence of ligand binding [Rousseau, el Ghouzzi et al 1996; Baitner et al 2000; Cohen 2002]. This activation leads to premature differentiation of proliferative chondrocytes into pre-hypertrophic chondrocytes and ultimately to premature maturation of the bone [Cohen 2002, Legeai-Mallet et al 2004]. The mechanism for other clinical findings in TD type I and TD type II (CNS and dermal abnormalities) is less clear. All reported mutations cause constitutive activation through the creation of new, unpaired cysteine residues that induce ligand-independent dimerization [Rousseau, el Ghouzzi et al 1996; Cohen 2002], activation of the tyrosine kinase loop [Gorlin 1997, Tavormina et al 1999, Cohen 2002], or creation of an elongated protein through destruction of the native stop codon [Rousseau et al 1995; Rousseau, el Ghouzzi et al 1996].

Studies have shown that the level of ligand-independent tyrosine kinase activity conferred by different *FGFR3* mutations is correlated with the severity of disorganization of endochondral ossification and therefore with the skeletal phenotype [Bellus et al 1999, Bellus et al 2000]. The K650E mutation causing thanatophoric dysplasia type II has been shown to cause accumulation of intermediate, activated forms of FGFR3 in the endoplasmic reticulum [Lievens & Liboi 2003]. This immature, cellular FGFR3 is able to signal through an FRS2α-independent pathway (via the JAK/STAT pathway) that is then not subject to FRS2α-mediated downregulation [Lievens et al 2006].

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
Thanatophoric Dysplasia

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

Medline Plus
Dwarfism

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: Jacky.Taylor@cmmc.nhs.uk
www.esdn.org

International Skeletal Dysplasia Registry
Medical Genetics Institute
8700 Beverly Blvd.
West Tower 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.

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Chapter Notes

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