GENEReviews

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X-Linked Spondyloepiphyseal Dysplasia Tarda

[*SED Tarda, X-Linked; SEDT; X-Linked SED*]

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Summary

Disease characteristics. In adults, X-linked spondyloepiphyseal dysplasia tarda (X-linked SEDT) is characterized by disproportionately short stature with short trunk and arm span significantly greater than height. At birth, affected males are normal in length and have normal body proportions. Affected males exhibit retarded linear growth beginning around six to eight years of age. Final adult height is typically 4'10" to 5'6". Progressive joint and back pain with osteoarthritis ensues; hip, knee, and shoulder joints are commonly involved but to a variable degree. Hip replacement is often required as early as age 30 years. Interphalangeal joints are typically spared. Motor and cognitive milestones are normal.

Diagnosis/testing. The diagnosis of X-linked SEDT, which relies upon a combination of clinical and radiographic features, is usually possible in childhood. Adolescent and adult males have disproportionately short stature with a relatively short trunk and barrel-shaped chest. Upper- to lower-body segment ratio is usually about 0.8. Arm span typically exceeds height by 10-20 cm. Characteristic radiographic findings, which typically appear prior to puberty, include multiple epiphyseal abnormalities; platyspondyly (flattened vertebral bodies) with characteristic superior and inferior "humping" seen on lateral view; narrow disc spaces in adulthood; scoliosis; hypoplastic odontoid process; short femoral necks; coxa vara; and evidence of premature osteoarthritis beginning in young adulthood. *TRAPPC2(SEDL)* is the only gene associated with X-linked SEDT. Molecular genetic testing reveals a mutation in *SEDL* in more than 80% of males with a clinical diagnosis of X-linked SEDT.

Management. Surgical intervention for X-linked SEDT may include joint replacement (hip, knee, shoulder) or spine surgery (correction of scoliosis or kyphosis). Standard chronic pain management preceding or following orthopedic surgery is often required. Surveillance includes: annual follow-up for assessment of joint pain and scoliosis; and cervical spine films prior to school age and before any surgical procedure involving general anesthesia to assess for clinically significant odontoid hypoplasia. Activities and occupations that place undue stress on the spine and weight-bearing joints should be avoided. Presymptomatic testing in males at risk may prevent unnecessary diagnostic testing for other causes of short stature and/or osteoarthritis.

Genetic counseling. X-linked SEDT is inherited in an X-linked recessive manner. In reported cases in which molecular genetic testing was performed, all mothers of affected sons, regardless of family history, were carriers of a mutation in *SEDL*. Carrier females have a 50% risk of transmitting the *SEDL* mutation in each pregnancy. Male sibs who inherit the mutation will be affected; female sibs who inherit the mutation will be carriers and will not be affected. None of the sons of an affected male will be affected; all daughters will be carriers of the *SEDL* mutation. Carrier testing of at-risk female relatives and prenatal testing for pregnancies at risk are available on a clinical basis if the *SEDL* disease-causing mutation has been previously identified in the family.

Diagnosis

Clinical Diagnosis

X-linked SEDT is suggested in males with the following findings:

- Disproportionately short stature in adolescence or adulthood and a relatively short trunk and barrel-shaped chest. Upper- to lower-body segment ratio is usually around 0.8. Arm span typically exceeds height by 10-20 cm. Short neck, dorsal kyphosis, and lumbar hyperlordosis may be evident by puberty.
- Early-onset osteoarthritis, especially in the hip joints
- A family history consistent with X-linked recessive inheritance. A positive family history is contributory but not necessary.
- Absence of cleft palate and retinal detachment

Testing

Routine laboratory test results are normal in affected males and carrier females.

Radiographic Findings —Affected males. The diagnosis of X-linked SEDT can be established by the observation of the following radiographic findings, which may not be manifest in early childhood and typically appear prior to puberty:

- Multiple epiphyseal abnormalities
- Platyspondyly (flattened vertebral bodies) with characteristic superior and inferior "humping" seen on lateral view; narrow disc spaces in adulthood
- Scoliosis
- Hypoplastic odontoid process
- Short femoral necks
- Coxa vara
- Evidence of premature osteoarthritis beginning in young adulthood

Radiographs of symptomatic males should be reviewed by a radiologist experienced with bone dysplasias.

Carrier females. Some phenotypically normal females with mild radiologically detectable osteoarthritic changes have been described.

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. *TRAPPC2(SEDL)* is the only gene associated with X-linked spondyloepiphyseal dysplasia tarda.

Molecular genetic testing: Clinical uses

- Confirmatory diagnostic testing
- Prenatal testing

Molecular genetic testing: Clinical method

- **Sequence analysis.** Deletions as well as splice, missense, and nonsense mutations have been identified in roughly 80% of males with clinically diagnosed X-linked SEDT [Gedeon et al 2001, Tiller et al 2001, Savarirayan et al 2003, Shaw et al 2003, Fiedler et al 2004]. Recurrent mutations account for roughly half of all mutations.

Table 1 summarizes molecular genetic testing for this disorder.

Table 1. Molecular Genetic Testing Used in X-Linked SEDT

Test Method	Mutations Detected	Mutation Detection Rate	Test Availability
Sequence analysis	*TRAPPC2(SEDL)* sequence alteration	80%	Clinical Testing

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

Genetically Related (Allelic) Disorders

No other phenotypes are known to be associated with mutations in *TRAPPC2(SEDL)*.

Clinical Description

Natural History

Males. At birth, affected males are normal in size and have normal body proportions. Affected males exhibit retarded linear growth beginning around grade school age (age 6-8 years). Final adult height is typically 137-163 cm [Whyte et al 1999, Beighton 2002, Jones 2006].

Adults with X-linked SEDT have disproportionately short stature with short trunk and arm span significantly greater than height.

Progressive joint and back pain with osteoarthritis ensues; hip, knee, and shoulder joints are commonly involved to variable degrees. Hip replacement is often required as early as age 30 years. Interphalangeal joints are typically spared.

Affected males achieve normal motor and cognitive milestones. Life span and intelligence appear normal.

Females. Carrier females typically show no phenotypic changes, but mild symptoms of osteoarthritis have been reported [Whyte et al 1999].

Genotype-Phenotype Correlations

Data are inadequate to reliably correlate clinical severity to a specific gene mutation. All mutations identified thus far, irrespective of their molecular basis, result in an almost identical phenotype, including the true null mutations.

Nomenclature

Spondyloepiphyseal dysplasia is a general term that describes the radiographic abnormalities seen in several skeletal dysplasias, including pseudoachondroplasia. The "congenita" form is evident at birth, whereas the "tarda" form is usually evident by school age.

SED tarda commonly refers to the X-linked recessive form of the disorder, although rare autosomal dominant and recessive forms have been described.

Prevalence

The prevalence is 1/150,000 - 1/200,000 [Wynne-Davies & Gormley 1985].

Mutations in *TRAPPC2(SEDL*) have been found in several ethnic groups including the Japanese, an observation suggesting that no specific population is at increased risk [Gedeon et al 2001].

Differential Diagnosis

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

X-linked spondyloepiphyseal dysplasia tarda is distinguished from other forms of spondyloepiphyseal dysplasia (SED) by its later onset and X-linked inheritance. These other forms of SED include the following:

- **SED congenita,** inherited in an autosomal dominant manner; evident at birth with disproportionately short stature and diagnostic radiographic changes. Affected individuals often have midline cleft palate and are at risk for hearing loss and high myopia with retinal detachment. SED congenita is caused by mutations in the *COL2A1* gene.
- **SED tarda,** autosomal forms (rare). A dominant form may be caused by mutations in the *COL2A1* gene; a recessive form has been described clinically but has not been molecularly defined.
- **Morquio syndrome** (mucopolysaccharidosis type IV), inherited in an autosomal recessive manner, is caused by deficiency in one of two enzymes: N-acetyl-galactosamine-6-sulfatase or beta-galactosidase. It is characterized by mild dysostosis multiplex, odontoid hypoplasia, short stature, and cloudy corneas.
- **Multiple epiphyseal dysplasia (MED),** inherited in an autosomal dominant manner, presents early in childhood, usually with pain in the hips and/or knees after exercise. Adult height is either in the lower range of normal or mildly shortened. The limbs are relatively short in comparison to the trunk. Pain and joint deformity progress, resulting in early-onset osteoarthritis particularly of the large weight-bearing joints. By definition, the spine is normal, although Schmorl bodies and irregular vertebral end plates may be observed. Mutations in five genes have been shown to cause dominant MED: *COMP*, *COL9A1*, *COL9A2*, *COL9A3*, and *MATN3*.
- **Scheuermann disease,** a term applied to premature osteoarthritis of the spine, regardless of the etiology

- **Spondyloperipheral dysplasia,** inherited in an autosomal dominant manner; also presents with short hands, feet, and ulnae. One family has been reported with a mutation in the *COL2A1* gene.
- **Stickler syndrome,** inherited in an autosomal dominant manner, is variable and can include myopia, cataract, and retinal detachment; hearing loss that is both conductive and sensorineural; midfacial underdevelopment and cleft palate (either alone or as part of the Robin sequence); and mild spondyloepiphyseal dysplasia and/or precocious arthritis. Most affected individuals have a truncation mutation in *COL2A1*; mutations in *COL11A1* and *COL11A2* have also been described. Some individuals do not have an identified mutation.

Management

Evaluations at Initial Diagnosis to Establish the Extent of Disease

As with all skeletal dysplasias, the radiographic survey necessary for an accurate diagnosis also serves to document the extent of disease at the time of presentation. In particular, individuals with X-linked SEDT need to be assessed for the possibility of clinically significant odontoid hypoplasia.

Treatment of Manifestations

- Surgical intervention may include joint replacement (hip, knee, shoulder) or spine surgery (correction of scoliosis or kyphosis).
- Chronic pain management preceding or following orthopedic surgery is standard and often required.

Surveillance

- Affected individuals should be followed annually for the development of joint pain and scoliosis.
- Cervical spinal films should be obtained prior to:
  - School age to assess for clinically significant odontoid hypoplasia;
  - Any surgical procedure involving general anesthesia to assess for clinically significant odontoid hypoplasia.

Agents/Circumstances to Avoid

Activities and occupations that place undue stress on the spine and weight-bearing joints should be avoided.

Testing of Relatives at Risk

Presymptomatic testing in males at risk, when available, may prevent unnecessary diagnostic testing for other causes of short stature and/or osteoarthritis.

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

X-linked spondyloepiphyseal dysplasia tarda is inherited in an X-linked recessive manner.

Risk to Family Members

Parents of a proband

- The father of a proband is unaffected and is not a carrier.
- A woman who has an affected son and one other affected male relative is an obligate carrier.
- In reported cases in which molecular genetic testing was available in a research laboratory, all mothers of affected sons were carriers of a mutation in *TRAPPC2 (SEDL*) regardless of family history [Gedeon et al 2001]. Mothers of affected sons who are not carriers have not yet been reported.

Sibs of a proband

- The risk to sibs depends upon the carrier status of the mother.
- If the mother is a carrier, the chance of transmitting the disease-causing mutation in each pregnancy is 50%. Male sibs who inherit the mutation will be affected; female sibs who inherit the mutation will be carriers and will usually not be affected.
- If the mother is not a carrier, the risk to sibs is low but greater than that of the general population; although research studies have not identified germline mosaicism in mothers who have one affected son and an otherwise negative family history, the risk of germline mosaicism in mothers is not known.

Offspring of a proband. None of the sons of an affected male will be affected. All daughters will be carriers of the *TRAPPC2(SEDL*) mutation.

Other family members of a proband. The proband's maternal aunts and their offspring may be at risk of being carriers or of being affected (depending upon their gender, family relationship, and the carrier status of the proband's mother).

Carrier Detection

Carrier testing of at-risk female relatives using molecular genetic techniques is available on a clinical basis if the mutation has been identified in an affected family member.

Related Genetic Counseling Issues

Family planning. The optimal time for determination of genetic risk, clarification of carrier status, and discussion of the availability of prenatal 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

Prenatal testing is possible for pregnancies of women who are carriers. The usual procedure is to determine sex by chromosome analysis on fetal cells obtained by chorionic villus sampling (CVS) at about 10-12 weeks' gestation or by amniocentesis usually performed at about 15-18 weeks' gestation. If the karyotype is 46,XY and if the disease-causing mutation has been identified in a family member, DNA from fetal cells can be analyzed for the known disease-causing mutation.

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

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 Spondyloepiphyseal Dysplasia Tarda, X-Linked

Gene Symbol	Chromosomal Locus	Protein Name
TRAPPC2	Xp22.2-p22.1	Trafficking protein particle complex protein 2

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 Spondyloepiphyseal Dysplasia Tarda, X-Linked

300202	SEDLIN; SEDL
313400	SPONDYLOEPIPHYSEAL DYSPLASIA TARDA, X-LINKED; SEDT

Table C. Genomic Databases for Spondyloepiphyseal Dysplasia Tarda, X-Linked

Gene Symbol	Entrez Gene	HGMD
TRAPPC2	6399 (MIM No. 300202)	TRAPPC2

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

Normal allelic variants: The *TRAPPC2(SEDL)* gene is composed of six exons, with the start site for translation located in exon 3. No normal allelic variants have been reported.

Pathologic allelic variants: Mutations in the *TRAPPC2(SEDL)* gene causing X-linked SEDT include splice site mutations, nonsense mutations, deletions, and rare missense mutations. Table 2 summarizes recurrent mutations. Mutations include: gross deletions of exons 3 and 6; dinucleotide deletions in exons 3, 4, and 5; tetranucleotide deletion in exon 6; pentanucleotide deletion in exon 5; splice donor site mutations 3' to exons 3 and 4; splice acceptor site mutations 5' to exons 2, 3, 4, 5, and 6; nonsense mutations in exons 3, 4, 5, and 6; missense mutations substituting W for D47, L for S73, S for F83, and D for V130.

Table 2. Recurrent Mutations in *TRAPPC2(SEDL*)

% of All Affected Individuals	Mutation
~16%	IVS3 +5G>A
~5%	157-158 del AT
~4%	191-192 del TG
~13%	271-275 del CAAGA
~11%	Other recurrent mutations

As reviewed by Gedeon et al (2001), Savarirayan et al (2003), Shaw et al (2003), and Fiedler et al (2004)

Normal gene product: The gene encodes a 140-amino acid protein of unknown function, which appears to be ubiquitously expressed [Gedeon et al 1999, Gecz et al 2000]. Functional motifs within the protein sequence have yet to be identified. Based on function of the yeast homolog, sedlin likely is involved with intracellular protein trafficking, as part of the TRAPP (transport protein particle) complex [Jang et al 2002].

Abnormal gene product: Almost all mutations identified in the *TRAPPC2(SEDL*) gene are predicted to generate a null allele or truncated protein product.

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.

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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

Revision History

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