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X-Linked Spondyloepiphyseal Dysplasia Tarda

Synonym: *TRAPPC2*-Related X-Linked Spondyloepiphyseal Dysplasia Tarda

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Summary

Clinical description

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 linear growth deficiency beginning around age six to eight years. Final adult height is typically 137-163 cm. 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 40 years. Interphalangeal joints are typically spared. Motor and cognitive milestones are normal.

Diagnosis/testing

The clinical diagnosis of X-linked SEDT can be established in a male proband with characteristic radiographic findings (which typically appear prior to puberty) including: multiple epiphyseal abnormalities, platyspondyly with characteristic superior and inferior "humping" seen on lateral view, scoliosis, hypoplastic odontoid process, short femoral necks, and coxa vara; evidence of premature osteoarthritis appears in young adulthood. The molecular diagnosis of X-linked SEDT can be established in a male proband with suggestive findings and a hemizygous pathogenic variant in *TRAPPC2* identified by molecular genetic testing. The molecular diagnosis of X-linked SEDT can be established in a female proband with osteoarthritis and a heterozygous pathogenic variant in *TRAPPC2* identified by molecular genetic testing.

Management

Treatment of manifestations: Treatment for scoliosis and kyphoscoliosis per orthopedic surgeon; surgical intervention may include spine surgery (correction of scoliosis or kyphosis). Pain management as needed for osteoarthritis; joint replacement (hip, knee, shoulder) as needed.

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Surveillance: Cervical spine films prior to school age and before any surgical procedure involving general anesthesia to assess for clinically significant odontoid hypoplasia. Annual follow up for assessment scoliosis and joint pain.

Agents/circumstances to avoid: Extreme neck flexion and extension in individuals with odontoid hypoplasia. Activities and occupations that place undue stress on the spine and weight-bearing joints.

Evaluation of relatives at risk: Presymptomatic testing in males at risk may obviate unnecessary diagnostic testing for other causes of short stature and/or osteoarthritis.

Genetic counseling

By definition, X-linked SEDT is inherited in an X-linked manner. When performed, molecular genetic testing of all mothers of affected sons determined that regardless of family history all were carriers of a pathogenic variant in *TRAPPC2*. Carrier females are at a 50% risk of transmitting the *TRAPPC2* pathogenic variant in each pregnancy: males who inherit the pathogenic variant will be affected; females who inherit the pathogenic variant 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 *TRAPPC2* pathogenic variant. Carrier testing of at-risk female relatives and prenatal testing for pregnancies at increased risk are possible if the pathogenic variant in the family has been identified.

Diagnosis

No consensus clinical diagnostic criteria for X-linked spondyloepiphyseal dysplasia tarda have been published.

Suggestive Findings

X-linked spondyloepiphyseal dysplasia tarda (X-linked SEDT) **should be suspected** in males with the following findings:

- Disproportionate short stature in adolescence or adulthood and 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. 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 (frequently present in SED congenita; see Differential Diagnosis)

Establishing the Diagnosis

The clinical diagnosis of X-linked SEDT **can be established** in a male proband with characteristic radiographic findings, or the molecular diagnosis can be established in a male proband with suggestive findings and a hemizygous pathogenic (or likely pathogenic) variant in *TRAPPC2* identified by molecular genetic testing (see Table 1) if radiographic findings are inconclusive.

Note: (1) Per ACMG/AMP variant interpretation guidelines, the terms "pathogenic variants" and "likely pathogenic variants" are synonymous in a clinical setting, meaning that both are considered diagnostic and both can be used for clinical decision making [Richards et al 2015]. Reference to "pathogenic variants" in this section is understood to include any likely pathogenic variants. (2) Identification of a hemizygous *TRAPPC2* variant of uncertain significance does not establish or rule out the diagnosis.

Radiographic Findings

The following radiographic findings may not be manifest in an affected male in early childhood and typically appear prior to puberty (Figure 1):

- Multiple epiphyseal abnormalities
- Platyspondyly (flattened vertebral bodies) with characteristic superior and inferior "humping" seen on lateral view; narrow disc spaces in adulthood
- Scoliosis / kyphoscoliosis
- 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.

Molecular Genetic Testing

Testing approaches can include **single-gene testing** and a **multigene panel**:

- **Single-gene testing.** Sequence analysis of *TRAPPC2* is performed first to detect small intragenic deletions/insertions and missense, nonsense, and splice site variants. Note: Depending on the sequencing method used, single-exon, multiexon, or whole-gene deletions/duplications may not be detected. If no variant is detected by the sequencing method used, the next step is to perform gene-targeted deletion/duplication analysis to detect exon and whole-gene deletions or duplications.
- **A multigene panel** that includes *TRAPPC2* and other genes of interest (see Differential Diagnosis) may also be considered. This method may be especially useful if expert radiographic interpretation is not available. Note: (1) The genes included in the panel and the diagnostic sensitivity of the testing used for each gene vary by laboratory and are likely to change over time. (2) Some multigene panels may include genes not associated with the condition discussed in this *GeneReview*; thus, clinicians need to determine which multigene panel is most likely to identify the genetic cause of the condition while limiting identification of variants of uncertain significance and pathogenic variants in genes that do not explain the underlying phenotype. (3) In some laboratories, panel options may include a custom laboratory-designed panel and/or custom phenotype-focused exome analysis that includes genes specified by the clinician. (4) Methods used in a panel may include sequence analysis, deletion/duplication analysis, and/or other non-sequencing-based tests.

  For an introduction to multigene panels click here. More detailed information for clinicians ordering genetic tests can be found here.

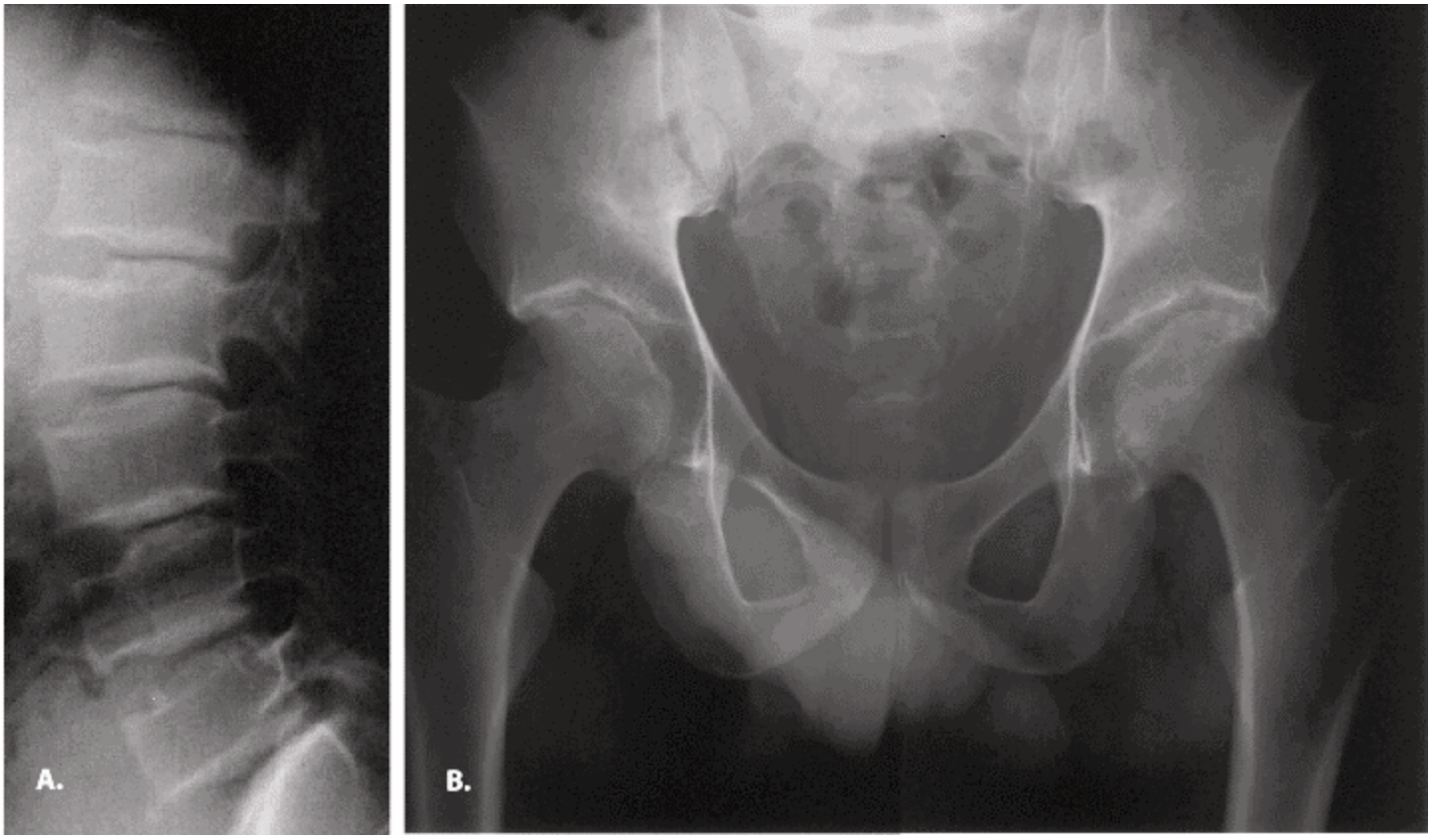

Figure 1. Radiographs of a male age 31 years with SEDT

A. Platyspondyly with superior and inferior humping of vertebral bodies

B. Severe degenerative changes in both hip joints.

Table 1. Molecular Genetic Testing Used in X-linked Spondyloepiphyseal Dysplasia Tarda

Gene [1]	Method	Proportion of Probands with a Pathogenic Variant [2] Detectable by Method
TRAPPC2	Sequence analysis [3]	84% [4]
	Gene-targeted deletion/duplication analysis [5]	16% [6]
Unknown [7]	NA	Rare

1. See Table A. Genes and Databases for chromosome locus and protein.
2. See Molecular Genetics for information on variants detected in this gene.
3. Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or pathogenic. Variants may include small intragenic deletions/insertions and missense, nonsense, and splice site variants; typically, exon or whole-gene deletions/duplications are not detected. For issues to consider in interpretation of sequence analysis results, click here.
4. Data derived from the subscription-based professional view of Human Gene Mutation Database [Stenson et al 2020]
5. Gene-targeted deletion/duplication analysis detects intragenic deletions or duplications. Methods used may include a range of techniques such as quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification (MLPA), and a gene-targeted microarray designed to detect single-exon deletions or duplications.
6. Males initially suspected on sequence analysis of having a deletion in whom the deletion is subsequently confirmed by deletion/duplication analysis
7. It is unknown whether negative molecular analysis reflects locus heterogeneity or clinical misdiagnosis.

Clinical Characteristics

Clinical Description

Males. At birth, affected males are normal in length and have normal body proportions. Affected males exhibit linear growth deficiency beginning around grade school (age 6-8 years). Adults with X-linked spondyloepiphyseal dysplasia tarda (X-linked SEDT) have disproportionately short stature with short trunk and arm span significantly greater than height. Final adult height is typically 137-163 cm [Whyte et al 1999, Jones et al 2013, Rimoin et al 2013].

Scoliosis/kyphoscoliosis and **odontoid hypoplasia** are known radiographic features. Data on the incidence, onset, and severity of these features have not been published.

Osteoarthritis. 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 40 years. Interphalangeal joints are typically spared.

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

Heterozygous 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 *TRAPPC2* pathogenic variant. All pathogenic variants identified thus far, irrespective of their molecular basis, result in an almost identical phenotype, including the true null variants.

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 autosomal recessive "tarda" forms have been described.

In the 2023 revision of the Nosology of Genetic Skeletal Disorders [Unger et al 2023], X-linked spondyloepiphyseal dysplasia tarda is referred to as *TRAPPC2*-related X-linked spondyloepiphyseal dysplasia tarda and included in the spondyloepi(meta)physeal dysplasias group.

Prevalence

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

Pathogenic variants in *TRAPPC2* have been found in several populations including European [Gedeon et al 2001], Japanese [Matsui et al 2001], and Chinese [Shu et al 2002], an observation suggesting that no specific population is at increased risk.

Genetically Related (Allelic) Disorders

No phenotypes other than those discussed in this *GeneReview* are known to be associated with germline pathogenic variants in *TRAPPC2*.

Differential Diagnosis

X-linked spondyloepiphyseal dysplasia tarda (X-linked SEDT) is distinguished from other forms of spondyloepiphyseal dysplasia (SED) by its later onset and X-linked inheritance (see Table 2).

Table 2. Forms of Spondyloepiphyseal Dysplasia of Interest in the Differential Diagnosis of X-Linked Spondyloepiphyseal Dysplasia Tarda

Gene(s)	Disorder	MOI	Clinical Features of Differential Diagnosis Disorder	Distinguishing Features/ Comment
CCN6 (*WISP3*)	Progressive pseudorheumatoid dysplasia (PED)	AR	Predominant involvement of articular cartilage w/ progressive joint stiffness & enlargement & w/o inflammation. Onset (age ~3-6 yrs) begins w/ involvement of interphalangeal joints; later involvement of large joints & spine causes significant joint contractures, gait disturbance, & scoliosis &/or kyphosis, → abnormal posture & significant morbidity. Short stature (<3rd centile) becomes evident in adolescence.	Unlike X-linked SEDT, joint swelling & hand involvement are common features of PED.
COL2A1	SED congenita (SEDC) (See Type II Collagen Disorders Overview.)	AD [1]	Usually evident at birth w/disproportionate short stature, short extremities, broad chest, characteristic facies, myopia, & ↑ incidence of cleft palate & hearing loss. Delayed/poor ossification of vertebrae & pubic bones; long bones are short w/hypoplastic epiphyses. ↑ risk for tracheolaryngomalacia & related respiratory complications & retinal detachment. ↑ risk for cervical instability.	SED congenita is most common form of SED.
	Spondyloperipheral dysplasia (See Type II Collagen Disorders Overview.)	AD	Mild-to-moderate disproportionate short stature & short extremities, brachydactyly type E, short ulnae, variable clubfeet, cleft palate, myopia, & hearing loss; ovoid vertebra, delayed ossification of pubic bones, & flattened & irregular epiphyses in long bones. Premature hip arthrosis causes joint pain.	
COL2A1 *COL9A1* *COL9A2* *COL9A3* *COL11A1* *COL11A2*	Stickler syndrome	AD AR [2]	Connective tissue disorder; can incl high myopia, hearing loss (both conductive & sensorineural); midfacial underdevelopment & cleft palate (either alone or as part of Pierre Robin sequence); & mild SED &/or precocious arthritis.	
COL9A1 *COL9A2* *COL9A3* *COMP* *MATN3*	Multiple epiphyseal dysplasia, autosomal dominant (MED)	AD	Presents early in childhood, usually w/pain in hips &/or knees after exercise; affected children complain of fatigue w/long-distance walking; waddling gait may be present. Adult height in lower range of normal or mildly shortened; limbs relatively short compared to trunk; progressive pain & joint deformity → early-onset osteoarthritis esp of large weight-bearing joints.	By definition, spine in MED is normal, although Schmorl bodies & irregular vertebral end plates may be observed.

Table 2. continued from previous page.

Gene(s)	Disorder	MOI	Clinical Features of Differential Diagnosis Disorder	Distinguishing Features/ Comment
GALNS *GLB1*	Morquio syndrome (MPS IVA & MPS IVB) (See *GLB1* Disorders.)	AR	Dysostosis multiplex, odontoid hypoplasia, short stature, hepatomegaly & cloudy corneas	

AD = autosomal dominant; AR = autosomal recessive; MOI = mode of inheritance; MPS = mucopolysaccharidosis; SED = spondyloepiphyseal dysplasia; SEDT = spondyloepiphyseal dysplasia tarda
1. Rare instances of autosomal recessive inheritance in SEDC have been reported (see Type II Collagen Disorders Overview).
2. Stickler syndrome caused by pathogenic variants in *COL2A1*, *COL11A1*, or *COL11A2* is inherited in an autosomal dominant manner; Stickler syndrome caused by pathogenic variants in *COL9A1*, *COL9A2*, or *COL9A3* is inherited in an autosomal recessive manner.

Other

- **SED tarda, autosomal forms** (rare). A dominant form (OMIM 184100) may be caused by pathogenic variants in *COL2A1*; a recessive form has been described clinically but not molecularly defined.
- **Scheuermann disease** (OMIM 181440) is a term applied to premature osteoarthritis of the spine regardless of etiology.

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with X-linked spondyloepiphyseal dysplasia tarda (X-linked SEDT), the evaluations summarized in Table 3 (if not performed as part of the evaluation that led to the diagnosis) are recommended:

Table 3. Recommended Evaluations Following Initial Diagnosis in Individuals with X-linked Spondyloepiphyseal Dysplasia Tarda

System/Concern	Evaluation	Comment
Skeleton	Complete radiographic survey to incl scoliosis series if clinically indicated	To assess extent of skeletal manifestations
Cervical spine	• Flexion-extension radiographs of cervical spine • Flexion-extension MRI if instability & compression seen on radiographs or interpretation on radiographs is limited (e.g., in young persons w/delayed ossification in upper cervical spine)	To assess for clinically significant odontoid hypoplasia
Genetic counseling	By genetics professionals [1]	To inform affected persons & their families re nature, MOI, & implications of SEDT to facilitate medical & personal decision making

MOI = mode of inheritance
1. Medical geneticist, certified genetic counselor, certified advanced genetic nurse

Treatment of Manifestations

Table 4. Treatment of Manifestations in Individuals with X-linked Spondyloepiphyseal Dysplasia Tarda

Manifestation/ Concern	Treatment	Considerations/ Other
Odontoid hypoplasia	Precautions during intubation/surgery to avoid hyperextension	Obtain cervical spinal films prior to any surgical procedure involving general anesthesia to assess for clinically significant odontoid hypoplasia.
Scoliosis/ Kyphoscoliosis	• Treatment per orthopedic surgeon • Spine surgery (correction of scoliosis or kyphosis) may be indicated.	
Osteoarthritis	• Chronic pain management • Surgical intervention may incl joint replacement (hip, knee, shoulder).	

Surveillance

Table 5. Recommended Surveillance for Individuals with X-linked Spondyloepiphyseal Dysplasia Tarda

System/Concern	Evaluation	Frequency
Odontoid hypoplasia	Flexion-extension radiographs of cervical spine	Obtain prior to school age to assess for clinically significant odontoid hypoplasia.
Scoliosis/ Kyphoscoliosis	Clinical eval w/spine radiographs if clinically indicated	Annually
Osteoarthritis	Clinical eval for osteoarthritis	Annually

Agents/Circumstances to Avoid

The following should be avoided:

- In individuals with odontoid hypoplasia, extreme neck flexion and extension
- Activities and occupations that place undue stress on the spine and weight-bearing joints

Evaluation of Relatives at Risk

If the *TRAPPC2* pathogenic variant in the family is known, presymptomatic genetic testing of at-risk males allows early diagnosis and may obviate unnecessary diagnostic testing for other causes of short stature and/or osteoarthritis.

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

Therapies Under Investigation

Search ClinicalTrials.gov in the US and EU Clinical Trials Register in Europe for access to information on clinical studies for a wide range of diseases and conditions. Note: There may not be clinical trials for this disorder.

Genetic Counseling

Genetic counseling is the process of providing individuals and families with information on the nature, mode(s) of inheritance, and implications of genetic disorders to help them make informed medical and personal decisions. The following section deals with genetic risk assessment and the use of family history and genetic testing to clarify genetic

status for family members; it is not meant to address all personal, cultural, or ethical issues that may arise or to substitute for consultation with a genetics professional. —ED.

Mode of Inheritance

By definition, X-linked spondyloepiphyseal dysplasia tarda (X-linked SEDT) is inherited in an X-linked manner.

Risk to Family Members

Parents of a proband

- The father of a male proband with X-linked SEDT will not have the disorder nor will he be hemizygous for the causative pathogenic variant; therefore, he does not require further evaluation/testing.
- In a family with more than one affected individual, the mother of an affected male is an obligate carrier. Note: If a woman has more than one affected child and no other affected relatives and if the familial pathogenic variant cannot be detected in her DNA, she most likely has germline mosaicism. Although no instances of maternal germline mosaicism have been reported, it remains a possibility.
- If a male is the only affected family member (i.e., a simplex case), the mother may be a carrier or the affected male may have a *de novo* pathogenic variant, in which case the mother is not a carrier.

  In reported individuals for whom molecular genetic testing was available in a research laboratory, all mothers of affected sons were carriers of a *TRAPPC2* pathogenic variant regardless of family history [Gedeon et al 2001]. Mothers of affected sons who are not carriers have not been reported to date.

Sibs of a proband. The risk to sibs of a male proband with X-linked SEDT depends on the genetic status of the mother:

- If the mother of the proband has a *TRAPPC2* pathogenic variant, the chance of transmitting the pathogenic variant in each pregnancy is 50%.
  - Males who inherit the pathogenic variant will be affected;
  - Females who inherit the pathogenic variant will be carriers and will usually not be affected (see Clinical Description, **Heterozygous females**).
- If the proband represents a simplex case and if the *TRAPPC2* pathogenic variant cannot be detected in the leukocyte DNA of the mother, the risk to sibs is presumed to be low but greater than that of the general population because of the theoretic possibility of maternal germline mosaicism.

Offspring of a male proband. Affected males transmit the *TRAPPC2* pathogenic variant to all of their daughters and none of their sons.

Other family members. The maternal aunts and maternal female cousins of a male proband may be at risk of being carriers and the aunts' offspring, depending on their sex, may be at risk of being carriers or of being affected.

Carrier Detection

Identification of female heterozygotes requires either prior identification of the *TRAPPC2* pathogenic variant in the family or, if an affected male is not available for testing, molecular genetic testing first by sequence analysis, and if no pathogenic variant is identified, by gene-targeted deletion/duplication analysis.

Note: Females who are heterozygotes (carriers) for X-linked SEDT may develop minimal clinical findings related to the disorder [Whyte et al 1999].

Related Genetic Counseling Issues

See Management, Evaluation of Relatives at Risk for information on evaluating at-risk relatives for the purpose of early diagnosis and treatment.

Family planning

- The optimal time for determination of genetic risk, clarification of genetic status, and discussion of the availability of prenatal/preimplantation genetic testing is before pregnancy.
- It is appropriate to offer genetic counseling (including discussion of potential risks to offspring and reproductive options) to young adults who are affected, are carriers, or are at risk of being carriers.

DNA banking. Because it is likely that testing methodology and our understanding of genes, pathogenic mechanisms, and diseases will improve in the future, consideration should be given to banking DNA from probands in whom a molecular diagnosis has not been confirmed (i.e., the causative pathogenic mechanism is unknown). For more information, see Huang et al [2022].

Prenatal Testing and Preimplantation Genetic Testing

Once the X-linked SEDT-causing pathogenic variant has been identified in an affected family member, prenatal and preimplantation genetic testing are possible.

Differences in perspective may exist among medical professionals and within families regarding the use of prenatal testing. While most centers would consider use of prenatal testing to be a personal decision, discussion of these issues may be helpful.

Resources

GeneReviews staff has selected the following disease-specific and/or umbrella support organizations and/or registries for the benefit of individuals with this disorder and their families. GeneReviews is not responsible for the information provided by other organizations. For information on selection criteria, click here.

- **Human Growth Foundation**
  www.hgfound.org
- **Little People of America**
  Phone: 888-LPA-2001; 714-368-3689
  Fax: 707-721-1896
  Email: info@lpaonline.org
  lpaonline.org
- **MAGIC Foundation**
  Phone: 800-362-4423
  Email: contactus@magicfoundation.org
  www.magicfoundation.org
- **UCLA International Skeletal Dysplasia Registry (ISDR)**
  Phone: 310-825-8998
  International Skeletal Dysplasia Registry

Molecular Genetics

Information in the Molecular Genetics and OMIM tables may differ from that elsewhere in the GeneReview: tables may contain more recent information. —ED.

Table A. X-Linked Spondyloepiphyseal Dysplasia Tarda: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
TRAPPC2	Xp22.2	Trafficking protein particle complex subunit 2	TRAPPC2 database	TRAPPC2	TRAPPC2

Data are compiled from the following standard references: gene from HGNC; chromosome locus from OMIM; protein from UniProt. For a description of databases (Locus Specific, HGMD, ClinVar) to which links are provided, click here.

Table B. OMIM Entries for X-Linked Spondyloepiphyseal Dysplasia Tarda (View All in OMIM)

300202	TRACKING PROTEIN PARTICLE COMPLEX, SUBUNIT 2; TRAPPC2
313400	SPONDYLOEPIPHYSEAL DYSPLASIA TARDA, X-LINKED; SEDT

Molecular Pathogenesis

TRAPPC2 (previously *SEDL*) encodes the 140-amino acid protein "sedlin," which appears to be ubiquitously expressed [Gedeon et al 1999, Gécz et al 2000]. Sedlin is an essential component of the TRAPP (*tra*fficking *p*rotein *p*article) complex that is required for the export of procollagen trimers (e.g., type II collagen) from the endoplasmic reticulum to the Golgi, which ultimately permits incorporation of these proteins into the extracellular matrix [Venditti et al 2012].

Mechanism of disease causation. Loss of function

***TRAPPC2*-specific laboratory technical considerations.** *TRAPPC2* contains six exons with the translation start site in exon 3. The exon and multiexon deletions (see also HGMD in Table A) would not be detected in heterozygous females by sequence analysis (see Table 1). Sequence analysis should include flanking intronic sequences, which is customary to evaluate splice junctions. This is particularly important with *TRAPPC2*, as there is an expressed pseudogene which is devoid of introns [Gécz et al 2000].

Notable *TRAPPC2* variants. X-linked SEDT-causing pathogenic variants in *TRAPPC2* include splice site, nonsense, and missense variants and deletions.

Table 6. Notable Recurrent *TRAPPC2* Pathogenic Variants

Reference Sequences	DNA Nucleotide Change	Predicted Protein Change	% of All Affected Individuals w/Variant	Comment [Reference]
NM_001011658.3	c.93+5G>A	--	~18%	Reviewed by Gedeon et al [2001], Tiller et al [2001], Shaw et al [2003], & Fiedler et al [2004]
NM_001011658.3 NP_001011658.1	c.157_158delAT	p.Met53ValfsTer35	~5%	
	c.191_192delTG	p.Val64GlyfsTer24	~4%	
	c.271_275delCAAGA	p.Gln91ArgfsTer9	~13%	

Variants listed in the table have been provided by the author. *GeneReviews* staff have not independently verified the classification of variants.
GeneReviews follows the standard naming conventions of the Human Genome Variation Society (varnomen.hgvs.org). See Quick Reference for an explanation of nomenclature.

Chapter Notes

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Revision History

- 6 April 2023 (sw) Revision: "*TRAPPC2*-Related X-Linked Spondyloepiphyseal Dysplasia Tarda" added as a synonym; Nosology of Genetic Skeletal Disorders: 2023 Revision [Unger et al 2023] added to Nomenclature
- 5 November 2020 (sw) Comprehensive update posted live
- 11 June 2015 (me) Comprehensive update posted live
- 15 February 2011 (me) Comprehensive update posted live
- 5 April 2006 (me) Comprehensive update posted live
- 10 February 2004 (me) Comprehensive update posted live
- 30 December 2003 (cd) Revision: change in test availability
- 1 November 2001 (me) Review posted live
- 16 May 2001 (gt) Original submission

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