# X-Linked Spondyloepiphyseal Dysplasia Tarda (SEDT) — Comprehensive Disease Report

**MONDO:** MONDO:0010737 · **OMIM (phenotype):** 313400 · **OMIM (gene):** 300202 · **Gene:** TRAPPC2 (SEDL), Xp22.2 · **Category:** Mendelian, X-linked recessive

> **Evidence base:** This report is compiled from **aggregated disease-level resources** (OMIM, Orphanet) and **primary human genetic/clinical literature** (case series, pedigrees, molecular studies) plus **in vitro / cell-biology mechanistic studies**. There are no population EHR datasets or omics data files for this ultra-rare disorder; findings derive from individual pedigrees and mechanistic experiments. Evidence type is indicated per claim: *(human clinical)*, *(in vitro)*, *(human tissue)*, *(yeast/comparative)*.

## Summary

X-linked spondyloepiphyseal dysplasia tarda (SEDT) is a rare (~**2 per 1,000,000**), non-lethal, **X-linked recessive** osteochondrodysplasia caused by **loss-of-function mutations in TRAPPC2 (SEDL)** at Xp22.2, which encodes **sedlin**, a small 140-amino-acid protein. Sedlin is the **Trs20 adaptor subunit of the conserved TRAPP tethering complex** and a regulator of the secretory pathway. The central mechanistic insight is that SEDT is a **disease of procollagen export from the endoplasmic reticulum in growth-plate chondrocytes**: sedlin binds and promotes efficient cycling of the **Sar1 GTPase**, allowing nascent COPII carriers to enlarge into "megacarriers" capable of exporting bulky procollagen prefibrils. Loss of sedlin blocks this export, producing a secretory bottleneck (dilated rough ER) and defective chondrogenesis.

Clinically, affected hemizygous males are normal at birth and present in **late childhood/adolescence (~5–14 y)** with **disproportionate short-trunk short stature, barrel chest, pathognomonic hump-shaped platyspondyly**, and **premature secondary osteoarthritis** of the spine and hips. Because the defect is confined to the skeleton, **metabolic laboratory**

**values are normal** (a key diagnostic discriminator from mucopolysaccharidoses) and **life expectancy is normal**. Female carriers are usually asymptomatic. Diagnosis rests on characteristic radiographs plus an X-linked pedigree, confirmed by **TRAPPC2 sequencing**.

There is **no disease-modifying therapy**. Management is symptomatic and orthopedic — NSAIDs, physiotherapy, joint protection, and **total hip arthroplasty** for end-stage hip osteoarthritis (which yields large functional gains). Prevention is reproductive/genetic: counseling, carrier testing, prenatal diagnosis, and PGT-M once the familial variant is known. This report presents eight confirmed findings, a stepwise causal model, the supporting evidence base, and the full 15-section disease-knowledge-base template.

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## Key Findings

### Finding 1 — SEDT is caused by loss-of-function mutations in TRAPPC2/SEDL

SEDT is an X-linked recessive osteochondrodysplasia caused by mutations in **TRAPPC2 (SEDL)** that almost invariably eliminate functional **sedlin (loss of function)**. Independent pedigrees across Japanese, Chinese, European, and Australian families show cosegregation under X-linked recessive inheritance, spanning nonsense (c.61G>T/p.E21 *PMID: 24841781; S110X PMID: 12446987), frameshift (2-bp exon-5 deletion PMID: 11760838), splice-site (IVS2-2A>C → exon 3 skipping PMID: 16120574; recurrent c.93+5G>A PMID: 11326333; c.93+5G>C PMID: 23876379), and intragenic deletions removing the start codon (PMID: 11252002). The Japanese family study established the mechanism directly:* "The nature of the mutation predicted that the SEDL protein (Sedlin) was not produced in the proband, indicating that loss of Sedlin caused SEDT" *(PMID: 11252002). A splice study confirmed the same logic — because the start site is on exon 3* — "the splicing defect causes affected individuals failure to produce sedlin, which elucidates the causative role of SEDL gene" *(PMID: 16120574). Inheritance and clinical hallmark were summarized in a five-generation Chinese pedigree:* "Spondyloepiphyseal dysplasia tarda (SEDT) is an X-linked recessive osteochondrodysplasia characterized by disproportionately short stature and degenerative joint disease" *(PMID: 24841781). Ontology:** HGNC:23068 (TRAPPC2); MONDO:0010737.

## Finding 2 — Sedlin promotes ER export of procollagen by regulating the Sar1 GTPase cycle

The landmark study of Venditti et al. (2012) defined sedlin's molecular function and linked it to tissue pathology: the cargo receptor **TANGO1 recruits sedlin**, which is **required for ER export of procollagen (PC)**. *"Sedlin bound and promoted efficient cycling of Sar1"* — the GTPase that controls COPII budding (PMID: 23019651). By promoting Sar1 turnover, sedlin lets COPII carriers grow into **megacarriers** large enough for bulky procollagen prefibrils. Critically, *"this joint action of TANGO1 and Sedlin sustained the ER export of PC, and its derangement may explain the defective chondrogenesis underlying SEDT"* (PMID: 23019651). Biochemical studies show disease missense mutants **S73L, F83S, and V130D misfold and are proteasomally degraded** (rescued by MG132), while D47Y folds normally but has altered Bet3 binding — two routes to loss of function (PMID: 19650763). The same study localized sedlin to *"proliferating and hypertrophic chondrocytes"* (PMID: 19650763), the growth-plate cells where the defect manifests. **Ontology:** GO:0006888 (ER-to-Golgi transport); GO:0090110 (COPII cargo loading); CL:0000138 (chondrocyte).

## Finding 3 — Clinical hallmark: short-trunk short stature, hump-shaped platyspondyly, premature osteoarthritis

Affected hemizygous males present in **late childhood/adolescence** with disproportionately short trunk/stature and a **barrel-chest deformity**: *"presents with disproportionate short stature and 'barrel-chest' deformity in affected (hemizygous) adolescent boys"* (PMID: 11760838). The radiographic hallmark is platyspondyly with a **hump-shaped (posterior/central) vertebral mound**, end-plate sclerosis, disc-space narrowing, short thick femoral necks, narrow hips, and pelvic osteosclerosis: *"His radiographs showed platyspondyly with posterior humping, narrow hip-joint surfaces, and pelvic osteosclerosis"* (PMID: 32471379), and *"Radiographically the disorder is characterized by a typical hump-shaped deformity of the vertebral bodies"* (PMID: 15221797). Early degenerative joint disease of spine and hips is near-universal; carriers are usually asymptomatic (PMID: 11760838). **Ontology (HPO):** HP:0000926 (Platyspondyly); HP:0004322 (Short stature); HP:0002758 (Osteoarthritis); HP:0002656 (Epiphyseal dysplasia).

## Finding 4 — Gene structure, epidemiology, and X-inactivation escape

SEDL/TRAPPC2 maps to **Xp22.2**, is a **2.8-kb transcript** expressed broadly including fetal cartilage, and encodes **sedlin, 140 aa**: *"SEDL encodes a 140 amino acid protein with a putative role in endoplasmic reticulum (ER)-to-Golgi vesicular transport"* (PMID: 10431248). Prevalence:

*"an X-linked recessive osteochondrodysplasia that occurs in approximately two of every one million people"* (PMID: 10431248). The gene **escapes X-inactivation** — *"RT-PCR experiments using mouse/human cell hybrids revealed that the SEDL gene escapes X inactivation"* (PMID: 11326333) — has a transcribed retropseudogene on chr19, and conserved orthologues from yeast (p20/Trs20) to mammals. The **recurrent c.93+5G>A allele** appears in multiple unrelated families (PMID: 11326333, PMID: 26252088).

## Finding 5 — Ultrastructural pathology confirms a secretory-pathway defect

Articular cartilage from an adult SEDT patient carrying c.93+5G>A contained chondrocytes with **abundant Golgi and dilated rough ER**: *"Articular cartilage from an adult who had SEDL and carried this mutation contained chondrocytes with abundant Golgi complexes and dilated rough endoplasmic reticulum (ER)"* (PMID: 11326333). The distended ER is the morphological signature of a secretory bottleneck (procollagen retention). The authors concluded: *"These data suggest that SEDL mutations may perturb an intracellular pathway that is important for cartilage homeostasis"* (PMID: 11326333). **Ontology:** GO:0005783 (ER); GO:0005794 (Golgi).

## Finding 6 — Sedlin (Trs20) is an essential TRAPP adaptor with Rab-GEF activity

TRAPP is a conserved modular "transport protein particle" complex acting as a **Ypt/Rab GTPase GEF**: *"TRAPP attracted attention when it was shown to act as a Ypt/Rab GTPase nucleotide exchanger, GEF"* (PMID: 27066478). Sedlin is the adaptor for higher-order assembly: *"Another small subunit, Trs20/Sedlin, is an adaptor required for the association of core TRAPP with larger subunits to form TRAPP II and TRAPP III"* (PMID: 27066478). TRAPP regulates **both secretion and autophagy**, so sedlin loss could in principle affect both; the secretory (procollagen) branch is the demonstrated driver of SEDT. **Ontology:** GO:0030008 (TRAPP complex); GO:0006914 (autophagy — inferred).

## Finding 7 — Management is orthopedic; total hip arthroplasty is effective for end-stage hip OA

No curative therapy exists; care is supportive/orthopedic. Because the dysplasia *"usually leads to premature secondary osteoarthritis often requiring hip arthroplasty"* (PMID: 10431248), THA is the mainstay for end-stage disease. In a series of SED patients with Tönnis grade 3 hip OA, THA improved mean **Harris hip score from 35.55 preoperatively to 89.56**, with reduced pain (VAS) and improved SF-12, and low short-term complications (PMID: 33550353). Registry data show THA durability in pediatric hip diseases is comparable to primary OA after adjustment

(PMID: 23043269). Life expectancy is normal: SEDT features *"disproportionate short stature with short neck and trunk, barrel chest and absence of systemic complications"* (PMID: 10431248). **Ontology (NCIT):** Total Hip Arthroplasty; NSAID Therapy; Physical Therapy.

### Finding 8 — Diagnosis rests on radiographs plus normal labs and X-linked pedigree, confirmed by sequencing

Clinical diagnosis is challenging: *"Clinical diagnosis can be challenging due to the late-onset of the disease and lack of systemic metabolic abnomalites [sic]. Genetic diagnosis is critical in both early diagnosis and management of the disease"* (PMID: 32471379). The diagnostic triad is platyspondyly with posterior humping, narrow hip-joint surfaces, and pelvic osteosclerosis (PMID: 32471379). Definitive diagnosis is by TRAPPC2 sequencing (ACMG-classified). Once the familial variant is known, *"Molecular testing of SEDL enables carrier detection and definitive diagnosis before clinical or radiographic expression of SEDT"* (PMID: 11760838). Key differential: SED tarda with progressive arthropathy (PPAC, WISP3/CCN6; PMID: 10870664), SED congenita (COL2A1), multiple epiphyseal dysplasia, and mucopolysaccharidoses (abnormal urinary GAGs — absent in SEDT).

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## Mechanistic Model / Interpretation

### Ordered causal chain (initiating lesion → clinical manifestation)

1. A **loss-of-function TRAPPC2 mutation** in a hemizygous male **leads to** absent or misfolded **sedlin** (NMD of null alleles; proteasomal degradation of destabilizing missense mutants). *(demonstrated — PMID: 11252002, PMID: 19650763)*
2. Loss of sedlin **results in** failure of its role as the **Trs20 adaptor** for TRAPP II/III assembly and loss of function at ER exit sites. *(demonstrated in vitro — PMID: 27066478)*
3. In chondrocytes, TANGO1 normally recruits sedlin, which **binds and promotes efficient cycling of Sar1**; without sedlin, Sar1 cycling is impaired and COPII carriers **cannot enlarge into megacarriers**. *(demonstrated in vitro — PMID: 23019651)*
4. Impaired megacarrier growth **leads to** defective **ER export of procollagen** (too large for standard COPII vesicles). *(demonstrated in vitro — PMID: 23019651)*
5. Procollagen **accumulates in a dilated rough ER** (with expanded Golgi) in patient chondrocytes — a secretory bottleneck. *(demonstrated, human tissue — PMID: 11326333)*

6. Reduced secretion of cartilage collagen matrix **results in** defective **chondrogenesis/endochondral ossification** at vertebral and epiphyseal growth plates (sedlin is expressed in proliferating/hypertrophic chondrocytes). *(inferred from mechanism + expression — PMID: 19650763, PMID: 23019651)*
7. Growth-plate dysfunction **leads to** the skeletal phenotype — **platyspondyly, epiphyseal dysplasia, short trunk** — visible only after years of growth (hence "tarda"). *(human clinical — PMID: 10431248, PMID: 15221797)*
8. Abnormal joint/vertebral architecture **results in** altered biomechanics and **premature secondary osteoarthritis** of spine and hips → chronic pain and disability, treated by arthroplasty. *(human clinical — PMID: 10431248, PMID: 33550353)*

**Branch point:** TRAPP also functions in **autophagy** and general ER–Golgi trafficking (PMID: 27066478); in principle sedlin loss could perturb these broadly, yet the phenotype is **skeleton-restricted** — inferred to reflect the exceptionally high demand for **large procollagen cargo export** in chondrocytes rather than a global trafficking collapse.

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TRAPPC2 (Xp22.2) loss-of-function mutation
        │  absent / misfolded sedlin (Trs20)
        ▼
Defective TRAPP assembly + impaired Sar1 GTPase cycling
        ▼
COPII "megacarriers" fail to form ──► procollagen cannot exit ER
        ▼
Dilated rough ER + expanded Golgi in growth-plate chondrocytes (CL:0000138)
        ▼
Defective chondrogenesis / abnormal endochondral ossification
        ├──► Platyspondyly (hump-shaped vertebrae) ──► short-trunk stature, barrel chest
        └──► Epiphyseal dysplasia (hips) ──► premature secondary osteoarthritis
                                                        ▼
                                        Total hip arthroplasty (symptomatic Tx)
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**Upstream vs downstream:** mutation and sedlin loss are upstream; the Sar1/COPII/procollagen-export defect is the proximal molecular mechanism; ER distension and defective chondrogenesis are the cellular midpoints; the skeletal phenotype with secondary OA is the downstream endpoint. **Cell type:** growth-plate chondrocyte (CL:0000138). **Anatomy:** vertebral column (UBERON:0001130), epiphyseal plate (UBERON:0006255/0002515), hip joint (UBERON:0001464).

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# Full Disease-Knowledge-Base Template (Sections 1–15)

## 1. Disease Information

**Overview.** SEDT is a rare, non-lethal X-linked recessive **osteochondrodysplasia** affecting primarily the **vertebrae (spondylo-)** and **epiphyses**. It is "tarda" (late) because affected boys are normal at birth, with skeletal signs emerging typically between ~5 and 14 years. Cardinal features are **disproportionate short-trunk short stature**, a **barrel/short chest**, and characteristic **platyspondyly with a hump-shaped mound** on the central/posterior vertebral bodies, leading to **premature secondary osteoarthritis** of spine and large joints (especially hips) without systemic metabolic complications (PMID: 10431248, PMID: 15221797) *(human clinical)*.

> *"Spondyloepiphyseal dysplasia tarda (SEDL; MIM 313400) is an X-linked recessive osteochondrodysplasia that occurs in approximately two of every one million people."* (PMID: 10431248)

**Key identifiers.** - **OMIM phenotype:** 313400 (Spondyloepiphyseal dysplasia tarda, X-linked) - **OMIM gene:** 300202 (TRAPPC2 / SEDL) - **Orphanet:** ORPHA:93284 (X-linked spondyloepiphyseal dysplasia tarda) - **ICD-10:** Q77.7 (Spondyloepiphyseal dysplasia) - **ICD-11:** ~LD24.1 (spondyloepiphyseal dysplasias) — verify exact code - **MeSH:** Osteochondrodysplasias (D010009); no unique dedicated descriptor - **MONDO:** MONDO:0010737 - **Gene:** TRAPPC2 (HGNC:23068; formerly SEDL); NCBI Gene ID 6399; cytoband Xp22.2; protein **sedlin**

**Synonyms.** SEDT; SED tarda; SEDL; X-linked spondyloepiphyseal dysplasia; spondyloepiphyseal dysplasia tarda, X-linked; sedlin deficiency. (Autosomal "SED tarda with progressive arthropathy" is genetically distinct — see §10.)

**Evidence source:** aggregated disease-level resources (OMIM, Orphanet) + individual pedigrees; not EHR/population data.

## 2. Etiology

**Primary cause — genetic (monogenic).** SEDT is caused by **loss-of-function mutations in TRAPPC2/SEDL** on Xp22.2 encoding sedlin (PMID: 10431248, PMID: 11252002) *(human clinical)*. It is **not** infectious, environmental, or multifactorial.

**Genetic risk factors.** Hemizygous pathogenic TRAPPC2 variants in males essentially fully determine disease. Male sex and an affected/carrier mother are the defining risk determinants (X-linked recessive). No susceptibility loci or modifier genes are established.

**Protective factors.** In heterozygous females, a normal X allele plus random X-inactivation renders most carriers asymptomatic (dosage protection). No protective modifier alleles described.

**Environmental risk/protective factors & gene–environment interactions.** None recognized — as expected for a fully penetrant Mendelian trafficking defect. Phenotypic variability exists (severe child vs mild adult, PMID: 11491516) but no molecular modifier has been mapped.

## 3. Phenotypes

All phenotypes are **physical manifestations** / **clinical signs** of a skeletal dysplasia; there are **no characteristic laboratory abnormalities** (normal blood/urine chemistry, normal mucopolysaccharides), a key diagnostic discriminator (PMID: 32471379). Onset is childhood (~5–14 y); course is chronic and slowly progressive; penetrance in hemizygous males is essentially complete with variable expressivity.

| Phenotype | Type | Onset / severity / frequency | Suggested HPO |
|---|---|---|---|
| Platyspondyly with hump-shaped vertebral mound | Radiographic sign (pathognomonic) | Childhood; near-universal | HP:0000926 (Platyspondyly) |
| Disproportionate short-trunk short stature | Physical | Childhood; mild–moderate | HP:0004322 (Short stature); HP:0004600 (short trunk, verify) |
| Short neck / barrel (short) chest | Physical | Childhood; common | HP:0000765 (Abnormal thorax) |
| Early-onset osteoarthritis (spine, hips) | Clinical sign | Adolescence–adulthood; progressive; near-universal | HP:0002758 (Osteoarthritis) |
| Chronic back pain | Symptom | Adolescence/adult; frequent | HP:0003418 (Back pain) |
| Hip pain / coxarthrosis | Symptom/sign | Adult; frequent; may need arthroplasty | Hip osteoarthritis (verify) |
| Epiphyseal dysplasia; short/thick femoral necks | Radiographic | Childhood; common | HP:0002656; HP:0100864 (short femoral neck) |
| Kyphosis / scoliosis | Physical | Childhood/adolescence; variable | HP:0002808; HP:0002650 |
| Narrow disc spaces, end-plate sclerosis | Radiographic | Childhood/adolescence | Abnormal vertebral morphology |
| Pelvic osteosclerosis, small iliac wings | Radiographic | Childhood | Abnormal pelvis morphology |

**Quality-of-life impact.** Morbidity is musculoskeletal: chronic back and hip pain, reduced mobility/stamina, and functional limitation from early OA dominate. Instruments used in SED hip-OA literature include **Harris Hip Score, WOMAC, VAS, SF-12** (PMID: 33550353). No cognitive, cardiac, respiratory-failure, or visceral involvement.

## 4. Genetic / Molecular Information

**Causal gene. TRAPPC2 (SEDL)**, Xp22.2, HGNC:23068, NCBI Gene 6399, OMIM 300202; encodes **sedlin (140 aa)**, a 2.8-kb transcript expressed broadly including fetal cartilage (PMID: 10431248). A near-identical paralog **TRAPPC2B** and a transcribed **retropseudogene on chr19** exist — relevant to assay design (PMID: 11326333).

**Pathogenic variant spectrum (all germline; LoF).** - **Frameshift/indels:** dinucleotide deletions with premature stops (PMID: 10431248); 2-bp exon-5 deletion (PMID: 11760838); additional small indels (PMID: 15221797). - **Nonsense:** c.61G>T/p.E21 *(PMID: 24841781); S110X (PMID: 12446987). - Splice-site: recurrent c.93+5G>A (IVS3+5G>A) hot spot causing exon-3 skipping (PMID: 11326333, PMID: 26252088); c.93+5G>C (PMID: 23876379); IVS2-2A>C (PMID: 16120574). - Missense: D47Y, S73L, F83S, V130D (PMID: 19650763); c.218C>T (PMID: 18247296) — rarer; mostly destabilize the protein. - Gross deletions:** intragenic deletion removing the start codon/exon 3 (PMID: 11252002); whole-exon deletions (PMID: 15221797).

**Functional consequence:** predominantly **loss of function / absence of sedlin** (NMD, no protein, or misfolded protein degraded by the proteasome) (PMID: 11252002, PMID: 19650763). No gain-of-function or dominant-negative mechanism. Missense S73L/F83S/V130D misfold and are proteasomally degraded (rescued by MG132); D47Y folds normally but shows altered Bet3 binding (PMID: 19650763) *(in vitro)*.

**Variant classification.** Reported variants are **Pathogenic/Likely pathogenic** under ACMG criteria (null variants in a LoF gene; cosegregation; absent from controls/gnomAD) (PMID: 32471379). **Allele frequency:** disease alleles absent/ultra-rare in gnomAD/1000 Genomes; absent from ≥100 control chromosomes in multiple studies (PMID: 11326333, PMID: 23876379).

**Somatic vs germline:** entirely germline. **Modifiers/epigenetic/chromosomal:** none established; the gene **escapes X-inactivation** (PMID: 11326333), possibly explaining subtle carrier changes. **Ontology:** GO:0005085 (GEF activity); GO:0030008 (TRAPP complex).

## 5. Environmental Information

**Not applicable.** SEDT is a pure monogenic disorder. No environmental toxins, radiation, occupational exposures, lifestyle factors, or infectious agents cause or trigger it. Mechanical joint loading over time contributes to the **progression** of secondary osteoarthritis (a biomechanical, not etiologic, factor); activity modification is advised clinically but is not an etiologic environmental factor.

## 6. Mechanism / Pathophysiology

(See the Mechanistic Model above for the numbered causal chain.)

**Category detail.** - **Molecular pathways:** COPII vesicle biogenesis / ER-to-Golgi anterograde transport; Sar1 GTPase cycle; TRAPP-mediated Rab (Ypt1/Rab1) GEF activity (Reactome "COPII-mediated vesicle transport"). GO:0006888; GO:0090110. - **Cellular processes:** secretory protein trafficking; possible autophagy modulation; ER cargo retention / plausible ER stress (dilated RER; GO:0030968 UPR not proven). - **Protein dysfunction:** LoF via misfolding/degradation or absent protein; altered partner binding (Bet3, TANGO1, Sar1) (PMID: 19650763, PMID: 23019651). - **Metabolic / immune changes:** none characteristic. - **Tissue damage mechanism:** structural/matrix insufficiency and biomechanical wear (osteoarthritic cartilage degeneration), not oxidative/ischemic/fibrotic primary injury. - **Molecular profiling (omics):** No large transcriptomic/proteomic/metabolomic disease datasets exist (rare disease); mechanistic data are from targeted in vitro procollagen-export and biochemical assays. - **Cell types (CL):** chondrocyte (CL:0000138), proliferating/hypertrophic growth-plate chondrocytes. **Subcellular (GO CC):** ER (GO:0005783), ER exit site (GO:0070971), Golgi (GO:0005794), COPII coat (GO:0030127), TRAPP complex (GO:0030008).

## 7. Anatomical Structures Affected

- **Organ/system level:** the **skeletal (musculoskeletal) system** is the sole primary system. Primary sites: **vertebral column** (UBERON:0001130) and **epiphyses/growth plates** (UBERON:0002515 epiphysis; UBERON:0006255 epiphyseal plate). Secondary: **hip joint** (UBERON:0001464), femoral head/neck, pelvis (UBERON:0001270), thorax/rib cage (UBERON:0001443). No cardiovascular, nervous, respiratory-failure, digestive, endocrine, ocular, or renal involvement.
- **Tissue/cell level:** cartilage/connective tissue (UBERON:0002418); target cell = **chondrocyte (CL:0000138)**.
- **Subcellular level:** ER (GO:0005783), Golgi (GO:0005794), COPII/ER-exit machinery.
- **Localization/lateralization:** generalized, **bilateral/symmetric** axial + appendicular involvement.

## 8. Temporal Development

- **Onset:** pediatric/childhood, typically 5–14 y; insidious/chronic; normal at birth (distinguishes from SED congenita). Presymptomatic diagnosis possible by imaging/DNA (PMID: 11760838).
- **Progression:** slowly progressive; growth-plate phenotype consolidates through skeletal growth, then **secondary osteoarthritis progresses** through adulthood (early → end-stage, e.g., Tönnis grade 3 hip OA, PMID: 33550353).
- **Course/duration:** chronic, lifelong, non-remitting; not episodic.
- **Critical period:** the **skeletal-growth years** are the biologically relevant window for any hypothetical disease-modifying therapy; none currently exists.

## 9. Inheritance and Population

- **Inheritance: X-linked recessive**; affected hemizygous males; obligate female carriers usually asymptomatic (gene escapes X-inactivation) (PMID: 10431248, PMID: 11326333).
- **Penetrance:** essentially complete in males (age-dependent expression). **Expressivity:** variable (PMID: 11491516).
- **Epidemiology:** prevalence ≈ **2 per 1,000,000 (0.2/100,000)** (PMID: 10431248); incidence not separately reported; pan-ethnic (Europe, China, Japan, Australia).
- **Sex ratio:** strongly male-predominant.
- **Founder effects/consanguinity:** no classical founder mutation, but **c.93+5G>A is a recurrent hot spot** (PMID: 11326333, PMID: 15221797); consanguinity not required.
- **Anticipation/mosaicism:** no anticipation (not a repeat disorder); germline mosaicism not specifically documented. **Carrier frequency:** not formally established; disease alleles ultra-rare in gnomAD.

## 10. Diagnostics

- **Imaging (primary modality):** spinal/pelvic radiographs show pathognomonic **platyspondyly with hump-shaped vertebral bodies**, end-plate sclerosis, narrow disc spaces, short/thick femoral necks, narrow hips, pelvic osteosclerosis (PMID: 10431248, PMID: 32471379).

- **Laboratory/biomarkers:** characteristically **normal** — no metabolic biomarker, normal urinary GAGs, normal blood chemistry; this normality is itself discriminating (rules out MPS; PMID: 32471379).
- **Histopathology/ultrastructure:** chondrocytes with dilated rough ER and abundant Golgi on EM (PMID: 11326333) — supportive, not routine.
- **Genetic testing (confirmatory):** single-gene sequencing of **TRAPPC2** (6 exons + splice sites); deletion/duplication analysis (CMA/MLPA) for gross deletions (PMID: 11252002, PMID: 15221797). WES/WGS or skeletal-dysplasia panels for atypical cases (PMID: 32471379). RT-PCR confirms splice effects (PMID: 16120574). Assays must avoid the chr19 pseudogene/TRAPPC2B paralog (PMID: 11326333). Karyotype/FISH/mtDNA/repeat testing not applicable.
- **Differential diagnosis:**

| Condition | Distinguishing feature |
|---|---|
| SED tarda with progressive arthropathy (PPAC) | WISP3/CCN6; inflammatory hand/wrist arthropathy; AR (PMID: 10870664) |
| SED congenita | COL2A1; neonatal onset; ocular/cleft palate |
| Multiple epiphyseal dysplasia | epiphyses without vertebral hump |
| Mucopolysaccharidoses (Morquio) | abnormal urinary GAGs; visceral/corneal involvement |
| Scheuermann / post-SCFE / Kashin-Beck | no X-linked pedigree; no generalized platyspondyly |

- **Screening:** no newborn/population screening; **cascade testing** of at-risk male relatives and **carrier testing** of females is appropriate; presymptomatic diagnosis feasible (PMID: 11760838).

## 11. Outcome / Prognosis

- **Survival/mortality: normal life expectancy**; no disease-specific mortality ("absence of systemic complications," PMID: 10431248).
- **Morbidity/disability:** significant musculoskeletal morbidity — chronic back/hip pain, restricted mobility, short stature, and early osteoarthritis often requiring **joint arthroplasty** (PMID: 10431248, PMID: 33550353). Disability is functional/orthopedic (ICF: mobility, pain), not cognitive/visceral.
- **QoL measures:** Harris Hip Score, WOMAC, VAS, SF-12 (PMID: 33550353).

- **Recovery:** the dysplasia is not reversible, but **arthroplasty markedly improves pain and function** (Harris Hip Score ~35.6 → 89.6; PMID: 33550353).
- **Prognostic factors:** severity/rate of joint degeneration and degree of short stature/kyphoscoliosis. No molecular prognostic biomarker; genotype–phenotype correlation weak (PMID: 11491516).

## 12. Treatment

**No curative or disease-modifying therapy exists.** Management is symptomatic, orthopedic, and rehabilitative (NCIT terms in brackets).

- **Pharmacotherapy:** analgesics and **NSAIDs** for joint/back pain [NCIT: Nonsteroidal Anti-inflammatory Agent; Analgesic Therapy]. No SEDT-specific pharmacogenomics.
- **Surgical/interventional: Total hip arthroplasty (THA)** for end-stage hip OA — effective, low short-term complications, large functional gains (PMID: 33550353) [NCIT: Total Hip Arthroplasty]. Spinal surgery for severe kyphoscoliosis; osteotomy in selected joints.
- **Supportive/rehabilitative:** physical therapy, weight management, activity modification, pain management, mobility aids [NCIT: Physical Therapy; Rehabilitation Therapy; Pain Management].
- **Advanced therapeutics (gene/cell/RNA/targeted/immuno):** none approved or in trials for SEDT. The LoF mechanism and defined Sar1/procollagen pathway make it a theoretical gene-replacement target, but no program exists.
- **Experimental/clinical trials:** no disease-specific interventional trials identified.
- **Strategy/personalized medicine:** genotype-guided therapy not applicable; management guided by orthopedic severity; **genetic counseling** is core [NCIT: Genetic Counseling].
- **Adverse events:** chronic NSAID risks and standard arthroplasty risks; SED THA survivorship favorable and comparable to other pediatric hip-disease groups after adjustment (PMID: 23043269).

## 13. Prevention

- **Primary prevention:** not possible for a germline monogenic disorder. **Reproductive/genetic prevention** is the principal lever: genetic counseling, carrier testing of at-risk females, prenatal diagnosis, and **PGT-M** once the familial TRAPPC2 variant is known (PMID:

24841781, PMID: 23876379). Carrier females have 50% transmission risk (affected sons, carrier daughters).

- **Secondary prevention:** cascade testing and early radiographic surveillance of at-risk boys enables early orthopedic monitoring; presymptomatic diagnosis feasible (PMID: 11760838).
- **Tertiary prevention:** joint protection, weight control, physiotherapy, timely orthopedic intervention to preserve function and optimize arthroplasty timing.
- **Immunization/public health/environmental:** not applicable.

## 14. Other Species / Natural Disease

- **Taxonomy:** disease described in **Homo sapiens (NCBI:txid9606)** only.
- **Orthologous genes:** sedlin/TRAPPC2 is deeply conserved: mouse **Trappc2**, rat, zebrafish **trappc2**, Drosophila, C. elegans, and S. cerevisiae **TRS20** (p20) (PMID: 11326333, PMID: 10431248). Yeast p20/Trs20 has a role in ER-to-Golgi transport (PMID: 11326333).
- **Natural disease in animals:** no naturally occurring animal model of SEDT is documented in OMIA (knowledge gap).
- **Comparative biology:** the **ER-to-Golgi TRAPP/Sar1 mechanism is conserved from yeast to humans**, so the molecular pathway is highly conserved even though the skeletal disease is human-specific (chondrocyte/procollagen context).
- **Transmission/zoonosis:** not applicable (non-infectious).

## 15. Model Organisms

- **In vitro/cellular models (primary evidence base):** patient-derived and transfected cell systems showing mislocalization, misfolding, and proteasomal degradation of mutant sedlin, and altered Bet3 binding (PMID: 19650763) *(in vitro)*; biochemical reconstitution of procollagen ER export demonstrating the TANGO1–Sedlin–Sar1 axis and megacarrier formation (PMID: 23019651) *(in vitro)*; mouse growth-plate tissue for in situ localization of sedlin to proliferating/hypertrophic chondrocytes (PMID: 19650763).
- **Yeast (S. cerevisiae) TRS20:** the tractable genetic model that defined TRAPP subunit architecture and Rab-GEF function (PMID: 27066478, PMID: 11326333).
- **Genetic vertebrate models: no widely reported mouse/zebrafish model faithfully recapitulates the human SEDT skeletal phenotype** — a notable knowledge gap. Orthologs are amenable to knockout via MGI/ZFIN resources.

- **Applications:** existing models best dissect the **secretory-trafficking mechanism** (procollagen export, Sar1 cycling) rather than whole-organism skeletal disease.
- **Limitations:** cell/yeast models do not reproduce growth-plate architecture, endochondral ossification, or biomechanical progression to OA.
- **Resource databases:** MGI (Trappc2), ZFIN (trappc2), SGD (TRS20), Alliance of Genome Resources.

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# Evidence Base

| PMID | Title (abbrev.) | Role in this report |
|---|---|---|
| 10431248 | *Identification of the gene (SEDL) causing SEDT* | Gene ID, prevalence, 140-aa protein, ER-Golgi role, normal lifespan/arthroplasty |
| 11252002 | *Loss of Sedlin causes X-linked SEDT (Japanese family)* | Loss of sedlin as disease mechanism |
| 11326333 | *Recurrent RNA-splicing mutation in SEDL* | c.93+5G>A hot spot; X-inactivation escape; dilated rough ER |
| 16120574 | *Novel splicing mutation IVS2-2A>C* | Exon-3 skipping abolishes sedlin |
| 24841781 | *Nonsense mutation, 5-gen Chinese pedigree* | X-linked recessive; clinical hallmark; p.E21* |
| 12446987 | *Novel nonsense mutation S110X* | Nonsense spectrum |
| 11760838 | *Preonset studies; 2-bp deletion* | Onset age/sex; barrel chest; carrier/prenatal testing |
| 23019651 | *Sedlin controls ER export of procollagen via Sar1* | Core molecular mechanism; chondrogenesis link |
| 19650763 | *Biochemical consequences of sedlin mutations* | Missense misfolding/degradation; chondrocyte expression |
| 15221797 | *Mutations in 13 European families* | Hump-shaped vertebral deformity as hallmark |
| 32471379 | *Novel TRAPPC2 deletion, Chinese family* | Diagnostic triad; normal labs; genetic diagnosis critical |
| 27066478 | *TRAPP Complexes in Secretion and Autophagy* | Sedlin/Trs20 adaptor; Rab-GEF; two pathways |
| 33550353 | *THA for Tönnis grade 3 hip OA in SED* | THA efficacy (Harris 35.6→89.6) |
| 23043269 | *Low revision rate THA, pediatric hip diseases* | THA durability |
| 10870664 | *SEDT with progressive arthropathy* | Differential (PPAC, WISP3/CCN6) |
| 23876379 | | c.93+5G>C; splice LoF |

| PMID | Title (abbrev.) | Role in this report |
|---|---|---|
| | *Novel splicing mutation, Chinese pedigree* | |
| 18247296 | *Missense mutation, Chinese family* | c.218C>T; carrier genotype-phenotype |
| 26252088 | *TRAPPC2 mutation analysis* | Independent confirmation of c.93+5G>A |
| 11491516 | *Severe child vs mild adult features* | Variable expressivity |

**Evidence-source distinction.** The mechanistic backbone (sedlin→Sar1→procollagen export) derives from **in vitro / cell-biology studies** (PMID: 23019651, PMID: 19650763, PMID: 27066478). Genotype–phenotype and clinical/radiographic data are **human clinical** studies from multiple independent pedigrees. Ultrastructural pathology is **human tissue** (PMID: 11326333). Treatment-efficacy data are **human clinical case series/registries** but drawn from SED broadly rather than SEDT specifically.

## Limitations and Knowledge Gaps

1. **Treatment evidence is indirect.** THA outcome data (PMID: 33550353, PMID: 23043269) come from mixed SED / pediatric hip-disease cohorts, not SEDT-specific series; effect sizes should be extrapolated cautiously.
2. **No validated animal model** faithfully reproduces the SEDT skeletal phenotype; steps 6–7 of the causal chain remain **inferred** in vivo.
3. **Weak genotype–phenotype correlation.** Variable expressivity is documented (PMID: 11491516) but no modifier genes identified.
4. **Carrier phenotype vs X-inactivation escape** incompletely reconciled — carriers are largely asymptomatic despite escape (PMID: 11326333).
5. **Autophagy branch of TRAPP** (PMID: 27066478) not evaluated in SEDT chondrocytes.
6. **Coarse epidemiology.** The ~2/1,000,000 estimate is legacy; incidence, geographic distribution, and true carrier frequency (gnomAD) not quantified.
7. **No SEDT-specific QoL data**; inferences rest on generic SED/THA instruments.
8. Exact ICD-11 code and some HPO term IDs should be verified against current ontology releases.

## Proposed Follow-up Experiments / Actions

1. **Interrogate gnomAD/ClinVar systematically** for TRAPPC2 LoF allele frequencies to refine carrier frequency, prevalence, and the ACMG-classified variant catalog.
2. **Generate a chondrocyte-specific Trappc2 conditional knockout mouse** (e.g., Col2a1-Cre) to test in vivo whether procollagen-export failure produces platyspondyly and epiphyseal dysplasia — closing the inferred gap in causal steps 6–7.
3. **Profile ER stress / UPR** (BiP, CHOP, XBP1 splicing) in patient- or iPSC-derived chondrocytes to test whether chronic ER distension activates a pathogenic UPR.
4. **Assess autophagic flux** (LC3-II, p62) in sedlin-deficient chondrocytes to determine whether the TRAPP III/autophagy role contributes to cartilage pathology.
5. **Explore proteostasis-directed therapeutics** for destabilizing missense alleles (S73L/F83S/V130D rescued by proteasome inhibition, PMID: 19650763) — chemical chaperones as a possible allele-specific disease-modifying route.
6. **Establish a SEDT natural-history registry** with standardized radiographic staging, disease-specific + SF-36 QoL, and long-term arthroplasty outcomes.
7. **Cryo-EM of the TANGO1–sedlin–Sar1–COPII assembly** to define, at atomic resolution, how disease mutations disrupt megacarrier formation, informing rational therapeutic design.

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*Report compiled from an autonomous multi-iteration literature investigation (8 confirmed findings, 24 papers reviewed). All mechanistic and clinical claims are anchored to the cited primary literature with verified abstract quotations.*

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