Dermatosparaxis Ehlers-Danlos Syndrome (dEDS): Comprehensive Disease Characterization

Disease: Dermatosparaxis Ehlers-Danlos Syndrome (dEDS) **Category:** Connective Tissue Disorder **Key identifiers:** OMIM **225410** · Orphanet **ORPHA:1901** · MONDO **0009159** · former name **EDS type VIIC** · ICD-11 LD28.0Y (Ehlers-Danlos syndrome, other specified) · MeSH Ehlers-Danlos Syndrome (D004535)

Summary

Dermatosparaxis Ehlers-Danlos syndrome (dEDS) is an ultra-rare, autosomal-recessive heritable connective tissue disorder caused by **biallelic loss-of-function variants in *ADAMTS2*** (chromosome 5q35.3), the gene encoding **procollagen I N-proteinase (pNPI)**. This zinc metalloproteinase excises the amino-terminal propeptide of type I, II, and III procollagens — a mandatory processing step that permits near-spontaneous assembly of collagen trimers into mature fibrils. When enzyme activity is abolished, unprocessed pN-collagen accumulates, producing structurally defective, ribbon-like or "hieroglyphic" collagen fibrils. The clinical consequence is a congenital, multisystem fragility syndrome dominated by extreme skin fragility, redundant/lax skin, easy bruising, a recognizable facial gestalt, and variable visceral, vascular, and skeletal complications (PMID: 10417273; PMID: 26765342; PMID: 39641471).

dEDS occupies a unique position in medical genetics because its animal counterpart — **dermatosparaxis** — was described in cattle decades before the human disorder was molecularly solved, and the *same gene* underlies naturally occurring disease across cattle, sheep, dogs, and cats. This cross-species conservation, combined with a well-characterized *Adamts2*-knockout mouse, makes dEDS a paradigmatic loss-of-function Mendelian disorder within the broader ADAMTS metalloproteinase superfamily (PMID: 24443030; PMID: 28856769; PMID: 29649548; PMID: 25770910).

There is **no disease-specific or curative therapy**. dEDS is placed within the 2017 international EDS classification as one of 12 molecularly defined subtypes, and management is symptomatic, protective, surgical, and multidisciplinary, supported by autosomal-recessive genetic counseling (25% sibling recurrence risk) and *ADAMTS2* molecular confirmation (PMID: 40887396).

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1. Disease Information

Overview. dEDS is a rare recessively inherited connective tissue disorder characterized by extreme skin fragility. It was historically designated **Ehlers-Danlos syndrome type VIIC** in the older Villefranche nomenclature and renamed **dermatosparaxis EDS** in the 2017 international classification. The name "dermatosparaxis" (Greek: *derma* = skin, *sparassein* = to tear) was coined for the analogous bovine disease, in which the skin tears easily. dEDS is defined by an absence of procollagen I N-proteinase activity (PMID: 10417273).

> *"Like the animal model dermatosparaxis, EDS type VIIC results from the absence of activity of procollagen I N-proteinase (pNPI), the enzyme that excises the N-propeptide of type I and type II procollagens."* — Colige et al., 1999 (PMID: 10417273)

Key identifiers:

Resource	Identifier
OMIM	225410
Orphanet	ORPHA:1901
MONDO	0009159
Former name	EDS type VIIC (Villefranche)
Gene	*ADAMTS2* (HGNC:217)
MeSH	Ehlers-Danlos Syndrome (D004535)

Synonyms / alternative names: dermatosparaxis type EDS; EDS dermatosparaxis type; EDS VIIC; Ehlers-Danlos syndrome type 7C; procollagen I N-proteinase deficiency; human dermatosparaxis.

Data source type. The knowledge summarized here is derived from **aggregated disease-level resources** — primary case reports, small case series (individual patient molecular and clinical data), OMIM/Orphanet, and model-organism studies — rather than from a single EHR cohort. Because dEDS is ultra-rare (well under 100 reported human cases worldwide), the literature is dominated by individual and small-series patient reports.

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2. Etiology

Primary cause (genetic). dEDS is caused exclusively by **biallelic (homozygous or compound heterozygous) loss-of-function variants in *ADAMTS2***. There is no environmental or infectious cause; the disorder is fully monogenic and recessive. The pathogenic mechanism is deficiency of procollagen I N-proteinase activity, which prevents removal of the procollagen N-propeptide.

Genetic risk factors. The only risk factor is inheritance of two defective *ADAMTS2* alleles. There are no known modifier loci or susceptibility variants in humans; carriers (heterozygotes) are unaffected. **Consanguinity** increases risk, consistent with a recessive disorder — several reported homozygous patients arose in consanguineous or geographically isolated families.

Environmental / protective factors. None established. Because the disorder is monogenic with a loss-of-function mechanism and near-complete penetrance, environmental modifiers, protective alleles, and gene–environment interactions have **not been described** and are not applicable in the conventional sense. (Not available for this disease.)

Gene–environment interactions. Not applicable / not documented for a fully penetrant recessive enzyme deficiency.

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3. Phenotypes

dEDS presents at birth (congenital onset) with a recognizable, multisystem phenotype. Severity is variable, with a classic severe form and a documented milder variant.

Phenotype	Type	Suggested HPO term	Onset / frequency notes
Extreme skin fragility	Physical manifestation	HP:0000974 (Hyperextensible skin) / HP:0000979 (Bruising susceptibility)	Congenital; near-universal; hallmark feature
Redundant/lax (sagging) skin, skin folds	Physical manifestation	HP:0000973 (Cutis laxa)	Congenital; often requires surgical resection in adults
Excessive/easy bruising	Clinical sign	HP:0000978 (Bruising susceptibility)	Congenital; frequent
Characteristic facial gestalt (puffy eyelids, epicanthal folds, micrognathia, blue sclerae)	Physical manifestation	HP:0001999 (Abnormal facial shape); HP:0000592 (Blue sclerae)	Congenital; recognizable "facies"
Joint laxity/ hypermobility	Clinical sign	HP:0001382 (Joint hypermobility)	Congenital
Umbilical/inguinal hernia	Physical manifestation	HP:0001537 (Umbilical hernia)	Congenital/ childhood
Delayed wound healing, atrophic scarring	Clinical sign	HP:0001058 (Poor wound healing)	Lifelong
Visceral/vascular fragility (e.g., gastric volvulus, diaphragmatic hernia)	Clinical sign	Hernia / GI terms	Variable; severe complications reported in adults
Multiple fractures / reduced bone mineral density	Laboratory/ imaging abnormality	HP:0002659 (Increased susceptibility to fractures); HP:0004349 (Reduced bone mineral density)	Adult natural history

Severity and course. Extreme skin fragility and laxity are the cardinal features; the disease is congenital and lifelong (chronic, non-remitting), with cumulative complications in adulthood. A **milder phenotypic variant** exists in addition to the typical severe form (PMID: 26765342).

> *"all presenting a recognizable phenotype with characteristic facial gestalt, extreme skin fragility and laxity, excessive bruising, and sometimes major complications due to visceral and vascular fragility."* — Van Damme et al., 2016 (PMID: 26765342)

The first adult natural-history case series (n = 5, ages 22–42 years) expanded the phenotype into adulthood:

> *"Complications include extreme skin fragility resulting in iatrogenic injury, redundant skin folds often requiring surgical resection, severe complications following a gastric volvulus secondary to a diaphragmatic hernia, and multiple fractures."* — Angwin et al., 2025 (PMID: 39641471)

The original molecular series described the classic constellation:

> *"characterized by extreme skin fragility, characteristic facies, joint laxity, droopy skin, umbilical hernia, and blue sclera."* — Colige et al., 1999 (PMID: 10417273)

Quality-of-life impact. No dEDS-specific EQ-5D/SF-36 data exist (ultra-rare disease). Extrapolating from the natural history, quality of life is affected by chronic skin fragility (requiring meticulous wound care and avoidance of trauma), disfiguring redundant skin folds and surgical scarring, hernias, fracture risk, and the psychosocial burden of a visible, chronic condition. Iatrogenic injury during routine medical procedures is a recurring, avoidable harm.

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4. Genetic / Molecular Information

Causal gene. ***ADAMTS2*** (a disintegrin and metalloproteinase with thrombospondin motifs 2), HGNC:217, located at **5q35.3**, encoding **procollagen I N-proteinase (pNPI)**. OMIM gene 604539; disease OMIM 225410.

Pathogenic variant spectrum. All confirmed dEDS variants are **loss-of-function**, abolishing enzyme activity. Documented classes:

Variant	Type	Consequence	Source
c.673C>T, p.(Gln225*) (Q225X)	Nonsense	Premature stop; mRNA decay	Colige 1999 (PMID: 10417273) — 5/6 patients homozygous
p.(Trp795*) (W795X)	Nonsense	Premature stop	Colige 1999 (PMID: 10417273) — 6th patient homozygous
c.2927_2928delCT, p.(Pro976Argfs*42)	Frameshift	Truncation	Van Damme 2016 (PMID: 26765342)
c.669_670dupG, p.(Pro224Argfs*24)	Frameshift (dup)	Truncation	Van Damme 2016 (PMID: 26765342)
c.2751-2A>T	Splice-site	Aberrant splicing	Van Damme 2016 (PMID: 26765342)
c.2T>C / c.884_887delTGAA	Start-loss / frameshift (compound het)	Loss of function	Van Damme 2016 (PMID: 26765342)
Genomic deletions → in-frame skipping of exons 3–5 and exons 14–16	Structural / splicing	Abolished enzyme activity despite in-frame	Colige 2004 (PMID: 15373769)

> *"Five of the individuals with EDS type VIIC were homozygous for a C-->T transition that results in a premature termination codon, Q225X."* — Colige et al., 1999 (PMID: 10417273)
>
> *"We identified three novel homozygous loss-of-function mutations (c.2927_2928delCT, p.(Pro976Argfs*42); c.669_670dupG, p.(Pro224Argfs*24); and c.2751-2A>T) and one compound heterozygous mutation."* — Van Damme et al., 2016 (PMID: 26765342)

A notable insight from the 2004 study is that even **in-frame exon-skipping** events (exons 3–5 or 14–16), affecting domains not previously thought essential, strongly impaired aminoprocollagen processing in vitro and in vivo — demonstrating that these domains are required for proper enzyme function (PMID: 15373769).

Variant classification (ACMG/AMP). Reported variants are **pathogenic** (nonsense, frameshift, canonical splice, structural), fulfilling loss-of-function criteria for a gene where LoF is the established mechanism.

Allele frequency / origin. All variants are **germline**; pathogenic alleles are exceedingly rare in gnomAD (consistent with an ultra-rare recessive disorder). No somatic contribution.

Functional consequence. Loss of function (enzyme deficiency). Not gain-of-function or dominant-negative — heterozygous carriers are healthy.

Modifier genes. No human modifier genes established. Mouse work implicates the paralog *Adamts14* as a minor contributor to dermal procollagen processing (see Section 15).

Epigenetics / chromosomal abnormalities. Not implicated. No methylation, histone, or large-scale cytogenetic mechanisms are described; dEDS is a point-mutation/small-indel recessive disorder. (Not applicable.)

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5. Environmental Information

dEDS is a **purely genetic** disorder. No environmental factors, toxins, radiation, occupational exposures, lifestyle factors, or infectious agents cause or trigger it. Physical trauma exacerbates the *manifestations* (skin tears, bruising, iatrogenic surgical injury) but does not cause the disease. Careful avoidance of mechanical stress and trauma is the practical corollary. (Environmental etiology: not applicable.)

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6. Mechanism / Pathophysiology

Causal chain (upstream → downstream):

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Biallelic ADAMTS2 LoF variant
        |
        ▼
Absent/deficient procollagen I N-proteinase (pNPI) activity
        |
        ▼
N-propeptide of type I (II, III) procollagen NOT excised
        |
        ▼
pN-collagen accumulates; trimers cannot assemble normally
        |
        ▼
Structurally defective, ribbon-like/"hieroglyphic" collagen fibrils
        |
        ▼
Weak dermal & connective tissue matrix
        |
        ▼
Extreme skin fragility, laxity, bruising, hernias,
visceral/vascular/skeletal fragility (clinical dEDS)
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Molecular pathway / biochemistry. Fibril-forming procollagens possess a central triple-helical domain flanked by N- and C-propeptides. **Both propeptides must be proteolytically removed** to permit spontaneous assembly of trimers into fibrils and fibers. The **N-propeptide is cleaved by procollagen N-proteinases ADAMTS2, ADAMTS3, and ADAMTS14**, while the C-propeptide is cleaved by tolloid-family (BMP1) proteinases (PMID: 25863161).

> *"the amino-propeptide is usually processed by procollagen N-proteinases: ADAMTS2, 3 and 14."* — Bekhouche & Colige, 2015 (PMID: 25863161)
>
> *"these two propeptides have to be proteolytically removed to allow the almost spontaneous assembly of the trimers into collagen fibrils and fibers."* — Bekhouche & Colige, 2015 (PMID: 25863161)

Protein dysfunction. ADAMTS2 is a secreted **zinc metalloproteinase** containing a catalytic (metalloprotease) domain plus ancillary thrombospondin/properdin repeats, a disintegrin-like domain, and a cysteine-rich domain. Loss-of-function variants remove or inactivate catalytic capacity (or destabilize the transcript via nonsense-mediated decay), yielding **enzyme deficiency** — a classic loss-of-function protein defect rather than aggregation or misfolding-toxicity. A short catalytic-only isoform and a long isoform exist (PMID: 25863161; PMID: 10417273).

Cellular processes and cell types. The principal effector cell is the **dermal fibroblast** (CL:0000057; fibroblast), which synthesizes and secretes procollagen. The affected biological process is extracellular collagen fibril organization.

- **GO biological process:** collagen fibril organization (GO:0030199); extracellular matrix organization (GO:0030198); collagen metabolic process (GO:0032963); proteolysis (GO:0006508).
- **GO molecular function:** metalloendopeptidase activity (GO:0004222); procollagen N-endopeptidase activity (GO:0004251).
- **GO cellular component:** extracellular space/matrix (GO:0005615, GO:0031012).
- **Cell types (CL):** fibroblast (CL:0000057); dermal fibroblast.

Metabolic / immune / tissue damage mechanisms. There is no primary metabolic derangement, and no autoimmune mechanism in human dEDS. Tissue "damage" is mechanical — a structurally weak matrix fails under normal shear/tensile stress, causing skin tears and connective-tissue rupture. (Of note, an immune-dysregulation phenotype emerges only in aged *Adamts2/14* double-knockout mice — see Section 15 — and is not a documented feature of human dEDS.)

Molecular profiling. No dedicated human transcriptomic/proteomic/metabolomic dEDS datasets are established; the diagnosis rests on biochemistry (accumulation of unprocessed pN-collagen), ultrastructure (abnormal fibrils on electron microscopy), and molecular genetics.

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7. Anatomical Structures Affected

- **Primary organ/system:** the **skin/integumentary system** (UBERON:0002097 skin of body; UBERON:0002199 dermis) — the dominant site of fragility and laxity.
- **Tissue type: connective tissue** (UBERON:0002384), specifically dense irregular connective tissue of the dermis, with a type I (and II, III) collagen-rich matrix.
- **Secondary/systemic involvement:** musculoskeletal (joints — hypermobility; bone — fractures, reduced BMD), gastrointestinal/abdominal wall (hernias — umbilical, diaphragmatic; gastric volvulus), vascular tissue (vascular fragility), and ocular tissue (blue sclerae, UBERON:0001773 sclera).
- **Cell populations:** dermal **fibroblasts** (CL:0000057) as collagen-producing cells.

- **Subcellular:** the pathology is **extracellular** — the defect manifests in the secreted extracellular matrix (GO:0031012), downstream of ER/Golgi collagen synthesis and secretion. No primary organelle defect.
- **Localization / lateralization:** generalized and **bilateral/systemic**; skin fragility is diffuse rather than focal.

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8. Temporal Development

- **Onset: congenital** — features are present at birth (skin fragility, laxity, characteristic facies, hernias). Onset pattern is chronic/constitutive.
- **Progression:** the underlying matrix defect is static (lifelong enzyme deficiency), but **complications accumulate with age** — redundant skin folds, surgical scarring, fractures, reduced bone mineral density, and visceral events (e.g., gastric volvulus) documented in adults (PMID: 39641471).
- **Course:** chronic, lifelong, non-remitting; no spontaneous remission. Not episodic or relapsing-remitting.
- **Critical periods:** the neonatal/pediatric period is critical for diagnosis and for instituting trauma-avoidance and wound-care protocols to prevent iatrogenic injury.

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9. Inheritance and Population

- **Inheritance: autosomal recessive** (biallelic *ADAMTS2* LoF). Sibling recurrence risk 25%.
- **Penetrance:** effectively **complete** for biallelic LoF genotypes (with variable expressivity — typical severe vs. milder variant).
- **Expressivity: variable**, including a recognized milder phenotype (PMID: 26765342).
- **Carrier state:** heterozygotes are asymptomatic. Carrier frequency is very low (ultra-rare disorder); no founder mutation of broad population impact is established, though recurrent variants (e.g., Q225X) occur.
- **Consanguinity:** contributes, as expected for a recessive disorder — many reported homozygous cases derive from consanguineous unions.

- **Epidemiology: ultra-rare** — fewer than ~60–100 human cases reported worldwide; precise prevalence/incidence figures are not reliably established (Orphanet lists prevalence as unknown/<1 per 1,000,000). No sex predilection (recessive, autosomal). No specific ethnic or geographic clustering beyond consanguineous kindreds.
- **Anticipation / germline mosaicism:** not applicable (no repeat expansion; no reported mosaicism of clinical relevance).

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10. Diagnostics

Diagnostic approach. Diagnosis is clinical (recognizable phenotype) **confirmed molecularly** by identification of biallelic pathogenic *ADAMTS2* variants. dEDS is one of the 12 EDS subtypes with a defined molecular etiology, for which molecular confirmation is expected under the 2017 classification (PMID: 40887396).

Biochemical / laboratory tests. - **Procollagen processing assay** on cultured dermal fibroblasts: accumulation of unprocessed **pN-collagen** (retained N-propeptide) is the biochemical hallmark, reflecting absent pNPI activity. - **Electron microscopy of skin:** abnormal collagen fibril morphology (irregular, ribbon-like/"hieroglyphic" cross-sections).

Genetic testing. - **Single-gene testing / targeted *ADAMTS2* sequencing** when the phenotype is recognized. - **EDS/connective-tissue gene panels** (NGS) including *ADAMTS2* — the pragmatic first-line molecular test given phenotypic overlap among EDS subtypes. - **Whole-exome/whole-genome sequencing** for atypical presentations or when panels are negative; useful to detect structural variants (e.g., the genomic deletions causing in-frame exon skipping described by Colige 2004, PMID: 15373769). - Karyotype/FISH/CMA and mitochondrial testing are **not indicated** (not a cytogenetic or mitochondrial disorder).

Clinical criteria & differential diagnosis. Diagnosis follows the **2017 international EDS classification**, which requires spotting clinical red flags and eliminating differential diagnoses, with molecular confirmation (PMID: 40887396). Differential diagnoses include other EDS subtypes (classical EDS, kyphoscoliotic EDS, cutis laxa syndromes) and *AEBP1*-related EDS (thin/hyperextensible skin, atrophic scarring, joint hypermobility, osteoporosis — PMID: 30668708). Distinguishing features of dEDS: congenital *extreme* skin fragility and laxity with redundant skin folds and characteristic facies, plus the specific pN-collagen biochemical signature.

Screening. For at-risk families, **cascade genetic testing** and **carrier testing** of relatives; prenatal/preimplantation genetic testing is feasible once the familial variants are known.

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11. Outcome / Prognosis

- **Survival / life expectancy:** dEDS is generally **not primarily life-limiting** in the way vascular EDS is, but severe visceral and vascular fragility can cause major, potentially life-threatening complications (e.g., gastric volvulus secondary to diaphragmatic hernia; vascular rupture) (PMID: 26765342; PMID: 39641471). Formal survival statistics are unavailable (ultra-rare).
- **Morbidity / disability:** substantial and lifelong — chronic skin fragility, disfiguring redundant skin folds (often requiring surgical resection), recurrent bruising, hernias, fractures, and reduced bone mineral density in adults (PMID: 39641471).
- **Complications:** iatrogenic skin injury during medical care, poor wound healing/atrophic scarring, hernias, gastric volvulus, fractures, and vascular events.
- **Prognostic factors:** severity of the phenotype (typical vs. milder variant) and the presence of visceral/vascular fragility. No validated molecular prognostic biomarkers exist.
- **Quality-of-life tools:** no dEDS-specific instruments; generic connective-tissue-disorder burden applies.

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12. Treatment

No curative or disease-specific therapy exists. Under the 2017 framework, non-vascular EDS management is symptomatic, multidisciplinary, and personalized (PMID: 40887396).

> *"There is no specific treatment for non-vascular EDS to date, so the care management is symptomatic, multidisciplinary and personalized."* — Benistan & Guichou, 2026 (PMID: 40887396)

Management pillars (NCIT term suggestions in parentheses): - **Protective / supportive care:** trauma avoidance, meticulous skin protection and wound care, padding, avoidance of unnecessary invasive procedures to prevent iatrogenic injury (NCIT: Supportive Care). - **Surgical intervention:** resection of redundant skin folds; careful surgical technique given fragile tissues and poor healing; hernia repair; management of visceral emergencies such as gastric volvulus (NCIT: Surgical Procedure). Surgery carries elevated risk due to tissue fragility and impaired wound healing. - **Skeletal / bone health:** monitoring and management of reduced bone mineral density and fractures (physiotherapy, fall/fracture prevention; consider bone-health surveillance). - **Rehabilitation:** physiotherapy/occupational therapy for joint hypermobility and function (NCIT: Physical Therapy). - **Pain and symptom management:** as needed, individualized. - **No pharmacogenomic, gene, cell, RNA, targeted, or immunotherapy** is established for dEDS. No approved drugs. No relevant clinical trials with NCT identifiers specific to dEDS.

Personalized medicine. Care is genotype-confirmed but not genotype-*directed* therapeutically; the value of molecular diagnosis lies in prognosis, counseling, and family planning rather than drug selection.

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13. Prevention

- **Primary prevention:** not possible for an inherited monogenic disorder. **Genetic counseling** is central: autosomal-recessive inheritance carries a 25% recurrence risk for siblings of an affected child; carrier testing and cascade screening inform reproductive decisions.
- **Reproductive options:** prenatal diagnosis and **preimplantation genetic testing** are available for families with known *ADAMTS2* variants.
- **Secondary/tertiary prevention:** early diagnosis to implement trauma-avoidance and wound-care protocols; surveillance for and early management of hernias, visceral complications, and bone fragility to prevent morbidity.
- **Immunization / public-health / environmental interventions:** not applicable (non-infectious, non-environmental).

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14. Other Species / Natural Disease

dEDS is remarkable for its **broad natural occurrence across mammals**, all traced to *ADAMTS2* — a strong argument for evolutionary conservation of the collagen-processing mechanism.

Species (NCBI Taxon)	Disease	*ADAMTS2* variant	Source
Cattle, *Bos taurus* (9913)	Bovine dermatosparaxis (original "dermatosparaxis")	17-bp deletion → frameshift	Colige 1999 (PMID: 10417273); Halper 2014 (PMID: 24443030)
Sheep, *Ovis aries* (9940)	Ovine dermatosparaxis (White Dorper)	Causative nonsense mutation	Joller 2017 (PMID: 28856769)
Sheep, *Ovis aries* (9940)	Dermatosparaxis in commercial flock	Catalytic-domain missense **V15M** (SIFT/ PolyPhen damaging)	Monteagudo 2015 (PMID: 25354687)
Dog, *Canis lupus familiaris* (9615)	EDS-like skin fragility	*ADAMTS2*-related and other collagen genes	Halper 2014 (PMID: 24443030)
Cat, *Felis catus* (9685)	Dermatosparaxis/EDS-like	*ADAMTS2*/collagen defects	Halper 2014 (PMID: 24443030)

> *"Several cases of bovine and ovine dermatosparaxis analogous to human Ehlers-Danlos syndrome type VIIC were found to be caused by mutations in the procollagen I N-proteinase (pnPI) or ADAMTS2 gene."* — Halper, 2014 (PMID: 24443030)
>
> *"A missense mutation was identified in the catalytic domain of ADAMTS2. The mutation is predicted to cause the substitution in the mature ADAMTS2 of a valine molecule by a methionine molecule (V15M) affecting the catalytic domain of the enzyme."* — Monteagudo et al., 2015 (PMID: 25354687)

The White Dorper study confirmed the causative nonsense mutation (PMID: 28856769).

Comparative pathology. In dogs and cats, EDS from collagen/ADAMTS2 defects predominantly affects the **skin** (thin, hyperextensible, hemorrhagic wounds, atrophic scars), generally **without** the systemic organ/vascular rupture seen in humans — an important species difference (PMID: 24443030). **Veterinary relevance** is significant in livestock (economic losses; animal welfare). **Zoonotic potential:** none (genetic, non-transmissible). **Orthologous genes:** *ADAMTS2* orthologs (mouse *Adamts2*, bovine/ovine/canine/feline *ADAMTS2*), reflecting deep evolutionary conservation of the N-proteinase mechanism.

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15. Model Organisms

Mouse (*Mus musculus*, NCBI Taxon 10090) is the principal genetic model.

- **Adamts2-knockout mouse:** recapitulates the human skin/collagen phenotype (skin fragility with abnormal collagen fibrils), validating *ADAMTS2* loss of function as sufficient to produce dermatosparaxis-like disease.
- **Paralog redundancy — Adamts14:** *Adamts14*-deficient mice are healthy, fertile, with normal aminoprocollagen processing. Crossing them with *Adamts2*-deficient mice produced double-knockout animals with essentially the same phenotype as *Adamts2*-single-knockouts, establishing **ADAMTS2 as the dominant dermal N-proteinase** and ADAMTS14 as a minor contributor (PMID: 29649548).

> *"showed the same phenotype as that of Adamts2-deficient mice, with no further reduction of procollagen processing and no significant aggravation of the structural alterations of collagen fibrils."* — Dupont et al., 2018 (PMID: 29649548)

- **Emergent immune phenotype:** aged *Adamts2/14* double-knockout **males** (from ~2 months) developed spontaneous atopic-dermatitis-like epidermal lesions driven by abnormal T-lymphocyte activation toward a Th1 profile — a model-specific finding not reported in human dEDS but of mechanistic interest (PMID: 29649548).

> *"the result of an abnormal activation and differentiation of T lymphocytes towards a Th1 profile."* — Dupont et al., 2018 (PMID: 29649548)

- **Division of labor within the ADAMTS2/3/14 subfamily:** *Adamts3*-null embryos die around E15 from failed lymphangiogenesis (VEGF-C dysregulation) with **normal** procollagen I/II/III processing — showing that ADAMTS3's essential role is in lymphatic development, not dermal collagen, while ADAMTS2 handles dermal procollagen (PMID: 26446156).

> *"The only documented activity of a subclass of ADAMTS proteases comprising ADAMTS2, 3 and 14 is the cleavage of the aminopropeptide of fibrillar procollagens."* — Janssen et al., 2016 (PMID: 26446156)

- **Naturally occurring large-animal models** (cattle, sheep — Section 14) provide gross, tissue, and biochemical parallels to human disease.

Model applications & limitations. Mouse and livestock models faithfully reproduce the collagen-processing defect and skin fragility, enabling study of fibrillogenesis, wound healing, and potential enzyme-replacement/gene approaches. Limitations: mice do not fully recapitulate the human facial gestalt or the full spectrum of visceral/vascular complications, and the Th1 atopic-dermatitis phenotype of double-knockouts is not a human dEDS feature.

Model resources: MGI (mouse *Adamts2*), OMIA (bovine/ovine dermatosparaxis), plus large-animal veterinary genetics resources.

Mechanistic Model / Interpretation

dEDS is a textbook **loss-of-function Mendelian enzymopathy of extracellular matrix assembly**. The single molecular lesion — abolished procollagen I N-proteinase activity — propagates deterministically to a macroscopic phenotype:

```
GENE (ADAMTS2, 5q35.3, biallelic LoF)
   → PROTEIN (procollagen I N-proteinase deficiency; loss of function)
      → BIOCHEMISTRY (N-propeptide not excised; pN-collagen accumulates)
         → ULTRASTRUCTURE (defective ribbon-like "hieroglyphic" fibrils)
            → TISSUE (weak dermal/connective matrix)
               → CLINICAL (extreme skin fragility, laxity, bruising,
                           facies, hernias, visceral/vascular/skeletal fragility)
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The disorder sits within the ADAMTS metalloproteinase superfamily paradigm: of 19 mammalian secreted ADAMTS proteinases, several cause **recessive, loss-of-function Mendelian disorders**, first delineated through spontaneous human and animal mutations — including bovine *ADAMTS2* (PMID: 25770910).

> *"These human and animal disorders are recessive and their manifestations appear to result from a loss-of-function mechanism."* — Dubail & Apte, 2015 (PMID: 25770910)
>
> *"spontaneous animal mutations, such as in bovine ADAMTS2."* — Dubail & Apte, 2015 (PMID: 25770910)

The cross-species conservation (human ↔ cattle ↔ sheep ↔ dog ↔ cat ↔ mouse) is the strongest external validation of the mechanism: identical enzyme deficiency yields analogous fragility phenotypes wherever it occurs, with species-specific attenuation of systemic (visceral/vascular) involvement in companion animals.

Evidence Base

PMID	Study	Role in this report
10417273	Colige 1999 — Human EDS VIIC & bovine dermatosparaxis caused by procollagen I N-proteinase mutations	**Foundational**: molecular proof that *ADAMTS2* LoF causes human dEDS and bovine dermatosparaxis; defines pNPI function; recurrent Q225X
26765342	Van Damme 2016 — Expanding clinical & mutational spectrum	Expands LoF variant spectrum; defines characteristic gestalt, extreme fragility, visceral/vascular complications, milder variant
39641471	Angwin 2025 — Natural history, adult case series	Adult complications: iatrogenic injury, redundant skin resection, gastric volvulus, fractures, low BMD
15373769	Colige 2004 — Novel mutation types	In-frame exon-skipping variants also abolish enzyme activity; broadens variant classes
25863161	Bekhouche & Colige 2015 — ADAMTS2/3/14 in pathophysiology	Places ADAMTS2 in the N-proteinase family; explains propeptide-removal requirement for fibrillogenesis
29649548	Dupont 2018 — Adamts2/14 double-KO mice	ADAMTS2 is dominant dermal N-proteinase; ADAMTS14 minor; emergent Th1 immune dysregulation
26446156	Janssen 2016 — Adamts3 & lymphangiogenesis	Division of labor within ADAMTS2/3/14 subfamily; ADAMTS3 essential for lymphatics
25770910	Dubail & Apte 2015 — ADAMTS genetics review	Frames dEDS as recessive LoF disorder in the ADAMTS superfamily
24443030	Halper 2014 — Connective tissue disorders in domestic animals	Establishes cattle/sheep/dog/cat natural disease; comparative pathology differences
28856769	Joller 2017 — White Dorper sheep	Confirms causative *ADAMTS2* nonsense mutation in ovine dermatosparaxis
25354687	Monteagudo 2015 — Ovine flock	Catalytic-domain missense V15M model
40887396	Benistan & Guichou 2026 — EDS diagnosis & care	

PMID	Study	Role in this report
		2017 classification framework; no specific treatment; symptomatic multidisciplinary care
30668708	Blackburn 2019 — *AEBP1* EDS	Differential diagnosis (EDS-like phenotype from a distinct gene)

All quoted snippets above were verified against the stored abstracts during the investigation.

Limitations and Knowledge Gaps

1. **Ultra-rarity limits epidemiology.** Fewer than ~100 human cases are reported; precise prevalence, incidence, sex/age distributions, penetrance quantification, and formal survival statistics are unavailable. Estimates are qualitative.
2. **No quality-of-life or PRO data** specific to dEDS (no EQ-5D/SF-36/PROMIS studies).
3. **No omics resources** (transcriptomic/proteomic/metabolomic/single-cell) dedicated to human dEDS; mechanism rests on biochemistry, EM, and genetics.
4. **UniProt/structural protein-level queries were unavailable during the investigation**, so ADAMTS2 domain-level structural detail is drawn from the primary literature rather than direct database interrogation.
5. **Genotype–phenotype correlation is incomplete** — the basis for the "typical severe" vs. "milder" variant distinction, and modifiers of expressivity, are not resolved in humans.
6. **Therapeutics gap:** no disease-modifying therapy; no dEDS-specific clinical trials identified.
7. **Model-to-human translation caveat:** the Th1 atopic-dermatitis phenotype of *Adamts2/14* double-KO mice is not a documented human feature and should not be over-interpreted.

Proposed Follow-up Experiments / Actions

1. **Establish a dEDS patient registry** (multicenter, international) to capture prevalence, natural history, complication rates, and standardized quality-of-life outcomes.

2. **Genotype–phenotype study** correlating variant class/location (e.g., catalytic vs. ancillary domains, complete vs. partial LoF) with severity, to explain the typical-vs-milder dichotomy.
3. **Deep phenotyping of visceral/vascular fragility** (imaging surveillance protocols) to define screening recommendations and prevent life-threatening events such as gastric volvulus.
4. **Bone-health natural history** — systematic assessment of BMD and fracture risk across the lifespan to guide surveillance and intervention.
5. **Preclinical therapeutic proof-of-concept** using existing *Adamts2*-KO mouse and livestock models: evaluate enzyme-replacement, gene-addition/AAV, or read-through strategies for nonsense alleles (e.g., Q225X, W795X).
6. **Molecular/EM diagnostic standardization** — validate the pN-collagen biochemical assay and fibril-morphometry as adjuncts to molecular testing.
7. **UniProt/structural follow-up** — retrieve ADAMTS2 domain architecture and map pathogenic variants onto structure (including the in-frame exon-skipping regions shown to be functionally essential) once the resource is available.
8. **Cross-species comparative study** to understand why companion animals are spared systemic organ/vascular rupture, potentially revealing protective modifiers relevant to human disease.

Report compiled from a 5-iteration autonomous investigation; 7 confirmed findings, 30 papers reviewed. All mechanistic and clinical claims are anchored to primary literature with verified abstract quotations.
