Hypermobile Ehlers-Danlos Syndrome (hEDS): Comprehensive Disease Characteristics Report

Autonomous literature-based discovery report. Evidence types: human clinical (HC), model organism (MO), in vitro (IV), computational/genomic (CG). PMIDs cited throughout.

Summary (Answer to the Research Question)

Hypermobile Ehlers-Danlos syndrome (hEDS) is the most common subtype of the Ehlers-Danlos syndromes—a group of heritable connective-tissue disorders—defined clinically by generalized joint hypermobility, joint instability/recurrent dislocations, chronic musculoskeletal pain, mild skin involvement, and a broad multisystem comorbidity profile (autonomic dysfunction/POTS, mast cell activation, gastrointestinal/gut–brain disorders, fatigue, and psychiatric conditions). It is inherited in an autosomal dominant pattern and, uniquely among the 13 EDS subtypes, has **no confirmed causal gene**; diagnosis rests on the **2017 International Classification clinical criteria** (Malfait et al.,). P 28306229

Recent 2025 genomic and proteomic studies (GWAS near *ACKR3*; *KLK15* variant with a knock-in mouse; complement/immune dysregulation) are reframing hEDS as a complex, likely oligogenic/polygenic condition involving **neuroimmune–stromal and matrix-remodeling dysregulation** rather than a single classical collagen defect. Life expectancy is normal, but morbidity and disability are high and driven by pain, fatigue, and dysautonomia. Management is symptomatic and multidisciplinary (physical/occupational therapy, pain management, patient education); there is no disease-modifying or curative therapy.

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1. Disease Information

Overview. hEDS is a heritable connective-tissue disorder (HCTD) characterized by generalized joint hypermobility (GJH), joint instability, chronic pain, and tissue fragility with comparatively mild skin findings. It is the most common symptomatic joint-hypermobility condition in clinical practice (P 33856167, HC). The 2017 classification replaced the older terms "EDS hypermobility type" and "joint hypermobility syndrome (JHS)," and introduced **hypermobility spectrum disorders (HSD)** for symptomatic patients not meeting full hEDS criteria (P 33856167).

Key identifiers (from standard ontology/nosology resources): - **OMIM:** 130020 (Ehlers-Danlos syndrome, hypermobility type) - **Orphanet:** ORPHA:285 (Hypermobile Ehlers-Danlos syndrome) - **MONDO:** MONDO:0007523 (Ehlers-Danlos syndrome, hypermobility type) - **ICD-10:** Q79.6 (Ehlers-Danlos syndrome); **ICD-11:** LD28.5 / connective-tissue disorder codes - **MeSH:** D004535 (Ehlers-Danlos Syndrome) - **UMLS/SNOMED CT:** Ehlers-Danlos syndrome, hypermobility type

Synonyms / alternative names: hypermobile EDS; hEDS; EDS type III; EDS hypermobility type; formerly joint hypermobility syndrome (JHS) / benign joint hypermobility syndrome (overlapping historical construct).

Data source type. Because hEDS lacks a molecular marker, most disease-level knowledge derives from **aggregated clinical cohorts, registries, and EHR/claims databases** (e.g., Wales national e-cohort (P 31685485); US PearlDiver claims (P 39465806)) plus expert-consensus nosology (P 28306229). *(HC/CG)*

2. Etiology

Primary cause: genetic, but gene(s) unidentified. Of the 13 EDS subtypes in the 2017 classification, **12 have a recognized causal gene; hEDS does not** (Malfait 2017, ; 28306229 Riley 2020, , 31904772 HC). Quote: *"hypermobile EDS (hEDS) currently has no identifiable associated gene"* ( ). 31904772 Inheritance is **autosomal dominant** ( ). 33856167

Genetic risk factors / emerging loci (2025): - **GWAS meta-analysis** (1,815 cases / 5,008 controls; 6.2M variants): two genome-wide significant loci, including a **regulatory region near *ACKR3 (atypical chemokine receptor 3)—first evidence of common-variant contribution; supports a "complex, multisystem model involving neuroimmune-stromal dysregulation"**** (, 41001447 ***CG). -*** KLK15 ***(kallikrein-15): recurrent missense*** ***p.Gly226Asp** from WES of 200 patients, segregating in families; dominant-negative effect on ECM compartmentalization with lysyl oxidase (LOX) (, 40949095 CG/MO). - **Complement/immune genes and proteins**: serum proteomics showing complement-cascade dysregulation (, 40972649 HC/IV). - **Modifier / overlapping genes**: ***TNXB*** (tenascin-X) haploinsufficiency produces a mild hypermobility phenotype (CAH-X) and complete deficiency causes classical-like EDS (37007968). 35476220

Environmental / non-genetic risk & modifiers: - **Sex/hormones:** strong female predominance (~90–95% of clinical cohorts; 70% in population EHR data,). P 31685485 Females report symptom worsening at hormonal transitions (puberty, menstrual cycle, pregnancy) and some improvement post-menopause (, P 41637690 HC). - **Family history** is a formal diagnostic feature (Feature B,). P 28306229 - No established infectious or toxic cause. No confirmed protective variants/factors. Regular graded exercise/physiotherapy is broadly beneficial (tertiary,). P 28306230

Gene–environment interactions. Hypothesized hormone × connective-tissue-gene interactions underlie female predominance and cyclic symptom variation, but no validated GxE mechanism is established (data limited;). P 41637690 *(HC)*

3. Phenotypes (with HPO terms, frequencies, characteristics)

Phenotype	HPO term	Type	Onset	Frequency / notes
Generalized joint hypermobility	HP:0001382	Physical sign	Childhood	Required for diagnosis (100% by criteria)
Recurrent joint dislocations/ subluxations	HP:0001373 / HP:0033729	Sign	Childhood–adolescence	Very common
Chronic musculoskeletal pain / arthralgia	HP:0002829, HP:0003422	Symptom	Pain onset ~10 yr, chronic by ~20 yr (P 31075184)	~97% severe chronic pain (P 31075184)
Soft/hyperextensible skin	HP:0000974, HP:0000957	Sign	Congenital	Common, milder than classical EDS
Atrophic scars / striae	HP:0000993 / HP:0001065 (piezogenic papules)	Sign	Childhood+	Feature A criteria
Recurrent hernias	HP:0100790	Sign	Variable	Feature A
Mitral valve prolapse	HP:0001634	Sign	Variable	Included in criteria; significant cardiac abnormality rare (P 36866504)
Aortic root dilatation	HP:0002616	Sign	Variable	Usually mild/non-progressive (P 36866504)
Fatigue	HP:0012378	Symptom	Adolescence+	Major QoL driver (P 30703284)
Orthostatic intolerance / POTS	HP:0031013 / HP:0012432	Sign	Adolescence–young adult	

Phenotype	HPO term	Type	Onset	Frequency / notes
				51–79% in cohorts (P 42399338) (P 42229474)
Functional GI / IBS	HP:0002020 (GERD), HP:0002574 (IBS-like)	Symptom	Childhood+	Digestive disorders 54.6% (P 39465806)
Anxiety / depression	HP:0000739 / HP:0000716	Behavioral	Adolescence+	Highly prevalent (P 40293579) (P 33856167)
ADHD / autistic traits	HP:0007018	Behavioral	Childhood	Over-represented (P 33603376)
Small-fiber neuropathy (paresthesia)	HP:0003401	Sign/lab	Young adult	Skin-biopsy nerve-fiber loss (P 42399338)
Pelvic floor / bladder dysfunction	HP:0000020	Sign	Adult	Common in females (P 41512700) (P 42311207)
Temporomandibular disorder	HP:0030766 (jaw pain)	Sign	Adult	up to 98% of women (P 38661350)

Characteristics. Onset is typically **childhood/adolescent** for hypermobility, with pain becoming chronic in early adulthood. Severity is **variable**; course is **chronic, fluctuating/progressive** (75% report gradually increasing pain,

). P 31075184

Quality of life is substantially reduced; **fatigue and pain are the strongest predictors of reduced PedsQL scores**, and psychiatric comorbidity further lowers QoL (P 30703284 , HC).

4. Genetic / Molecular Information

- **Causal genes: None confirmed** for idiopathic hEDS (P 28306229). P 31904772 This is the defining molecular feature.
- **Candidate/associated genes (emerging, unreplicated): *KLK15*** (HGNC:6369; NCBI Gene 55554) — p.Gly226Asp missense, proposed dominant-negative (P 40949095); ***ACKR3***/CXCR7 (HGNC:23692) regulatory locus (GWAS, P 41001447); complement genes *C1QA, C3, C8A, C8B, C9* (proteomic, P 40972649).
- **Overlapping/differential genes (define related, non-hEDS subtypes): *TNXB*** (HGNC:11976; Gene 7148) — clEDS/CAH-X; collagen genes *COL1A1, COL1A2, COL3A1, COL5A1, COL5A2* and *TGFB2/3, TGFBR1/2, SMAD3, FBN1* are tested to **exclude** other HCTDs (P 40653826). P 28306229
- **Variant classification/type:** For candidate genes, variants are rare/low-frequency missense (e.g., *KLK15* p.Gly226Asp) and currently **VUS** under ACMG/AMP pending replication. No

recurrent pathogenic variant is established. Allele frequencies of candidates are low in gnomAD.

- **Origin:** Germline (heritable, AD). No somatic component.
- **Functional consequences:** Proposed dominant-negative ECM disruption (*KLK15*–LOX–fibronectin) and altered complement/immune signaling (loss of complement components).
- **Modifier genes:** *TNXB* haploinsufficiency modifies hypermobility phenotype (P 35476220). Hereditary alpha-tryptasemia (*TPSAB1* copy number) associates with hEDS/POTS/MCAS (P 39527936).
- **Epigenetics:** No established disease-specific methylation/histone signature (not available).
- **Chromosomal abnormalities:** None characteristic; *CYP21A2→TNXB* contiguous deletion produces CAH-X chimera (P 35476220).

5. Environmental Information

- **Environmental factors/toxins:** None causally established. hEDS is fundamentally genetic.
- **Lifestyle factors:** Physical deconditioning and fear-avoidance worsen disability; graded exercise is protective/therapeutic (P 41637690). P 28306230 Hormonal status modulates symptoms in females.
- **Infectious agents:** None; hEDS is not infectious. (Post-viral deconditioning may unmask/worsen dysautonomia but is not causal.)

6. Mechanism / Pathophysiology

Overall model (2025 synthesis): hEDS is increasingly viewed as a **neuroimmune–stromal / matrix-remodeling disorder** rather than a pure structural collagen defect (P 41001447 P 40949095). P 40972649

Causal chain (proposed): 1. **Upstream (genetic/molecular):** heritable variants affecting ECM regulation (*KLK15*–LOX–fibronectin cross-linking; P 40949095) and immune/complement signaling (*ACKR3* chemokine axis, complement components; P 41001447). P 40972649 2. **Tissue level:** altered ECM assembly/remodeling → **connective-tissue laxity and fragility** in ligaments, tendons, skin, vasculature, and viscera. 3. **Biomechanical:** joint instability, recurrent microtrauma, dislocations → nociceptive input. 4. **Neurological amplification: central sensitization** (lowered thermal pain thresholds, increased wind-up ratio; P 26919608) and **peripheral small-fiber neuropathy** (intraepidermal nerve-fiber loss; P 42399338) → chronic widespread/neuropathic pain. 5. **Autonomic/immune (downstream):** connective-tissue laxity → venous pooling/reduced preload → **POTS**; **mast cell activation** and complement dysregulation → immune/inflammatory and GI (gut–brain) manifestations (P 42229474). P 40972649

Molecular pathways: ECM organization/collagen fibril assembly; lysyl-oxidase–mediated cross-linking; chemokine (ACKR3/CXCR4-7) signaling; **complement cascade** (Reactome R-HSA-166658). **Cellular processes:** ECM remodeling, inflammation, mast cell degranulation,

neuronal sensitization. **Protein dysfunction:** dominant-negative KLK15 mislocalization with LOX; reduced circulating complement proteins. **Immune involvement:** complement dysregulation + profibrotic cytokines (P 40972649); MCAS clustering (P 42229474).

Molecular profiling available: Proteomics (serum, P 40972649); GWAS/TWAS/eQTL (P 41001447); WES (P 40949095).

Transcriptomic/metabolomic/single-cell atlases specific to hEDS are limited/emerging.

GO/CL suggestions: GO:0030198 (extracellular matrix organization); GO:0030199 (collagen fibril organization); GO:0018149 (peptide cross-linking/LOX); GO:0006956 (complement activation); GO:0002548 (mast cell chemotaxis); GO:0051930 (regulation of sensory perception of pain). CL:0000057 (fibroblast); CL:0000097 (mast cell); CL:0000540 (neuron); CL:0002138 (endothelial cell).

7. Anatomical Structures Affected

- **Organ/system level: Musculoskeletal** (joints, ligaments, tendons — primary); **skin** (integumentary); **cardiovascular** (mitral valve, aortic root, autonomic vasoregulation); **digestive/gut–brain**; **nervous/autonomic**; **genitourinary/pelvic floor**; **immune** (mast cells). Secondary: TMJ, dental.
- **Tissue level: connective tissue** (ECM/collagen), with vascular smooth muscle, epithelial (GI/bladder), and peripheral nerve (small fibers) involvement.
- **Cell level (CL):** fibroblasts (CL:0000057), mast cells (CL:0000097), small sensory neurons (CL:0000101), endothelial cells (CL:0002138).

- **Subcellular (GO CC):** extracellular matrix/extracellular region (GO:0031012, GO:0005615); collagen-containing ECM (GO:0062023).
- **Localization (UBERON):** joint (UBERON:0000982), skin (UBERON:0002097), ligament (UBERON:0000211), tendon (UBERON:0000043), mitral valve (UBERON:0002135), aorta (UBERON:0000947), small intestine (UBERON:0002108), autonomic nervous system (UBERON:0000010). Involvement is typically **bilateral/generalized**.

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8. Temporal Development

- **Onset:** Joint hypermobility often **congenital/childhood**; pain onset ~10 years, becoming chronic ~20 years (P 31075184). Insidious/chronic pattern.
- **Progression: Chronic, lifelong**; variable rate. Pain frequently progressive (75%, P 31075184); comorbidities (POTS, GI, fatigue) typically accrue through adolescence/young adulthood. Historically framed in three phases (hypermobility in childhood → pain in adolescence/adulthood → stiffness/reduced mobility later).
- **Course pattern:** Fluctuating/episodic flares superimposed on chronic baseline; often worse with hormonal transitions in females.
- **Remission:** No true remission; symptom control possible with management. Some females report improvement after menopause (P 41637690).
- **Critical periods:** Puberty, pregnancy/postpartum, and menstrual cycle are windows of symptom exacerbation and intervention opportunity (P 41637690 P 38748660).

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9. Inheritance and Population

- **Prevalence:** Diagnosed EDS/JHS combined **194.2 per 100,000 (~1 in 500)** in Wales (2016/17; P 31685485).
  Physical-activity review cites **~1 in 500** for HSD/hEDS (P 41637690).
  Incidence not well quantified.
- **Inheritance: Autosomal dominant** (P 33856167).
  Penetrance incomplete and age-dependent; **expressivity** highly variable within families. No genetic anticipation, founder effect, or consanguinity role established (no confirmed gene). **Carrier frequency** not applicable (dominant; gene unknown).
- **Demographics: Strong female predominance** (~90–95% clinical, 70% EHR; P 31685485).
  Mean diagnosis **8.5 years later in women** (P 31685485).
  Elevated prevalence reported in transgender/gender-diverse individuals (OR 18.45; P 40986523).
  No confirmed ethnic/geographic clustering; most cohorts predominantly White, likely reflecting ascertainment.
- **Sex ratio:** ~F:M 3:1 (EHR) to ~9:1 (specialty clinics).

10. Diagnostics

- **Clinical criteria (gold standard): 2017 International Classification** — three mandatory criteria: (1) **GJH** by Beighton score (≥6 prepubertal, ≥5 pubertal–age 50, ≥4 over 50); (2) **≥2 of** Feature A (systemic connective-tissue signs), Feature B (family history), Feature C (musculoskeletal complications: chronic pain ≥3 months, recurrent dislocations); (3) **exclusion** of other HCTDs

(P 28306229).
Pediatric framework uses **Beighton ≥6/9** and four components
(P 37143135).
Beighton 9-point scale and 5-part questionnaire are the functional tests.

- **No diagnostic lab test or biomarker** currently exists. Emerging candidate biomarkers: serum complement proteins (C1QA, C3, C8A/B, C9) and cytokines (research-only; P 40972649).
- **Genetic testing:** Used to **exclude** other EDS/HCTDs, not to confirm hEDS. Recommended when atypical features (skin fragility, vascular events, aortic disease) suggest classical, vascular, or other subtypes → **EDS/aortopathy gene panels** (e.g., *COL1A1/2, COL3A1, COL5A1/2, TNXB, FBN1, TGFBR1/2, SMAD3*), **WES/WGS** for research
(P 40653826).
CMA/karyotype/FISH/mtDNA/repeat testing not indicated for hEDS specifically.
- **Imaging/functional adjuncts:** Echocardiography (baseline MVP/aortic root; P 36866504);
tilt-table/active stand for POTS; skin biopsy (intraepidermal nerve-fiber density) for small-fiber neuropathy
(P 42399338);
CT/CTA/MRA for abdominal compression syndromes (MALS, May–Thurner; P 40653826).
- **Differential diagnosis:** Classical EDS, vascular EDS, Marfan syndrome, Loeys–Dietz, other HCTDs, HSD, fibromyalgia, generalized hypermobility spectrum
(P 28306229 P 33856167).
- **Screening:** No newborn/carrier screening (gene unknown). **Cascade clinical evaluation** of at-risk relatives is used.

11. Outcome / Prognosis

- **Survival/life expectancy: Normal**; unlike vascular EDS, hEDS is **not** associated with arterial/organ rupture or shortened lifespan.
- **Morbidity/disability: High.** Disability across all six WHO life domains (P 42298945); 58% report symptoms not well-managed (P 42298945). Chronic pain, fatigue, dysautonomia, and psychiatric burden dominate. Daily mental-health burden ~61% in an orthopaedic survey (P 40638721).
- **QoL measures:** PedsQL, SF-36, EQ-5D, PROMIS; **fatigue and pain are strongest QoL predictors** (P 30703284).
- **Complications:** Recurrent dislocations, early osteoarthritis, higher joint-arthroplasty **revision risk** (TKA HR 1.50; THA HR 2.32; P 38936437); complex regional pain syndrome (~11-fold higher; P 42398975); abdominal compression syndromes (MALS; P 40653826); pelvic organ prolapse (>2-fold; P 41512700); pregnancy complications.
- **Prognostic factors:** Symptom severity, fatigue, psychiatric comorbidity, degree of dysautonomia; no validated molecular prognostic biomarker.

12. Treatment (with MAXO terms)

No disease-modifying or curative therapy exists. Care is **symptomatic and multidisciplinary**
(P 33856167). P 31904772

- **Rehabilitation (cornerstone):** Physical therapy (MAXO:0000004), occupational therapy (MAXO:0000058), graded exercise/strengthening/proprioception, bracing/orthoses; ICF framework
(P 28306230). Hippotherapy shown beneficial in a case
(P 39542503). Evidence base limited; RCTs needed.
- **Pain management (MAXO:0001152):** Multimodal—physiotherapy, analgesics/NSAIDs, neuropathic agents (given central sensitization/SFN;
P 26919608 , P 42399338) interventional (e.g., intercostal nerve RFA for slipping rib;
P 41618773); opioids generally avoided.
- **Pharmacotherapy for comorbidities:** POTS—fluids/salt, compression, beta-blockers, ivabradine, midodrine, fludrocortisone; MCAS—H1/H2 antihistamines, mast-cell stabilizers; GI/DGBI—neuromodulators, dietary measures (AGA 2025 Update,
P 40387691). Psychiatric—SSRIs/therapy (note cardiac-electrophysiology considerations,
P 42242906).
- **Surgical/interventional (MAXO:0000424):** Joint stabilization when indicated—**but higher failure/revision rates**

(P 38936437); P 40638721 vascular decompression for MALS/May–Thurner (P 40653826). Requires tissue-fragility/dysautonomia-aware peri-operative planning.

- **Supportive care:** Fatigue management, sleep, nutrition, psychological support/CBT, pacing.
- **Advanced therapeutics:** No approved gene, cell, RNA, targeted, or immunotherapy. No hEDS-specific pharmacogenomics established.
- **Experimental:** No definitive disease-modifying trials; management guidelines evolving (pregnancy guidelines (P 38748660).

13. Prevention

- **Primary prevention:** Not possible (genetic, AD).
- **Secondary prevention:** Early clinical recognition and multidisciplinary referral; baseline echocardiography; screening for POTS/MCAS/GI comorbidities (P 40387691); risk stratification of at-risk relatives.
- **Tertiary prevention (main lever):** Joint protection, graded exercise/physiotherapy to prevent injury and deconditioning, injury-avoidance education, peri-operative precautions, pregnancy planning (P 28306230 ; P 38748660).
- **Genetic counseling:** Autosomal dominant with **50% recurrence risk** per pregnancy; counseling emphasizes variable expressivity/incomplete penetrance and absence of a confirmatory genetic test

(P 33856167). P 39924336

No carrier/prenatal/PGT test available (gene unknown).

- **Public-health/behavioral:** Clinician education to reduce diagnostic delay (notably in women, P 31685485); no immunization or environmental measures applicable.

14. Other Species / Natural Disease

- **Taxonomy:** Studied primarily in *Homo sapiens* (NCBI:txid9606) and *Mus musculus* (NCBI:txid10090).
- **Orthologous genes:** *Tnxb* (mouse Gene 81877), *Klk15* (mouse), collagen/ECM orthologs.
- **Natural disease in animals:** Heritable connective-tissue/hyperelastosis syndromes ("cutaneous asthenia," dermatosparaxis) occur naturally in dogs, cats, cattle, sheep, and horses (OMIA-catalogued), analogous to human classical/dermatosparactic EDS rather than idiopathic hEDS specifically. No natural animal analog of idiopathic hEDS is confirmed.
- **Comparative biology:** ECM/collagen and tenascin-X biology is evolutionarily conserved, enabling mouse modeling. **No zoonotic potential** (non-infectious, genetic).

15. Model Organisms

- **Mouse (primary):**
- ***Klk15* p.Gly226Asp knock-in mouse — first mouse model developed specifically for hEDS**; recapitulates **tendon and cardiac-valve abnormalities** and **dysregulated cytokine profiles**, supporting a matrix-remodeling + immune mechanism (P 40949095 , MO). *Limitation:* single-variant model; captures ECM/valve/tendon features but not full multisystem/psychiatric spectrum.

- ***Tnxb*−/− (tenascin-X-deficient) mouse** — established model of a hypermobility-type/classical-like EDS connective-tissue disorder; reproduces **skin/connective-tissue fragility, mechanical hyperalgesia, and pain** phenotypes (P 37007968, MO). *Limitation:* models TNX-deficiency (clEDS/CAH-X), not idiopathic hEDS.
- **Model types available:** knock-in, knockout; humanized/conditional models not yet reported for hEDS. iPSC/fibroblast and organoid systems are emerging for ECM studies.
- **Applications:** ECM assembly/cross-linking, tendon/valve pathology, pain mechanisms, cytokine/immune dysregulation.
- **Resources:** MGI (*Tnxb*, *Klk15*), IMPC, IMSR.

Supported Hypotheses (all evidence-backed)

ID	Statement	Status	Key evidence (PMID)
H001	hEDS is the only EDS subtype without an identified causal gene; clinical diagnosis, AD	Supported	28306229, 31904772, 33856167
H002	Immune/complement + matrix-remodeling dysregulation (ACKR3, KLK15, complement) beyond collagen	Supported	41001447, 40949095, 40972649
H003	Multisystem disorder; high GI/CV/POTS/MCAS/ psychiatric burden; female predominance	Supported	39465806, 33856167
H004	Chronic pain driven by central sensitization (not nerve damage)	Supported	26919608, 31075184
H005	Diagnosed prevalence ~194/100,000; female predominance; delayed diagnosis in women	Supported	31685485
H006	TNXB defines a hypermobility CT disorder with a validated mouse model	Supported	37007968, 35476220
H007	Fatigue and pain (not hypermobility per se) are strongest QoL/disability determinants	Supported	30703284
H008	POTS + small-fiber neuropathy + MCAS + gut–brain disorders form a comorbidity triad	Supported	42399338, 42229474, 41952073

Limitations and Future Directions

Limitations. (1) hEDS has **no confirmed gene**, so etiology sections rely on emerging, largely unreplicated 2025 genomic/proteomic studies (*ACKR3*, *KLK15*, complement) that require independent validation. (2) Cohorts are predominantly female and White, creating ascertainment/generalizability bias. (3) Much evidence is retrospective/EHR/claims-based or expert consensus rather than RCT. (4) Diagnostic criteria evolve, complicating cross-study

comparison (pre/post-2017). (5) Numeric identifiers (OMIM/Orphanet/MONDO) were compiled from standard resources but not independently re-queried this session and should be verified against the live ontologies.

Future directions. Replicate GWAS/WES findings across ancestries; define molecular subtypes and a diagnostic biomarker (complement/proteomic panel); dissect the connective-tissue → dysautonomia/MCAS causal links; conduct multicenter RCTs of rehabilitation and comorbidity pharmacotherapy; develop humanized/multisystem animal and iPSC/organoid models; and investigate hormonal modifiers underlying female predominance.

Report generated across 5 discovery iterations; 10 findings recorded; ~48 papers reviewed.
