



Skin Ultrastructure as a Window into Arterial Vulnerability in Vascular Ehlers–Danlos Syndrome: A Comparative Two-Case Report

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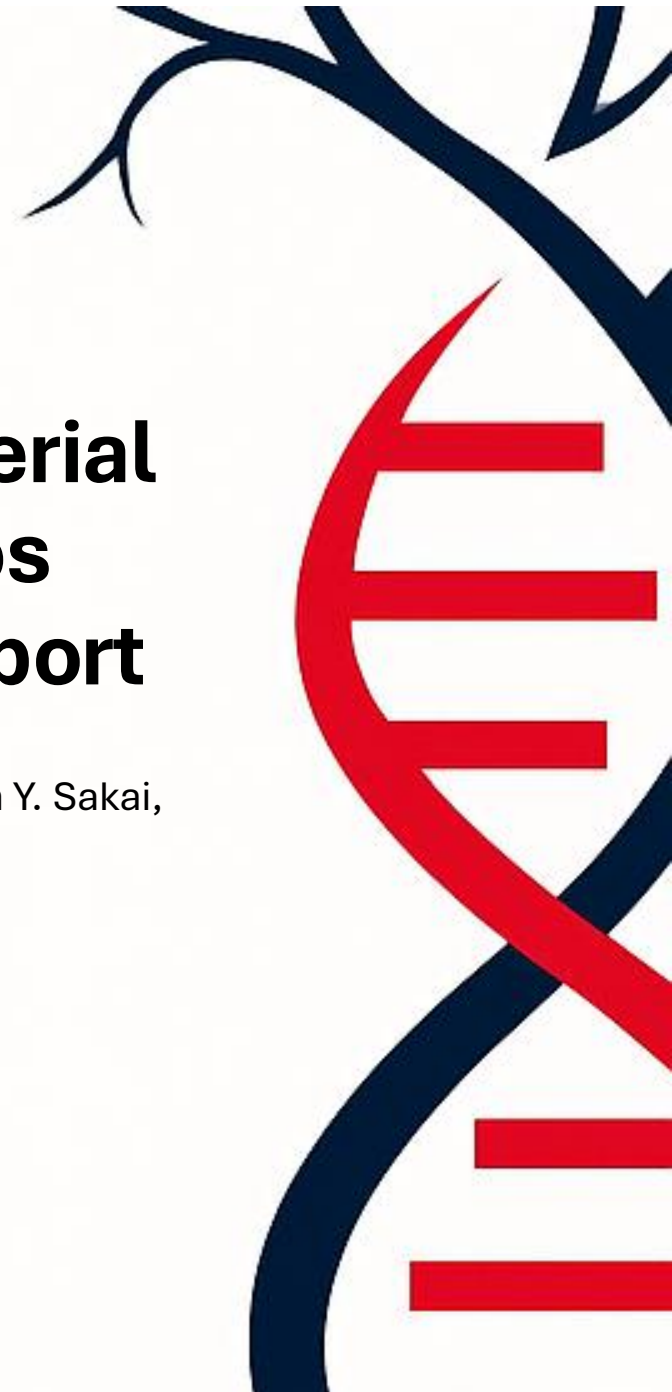
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Disclosures

A cable car is suspended from cables, overlooking a city at dusk. In the background, a large, snow-capped mountain is visible under a pink and purple sky. The city below is illuminated with lights, and several tall buildings are prominent in the foreground.

A.B., D.R.K, S.F.T., L.Y.S., & C.F. have no relevant disclosures or COI.

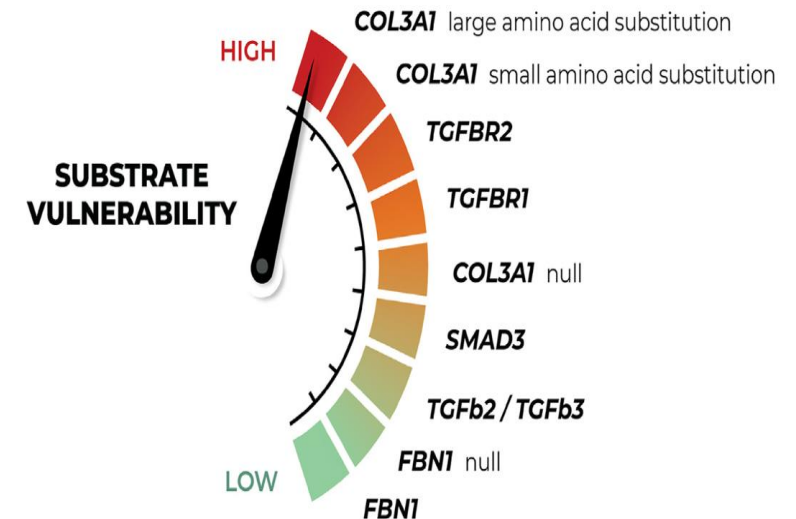
S.S. Advisory Boards: The Ehlers-Danlos Society;
Marfan Foundation; Vascular Cures

Background & Concept

- Vascular Ehler-Danlos Syndrome (VEDS) shows marked heterogeneity in arterial fragility
- Rupture can occur at small diameters
- Others tolerate large aneurysms
- Need biologic markers beyond anatomy

Concept: *Aortic & Arterial Vulnerability Spectrum (AAVS)*

- Arterial risk reflects substrate vulnerability
- Genotype influences ECM architecture
- Biology shapes arterial behavior



Shalhub et al., J Vasc Surg 2025

Case 1

High-Vulnerability Phenotype

- 26-year-old male, *COL3A1* c.1347+1G>A (splice donor)
- Spontaneous left common iliac artery rupture → endovascular repair (VIABAHN stents)
- 1 year later: new right CIA aneurysm (2.6cm) with dissection
- Underwent elective open infrarenal aortic replacement with bifurcated Dacron graft
- Marked intraoperative tissue fragility requiring technical adaptation

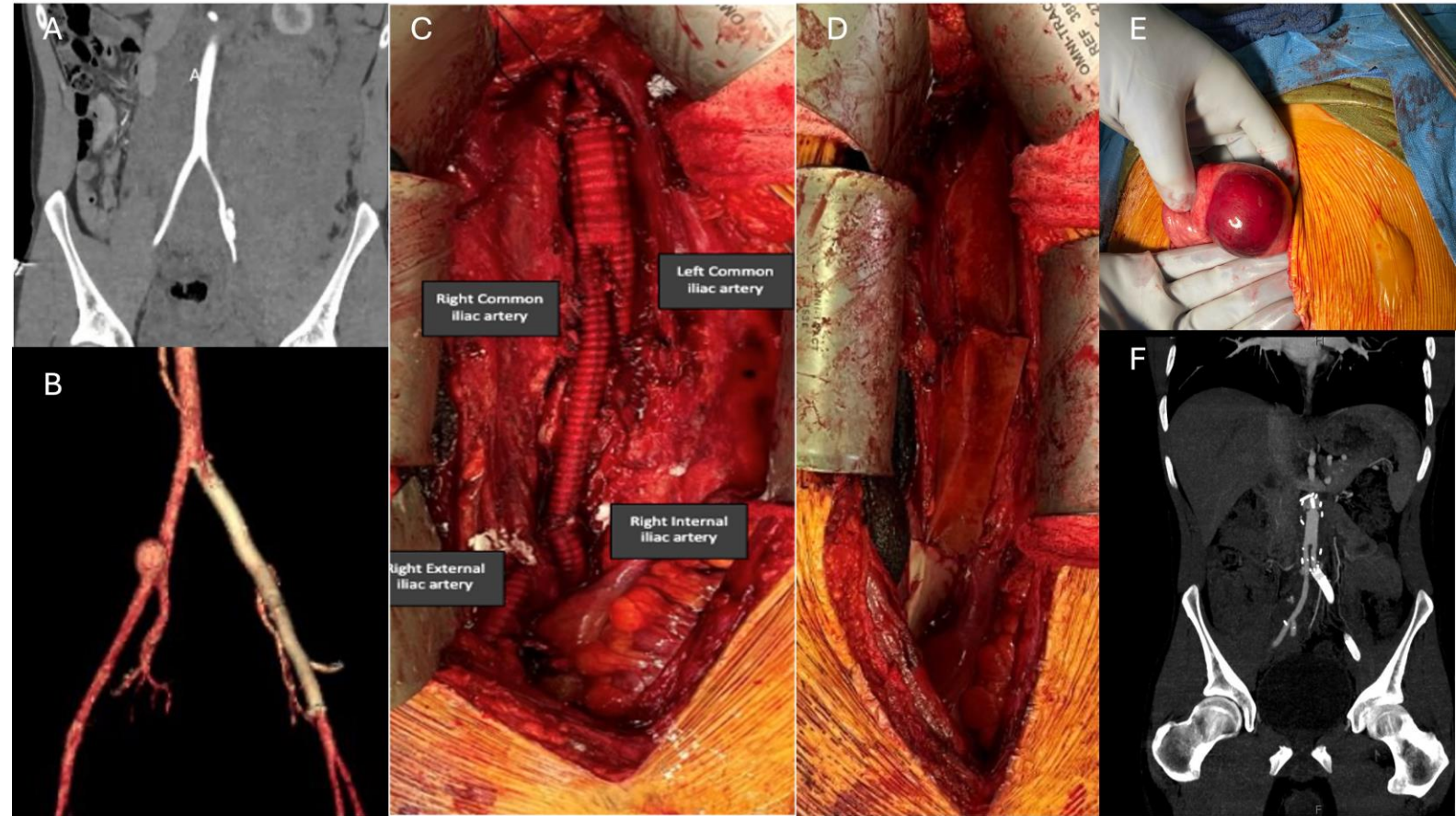


Figure 1. Sequential iliac artery pathology and operative management in case 1, 25-year-old patient with Vascular Ehlers–Danlos syndrome (*COL3A1* c.1347+1G>A, exon skip variant). (A) Computed tomography angiography (CTA) demonstrating spontaneous rupture of the left common iliac artery with a large retroperitoneal hematoma. (B) Surveillance CTA one year later showing interval development of a 2.6 cm right common iliac artery aneurysm with dissection extending into the common femoral artery. (C) Completed bifurcated Dacron aortobiiliac graft incorporating the prior left iliac stent graft with reimplantation of the right internal iliac artery. (D) Neo-retroperitoneal reconstruction using bovine pericardial patches to cover the graft. (E) Intraoperative proximal jejunal serosal hematoma secondary to traction injury. (F) Postoperative CTA demonstrating durable reconstruction without a nastomotic pseudoaneurysm.

Case 2

Low -Vulnerability Phenotype

- 44-year-old male, *COL3A1* c.852+1 G>A, Ala280*, null variant
- Intact AAA (5.5cm) + right CIA aneurysm (7.9cm) with bilateral iliac dissection
- Elective open transperitoneal repair (16x8mm bifurcated Dacron graft)
- Complex iliac reimplantation performed
- No intraoperative tissue fragility
- Outcome
 - EBL 5L (lumbar back-bleeding), operative time 2 hrs
 - Discharged POD8
 - Alive 6 years without new vascular complications

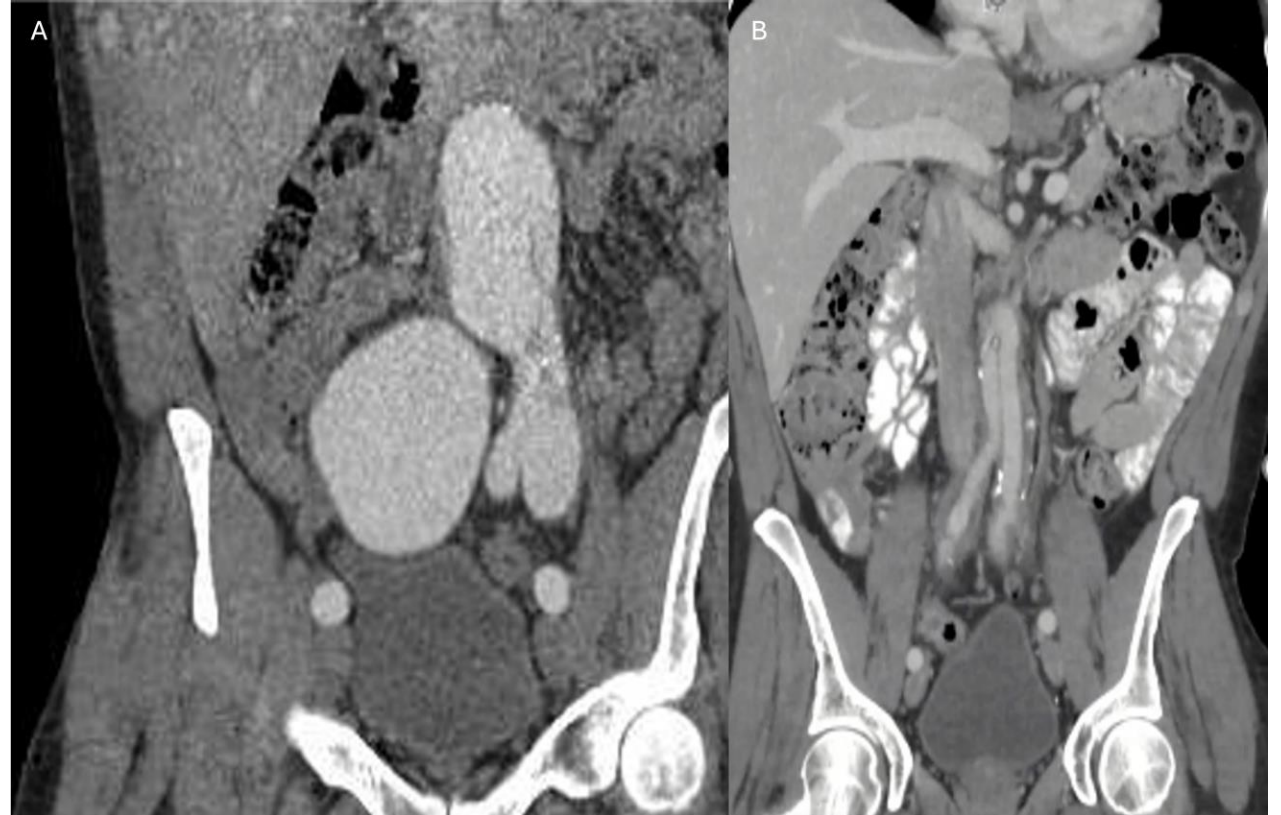


Figure 2. Iliac and aortic aneurysmal disease with dissection

(A) Computed tomography angiography demonstrating an intact right common iliac artery aneurysm measuring 7.9×6.8 cm and an intact infrarenal abdominal aortic aneurysm measuring 5.5×5.2 cm, with an associated dissection extending into both common iliac arteries.

(B) Postoperative computed tomography angiography demonstrating 6 years post repair demonstrating durable reconstruction without anastomotic pseudoaneurysm.

Dermal Ultrastructure

Skin extracellular matrix (ECM) Mirrors Clinical Behavior

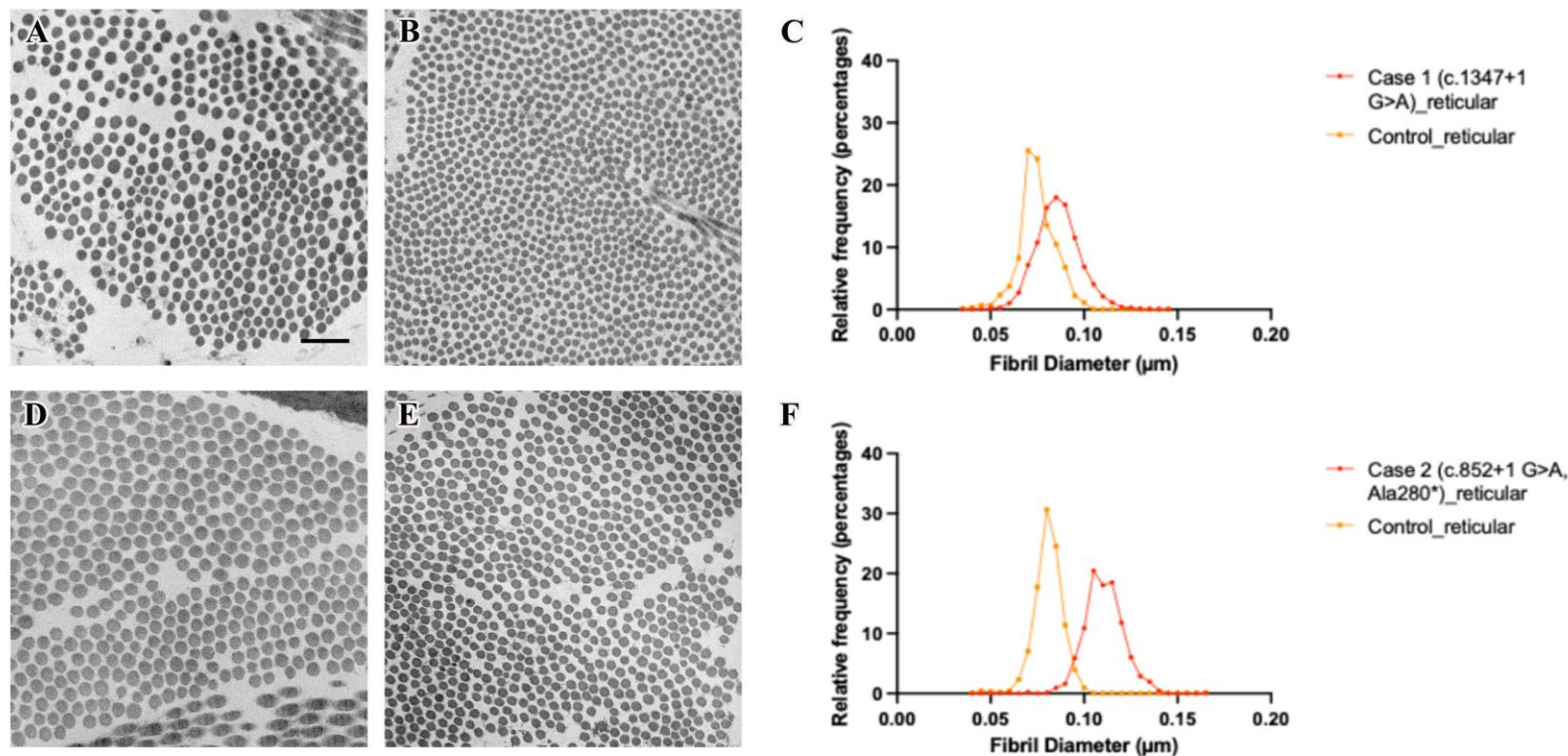


Figure 3. Collagen fibrils in reticular dermis from two patients with vascular Ehlers-Danlos syndrome compared with age- and sex-matched controls.

(A) Representative transmission electron micrograph of reticular dermal collagen from Case 1 (COL3A1 c.1347+1G>A, exon skip variant).
(B) Representative transmission electron micrograph of reticular dermal collagen from an age- and sex-matched control corresponding to Case 1.
(C) Histogram of collagen fibril diameter measurements demonstrating a right-shifted and broadened distribution in Case 1 compared with control.
(D) Representative transmission electron micrograph of reticular dermal collagen from Case 2 (COL3A1 c.852+1G>A, null variant).
(E) Representative transmission electron micrograph of reticular dermal collagen from an age- and sex-matched control corresponding to Case 2.
(F) Histogram of collagen fibril diameter measurements demonstrating an altered and heterogeneous fibril diameter distribution in Case 2 compared with control.

Histograms display area-equivalent collagen fibril diameters measured from true cross-sections in the reticular dermis using a standardized semi-automated Fiji/ImageJ workflow. Patient and control distributions are overlaid to facilitate direct comparison within each age- and sex-matched pair. Scale bar = 500 nm.

Arterial Ultrastructure

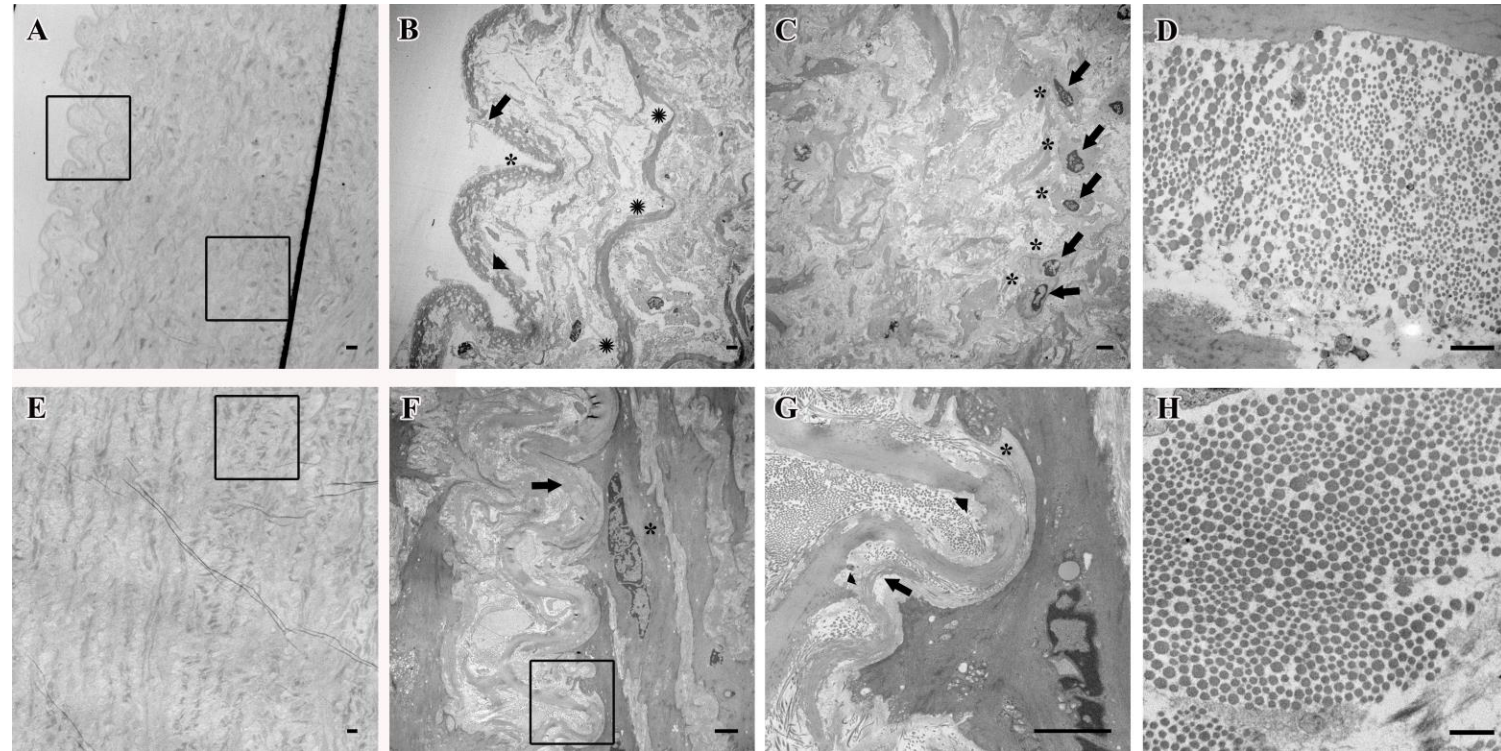
Skin-Artery Correlation — Case 1 (COL3A1 c.1347+1G>A, exon skip)

Iliac artery aneurysm (A–D)

- Severe disruption of medial lamellar architecture
- Fragmented, fenestrated intima
- Dysmorphic smooth muscle cells
- Marked collagen fibril heterogeneity

Non-aneurysmal abdominal aorta (E–H)

- Preserved overall lamellar structure
- Focal elastic fiber fragmentation
- Persistent collagen fibril variability



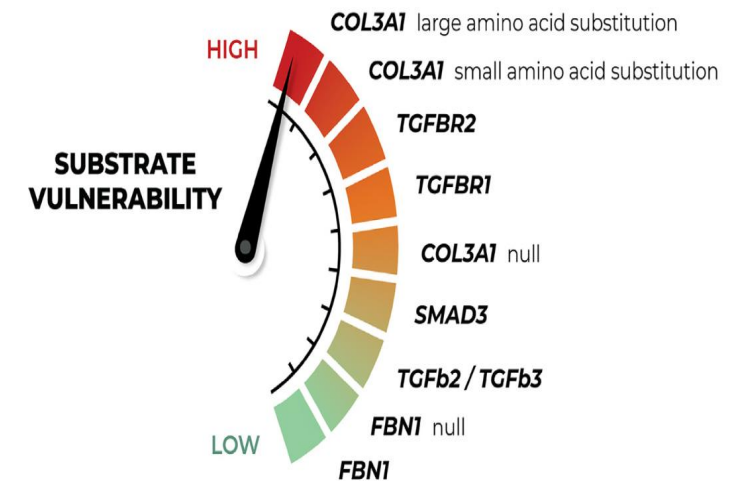
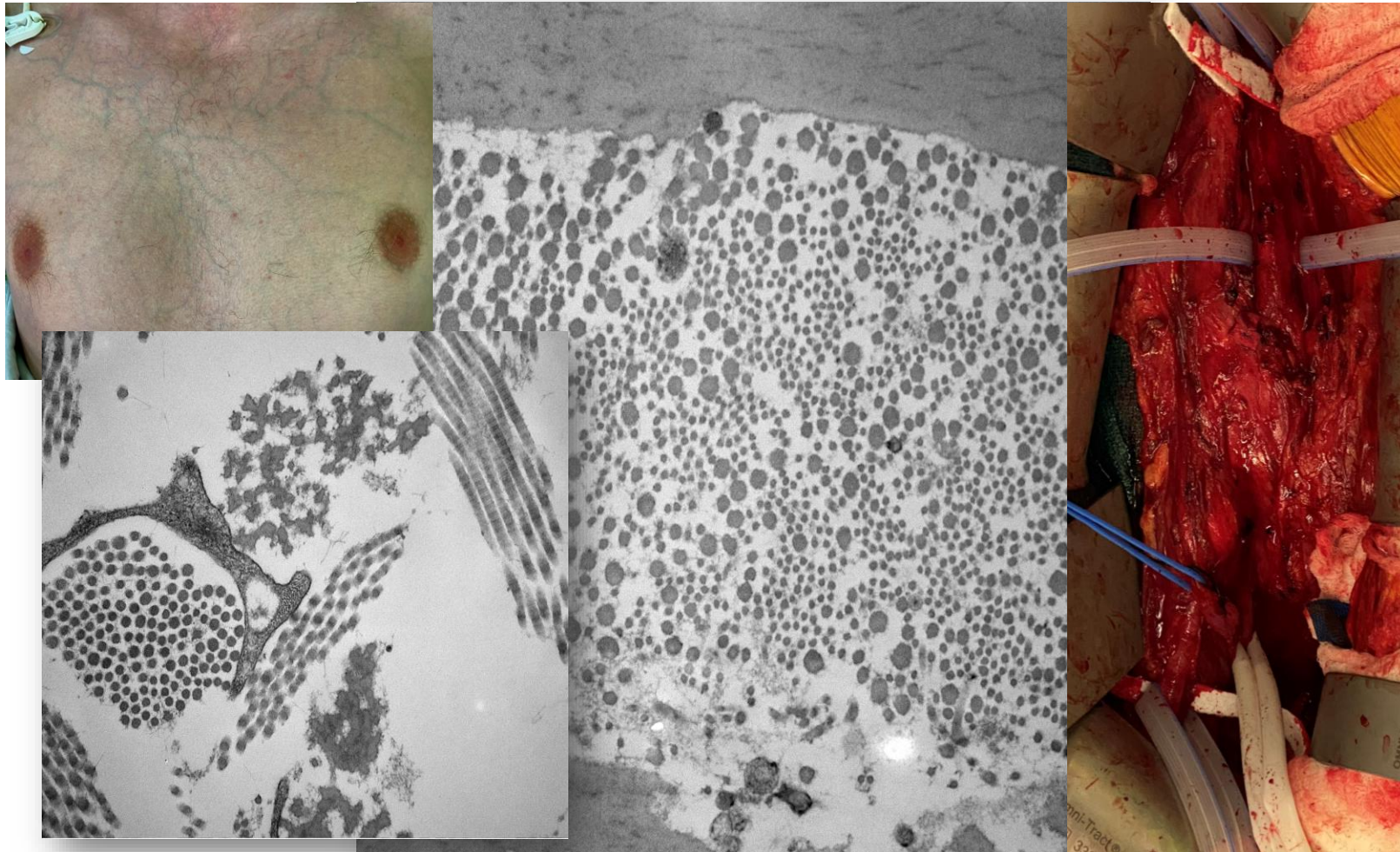
Key Insight: Collagen disorganization present in both aneurysmal and non-aneurysmal segments → supports a systemic ultrastructural abnormality

Key Lessons

- Open repair in VEDS can be successful with meticulous handling.
- Reinforcement and gentle clamp techniques are critical.
- Integrating ultrastructural data may enable genotype-specific surgical planning.

Conceptual Model

Genotype → ECM → Tissue Behavior → Surgical Phenotype



Conceptual illustration of genotype-surgical phenotype correlations (Shalhub, 2025)

Diameter alone does not predict rupture!

Conclusion

- VEDS demonstrates profound biologic heterogeneity
- Dermal ultrastructure correlates with vascular phenotype
- Skin biopsy may provide a biologic window into arterial risk
- Supports precision surgical decision-making