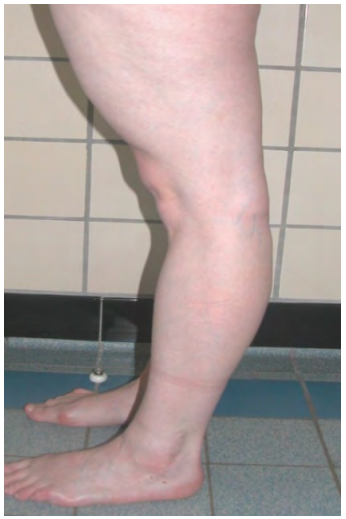
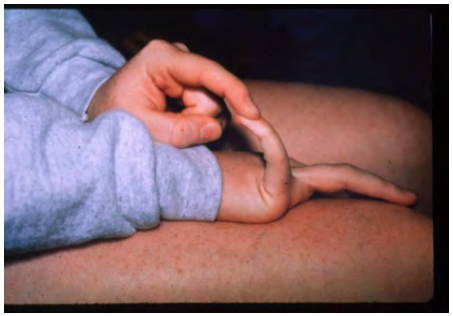
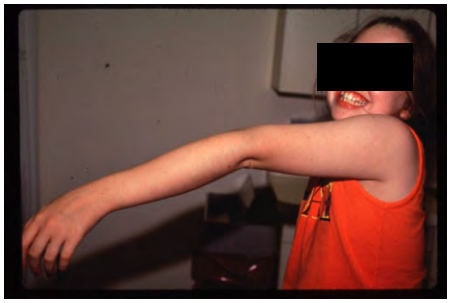
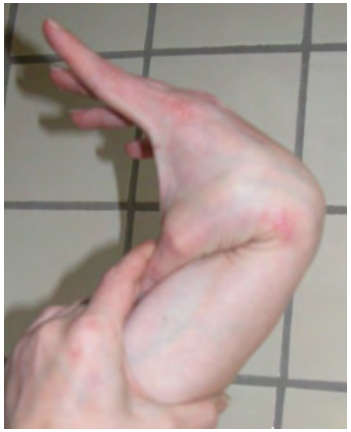
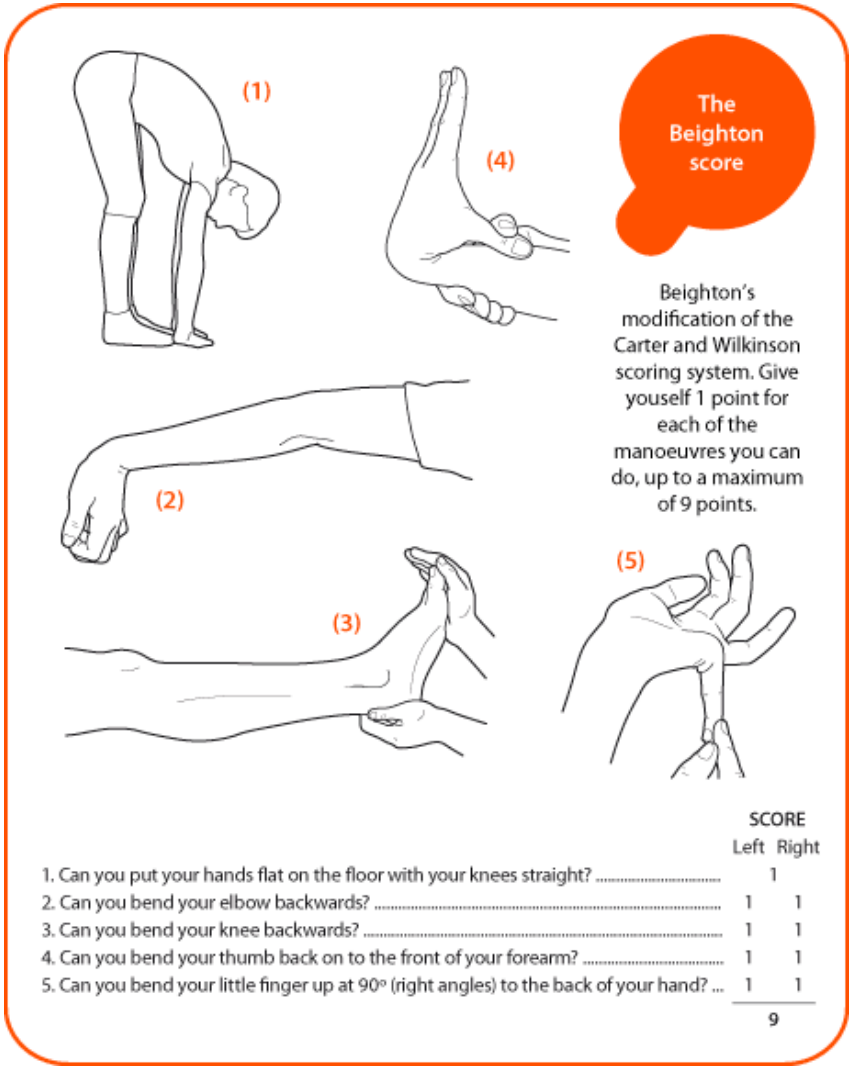
Beighton score









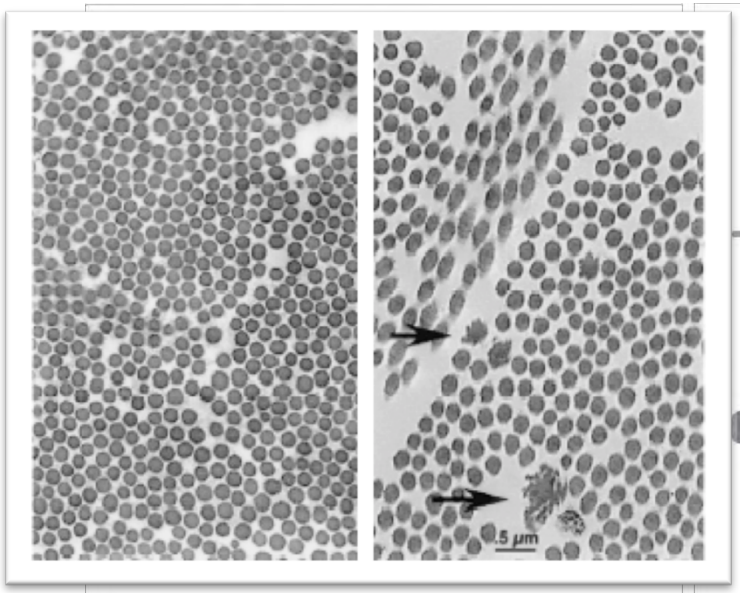


Source: Arthritis Research UK

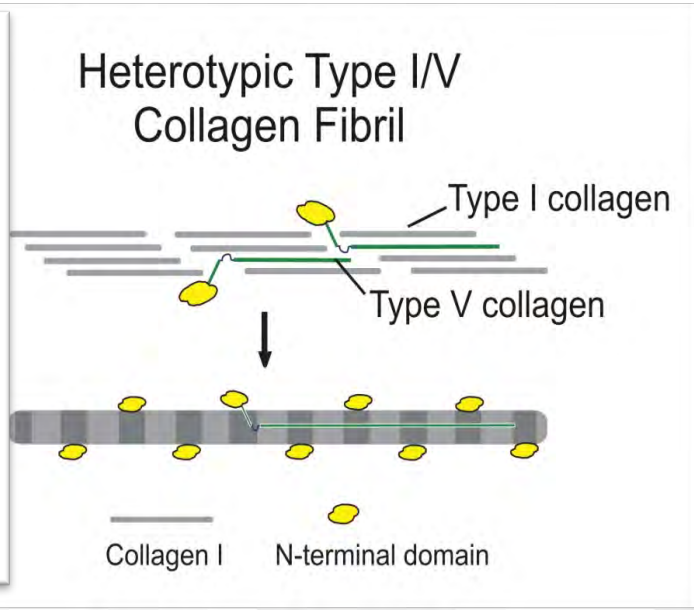
Classic EDS: molecular basis

Type V collagen deficiency

- Member of the fibrillar collagens
- Present in collagen type I-rich tissues (skin, tendon, bone)
- Key role in type I collagen fibrillogenesis via huge N-propeptide

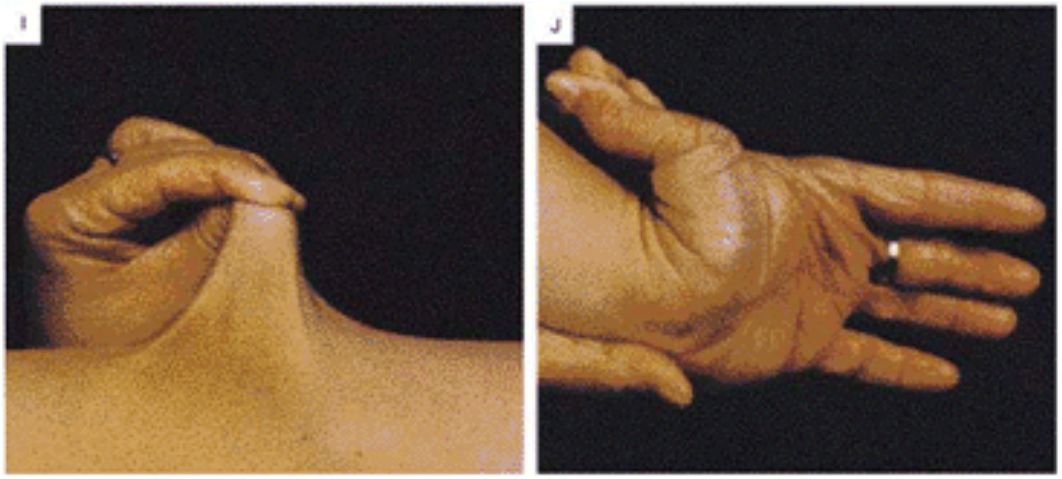


normal EDS



Classic EDS-like EDS: Tenascin-X deficiency

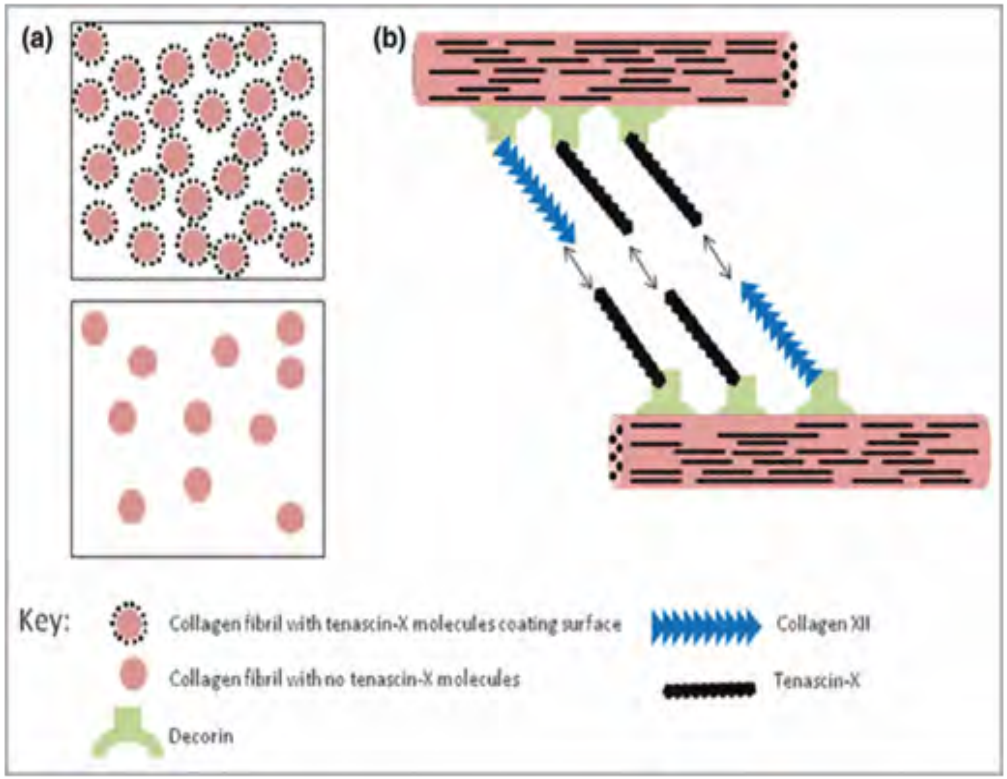
- Complete deficiency of tenascin-X causes an AR condition with great similarity to classic EDS, with:
  - Hyperelastic skin, tissue fragility
  - Hypermobile joints, joint pain, (sub)luxations
  - Easy bruising
  - No atrophic scarring



Schalkwijk et al. N Engl J Med. 2001 Oct 18;345(16):1167-75.

Classic EDS-like EDS: Tenascin-X deficiency

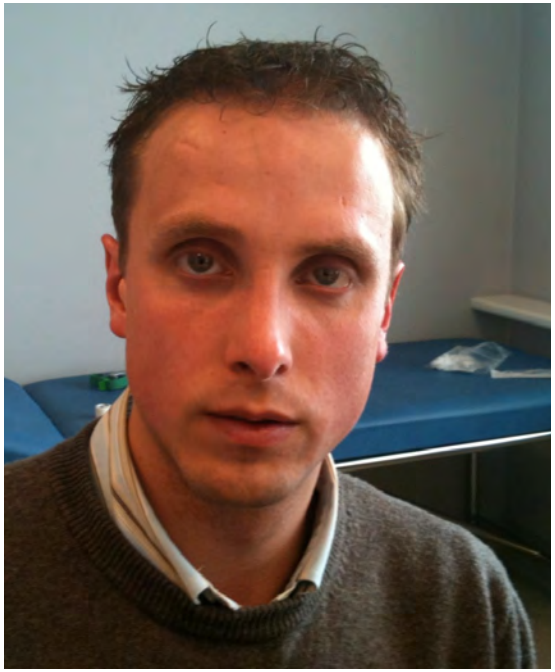
- Caused by truncating mutations or large deletions in both alleles of the TNX-B gene
- Tenascin-X interacts with collagen and other ECM molecules



ECM: Extracellular matrix.

Case History

- male, aged 24 years
- Born with unilateral clubfoot, surgically corrected
- Multiple ‘spontaneous’ ecchymoses since early age, but no wound healing problems, hyperlaxity confined to the small joints
- No specific medical problems up to age 24 years
- At age 24: hospitalisation after sudden collapse due to spontaneous bilateral rupture of two intercostal arteries
- Angiography reveals presence of multiple aneurysms of A. carotis and A. renalis
- → Genetic consultation: diagnosis of EDS, type III collagen defect

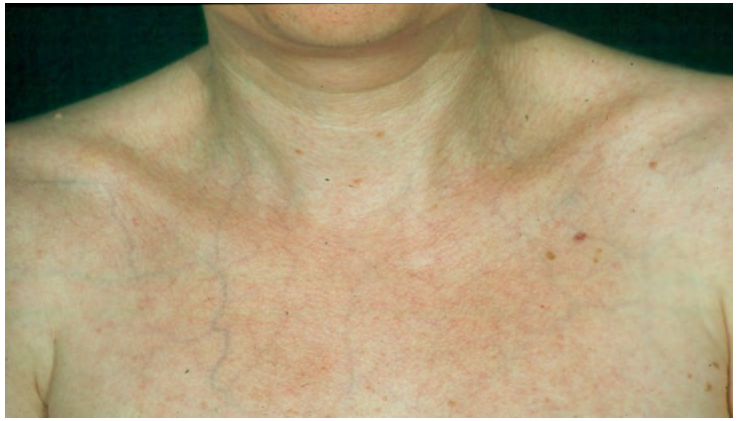


Vascular Ehlers–Danlos syndrome (vEDS)

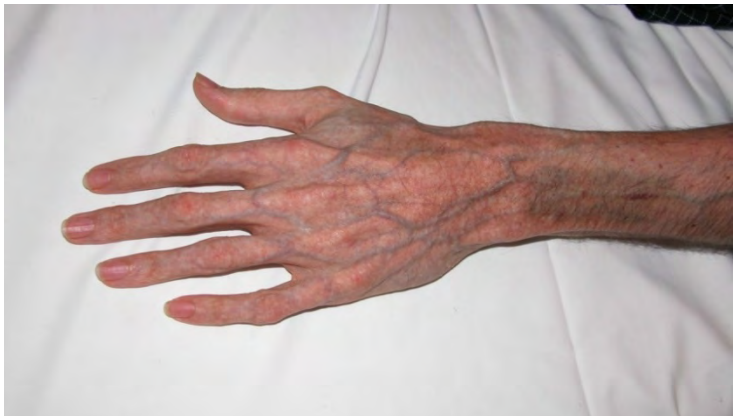
- **Disease prevalence:** 1:200,000–1:50,000

- **Major diagnostic criteria:**
  - Thin translucent skin
  - Arterial / intestinal / uterine fragility or rupture
  - Extensive bruising
  - Characteristic facial appearance

- **Minor diagnostic criteria:**
  - Acrogeria
  - Hypermobility of small joints
  - Tendon and muscle rupture
  - Talipes equinovarus
  - Early-onset varicose veins
  - Arteriovenous, carotid-cavernous fistel
  - Pneumothorax / pneumohaemothorax
  - Gingival recession
  - Positive family history, sudden death in a close relative

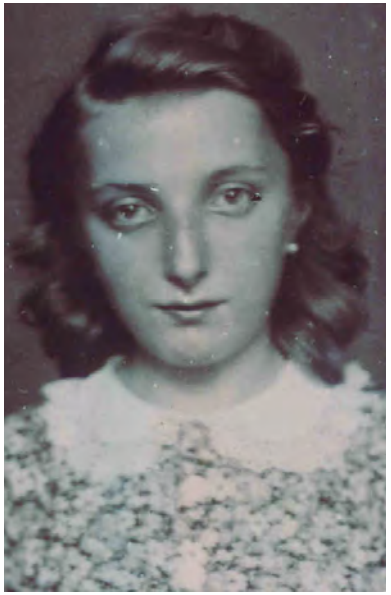


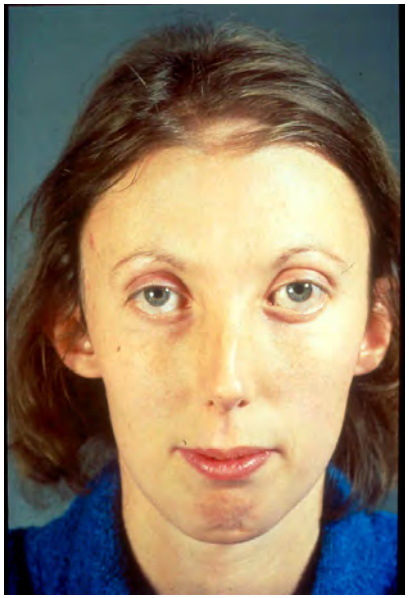
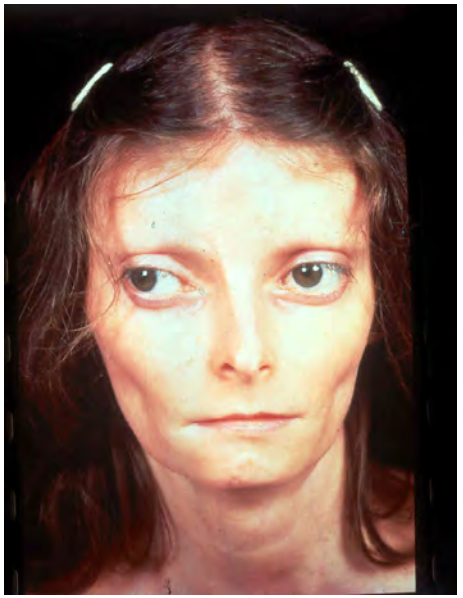
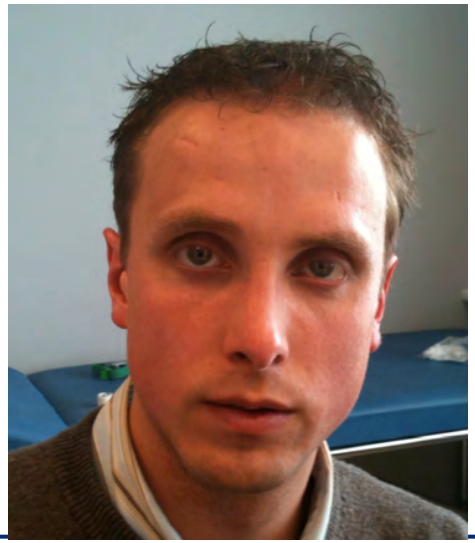
Thin, translucent skin



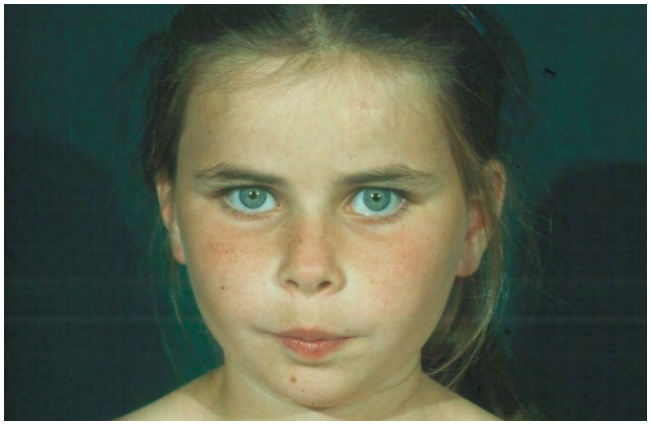
Acrogeria

vEDS: facial characteristics



Characteristic face



Consent from patients received.

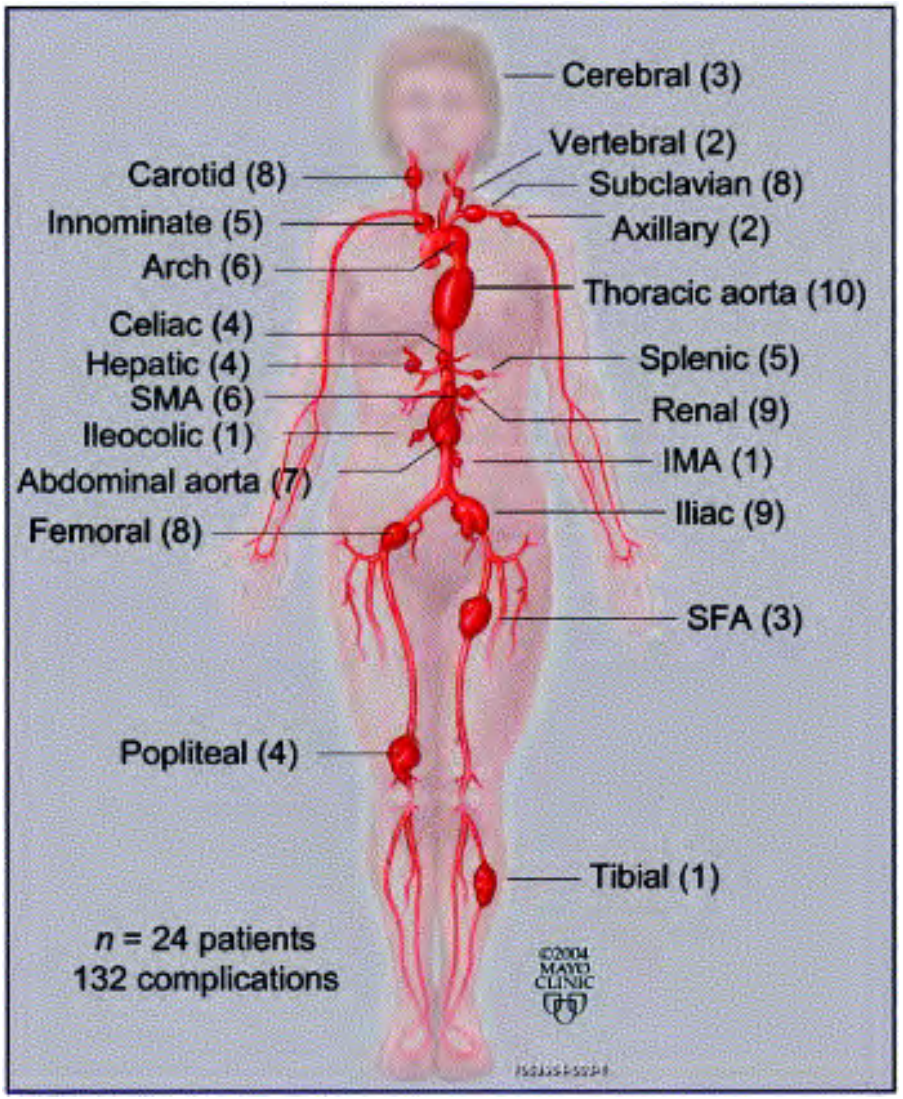
vEDS: natural history

- Life span significantly reduced, death mainly in 3rd or 4th life decade

- Most deaths result from arterial rupture/ dissection
  - Abdominal > thoracic > cerebral
  - Aorta often involved
  - Not always preceded by dilatation

- Bowel rupture (sigmoid): 20–25% of all complications

- Pregnancy-related complications are rare, but life-threatening



J Vasc Surg. 2005 Jul;42(1):98-106.

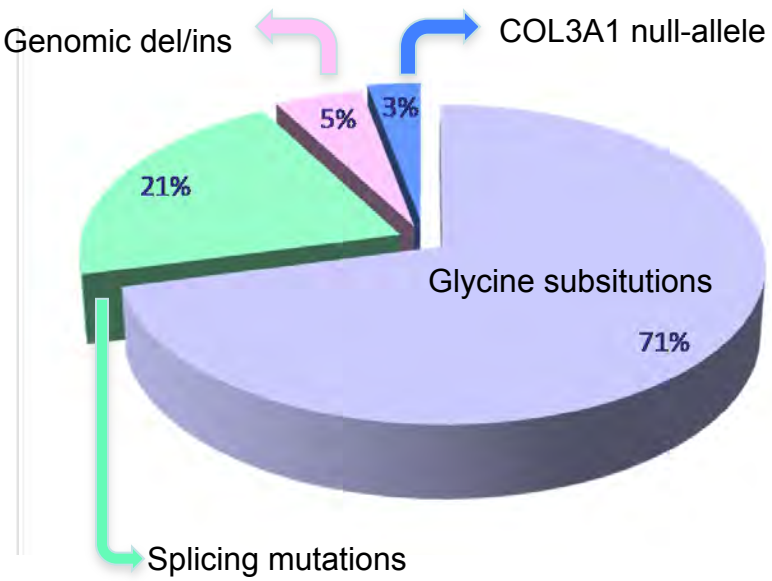
Clinical characteristics of 100 vEDS patients

- Total number of major complications: n= 129 in 60 patients
  - 7% first major complication by age 20 yrs
  - 75% first for major complication by age 40 yrs
  - Majority (35/60) experienced more than 1 complication

- Arterial complications: 82 %
- Gastro-intestinal complications: 15%
- Pregnancy-related complications

  34 reported pregnancies in 21 women: major complications in 5/34 pregnancies
- Organ ruptures: 3% (spleen, liver)

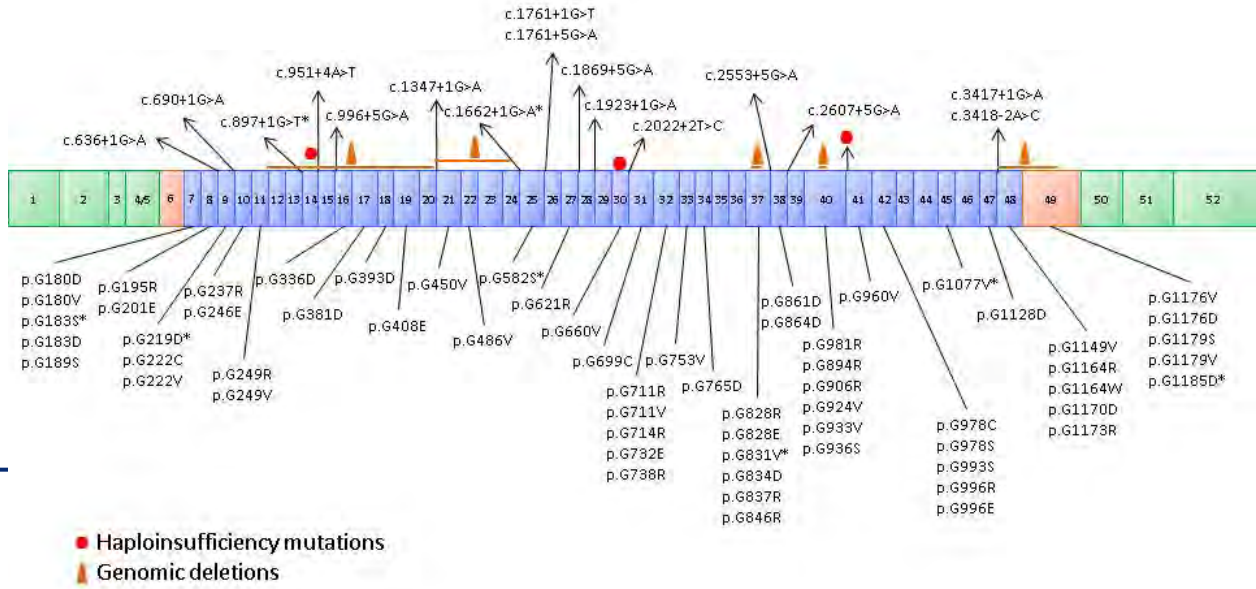
vEDS: molecular basis



Type III collagen defect

Majority are substitutions for glycine residue within triple helical domain

Wide range of *COL3A1* mutations throughout the gene



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Case History

- Male, 56 yrs
- Bilateral clubfeet
- Easy bruising
- Varicose veins at young age
- Repetitive dislocations at age 25 yrs
- Joint hyperlaxity of small joints
- Limited extension of elbows
- Soft skin, mildly dilated scars
- 51 yr: diagnosis MVP, surgery at age 56 yrs,
  mild dilatation proximal aorta

Familial Thoracic Aorta Aneursym

- *COL3A1, FBN1, TGFBR1, TGFBR2, ACTA2, Smad3,* : negative

- *TBFB2 mutation*

Diagnostic evaluation

- Clinical Hx
- Clinical examination
  - Skin
  - Joint hyperlaxity (Beighton score)
  - Skeletal manifestations
  - Craniofacial features
  - Echocardiography
  - CT/MRA: Arterial tortuosity, arterial aneurysms
  - Ophthalmologic examination
  - Skeletal X-rays

  - Family history (three generations)

Diagnostic evaluation: arterial fragility

- If clinical suspicion of vascular EDS → sequencing of *COL3A1* gene (genomic DNA)

- If negative: consider other EDS-subtypes….
  - Classic EDS: *COL5A1*, *COL5A2*
  - Cardiac-vascular-like EDS (R-to-C): *COL1A1*
  - EDS kyphoscoliotic type: *PLOD1*

- … or other heritable disorders of connective tissue
  - Especially in presence of aortic dilatation and/or arterial tortuosity
    → Consider FTAA

NGS panel*[1]	Genes	TAT (months)
FTAA panel 1	*FBN1, TGFBR1/2, ACTA2, TGFB2, SMAD3, COL3A1*	3
FTAA panel 2	*MYH11, MLCK, SLC2A10, NOTCH1, FBN2*[2], ADAMTS10, FBLN4, FLNA, ELN*[3]*	3
EDS panel 1	*COL3A1, COL5A1, COL5A2, ADAMTS2*	3
EDS panel 2	*PLOD1, ZNF469, PRDM5, CHST14, SLC39A13, FKBP14, B4GALT7*	4
OI panel 1	*COL1A1, COL1A2*	3
OI panel 2	*LEPRE1, PPIB, CRTAP, SP7, PLOD2, FKBP10, BMP1, SERPINH1, SERPINF1*	4
CL panel 1	*ATP6V0A2, ELN*[3], FBLN4, FBLN5, LTBP4, PYCR1, ALDH18A1, GORAB, RIN2*	3
Stickler panel 1	*COL2A1, COL11A1, COL11A2*	3
PXE panel 1	*ABCC6, ENPP1, GGCX, VEGFA*	3

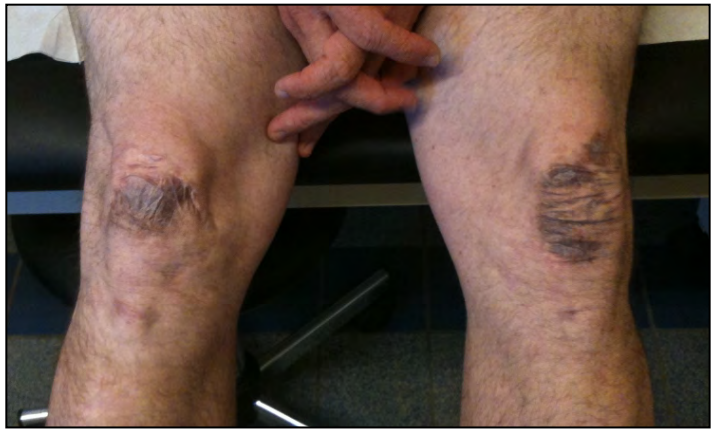
EDS: general management guidelines

- Patients with EDS require a **multi-disciplinary approach** with:
  - Genetic counselling
  - Cardiovascular work-up
  - Physiotherapy
  - Orthopaedic surgeon
  - Pain management
  - Psychological support
  - …

EDS: general management guidelines

Skin Care:

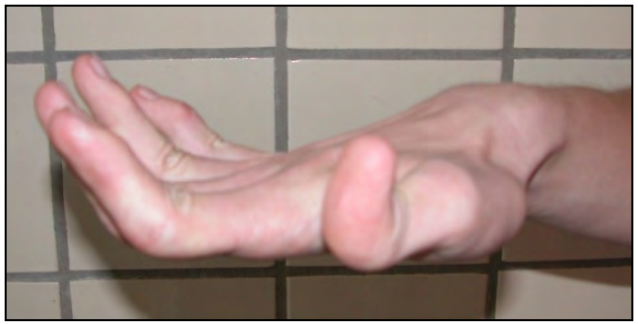
- Avoid undue trauma to the skin
- Children should wear protective bandages and paths
- Dermal wounds should be closed without tension
- Cutaneous stitches should be left in place twice as long as usual
- Fixation of skin adjacent to stitches with adhesive tape to prevent stretching of the scar



EDS: general management guidelines

Joint Protection

- In children with hypotonia and delayed motor development: physiotherapeutic programme
- Avoid excessive or repetitive heavy lifting that produces undue strain to the joints
- Avoid “showing off” joint hyperlaxity, and excessive stretching of the already hypermobile joints
- Provide assisting devices, such as ring splints and braces
- Delay surgery in favour of physical therapy and bracing

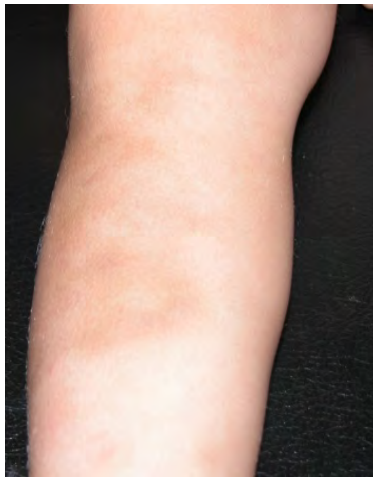


EDS: general management guidelines

- **Pain management** should be tailored to the individual's subjective symptoms
- **Cognitive behavioural therapy** can be beneficial
- **Psychological follow-up** to explore coping strategies and recognise depression
- Follow-up and monitoring of **pregnancy** is recommended

EDS: general management of bleeding and bruising

- **Control the risk for bruising** by avoidance of contact sports and heavy exercises and by wearing protective pads and bandages
- **Control the risk of vascular damage** by avoidance of risk factors for atherosclerotic cardiovascular disease (smoking, hypertension, obesity, etc.)
- **Supplementation of ascorbic acid** (cofactor for cross-linking of collagen fibrils)



EDS: general management of bleeding and bruising

- Vasopressin analogue **DDAVP** has been reported to reduce bleeding tendency temporarily in subjects undergoing dental of surgical procedures

- Case report of successful use of **recombinant factor VIIa** in a patient with vascular EDS with continued bleeding[1]

DDAVP: Desmopressin.

1. Faber *et al. Acta Anaesthesiol Scand*. 2007;51:1277–9.

EDS: preventive measures in vascular EDS

- **Avoid drugs that interfere with haemostatic process:** aspirin (acetylsalicylic acid), non-steroidal anti-inflammatory drugs, anticoagulant drugs (oral vitamin K antagonists, heparin, low molecular weight heparin, oral thrombin inhibitors)

- **Avoid invasive vascular procedures** (catheterisation, arteriography)

- **Avoid surgical intervention,** if possible

Beta-blockers in treatment of vascular EDS

- **Purpose:** to test the ability of celiprolol, a β1-adrenoceptor antagonist with a β2-adrenoceptor agonist action, of preventing arterial dissections and ruptures of vEDS in a multicentre, prospective, randomised, open, blinded endpoints trial
- **Design:** 53 patients with clinical vEDS (33 patients COL3A1 mutation positive), randomised to celiprolol (n=25) or no treatment (n=28); uptitration from 100 to 400mg, 5 years treatment
- Primary endpoints: arterial events (rupture or dissection, fatal or not)
- Secondary endpoints: intestinal/uterine rupture, major clinical event related to vEDS

Beta-blockers in treatment of vascular EDS

- Mean duration of follow-up: 47 months
- Primary endpoints: 5 patients in celiprolol (20%) and 14 patients in control group (50%)
- Primary and secondary endpoints: 6 celiprolol (24%) and 17 control group (61%)
- Study was ended prematurely since significant differences between the two groups were reached after 64 months
- Treatment was well-tolerated and target dose of 400 mg was reached in all but 2 patients
- Results were nearly identical in COL3A1 mutation positive group
- Conclusion: Treatment with celiprolol compared to no treatment reduced by threefold arterial events such as rupture or dissection in vEDS patients

Key messages

1. EDS is a **multisystemic** disorder
2. EDS is a clinically recognisable but **underdiagnosed** disorder!
3. EDS is clinically and genetically very heterogeneous
4. Diagnosis of **correct EDS subtype** may require combination of clinical, biochemical and molecular studies
5. EDS has a serious impact on **Quality of Life**, morbidity and mortality
6. Management and therapy → comprehensive and **multidisciplinary**
7. Genetic counselling is mandatory

ACKNOWLEDGEMENTS

- **Thanks to the EDS team in Ghent, Centre for Medical Genetics, Ghent, Ghent University:**

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- **Thanks to all EDS patients and referring physicians**

- **Thanks to all collaborating physicians and scientists worldwide**