Genetics and Inheritance of Ehlers-Danlos Syndromes

John W. Belmont, MD, PhD
Encyclopedia=Genetic Material

- Genes are the parts list for the assembly of the body
- Arranged in volumes – the chromosomes
- We get one entire set from each parent
Human chromosomes

Female
Paragraphs=Genes

• About 22,000 genes

• Paragraphs in the genetic encyclopedia

• >300 genes known to play a role in normal heart development
Alphabet=Genetic Code

- Genes are composed of words made with the genetic material - DNA
- The words are spelled with 4 letters – A C G T
Misspellings in Single Genes
DNA Sequencing

- Applied Biosystems 3730xl
  - 96 capillary
Types of gene mutations

Normal: Put the puppy in the box.

Deletions: Put the in the box.

Duplications: Put the puppy puppy in the box.

Misspellings: Put the poppy in the box.
A visit to the genetics specialist

- History
  - Pregnancy history
  - Family history - pedigree

- Physical exam
  - Beighton Score
  - Etc

- Genetic testing
  - Blood sample

- Ultrasound or MRI examinations
  - Are other organs affected?
The Genetics Family History

- A three generation pedigree

[Pedigree diagram showing relationships and conditions such as Male, Female, Pregnant, Joint Laxity, Migraine]
Positive Family History – Affected Parent

DOMINANT INHERITANCE
Villefranche classification of EDS

Beighton et al., 1998

- classic type (EDS I and EDS II, 130010)
- hypermobility type (EDS III, 130020)
- vascular type (EDS IV, 130050)
- kyphoscoliosis type (EDS VI, 225400)
- arthrochalasia type (EDS VIIA and VIIIB, 130060)
- dermatosparaxis type (EDS VIIIC, 225410)
# Updated Classification of EDS

<table>
<thead>
<tr>
<th>EDS subtype</th>
<th>Inheritance pattern</th>
<th>Protein</th>
<th>Gene</th>
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<tbody>
<tr>
<td>Classic</td>
<td>AD</td>
<td>Procollagen type V</td>
<td>COL5A1/COL5A2</td>
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<td>Procollagen type I</td>
<td>COL1A1</td>
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<tr>
<td></td>
<td>AR</td>
<td>Tenascin-X</td>
<td>TNX-B</td>
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<tr>
<td>Cardiac-valvular</td>
<td>AR</td>
<td>Deficiency of α2(I) collagen chain</td>
<td>COL1A2</td>
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<td>?</td>
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<td>Procollagen type I (R-to-C)</td>
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<td>Dermatan-4-sulfotransferase-1</td>
<td>CHST14</td>
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<td>ZIP13</td>
<td>SLC39A13</td>
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<td>Brittle cornea syndrome</td>
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<td>ZNF469</td>
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<td>PRDM5</td>
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<td>Dermatosparaxis</td>
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<td>Procollagen-I-N-proteinase</td>
<td>ADAMTS2</td>
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</table>

De Paepe et al The Ehlers–Danlos syndrome, a disorder with many faces Clin Genet 2012: 82: 1–11
Classic Type

- Classic Ehlers-Danlos syndrome (EDS) is a heritable connective tissue disorder characterized mainly by skin hyperextensibility, abnormal wound healing, and joint hypermobility.

- The prevalence of classic EDS has been estimated to be 1:20,000.

- It includes two previously designated subtypes (EDS type I or “gravis type” and EDS type II or “mitis type”) that are now recognized to form a clinical continuum.
Classic Type EDS

atrophic scars

swan neck deformities
COL5A1 and COL5A2 mutations

Symoens et al Comprehensive Molecular Analysis Demonstrates Type V Collagen Mutations in over 90% of Patients with Classic EDS and Allows to Refine Diagnostic Criteria Hum Mutat 33:1485–1493, 2012
Most COL5A1 Mutations are unique in a family

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<td>Raymond Dalgleish</td>
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<td>Total number of variants reported</td>
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NOTE

The work leading to the establishment of this LSDB was supported by the European Commission’s Seventh Framework Programme (FP7/2007-2013) under grant agreement no 200754 - the GEN2PHEN project.
Type V Collagen

• Type V collagen is a quantitatively minor fibrillar collagen,
• widely distributed - skin, tendon, bone, cornea, placenta, and fetal membranes

• EDS Mutations
  • typical collagen fibril abnormalities in the skin
  • variability in collagen fibril diameter
  • presence of large collagen aggregates, known as “collagen cauliflowers”
Vascular Type

- estimated prevalence of 1 : 50 000
- accounts for fewer than 5% of all cases of EDS
- autosomal dominant disorder resulting from mutations in the gene (COL3A1) encoding for type III procollagen synthesis
- 50% of cases represent new mutations
- life expectancy of patients with vascular EDS is dramatically shortened largely as a result of vascular rupture - median life span of 48 years (range 6 to 73 years)
Distribution of 132 vascular complications in 24 patients with a clinical diagnosis of vascular Ehlers–Danlos syndrome.
COL3A1 Mutations

- mutations in the COL3A1 gene
- encodes a protein for type III collagen assembly
- Type-III collagen is in bone, cartilage, dentin, tendon, bone marrow stroma and other connective tissue
- abnormal collagen III molecule cannot fold stably into a triple helix
Collagen III mutations are mostly unique to individuals and families.
EDS – Hypermobility Type
1998 Brighton criteria for classification of joint hypermobility syndrome

• Joint hypermobility syndrome is diagnosed in the presence of two major criteria; one major criterion plus two minor criteria; or four minor criteria. Two minor criteria will suffice where there is an unequivocally affected first degree relative.

• Major criteria
  • Beighton score of ≥4 (either currently or previously)
  • Arthralgia for longer than three months in four or more joints

• Minor criteria
  • Beighton score of 1, 2, or 3 (0, 1, 2, or 3 if aged >50 years)
  • Arthralgia in one to three joints or back pain or spondylosis, spondylolysis and/or spondylolisthesis
  • Dislocation in more than one joint or in one joint on more than one occasion
  • Three or more soft tissue lesions (eg, epicondylitis, tenosynovitis, bursitis)
  • Marfanoid habitus (tall, slim, ratio of span to height greater than 1.03 and/or ratio of upper segment to lower segment less than 0.89, arachnodactyly)
  • Abnormal skin: striae, hyperextensibility, thin skin, papyraceous scarring
  • Eye signs: drooping eyelids, myopia, or antimongoloid slant
  • Varicose veins, hernia, or uterine or rectal prolapse
Beighton Scale
Associated Findings – Adolescents and Adults

- Non-inflammatory joint or spinal pain
- Joint dislocations
- Multiple soft tissue (including sporting) injuries
- Increase in pain or progressive intensification of pain that is largely unresponsive to analgesics
- Progressive loss of mobility owing to pain or kinesiophobia (pain avoidance through movement avoidance)
- Premature osteoarthritis
- Autonomic dysfunction, such as orthostatic intolerance (dizziness or faintness) or postural tachycardia syndrome (in this form of dysautonomia, in 60° upright tilt the blood pressure remains constant while the pulse rate rises by a minimum of 30 beats/min)
- Functional gastrointestinal disorders (sluggish bowel, bloating, rectal evacuatory dysfunction)
- Laxity in other supporting tissues—for example, hernias, varicose veins, or uterine or rectal prolapse
Tenascin X Deficiency

- TNXB gene

- Homozygous mutations have been identified in TNXB in a few individuals with an autosomal-recessive EDS phenotype characterized by joint hypermobility, skin hyperextensibility without atrophic scarring, easy bruising and occasionally increased laxity of the genitourinary tract causing uterine and vaginal prolapse, and increased risk for postpartum hemorrhage

- Heterozygotes for the same mutation, especially females, appear to have an EDS hypermobility phenotype
Positive Family History – Affected Sibling

RECESSIVE INHERITANCE
Kyphoscoliosis Type

- **Major diagnostic criteria**
  - Generalized joint laxity
  - Severe muscle hypotonia at birth
  - Scoliosis at birth, progressive
  - Scleral fragility and rupture of the ocular globe

- **Minor diagnostic criteria**
  - Tissue fragility, including atrophic scars
  - Easy bruising
  - Arterial rupture
  - Marfanoid habitus
  - Microcornea
  - Radiologically considerable osteopenia
  - Family history, i.e., affected sibs
Kyphoscoliosis Type

Remarkable distal joint hypermobility (metacarpophalangeal and metatarsophalangeal joints) in a 4-year old male patient with the kyphoscoliatic type of Ehlers-Danlos syndrome (left images)

elbow contractures and mild knee contractures in a 16-year old male patient with the kyphoscoliatic type of Ehlers-Danlos syndrome (right image)

Kyphoscoliosis EDS (VIA)

• EDS kyphoscoliotic type or EDS type VI is an autosomal recessive
• caused by deficient activity of the enzyme procollagen-lysine, 2-oxoglutarate 5-dioxygenase 1 (PLOD1 or lysyl hydroxylase-1 [LH-1])
• This enzyme hydroxylates lysyl residues in Xaa-Lys-Gly- triplets of the helical region of collagens and collagen-like sequences of noncollagenous proteins
• hydroxyllysyl residues are essential for the formation of stable intermolecular crosslinks -> tensile strength and mechanical stability to the collagen fibrils, serve as attachment sites for carbohydrate units

• The diagnosis of EDS type VIA
  • increased ratio of lysylpyridinoline (LP) to hydroxyllysylpyridinoline (HP) crosslinks in the urine
  • a reduction of LH-1 enzyme activity in skin and mutation analysis of the PLOD1 gene (MIM] 153454)
Kyphoscoliosis Type VIB

- EDS type VI has been reported, in whom lysyl hydroxylase activity and urinary LP/HP ratio appear to be
- mutations in CHST14 (MIM 608429) coding for carbohydrate (N-acetylgalactosamine 4-O) sulfotransferase 14 (D4ST1)
  - adducted thumb-club foot syndrome (ATCS),
  - musculocontractural EDS (MCEDS [MIM 601776])
  - EDS Kosho Type (EDSKT)
- a single clinical entity with variable expression
Noriko Miyake
Loss-of-Function Mutations of CHST14 in a New Type of Ehlers-Danlos Syndrome
Hum Mutat 31:966–974, 2010
Variant Kyphoscoliosis Type EDS

- autosomal-recessive

- Clinically, the disorder shares many features with the kyphoscoliotic type of EDS (EDS VIA) and Ullrich congenital muscular dystrophy

- homozygous frameshift mutation in FKBP14 in two affected individuals.
Clinical findings in individuals with FKBP14-deficient EDS.

(A and B) Severe kyphoscoliosis in P1 (age 15 years) (A) and lumbar scoliosis in P6 (3 years) (B).

(C–G) Genu recurvatum in P3 (C) and distally pronounced joint hypermobility in P3 (D, 10 years), P5 (E, 3 years), and P6 (F and G, 3 years).

(H and I) Muscle hypotonia and weakness in P6 (H, 3 months) and P5 (I, 1.5 years).

(J) Moderate atrophy of intrinsic hand muscles in P2 (47 years).

(K and L) Hyperelastic skin of the forearm of P3 (K, 10 years) and the neck region of P1 (L, 16 years).

(M) Follicular hyperkeratosis in the pretibial region of P3 (10 years).
Gene Mutations That Cause EDS

<table>
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<tr>
<th>Numerical type</th>
<th>Descriptive type</th>
<th>Genes</th>
<th>OMIM</th>
<th>Inheritance</th>
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<tr>
<td>I (Gravis)</td>
<td>Classical(^1)</td>
<td>COL5A1</td>
<td>130000</td>
<td>AD</td>
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<td>II (Mitis)</td>
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<td>III</td>
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<td>130020</td>
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<td>IV</td>
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<td>VIA</td>
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<td>VIIA</td>
<td>Arthrochalasia multiplex congenita</td>
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## Gene Mutations That Cause EDS

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<td>ADAMTS2</td>
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<td>VIII Periodontitis</td>
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<td>Progeroid</td>
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<td>Periventricular heterotopia</td>
<td>FLNA</td>
<td>300537</td>
<td>XL</td>
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DNA Sequencing

- Applied Biosystems 3730xl
  - 96 capillary
Exome Technology

1.5 billion reads per flow cell
100 bp reads -> 300 Gb per lane
Sequencing By Synthesis
Recommendations for families with EDS:

- Know your family history & update as family grows
- Ask about problems with blood vessels, aneurysms, unusual surgical complications, sudden unexplained deaths
- Be an advocate for research!
Thank you!
Arthrochalasia Type

• Major diagnostic criteria
  • Severe generalized joint hypermobility, with recurrent subluxations
  • Congenital bilateral hip dislocation

• Minor diagnostic criteria
  • Skin hyperextensibility
  • Tissue fragility, including atrophic scars
  • Easy bruising
  • Muscle hypotonia
  • Kyphoscoliosis
  • Radiologically mild osteopenia
Arthrochalasia Type

- Congenital hip dislocation has been present in all biochemically proven individuals
- Short stature is not a manifestation, unless it is a complication of severe kyphoscoliosis and/or hip dislocation
- Larsen syndrome should be considered in the differential diagnosis
Fig. 4. Extreme hyperlaxity of the finger joints in a patient with Ehlers–Danlos syndrome, arthrochalasis type.
EDS arthrochalasia type (EDS type VIIA and B)

- EDS arthrochalasia type is an autosomal-dominant
- severe joint hypermobility at birth and congenital bilateral hip dislocation
- Tissue fragility (including atrophic scars) and skin hyperextensibility are usually present; severity ranges from mild to severe
- caused by mutations in COL1A1 or COL1A2 leading to skipping of all or part of exon 6 of the messenger RNA (mRNA) coding for one of the alpha1 chains (EDS VIIA) or the alpha2 chain (EDS VIIB) of type I collagen, respectively
Arthrochalsis Type
Transversely sectioned cutaneous collagen fibrils from EDS VII skin compared with normal control. (a) Microscopy of regularly sized, circular collagen fibrils in a control patient (Magnification x50 000). (b) Microscopy of misshapen, thinner angulated fibrils in the EhlerseDanlos Type VII patient. These differences indicate mispacking and assembly of the fibrils caused by the persisting pNalpha1(I) extensions (Magnification x55 000).
EDS dermatosparaxis type (EDS type VIIC)

- autosomal-recessive
- characterized by extreme skin fragility and skin laxity, but the skin has a sagging, redundant appearance
- distinctive features - delayed closure of the fontanels, characteristic facies, edema of the eyelids, blue sclerae, umbilical hernia, short fingers, and short stature
- deficient activity of procollagen-N-proteinase, the enzyme that excises the amino (N)-terminal propeptide in procollagen types I, II, and III
Dermatosparaxis Type

- Major diagnostic criteria
  - Severe skin fragility
  - Sagging, redundant skin

- Minor diagnostic criteria
  - Soft, doughy skin texture
  - Easy bruising
  - Premature rupture of fetal membranes
  - Large hernias (umbilical, inguinal)
Fig. 5. Patient with Ehlers–Danlos syndrome, dermatosparaxis type. Note the typical facial appearance with epicanthic folds, downslanting palpebral fissures, blue sclera, micrognathia, prominent lips and facial scars especially around the mouth. There is a large bruise on the thorax from minor trauma.
EDS progeroid form

- rare autosomal-recessive disorder characterized by progeroid appearance with wrinkled facies, curly and fine hair, scanty eyebrows and eye lashes, and periodontitis, in addition to typical signs of EDS
- It is caused by homozygous mutations in B4GALT7, the gene encoding galactosyltransferase I
- This enzyme catalyzes the second glycosyl-transfer reaction in the assembly of the dermatan sulfate chain
EDS cardiac valvular form

• The cardiac valvular form of EDS is characterized by joint hypermobility, skin hyperextensibility with variable atrophic scarring, and cardiac valvular defects

• Total absence of the pro alpha2(I) chains of type I collagen as a result of homozygous or compound heterozygous mutations in the COL1A2 gene is causative

• Inheritance is autosomal recessive
EDS/OI overlap phenotype

• Some defects in the most amino-terminal region of either the alpha1(I)- or the alpha2(I)-collagen triple helix have been shown to result in an EDS/OI overlap phenotype.

• Characterized on the one hand by joint hypermobility, skin hyperextensibility with mildly atrophic scarring, and easy bruising and on the other hand by a variable degree of bone fragility, short stature, and blue sclerae.

• Some patients also suffered from severe bleeding problems, suggesting vascular fragility.
Occipital horn syndrome (formerly known as EDS type IX)

- Occipital horn syndrome (OHS) is characterized by “occipital horns,” distinctive wedge-shaped calcifications at the sites of attachment of the trapezius muscle and the sternocleidomastoid muscle to the occipital bone.
- Occipital horns may be clinically palpable or observed on skull radiographs.
- Lax skin and joints, bladder diverticula, inguinal hernias, and vascular tortuosity.
- No easy bruising or fragility of the skin.
- Serum copper concentration and serum ceruloplasmin concentrations are low.
- Mutations in ATP7A in >95% of affected individuals.
- Inheritance is X linked.
Periventricular Nodular Heterotopia - EDS

• two families had BPNH-EDS with mutations in FLNA (FLNA-BPNH-EDS)
• The EDS-associated signs were variable in their distribution and severity
• Valvular dystrophy, joint hypermobility and dislocations, skin anomalies and dysmorphic facial features were variably observed.
• Aortic aneurysm is the most severe cardiovascular complication associated with this condition was present in all three FLNA-BPNH-EDS patients
Reinstein et al Vascular and connective tissue anomalies associated with X-linked periventricular heterotopia due to mutations in Filamin A.
Classic-like EDS with propensity for arterial rupture

• One arginine-to-cysteine (R-to-C) substitution in pro alpha1(I) chain of type I collagen (R134C) has been identified in a series of patients with a condition reminiscent of classic EDS, with skin hyperextensibility, easy bruising, atrophic scarring, and joint hypermobility but with propensity for arterial rupture at adult age.

• Two other pro1(I) R-to-C substitutions (R396C and R915C) were also associated with rupture of medium sized arteries, but affected individuals did not present EDS-like skin features.

• pro alpha1(I)-R888C substitution was reported in a family presenting an EDS/osteogenesis imperfecta (OI) overlap phenotype,26 and a proalpha1(I)-R836C was shown to be associated with autosomal-dominant Caffey disease.
Type VIII

- Ehlers–Danlos syndrome (EDS) type VIII (OMIM #130080)
- distinct, largely unrecognized form of EDS characterized primarily by generalized periodontal disease causing progressive loss of the alveolar bone and subsequent dental loss
- associated clinical abnormalities include joint and skin manifestations and with much clinical overlap to other EDS subtypes, mainly the hypermobility and classic types
- diagnosis - established in an individual presenting with dental and connective tissue findings and a typical pattern of inheritance (AD)
FIG. 1. Facial and dental appearance of family with EDS type VIII. A, B, D: Proposita; C—her mother. Note long nose with narrow root and prominent tip that have been reported in patients with this type of EDS. Proposita’s mother wears dentures.

FIG. 5. Coronal MR imaging of the right knee joint. The lateral joint compartment demonstrates a distinct cyst [arrow] of the subchondral bone (A), and multiple surface and subchondral irregularities [arrowheads], as well as osteophytic spurs [arrows] (B), which are overall the result of marked degeneration.