Symposium: Integrated morphologic and molecular approach to diagnosis of cardiovascular disease

Familial aortic dissection

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Disclosure:

No conflicts of interest to declare.
Content

• Definitions
• Pathology of aortic dissection
• Genetics: main genes involved
• Pathophysiology: from genes to aorta wall damage
• Integrated diagnosis: characterization of different entities by combining clinical features (+++), genetics (+++) and pathology:
  • Syndromic entities:
    • Marfan syndromes, classical and type II
    • Loeys-Dietz syndromes
    • Ehlers-Danlos syndrome, vascular type (former type IV)
    • miscellaneous
  • Non-syndromic entities:
    • Mutations of genes coding for contractile proteins in the VSMC (MYH11, ACTA2,...)
    • Other genes: non-syndromic thoracic aortic aneurysm & dissection (TAAD)
• Discussion
• Conclusion
Definitions

**Dissection:** Passage of blood in the media forming a splitting of the media, usually in the deeper part of the media and entry of blood via intimal tear

- **Acute:** recent, non organized blood (hematoma) in the media
- **Chronic:** remote, organized

**Syndromic vs. non-syndromic forms of familial dissections:**

- **Syndromic:** dissection in the setting of a complex clinical feature involving other organs (eyes, face, limbs, skeleton, skin...) or immunity
- **Non-syndromic:** aorta involvement is isolated

**In**

- a well-established familial background of thoracic aorta aneurysm/dissection (TAAD)
- or apparently sporadic in young patient <45 y.o. = index patient (leading to the discovery of affected relatives)
Pathology of aortic dissection

Classification: The Stanford classification is the most frequently used; it has a therapeutic input [Daily et al. Ann Thorac Surg 1970].

- **Type A** involving ascending aorta (tear in the ascending aorta), at least or more extensive → life threatening (rupture, hemopericardium, tamponade, myocardial/cerebral ischemia) → emergency, surgical replacement of the aorta

- **Type B**: no involvement of the ascending aorta → medical treatment (control blood pressure) and imaging at follow-up
Pathology of acute aortic dissection

**Hemorrhagic cleft in the media** in a variable % circumference and variable length (up to complete aorta and aorta branches). ± rupture in the pericardium, adventicia
Pathology of acute aortic dissection

Entry:
- Most often entry is present
- Transversal intimal tear, intimo-medial flap

If no entry → intramural hematoma
Pathology of chronic aortic dissection

Media cleft organized, often circulating false channel
Histopathology of aortic dissection

- Dissection is supported by changes at histology in the aortic media
- Media abnormalities involve vascular smooth muscle cells and extracellular matrix components
- Elementary lesions similar to “degenerative” features, but they occur in the aortic media of a young patient
  - [Jain et al. Cardiovasc Pathol 2011]
Definition and Grading of Elementary Lesions

Consensus terms of degenerative aortic histopathology

- EFFL (elastic fiber fragmentation and/or loss)
- SMNL (smooth muscle nuclei loss)
- MEMA-I (mucoid extracellular matrix accumulation-intralamellar)
- MEMA-T (mucoid extracellular matrix accumulation-translamellar)

[from Halushka et al. Cardiovasc Pathol 2016]
Genetics: main genes involved

• A ten of genes are definitely associated with familial dissections:
  • Genes coding for ECM proteins: fibrillin-1, col3A1, LOX (lysyl oxidase for ECM elastic and collagen fibers)
  • Genes coding for contractile proteins within VSMC: ACTA2, MYH11, MYLK (myosin light chain kinase), PRKG1 (type I cGMP-dependent protein kinase)
  • Genes coding for TGF-β1 pathway: TGFB2, TGFBR1, TGFBR2, SMAD3
• Others genes have moderate, limited or no association with aortic dissections in humans
• Recommendations
  • in a given syndrome, test first respective associated genes
  • If no syndrome, test genes in a stepwise approach or wider approach if NGS available
• [Clinical validity of genes for heritable thoracic aneurysm and dissection. Renard et al. JACC 2018;
• Clinical utility gene card for hereditary thoracic aneurysm and dissection including NGS approach. Arslan-Kirchner et al. Eur J Hum Genetics 2016;
• Familial thoracic aneurysms. Jondeau G and Boileau C. Curr Opin Cardiol 2014]
• Note: A given mutated gene can be associated with different diseases
CENTRAL ILLUSTRATION. Evaluation of the Clinical Validity of Genes for Heritable Thoracic Aortic Aneurysms and Dissections (HTAAD)
<table>
<thead>
<tr>
<th>HGNC Gene Symbol</th>
<th>OMIM ID</th>
<th>Phenotype</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACTA2</td>
<td>Aortic aneurysm familial thoracic, 6 (#611788)</td>
<td>Familial thoracic aneurysm and dissection (91387); rare disease with thoracic aortic aneurysm and aortic dissection (285014)</td>
</tr>
<tr>
<td>COL3A1</td>
<td>Ehlers-Danlos syndrome type IV (#130050)</td>
<td>Ehlers-Danlos syndrome, vascular type (286); rare disease with thoracic aortic aneurysm and aortic dissection (285014)</td>
</tr>
<tr>
<td>FBN1</td>
<td>Marfan syndrome (#154700)</td>
<td>Familial thoracic aneurysm and dissection (91387); Marfan syndrome type 1 (284963); rare disease with thoracic aortic aneurysm and aortic dissection (285014)</td>
</tr>
<tr>
<td>MYH11</td>
<td>Aortic Aneurysm familial thoracic, 4 (#132900)</td>
<td>Familial thoracic aneurysm and dissection (91387); rare disease with thoracic aortic aneurysm and aortic dissection (285014)</td>
</tr>
<tr>
<td>SMAD3</td>
<td>Loey-Dietz syndrome 3 (#613795)</td>
<td>Familial thoracic aneurysm and dissection (91387); aneurysm-osteoarthritis syndrome (284984)</td>
</tr>
<tr>
<td>TGFBR1</td>
<td>Loey-Dietz syndrome 1 (#609192)</td>
<td>Familial thoracic aneurysm and dissection (91387); rare disease with thoracic aortic aneurysm and aortic dissection (285014); Loey-Dietz syndrome (60030)</td>
</tr>
<tr>
<td>TGFBR2</td>
<td>Loey-Dietz syndrome 2 (#610168)</td>
<td>Familial thoracic aneurysm and dissection (91387); rare disease with thoracic aortic aneurysm and aortic dissection (285014); Loey-Dietz syndrome (60030); Marfan syndrome type 2 (284973)</td>
</tr>
<tr>
<td>MYLK</td>
<td>Aortic aneurysm familial thoracic, 7 (#613780)</td>
<td>Familial thoracic aneurysm and dissection (91387); rare disease with thoracic aortic aneurysm and aortic dissection (285014)</td>
</tr>
<tr>
<td>LOX</td>
<td>Aortic aneurysm familial thoracic, 10 (#617168)</td>
<td>Familial thoracic aneurysm and dissection (91387); rare disease with thoracic aortic aneurysm and aortic dissection (285014)</td>
</tr>
<tr>
<td>PRKGI</td>
<td>Aortic aneurysm familial thoracic, 8 (#613436)</td>
<td>Familial thoracic aneurysm and dissection (91387); rare disease with thoracic aortic aneurysm and aortic dissection (285014)</td>
</tr>
</tbody>
</table>

Strong and definitive genes with their respective OMIM and ORPHA disease codes (if available), the reason for listing them, and relevantadc the rightmost column in italics.

AD = aortic dissection; TAA = thoracic aortic aneurysm.

[Clinical validity of genes for heritable thoracic aneurysm and dissection. Renard et al. JACC 2018]
Pathophysiology: From genes to aorta wall damage

• Opposite roles of TGF-β1 in the aortic wall:
  • contribute to extracellular matrix synthesis
  • increase in matrix degradation via plasminogen activators and release of MMP

• TGF-β1 is a key growth factor in the pathophysiology of aortic aneurysm/dissection: its overactivity being responsible for aortic media damage

• However endless debate that TGF-β1 increase is not the culprit and has a compensatory role, depending on the severity of the disease, possibly involved in healing of the aortic wall
Pathophysiology: From genes to aorta wall damage

• when the aortic media is in steady state conditions, most of TGF-β1 is inactive in large latent complex (LLC): latent TGF-β-binding protein (LTBP) associated with ECM components, fibrillin-1

• TGF-β1 is involved in most of the gene mutations/entities resulting in TGF-β1 pathways activation, often in a well-established manner or in some entities through still-unexplained signaling and leading to increased phospho-Smad2 in VSMC

Pathophysiology:
From genes to aorta wall damage

Overactivity of TGF-β1 [Gomez et al. J Pathol 2009]:

- X Fibrillin-1 mutations: abnormal or decreased fibrillin-1: release of TGF-β1 from LTBP-1
- X TGF-βR1, TGF-βR2, Smad3 mutations: alternative pathways of TGF-β1 including non-canonic signaling explain TGF-β1 overactivity
- X Mutations of genes coding for contractile proteins in VSM (vascular smooth muscle actin, myosin heavy chain 11): TGF-β1 is active by indirect mechanisms (cytoskeleton-integrins-ECM)

[Jondeau & Boileau. Curr Opin Cardiol 2014]
Pathophysiology:
From genes to aorta wall damage

Increased proteolysis of extracellular matrix components by MMPs: due to TGF-β1, active plasmin, abnormal ECM components (for ex. mutated fibrillin-1):

- Accumulation of MMPs in MEMA lesions
- Activation of MMPs (zymography)

[Borges et al. Hum Pathol 2009]
Syndromic aortic dissections
Marfan syndrome

- The most frequent familial connective tissue disorder: 1/5,000 births
- Autosomal dominant
- The first familial connective tissue disorder with genetic characterization: mutation in \textit{FBN1} coding for fibrillin-1 \cite{Lee1991, Dietz1991}
- Characterized by a well-established panel of clinical features: see updated “revised Ghent nosology for the Marfan syndrome” \cite{Loeys2010}. (predated by “Berlin nosology” \cite{Beighton1988} and “Ghent nosology” \cite{dePaepe1996})
- However distribution and intensity of organ involvement quite variable making the \textbf{clinical diagnosis difficult}
- Use genetic testing
Marfan syndrome

Cardiovascular System

Major criteria.
- dilatation of the ascending aorta with or without aortic regurgitation and involving at least one sinus of Valsalva; or
- dissection of the ascending aorta

Minor criteria.
- mitral valve prolapse with or without mitral valve regurgitation;
- dilatation of the main pulmonary artery, in the absence of valvular or peripheral pulmonic stenosis or any other obvious cause, below the age of 40 years;
- calcification of the mitral annulus below the age of 40 years; or
- dilatation or dissection of the descending thoracic or abdominal aorta below the age of 50 years

Requirements of the Diagnosis of the Marfan Syndrome

For the index case:
- If the family/genetic history is not contributory, major criteria in at least 2 different organ systems and involvement of a third organ system
- If a mutation known to cause Marfan syndrome in others is detected, one major criterion in an organ system and involvement of a second organ system

For a relative of an index case:
- presence of a major criterion in the family history and one major criterion in an organ system and involvement of a second organ system

Pulmonary System

Major criteria.
- none

Minor criteria.
- spontaneous pneumothorax [Hall et al., 1984], or apical blebs (ascertained by chest radiography)

Ocular System

Major criterion.
- ectopia lentis

Skeletal System

Major criterion. Presence of at least 4 of the following manifestations.
- pectus carinatum
- pectus excavatum requiring surgery
- reduced upper to lower segment ratio or arm span to height ratio greater than 1.05
- wrist and thumb signs
- scoliosis of > 20° or spondylolisthesis
- reduced extension at the elbows (< 170°)
- medial displacement of the medial malleolus causing pes planus
- protrusio acetabulae of any degree (ascertained on radiographs)

Skin and Integument

Major criterion.
- none

Minor criteria.
- striae atrophicae (stretch marks) not associated with marked weight changes, pregnancy or repetitive stress, or recurrent or incisional herniae

Dura

Major criterion
- lumbosacral dural ectasia by CT or MRI

Family/Genetic History

Major criteria.
- having a parent, child or sib who meets these diagnostic criteria independently;
- presence of a mutation in FBN1 known to cause the Marfan syndrome; or
- presence of a haplotype around FBN1, inherited by descent, known to be associated with unequivocally diagnosed Marfan syndrome in the family

Genetics in Marfan syndrome

1. **FBN1** (65 coding exons): coding for a large ECM molecule, fibrillin-1: 320 kDa. Structural glycoprotein, forming assembly with LTBP, other fibrils (fibulins 2, 4, 5) and **elastin to build elastic fibers**

1,847 different mutations so far reported [http://www.umd.be/FBN1/] in any exon. Private mutations, but 12% are recurrent. Mutations influence clinical expression: exons 26-28: neonatal forms, adult severe forms; exon 59 and 65: lack of aortic pathology; but no clearly-established predictive genotype-phenotype correlation

2 classes of mutations [Boileau et al. Curr Op Cardiol 2005]:
   - ≈ 40% shortened fibrillin-1 molecule, act as dominant negative, variable clinical phenotype
   - ≈ 60% missense mutation, mostly affecting EGF modules, complex cellular pathology: impaired trafficking, delayed secretion, rigidity, or enhanced protease susceptibility

Intrafamilial variability of Marfan phenotype: suggesting gene modifiers
Genetics in Marfan syndrome

in Marfan syndrome type II: clinical pattern of Marfan syndrome (*ectopia lentis*), different from Loeys-Dietz syndrome type 2 and aorta involvement less severe than Loeys-Dietz syndrome type 2
Aortic pathology in Marfan syndrome

MEMA-T, MEMA-I, EFFL, SMNL: non specific, but severe grades; heterogeneous distribution → large sampling
Loeys-Dietz syndromes

- Rare familial connective tissue disorder: 1/20,000-100,000 births
- Autosomal dominant
- Some clinical abnormalities (skeletal) shared with Marfan syndrome and some (skin) with Ehlers-Danlos syndrome

- LDS type 1: *TGFBR1*
- LDS type 2: *TGFBR2*
- LDS type 3: *SMAD3*
- LDS type 4: *TGFB2*
Loeys-Dietz syndromes 1 and 2 (*TGFBR1* and *TGFBR2*)

- Loeys *et al.*. NEJM 2006

### Table 1. Clinical Characteristics of 40 Probands with Loeys–Dietz Syndrome Type L

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Current Cohort (N=30)</th>
<th>Previous Cohort (N=10)</th>
<th>Total (N=40)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>no. of patients (%)</td>
<td>no. (%)</td>
<td>no. (%)</td>
</tr>
<tr>
<td>Clinical</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertelorism†</td>
<td>26 (80)</td>
<td>10 (60)</td>
<td>36 (90)</td>
</tr>
<tr>
<td>Cleft palate or abnormal usta†</td>
<td>27 (89)</td>
<td>9 (60)</td>
<td>36 (90)</td>
</tr>
<tr>
<td>Anterior–root aneurysm†</td>
<td>29 (97)</td>
<td>10 (60)</td>
<td>39 (98)</td>
</tr>
<tr>
<td>Arterial or other lesions†</td>
<td>13 (43)</td>
<td>8 (50)</td>
<td>21 (53)</td>
</tr>
<tr>
<td>Arterial tortuosity†</td>
<td>11 (37)</td>
<td>10 (60)</td>
<td>21 (53)</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Craniosynostosis</td>
<td>15 (50)</td>
<td>4 (40)</td>
<td>19 (48)</td>
</tr>
<tr>
<td>Malformations</td>
<td>17 (57)</td>
<td>7 (70)</td>
<td>24 (60)</td>
</tr>
<tr>
<td>Retinopathy</td>
<td>15 (50)</td>
<td>5 (50)</td>
<td>20 (50)</td>
</tr>
<tr>
<td>Blue sclera†</td>
<td>10 (33)</td>
<td>6 (60)</td>
<td>16 (40)</td>
</tr>
<tr>
<td>Ectopia lentis†</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Skeletal</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Deformities</td>
<td>4 (13)</td>
<td>3 (30)</td>
<td>7 (18)</td>
</tr>
<tr>
<td>Anomalousity</td>
<td>22 (73)</td>
<td>6 (60)</td>
<td>28 (70)</td>
</tr>
<tr>
<td>Perimetal deformity</td>
<td>21 (69)</td>
<td>6 (60)</td>
<td>27 (68)</td>
</tr>
<tr>
<td>Scleosis</td>
<td>14 (47)</td>
<td>6 (60)</td>
<td>20 (50)</td>
</tr>
<tr>
<td>Talipes equinovarus†</td>
<td>15 (50)</td>
<td>3 (30)</td>
<td>18 (45)</td>
</tr>
<tr>
<td>Campodactyly</td>
<td>10 (33)</td>
<td>5 (50)</td>
<td>15 (38)</td>
</tr>
<tr>
<td>Joint laxity</td>
<td>18 (60)</td>
<td>9 (60)</td>
<td>27 (68)</td>
</tr>
<tr>
<td>Cervical–spine instability†</td>
<td>6 (20)</td>
<td>1 (0)</td>
<td>7 (18)</td>
</tr>
<tr>
<td>Curative</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Velecre skin</td>
<td>9 (30)</td>
<td>2 (20)</td>
<td>11 (28)</td>
</tr>
<tr>
<td>Translucent skin†</td>
<td>9 (30)</td>
<td>4 (20)</td>
<td>13 (32)</td>
</tr>
<tr>
<td>Other</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patent ductus arteriosus</td>
<td>10 (33)</td>
<td>4 (40)</td>
<td>14 (35)</td>
</tr>
<tr>
<td>Atrial septal defect</td>
<td>5 (17)</td>
<td>4 (40)</td>
<td>9 (22)</td>
</tr>
<tr>
<td>Developmental delay</td>
<td>3 (10)</td>
<td>3 (30)</td>
<td>6 (15)</td>
</tr>
</tbody>
</table>

### Table 2. Characteristics of 12 Probands with Loeys–Dietz Syndrome Type II

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Proband No.</th>
<th>No. of Proband</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Mutations</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>R1, R4870</td>
</tr>
<tr>
<td>Aortic root aneurysm</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Other arterial aneurysm</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Arterial tortuosity</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Vascular rupture during pregnancy</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Uterine rupture</td>
<td>−</td>
<td>+</td>
</tr>
<tr>
<td>Uterine hernorhage</td>
<td>−</td>
<td>−</td>
</tr>
<tr>
<td>Splenic or bowel rupture</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Inguinal hernia</td>
<td>−</td>
<td>+</td>
</tr>
<tr>
<td>Easy breaching</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Translucent skin†</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Velvety skin</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Skin hyperr efficiency</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Atrophic scars</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Joint laxity</td>
<td>+</td>
<td>+</td>
</tr>
</tbody>
</table>

* R1 denotes TGFBR1, R2 TGFBR2; plus sign the presence of a characteristic minus sign the absence of a characteristic, ND not determined, and NA not applicable.
* † This abnormality or condition is considered rare in the general population.
* All probands had splenic rupture except proband 6, who had bowel rupture.

No craniosynostosis
No hypertelorism
No cleft palate
Loeys-Dietz syndromes 1 and 2 (*TGFBR1* and *TGFBR2*)

[Loeys *et al.* NEJM 2006]

- Severe aortic involvement
- Involvement of other medium-sized arteries (carotid arteries)
- Arterial tortuosity, frequent
- → more diffuse arteriopathy than in Marfan Sd

**Table 3. Cardiovascular Involvement in 90 Patients with Loeys–Dietz Syndrome Type I or II from 52 Families.**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Type I (N=64)</th>
<th>Type II (N=25)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean craniofacial-severity-index score</td>
<td>4.8</td>
<td>0.8</td>
</tr>
<tr>
<td>Mean age at first major event (yr)</td>
<td>24.5</td>
<td>29.8</td>
</tr>
<tr>
<td>Age at death (yr)</td>
<td>22.6</td>
<td>31.8</td>
</tr>
<tr>
<td>Range</td>
<td>0.5–45.0</td>
<td>18.0–47.0</td>
</tr>
<tr>
<td>Cause of death (no.)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thoracic aortic dissection</td>
<td>12</td>
<td>6</td>
</tr>
<tr>
<td>Abdominal aortic dissection</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Subclavian-artery dissection</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Cerebral bleeding</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Age at first cardiovascular surgery (yr)</td>
<td>16.9</td>
<td>26.9</td>
</tr>
<tr>
<td>Range</td>
<td>1.2–46.0</td>
<td>14.0–38.0</td>
</tr>
<tr>
<td>Distribution of aneurysms (no.)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ascending aorta</td>
<td>54</td>
<td>22</td>
</tr>
<tr>
<td>Transverse aorta</td>
<td>3</td>
<td>6</td>
</tr>
<tr>
<td>Descending thoracic aorta</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>Abdominal aorta</td>
<td>5</td>
<td>4</td>
</tr>
<tr>
<td>Thoracic arterial branches</td>
<td>17</td>
<td>2</td>
</tr>
<tr>
<td>Head or neck arterial branches</td>
<td>7</td>
<td>2</td>
</tr>
<tr>
<td>Abdominal arterial branches</td>
<td>2</td>
<td>4</td>
</tr>
</tbody>
</table>

[Phosphorylated Smad2, CTGF]

Degenerative pattern in aortic aneurysm in LDS 1

[Nakajima *et al.* Ann Thorac Surg 2014]

TGFB pathway activation

[Loeys *et al.* NEJM 2006]
Loeys-Dietz syndromes 1 and 2 (*TGFBR1* and *TGFBR2*)

- Arterial tortuosity
Loeys-Dietz syndrome 3 (SMAD3)

Loeys-Dietz syndrome 4 (TGFB2)

[Lindsay et al. Nat Genet 2012]

≈ 10 families; ≈ 30 cases
Ehlers-Danlos syndrome, vascular type (former type IV)

- Gene mutation: \textit{COL3A1} coding for collagen III\(\alpha_1\); Autosomal dominant

- The type of mutation influences the severity of organ involvement \cite{Frank2015}

- Arterial rupture and dissection in dilated or non-dilated arteries

- Rupture of arteries with normal histology

- In experimental models, decreased collagen in mouse aorta \cite{Faugeroux2013}

\begin{itemize}
  \item Inheritance
    \begin{itemize}
    \item Autosomal dominant
    \end{itemize}
  \item Major criteria
    \begin{enumerate}
    \item Family history of vEDS with documented causative variant in \textit{COL3A1}
    \item Arterial rupture at a young age
    \item Spontaneous sigmoid colon perforation in the absence of known diverticular disease or other bowel pathology
    \item Uterine rupture during the third trimester in the absence of previous C-section and/or severe peripartum perineum tear
    \item Carotid-external jugular vein (CCSV) formation in the absence of trauma
    \end{enumerate}
  \item Minor criteria
    \begin{enumerate}
    \item Bruising unrelated to identified trauma and/or in unusual sites such as cheeks and back
    \item Thin, translucent skin with increased venous visibility
    \item Characteristic facial appearance
    \item Spontaneous pneumothorax
    \item Acrorrhagia
    \item Talar exostosis
    \item Hypermobility of small joints
    \item Tendon and muscle rupture
    \item Keratoconus
    \item Gingival recession and gingival fragility
    \item Early onset varicose veins (under age 30 and mulliparous if female)
    \end{enumerate}
\end{itemize}

Miscellaneous gene mutations/syndromes with possible familial aortic involvement

- **SLC2A10**: coding for Glut10: arterial tortuosity
- **COL1A1, COL1A2, COL5A1, COL5A2**: other Ehlers-Danlos syndromes
- **FBLN4**: fibulin 4: cutis laxa syndrome
- **FBLN5**: fibulin 5
Non-syndromic aortic dissections
Mutations in **MYH11**

- **MYH11**: gene coding for smooth muscle heavy chain (SM-MHC)
- **2 families** (one French and one American): deletions in exons 32 and 37 in the French family and exon 32 in the American family → loss in the C terminal SM-MHC involving coiled-coil structure and assembly of thick myosin filaments [Zhu et al. Nature Genet 2006]
- **Marked decreased aorta compliance** (at MRI): aorta stiffness increases rapidly with aging

*Images of various tissues and histological sections with annotations.*

*Aorta from 2 affected individuals from the French kindred* [Zhu et al. Nature Genet 2006]
Mutations in ACTA2

- Thoracic aorta aneurysm/dissection frequently associated with livedo reticularis [Guo et al. Nat Genet 2007]
- ACTA2: gene coding for vascular smooth muscle actin isoform
- After discovery of that mutation in one family, other ACTA2 mutations discovered in other families ± livedo, ± PDA
  Autosomal dominant; variable penetrance (low)
- → authors estimate that ACTA2 mutations are responsible for 14% familial TAAD [Guo et al. Nat Genet 2007]
Other non-syndromic familial aortic dissections

• Cohorts of TAAD patients in referral centers
• Several studies showed a significant % of TAAD patients harboring pathogenic variants of targeted genes:
  • for ex. in a cohort of 226 TAAD and testing of 23 genes: mutated genes in 18% (mean), 22% in familial cases vs. 11% in sporadic cases; High prevalence of SMAD3 and FBN1 mutations; Positivity of pathogenic variants impacts prognosis with higher % of dissections and lower survival [Arnaud et al. Genet Med, 2019 online]

![Gene distribution diagram with gene labels and counts](image-url)
Familial aortic dissection associated with BAV with gene mutation

- **NOTCH1** mutations:
  - in 5/48 patients with BAV and thoracic aorta aneurysm [McKellar et al. JTCS 2007]
  - In 2/48 [Mohamed et al. Biochem Biophys Res Com 2006]
  - Notch1 signaling interacts with TGFβ

- **TGFBR2** mutation:
Discussion

• Is histopathology of aorta able to differentiate syndromic or non-syndromic, familial or genetic TAAD from degenerative (aging, hypertension) TAAD or from BAV associated aortopathy?

• Marfan aorta has higher degenerative score and MEMA score vs. Loeys-Dietz or BAV; EFFL (elastic fiber) score did not vary significantly among entities; SMCNL (loss of smooth muscle cells) score was higher in degenerative aorta [Waters et al. Cardiovasc Pathol 2017]

• But wide range of histopathology changes hampering specific diagnosis of entities at histopathology.
Conclusion

• **Dissection in youth (<45 y.o.):** always think of inherited disease (if no aortitis, no trauma)

• **Pathology including histology is not specific:** ask for specialized cardiovascular genetic consultation → family tree, syndrome or no…

• **Genetic testing only after clinical assessment to target the genes to be sequenced:** however genetic testing not always positive, mainly in sporadic non-syndromic TAAD in young: gene discovery still mandatory

• **Specific diseases are finally defined by clinical features and gene mutation, and not by pathology**
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