Marfan syndrome and related heritable aortic disease

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Overview

• Definition and Diagnostic Criteria

• Differential Diagnosis

• Genes in Practice
Overview

• Definition and Diagnostic Criteria

• Differential Diagnosis

• Genes in Practice
Definition

• Connective Tissue Disorder – autosomal dominant

• Incidence: 2-3/10,000

• Diagnosis: based on the identification of
  
  10 a combination of

  10 **Clinical** manifestations

  10 In **different** organ systems

• Caused by mutations in the **fibrillin-1 gene** (*FBN1*)
Revised Nosology – Basic rules

In the absence of family history:

(1) Ao (Z≥2) + EL = MFS
(2) Ao (Z≥2) + FBN1 = MFS
(3) Ao (Z≥2) + Syst (≥7pts) = MFS
(4) EL + FBN1 with known Ao = MFS

In the presence of family history:

(5) EL + FH of MFS (as defined above) = MFS
(6) Syst (≥7 pts) + FH of MFS (as defined above) = MFS
(7) Ao (Z≥2 in adults, Z≥3 in children) + FH of MFS (as defined above) = MFS

EL with or without Syst AND with an FBN1 not known with Ao or no FBN1=ELS
MVP AND Ao (Z <2) AND Syst (<5) without EL=MVPS

Revised nosology – Systemic score

3 points
Revised nosology – Systemic score

1 point
Systemic Score

- Wrist AND thumb sign - 3 (Wrist OR thumbs - 1)
- Pectus carinatum deformity - 2 (excavatum/asymm - 1)
- Pneumothorax - 2
- Dural Ectasia - 2
- Protrusio acetabuli - 2
- Reduced US/LS AND increased arm/height AND no severe scoliosis - 1
- Scoliosis or thoracalumbar kyphosis - 1
- Reduced elbow extension - 1
- Facial features (3/5) - 1
- Skin striae - 1
- Myopia >3 diopters - 1
- Mitral Valve Prolapse (all types) - 1

Maximum total: 20 points

≥7
Alternative diagnosis in Children

• If insufficient systemic features (<7) and/or borderline aortic root measurements (Z < 3) are present (without $FBN1$ mutation)
  - -> use “non-specific connective tissue disorder” until follow-up echocardiographic evaluation shows aortic root dilation (Z≥3).

• If an $FBN1$ mutation is identified in sporadic or familial cases but aortic root measurements are still below Z=3,
  - -> use the term “potential MFS” until the aorta reaches threshold.

• CAVE: Neonatal MFS is not considered as a separate category, but rather represents the severe end of the MFS spectrum.
Case 1

- 6y
- Bilateral lens luxation
- Ao Z-score: 1.7
- Systemic score: 5/20

Ectopia Lentis Syndrome? Potential Marfan syndrome?
Case 1

- 6y
- Bilateral lens luxation
- Ao Z-score 1.7
- Systemic score 5/20

- Mother: 30y
  - Bilateral lens luxation
  - Systemic score 9/20
  - Ao Z-score 2.3

*FBN1*+ Marfan syndrome
Fibrillin1 - structural
Fibrillin1 - functional

- fibrillin-1 is homologous with the family of latent TGFβ binding proteins (LTBPs)
  - Serve to hold TGFβ in an inactive complex in various tissues, including the extracellular matrix
- fibrillin-1 can bind TGFβ and LTBPs

TGFβ

Tβ-RII

LTBP

LAP

LAP

Microfibril/Fibrillin

Tβ-RI

Receptor Complex

TGFβ
Co-Activators
Co-repressors
Transcription Factors
↓
Gene transcription

Nucleus

Microfibril/Fibrillin

LAP

LTBP

TGFβ

Tβ-RI

Tβ-RII

Smad2

Smad3

Smad4

Receptor Complex

P

P

P

P
Marfan
Overview

• Definition and Diagnostic Criteria

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Case 2

- ° 1982
- TAA (known since 12 y)
  - David in 1996 ➔ Homograft in 1997  ➔ Bentall in 2005
- PDA
- Tall stature, Varicositas, Uvula raphe
- Family History
  - Father: died at age 27 y (aortic dissection)
  - Brother: aortic aneurysm (David at age 27y)
Case 2

Loeys-Dietz Syndrome

$FBN1 - TGFBR1+$
Case 2

Loeys-Dietz syndrome

Combination of vascular lesions

- Asending aortic aneurysm
- Aortic arch aneurysm
- Descending thoracic aortic aneurysm
- Abdominal aortic aneurysm
- Aortic dissection
- Head and neck artery anomalies
- Thoracic artery anomalies
- Abdominal artery anomalies
- Pulmonary artery dilatation
- Cardiac anomalies: MVP; ASD; PDA; LV dilatation; HCMP
Loeys-Dietz

Microfibril/Fibrillin

Co-Activators
Co-repressors
Transcription Factors
↓
Gene transcription

Nucleus

Receptor Complex

Smad2

Smad3

Smad4

P

S

P

TGFβ

Tβ-RII

Tβ-RI

LAP

LTBP

-
Case 3

- ♀, ° 1980
- Lumbar hernia at age 22
- 2011: Pulsatile sensations in both groins
Case 3

Aneurysm-Osteoarthritis Syndrome

van de Laar et al, Nature Genetics 2011
Aneurysm- Osteoarthritis

Microfibril/Fibrillin

Tβ-RII

Tβ-RI

TGFβ

LAP

Receptor Complex

Smad2

Smad2

Smad3

Smad3

Smad4

Smad4

Nucleus

Gene transcription

Co-Activators

Co-repressors

Transcription Factors
Case 4

• ♂, ° 1964
• Varicectomy
• Referral to Genetics outpatient Clinic

Jurgent referral for ARR??

• “Aspecific CTD/Hypermobile EDS”

TAAD NGS: TGFβ2 mutation
<table>
<thead>
<tr>
<th>nr</th>
<th>age/sex</th>
<th>age at diagnosis presenting symptom</th>
<th>cardiovascular features</th>
<th>skeletal</th>
<th>craniofacial</th>
<th>skin</th>
<th>ocular</th>
<th>cerebrovascular</th>
<th>family</th>
<th>mutation</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>69/F</td>
<td>60y</td>
<td>type A dissection</td>
<td>normal</td>
<td>flat feet, hallux valgus</td>
<td>/</td>
<td>/</td>
<td>/</td>
<td>mother died in childbirth, sister died from dissection at age 41</td>
<td>(p.Arg159X)</td>
</tr>
<tr>
<td>2</td>
<td>60/M</td>
<td>56y</td>
<td>MVP - MVR</td>
<td>clubfeet, joint laxity, mild pectus carinatum</td>
<td>high arched palate</td>
<td>varicose veins</td>
<td>myopia</td>
<td>/</td>
<td>negative</td>
<td>(p.Arg159X)</td>
</tr>
<tr>
<td>3</td>
<td>53/F</td>
<td>18y (Dx at 43 y)</td>
<td>MVP, mild MR</td>
<td>joint laxity as a child</td>
<td>high palate, retrogнатia</td>
<td>local translucency</td>
<td>myopia, astigmatism, cataract</td>
<td>recurrent strokes, corneos jailed vertebral Aa</td>
<td>daughter Marfanoid</td>
<td>{p.Arg327Trp}</td>
</tr>
<tr>
<td>4</td>
<td>38/M</td>
<td>38y</td>
<td>MVP</td>
<td>joint laxity</td>
<td>/</td>
<td>/</td>
<td>myopia, strabismus</td>
<td>/</td>
<td>negative</td>
<td>(p.Arg327Trp)</td>
</tr>
<tr>
<td>5</td>
<td>60/M</td>
<td>41y</td>
<td>trivial MR</td>
<td>arachnodactyly, camptodactyly, kyphoscoliosis</td>
<td>hypertelorism, downsllanting palpebral fissures, malar hypoplasia, high palate, retrogнатia</td>
<td>/</td>
<td>/</td>
<td>/</td>
<td>spontaneous pneumothorax in daughter, father sudden death at 43y</td>
<td>(p.Arg327Gln)</td>
</tr>
<tr>
<td>6</td>
<td>46/M</td>
<td>32y</td>
<td>type A dissection</td>
<td>MVP - MVR</td>
<td>pectus carinatum, arachnodactyly, joint hypermobility</td>
<td>/</td>
<td>/</td>
<td>/</td>
<td>negative</td>
<td>(p.Gly376Glu fsX17)</td>
</tr>
</tbody>
</table>

Renard et al, Int J Cardiol 2012
Microfibril/Fibrillin

Nucleus

Co-Activators
Co-repressors
Transcription Factors
↓
Gene transcription

Tβ-RI

Receptor Complex

Smad2

Smad3

Smad4

Smad4

P

P

TGFβ2

Tβ-RII

Co-repressors
Case 5

- 11y
- Craniosynostosis
- Skeletal abnormalities
- Facial dysmorphism
- Aortic root dilatation
- Intellectual disability

Whole exome sequencing: **SKI** mutations (exon1)

**SKI** = repressor of the TGFβ pathway
SKI

Co-Activators
Co-repressors
Transcription Factors
↓
Gene transcription
Co-Activators
Co-repressors
Transcription Factors
↓
Gene transcription

TGFβ2

Receptor Complex

Smad2
Smad3
Smad4

Losartan

Aneurysm/osteoarthritis

TGFβ related vasculopathies
Case 6

- Male, ° 1972
- 2000: Rupture Splenic artery
- 2004: Acute Myocardial Infarction - Dissection LAD
- 17/5/2010: Acute Abdominal Pain w hemodynamic shock
- Autopsy shows profuse hemoperitoneum with dissection of the entire aorta - ? originating from splenic artery rupture

Vascular Ehlers-Danlos Syndrome

- COL3A1+
Case 7

Isolated TAA

ACTA2
15% of all FTAA
Mutations in genes for contractile proteins in TAAD

- The contractile unit of vascular smooth muscle cells functions to maintain vascular tonus
- Consists of thick myosin filaments and thin actin filaments, encoded by:
  - **MYH11**
    - Associated with TAAD and patent ductus arteriosus (PDA)
    - Direct sequencing revealed 1 heterozygous splice site mutation in a family with TAAD + PDA
  - **ACTA2**
    - Associated with familial TAAD and variable association of:
      - Bicuspid aortic valve (BAV)
      - Patent ductus arteriosus (PDA)
      - Iris flocculi
      - Vascular occlusive disease: livedo reticularis, coronary artery disease, stroke, Moyamoya
    - Direct sequencing revealed ACTA2 mutations in 7 families with TAAD (16%) infrequently associated with BAV, PDA or livedo reticularis
Case 7

• ♂, ° 1960
• Small stature
• Hypothyreosis
• Lymphedema
• Infertility
Case 7

- ♀, ° 1960
- Small stature
- Hypothyreosis

**Turner Syndrome**

46 X0
## Syndromic TAAD

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Gene(s)</th>
<th>Additional Clinical Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Marfan</td>
<td>FBN1</td>
<td>Lens luxation, skeletal features (arachnodactyly, pectus deformity, scoliosis, flat feet, increased arm span, dolichocephalia)</td>
</tr>
<tr>
<td>Ehlers-Danlos (vascular, valvular)</td>
<td>COL3A1, COL1A2</td>
<td>Thin, translucent skin, dystrophic scars, facial characteristics (Madonna face, thin lips, deep-set eyes)</td>
</tr>
<tr>
<td>Loeys-Dietz</td>
<td>TGFBR1/2</td>
<td>Bifid uvula/cleft palate, hypertelorism, pectus abnormalities, scoliosis, club feet</td>
</tr>
<tr>
<td>Aneurysm-Osteoarthritis</td>
<td>SMAD3</td>
<td>Osteoarthritis, soft skin, flat feet, scoliosis, recurrent hernia's, hypertelorism, pectus abnormalities</td>
</tr>
<tr>
<td>TGFβ-related vasculopathies</td>
<td>TGFβ2</td>
<td>Club feet, soft translucent skin</td>
</tr>
<tr>
<td>Shprintzen-Goldberg syndrome</td>
<td>SKI</td>
<td>Craniosynostosis, distinctive craniofacial features, skeletal changes, neurologic abnormalities, mild-to-moderate intellectual disability</td>
</tr>
<tr>
<td>Arterial Tortuosity Syndrome</td>
<td>SLC2A10</td>
<td>Hyper lax skin and joints</td>
</tr>
<tr>
<td>Cutis Laxa Syndromes</td>
<td>FBLN4, ELN</td>
<td>Hyper lax skin and joints, mild emphysema</td>
</tr>
<tr>
<td>Turner Syndrome</td>
<td>X0</td>
<td>Hypothyreosis, lymphedema, short stature, infertility</td>
</tr>
<tr>
<td>Non Syndromic TAAD</td>
<td></td>
<td></td>
</tr>
<tr>
<td>-------------------</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Familial thoracic aortic aneurysm syndrome (FTAA)</strong></td>
<td><strong>TGFBR1/2 (3-5%)</strong></td>
<td>Lack of syndromal features</td>
</tr>
<tr>
<td></td>
<td><strong>ACTA2 (10-14%)</strong></td>
<td>Lack of Marfanoid skeletal features, livedo reticularis, iris flocculi, coronary artery/cerebrovascular disease</td>
</tr>
<tr>
<td></td>
<td><strong>MYLK</strong></td>
<td>Gastro-intestinal abnormalities</td>
</tr>
<tr>
<td></td>
<td><strong>SMAD3 (2%)</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>TGFβ 2</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>PRKG1</strong></td>
<td></td>
</tr>
<tr>
<td><strong>FTAA with bicuspid aortic valve (BAV)</strong></td>
<td><strong>ACTA2</strong></td>
<td>Lack of Marfanoid skeletal features, livedo reticularis, iris flocculi</td>
</tr>
<tr>
<td></td>
<td><strong>NOTCH1</strong></td>
<td></td>
</tr>
<tr>
<td><strong>FTAA with patent ductus arteriosus (PDA)</strong></td>
<td><strong>MYH11</strong></td>
<td></td>
</tr>
</tbody>
</table>
Overview

• Definition and Diagnostic Criteria

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• Genes in Practice
Genes in Practice

**Pedigree Drawing**
Clinical evaluation in 1st degree relatives

**TAA**
- Z-score >2 in adults, >3 in children
- Age <60 – 65 (?)
- Absence of other risk factors

**Non-Syndromal**
- Isolated TAA
  - NGS?
  - Clinical follow-up

**Syndromal**
- Marfan: FBN1
- Vascular EDS: COL3A1
- TGFB-related vasculopathies: TGFB1/2, SMAD3, TGFB2
- Arterial Tortuosity Syndromes
- SLC2A10
- Cutis Laxa: Fbln4

**Non-Syndromal**
- FTAA
- NGS

**Detailed clinical evaluation**
1. Clinical examination
   - Facial characteristics: hypertelorism, high palate, bifid uvula
   - Skeletal manifestations: arm span, pectus, arachnodactyly, flat feet, club feet
2. Echocardiography
   - Mitral Valve Prolapse
   - Bicuspid Aortic Valve
   - Patent Ductus Arteriosus
3. Ocular examination
   - Lens luxation
   - Iris Flocculi
4. X-ray, CT/MRI
   - Osteoarthritis
   - Arterial Tortuosity
   - Arterial Aneurysms
Monogenetic Disease

Sanger Sequencing

~ 2mln bp/d (human genome: 3 bln bp!)
Gene per gene
600 - 1000 €/gene

1. Select the right book (gene)
2. Careful proofreading

Ehlers Danlos
Marfan
Loeys-Dietz
Aneurysm-Osteoarthritis
...

1. Select the right book (gene)
2. Careful proofreading
Monogenetic Disease

Next Generation Sequencing
50 bln bp/d
Several genes/run
600 - 2000 €/set

Efficient browsers
Spelling Checker
Storage Capacity
Back-up
Next Generation Sequencing

Panel Sequencing

TAA Panel 1
- FBN1
- TGFBR1
- TGFBR2
- ACTA2
- COL3A1
- TGFB2
- SMAD3
- MYH11

TAA Panel 2
- MYLK
- NOTCH1

**Marfan**
Surgery at 50 (45) mm
No involvement outside the Ao
Ocular Problems

**Loeys-Dietz**
Surgery at 40 (45) mm
Extensive vascular involvement

- Available since 1/1/2013
- Cost 1800 € - 9 € for the patient
- TAT 3 months
# Genes in Practice

## Table of Genes

<table>
<thead>
<tr>
<th>Gene</th>
<th>Marfan</th>
<th>Loeys-Dietz</th>
<th>Aneurysm-OsteoA</th>
<th>Ehlers-Danlos</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gene</td>
<td>FBN1</td>
<td>TGFB1/2</td>
<td>SMAD3</td>
<td>COL3A1</td>
</tr>
<tr>
<td>Survival</td>
<td>72y (+R/)</td>
<td>45y (- R/)</td>
<td>45y</td>
<td>45y</td>
</tr>
<tr>
<td>Diameter Dissection (mm)</td>
<td>&gt;50</td>
<td>40-45</td>
<td>40-45</td>
<td>?</td>
</tr>
<tr>
<td>Disease outside aorta</td>
<td>rare</td>
<td>frequent</td>
<td>frequent</td>
<td>frequent</td>
</tr>
<tr>
<td>Outcome surgery</td>
<td>Good</td>
<td>Good</td>
<td>Good</td>
<td>Bad!</td>
</tr>
</tbody>
</table>

## Conditions
- **Surgery >50mm**
- **MRI/CT q 5j**
- **BBI - ARB**

- **Surgery >42mm**
- **MRI/CT yearly**
- **BBI - ARB**

- **Surgery?**
- **MRI/CT ?**
- **Selectol**
Take Home Messages

- Marfan syndrome is a clinical diagnosis
- TGF$_{\beta}$ is an important molecule in the pathogenesis
- Other TGF$_{\beta}$ associated disorders should be considered in the differential diagnosis
- Knowledge of the underlying gene defect is important for
  - Guidance of Medical / Surgical management
  - Family counselling