Diagnosis and Treatment of Genetic Aortopathies for the Practicing Cardiologist

Juan Bowen, MD
Charles Wooley, MD

Harisios Boudoulas, MD
Diagnosis and treatment of genetic aortopathies

• Milestones and important discoveries
• Structure and function of the ascending aorta
• Making a specific genetic diagnosis – a guide for clinicians
• Medical management of genetic aortopathies
• Surgical management of genetic aortopathies
Marfan Syndrome Milestones

1896
Antoine Marfan
Clinical description

1952
Cooley & DeBakey
Thoracic aneurysm repair

1956
Victor McKusick
Heritable Disorders of Connective Tissue

1968
Hugh Bentall
Composite graft

Hal Dietz
Fibrillin gene TGFB

2007
Dianna Milewicz
VSMC mutations
Basic and Clinical Research

2003
TGFB

1991
FBN1

2007
ACTA2
GenTAC

2013
MAC
Aorta Journal

2014
PHN TRIAL
AVR TRIAL
The elastic fiber network and aortic function
Elastic fiber fragmentation
Verhoeff van Gieson Stain (Elastic Stain)
Structure of the Elastin-Contractile Units in the Thoracic Aorta and How Genes That Cause Thoracic Aortic Aneurysms and Dissections Disrupt This Structure
Ashkan Karimi, MD, and Dianna M. Milewicz, MD, PhD
Canadian J of Cardiology  2016
**Vessel wall homeostasis**

**TGF-β**
- Prenatally and perinatally:
  - Required for formation of the vascular plexus and differentiation of endothelial and vascular smooth muscle cells
  - Required for elastogenesis
  - Required for normal morphogenesis of the cardiac outflow tract

**Postnatally**
- Increased signaling is associated with development of thoracic aortic aneurysm (TAA)
- Increased signaling is associated with increased matrix deposition (i.e., collagen) as well as increased matrix degradation (i.e., increased expression of MMP2 and MMP9 leading to elastin degradation)

**Palate development**

**TGF-β**
- Promotes fusion of palatal shelves through apoptosis-dependent disintegration of the midline epithelial seam

**BMP**
- Promotes proliferation of palatal mesenchymal cells

**Endochondral ossification and longitudinal bone growth**

**TGF-β**
- Induces commitment to osteoblastic cell lineage
- Stimulates mesenchymal condensation; commitment to the chondrogenic lineage
- Prevents terminal osteoblastic and chondrogenic differentiation

**BMP**
- Required for terminal osteoblastic and chondrogenic differentiation
- Promotes maturation of cartilaginous elements in growth plate

**Limb and digit development**

**TGF-β**
- Digit patterning/establishment of phalanx-forming region (PFR)

**BMP**
- Induction of apical ectodermal ridge (AER)
- Proximodistal elongation of digits
- Induction of apoptosis for formation of joint cavity
- Induction of apoptosis of interdigital mesenchyme

**Bone remodeling**
(see Fig. 5)
Diagnosis: As specific as possible

- History
- Exam
- Imaging
- Genetics

DIAGNOSIS

PLAN

Prognosis
Management
Lifelong Care
Comments on the medical history

• Personal history
  • Cardiac
  • Noncardiac
    • Skin, eye, musculoskeletal
• Family history – Aortic and aortic valve disease, early death
• Symptoms
Comments on the physical examination

- Phenotype can be normal.
- Many features of connective tissue dysplasia are nonspecific.
- “Hard” findings are more meaningful than “soft” findings.
- CV – aortic and mitral valves.
- Non-CV – Skin, eye, musculoskeletal.
Ectopia lentis
Comments on imaging

• Echocardiography - aortic root Z score
• CTA and MRA - gated
• First evaluation - chest/abdomen/pelvis
• Follow up imaging - individualized
Multimodality Imaging

40 mm

48 mm
<table>
<thead>
<tr>
<th>Gene (Protein)</th>
<th>Syndrome or Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Extracellular matrix protein genes</td>
<td></td>
</tr>
<tr>
<td><em>FBN1</em> (fibrillin-1)</td>
<td>Marfan syndrome</td>
</tr>
<tr>
<td><em>COL3A1</em> (type 3 procollagen)</td>
<td>Vascular Ehlers-Danlos syndrome</td>
</tr>
<tr>
<td><em>COL4A5</em> (type 4 procollagen)</td>
<td>Alport syndrome</td>
</tr>
<tr>
<td><em>EFEMP2</em> (fibrillin-4)</td>
<td>Cutis laxa</td>
</tr>
<tr>
<td>TGF-β signaling pathway genes</td>
<td></td>
</tr>
<tr>
<td><em>TGFBR1</em> (TGF-β receptor-1)</td>
<td>LDS or FTAAD</td>
</tr>
<tr>
<td><em>TGFBR2</em> (TGF-β receptor-2)</td>
<td>LDS or FTAAD</td>
</tr>
<tr>
<td><em>SMAD3</em> (SMAD3)</td>
<td>Osteoarthritis-aneurysm syndrome or LDS 3</td>
</tr>
<tr>
<td><em>TGFBL2</em> (TGF-β2)</td>
<td>FTAAD or LDS 4</td>
</tr>
<tr>
<td><em>SKI</em> (v-SKI sarcoma oncogene homolog)</td>
<td>Shprintzen-Goldberg syndrome</td>
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<tr>
<td><em>SLC2A10</em> (glucose transporter 10)</td>
<td>Arterial tortuosity syndrome</td>
</tr>
<tr>
<td>Vascular smooth muscle contraction</td>
<td></td>
</tr>
<tr>
<td>components or cytoskeleton genes</td>
<td></td>
</tr>
<tr>
<td><em>ACTA2</em> (alpha-actin)</td>
<td>FTAAD</td>
</tr>
<tr>
<td><em>MYH11</em> (myosin heavy chain-11)</td>
<td>FTAAD</td>
</tr>
<tr>
<td><em>MLK</em> (myosin light chain kinase)</td>
<td>FTAAD</td>
</tr>
<tr>
<td><em>PRKG1</em> (protein kinase cGMP-dependent)</td>
<td>FTAAD</td>
</tr>
<tr>
<td><em>FLNA</em> (filamin A)</td>
<td>Periventricular nodular heterotopia, aortic aneurysm, valvular dystrophy</td>
</tr>
</tbody>
</table>
Marfan syndrome
MFS facial features

- Dolicocephaly
- Enophthalmos
- Downslanting palpebral fissures
- Malar hypoplasia
- Retrognathia
Aortic root aneurysm
MFS Systemic Score
Maximum score 20
Score ≥ 7 means systemic involvement

FAMILY HX MFS

One of the following
Ectopia lentis
  Aortic dilation
    Z-score ≥ 2 (age ≥ 20)
    Z-score ≥ 3 (age < 20)
Systemic score ≥ 7

NO FAMILY HX MFS

Z-score ≥ 2 or dissection + EL
Z-score ≥ 2 or dissection + FBN1 mutation
Z-score ≥ 2 or dissection + SS ≥ 7
Aorta + Ectopia lentis + FBN1 mutation
<table>
<thead>
<tr>
<th>Condition</th>
<th>Score</th>
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<tbody>
<tr>
<td>Wrist and thumb sign</td>
<td>3</td>
</tr>
<tr>
<td>Wrist OR thumb sign</td>
<td>2</td>
</tr>
<tr>
<td>Pectus carinatum</td>
<td>2</td>
</tr>
<tr>
<td>Pectus excavatum or chest asymmetry</td>
<td>1</td>
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<tr>
<td>Hindfoot deformity</td>
<td>2</td>
</tr>
<tr>
<td>Pes planus</td>
<td>1</td>
</tr>
<tr>
<td>Pneumothorax</td>
<td>2</td>
</tr>
<tr>
<td>Dural ectasia</td>
<td>2</td>
</tr>
<tr>
<td>Protrusio acetabulae</td>
<td>2</td>
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<tr>
<td>US/LS ratio AND Arm span/height</td>
<td>1</td>
</tr>
<tr>
<td>Scoliosis OR thor-lumb kyphosis</td>
<td>1</td>
</tr>
<tr>
<td>Elbow extension</td>
<td>1</td>
</tr>
<tr>
<td>3/5 Facial features</td>
<td>1</td>
</tr>
<tr>
<td>Skin striae</td>
<td>1</td>
</tr>
<tr>
<td>Myopia &gt;3 diopters</td>
<td>1</td>
</tr>
<tr>
<td>Mitral valve prolapse</td>
<td>1</td>
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</table>
Risk assessment by genotype

- Truncating/splicing variants associated with aortic events.
- Haploinsufficiency mutations have more risk for aortic events than dominant negative mutations.
FBN Mutation: haploinsufficiency vs. dominant-negative

Aortic root (mm)

Age

Loeys-Dietz syndrome
Arterial tortuosity
Multiple aneurysms
Are all TGF beta pathway mutations clinically equivalent?

Montalcino Aortic Consortium data

- TGFBR1 and TGFBR2 (n=441) - aggressive aneurysmal disease, hypertelorism, bifid uvula
- TGFBR2 and TGFBR3 – usually not as severe
- SMAD 3 (n=210) – later onset aortic events, osteoarthritis
Vascular Ehlers-Danlos syndrome
Age 33 renal artery dissection

Age 41 ruptured hepatic artery aneurysm

Age 46 carotid-cavernous sinus fistula
Aneurysms are often minimal
COL3A1 haploinsufficiency results in a variety of Ehlers-Danlos syndrome type IV with delayed onset of complications and longer life expectancy

Dru F. Leistritz, MS1, Melanie G. Pepin, MS1, Ulrike Schwarze, MD1, and Peter H. Byers, MD1,2

Molecular diagnosis in vascular Ehlers-Danlos syndrome predicts pattern of arterial involvement and outcomes

BAV Aortopathy
Ascending aorta
BAV Aneurysm and Dissection Risk

No. at Risk

<table>
<thead>
<tr>
<th>Years after diagnosis</th>
<th>TAA</th>
<th>Dissection</th>
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<tr>
<td>0</td>
<td>384</td>
<td>416</td>
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<tr>
<td>5</td>
<td>352</td>
<td>387</td>
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<td>10</td>
<td>309</td>
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<td>186</td>
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<td>20</td>
<td>88</td>
<td>110</td>
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<td>25</td>
<td>39</td>
<td>53</td>
</tr>
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</table>

Michelena et al: JAMA, 2011
BAV etiology and genetics

- Etiology of aneurysm is both developmental and hemodynamic.

- No single genetic/developmental cause
Intrinsic weakness + hemodynamic stress

Non-syndromic familial TAA genetic testing
Mutations found in 15-20%

<table>
<thead>
<tr>
<th>Gene</th>
<th>FTAAD (%)</th>
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<tr>
<td>ACTA2</td>
<td>10-14</td>
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<tr>
<td>TGFBR2</td>
<td>4</td>
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<tr>
<td>SMAD3</td>
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<td>TGFBR1</td>
<td>1</td>
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<tr>
<td>MYH11</td>
<td>1</td>
</tr>
<tr>
<td>MYLK1</td>
<td>1</td>
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<tr>
<td>TGFB2</td>
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</table>
Familial TAA 8%
Marfan 56%
EDS 9%
LVSD 3%
BAV 11%
GCA 2%
Arteritis 1%
MYLk 1%
MYH11 1%
ACTA2 1%
SMAD3 1%
TGFB1 1%
TGFB2 1%
COL3A1 2%
COL5A1 1%
Management
Protection of the aorta

• Physical activity recommendations

• Medication
Exercise and Physical Activity in Marfan Syndrome and Related Disorders

Alan C. Braverman, MD

www.marfan.org
Mild aerobic exercise blocks elastic fiber fragmentation and aortic dilatation in a mouse model of Marfan syndrome associated aortic aneurysm.

Can the disease be modified?

Beta blockade - Grade B evidence
AT1R blockade - Mouse model followed by clinical trials
Losartan prevents MFS complications in the mouse model

Habashi, Dietz et al: Science 2006
PHN Trial 2014: Changes in Aortic-Root Z Score and Aortic-Root Diameter, According to Treatment Group

No. at risk

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Years Since Randomization</th>
<th>Atenolol</th>
<th>Losartan</th>
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<td>303</td>
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<td>3</td>
<td>268</td>
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P=0.08

No. at risk

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Years Since Randomization</th>
<th>Atenolol</th>
<th>Losartan</th>
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<tbody>
<tr>
<td></td>
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<td>303</td>
<td>304</td>
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<tr>
<td></td>
<td>3</td>
<td>268</td>
<td>267</td>
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P=0.20

MFS Clinical trials

<table>
<thead>
<tr>
<th>Country (trial)</th>
<th>Design</th>
<th>Treatment</th>
<th>Follow-up (months)</th>
<th>Mean age (years)</th>
<th>Number of patients*</th>
<th>Imaging</th>
<th>Aortic root dilatation (mm per year)</th>
<th>Death and aortic dissection (n)</th>
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<tbody>
<tr>
<td>Taiwan (Mayo)</td>
<td>Open-label (blinded</td>
<td>Losartan and β-blockers vs β-blockers</td>
<td>35</td>
<td>13±6.3</td>
<td>29 (28)</td>
<td>Ultrasonography</td>
<td>0.10 vs 0.89 (P=0.02)</td>
<td>1 vs 0</td>
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<tr>
<td></td>
<td>end points)</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>The Netherlands (COMPARE trial)</td>
<td>Open-label (blinded end points)</td>
<td>Losartan vs no losartan‡</td>
<td>37</td>
<td>38 (range 18–71)</td>
<td>233 (145)</td>
<td>MRI/ultrasonography</td>
<td>0.26 vs 0.45 (P=0.014)</td>
<td>0 vs 2</td>
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<tr>
<td>USA (Pediatric Heart Network Study)</td>
<td>Double-blind</td>
<td>Losartan vs atenolol</td>
<td>36</td>
<td>11 (range 0.5–25.0)</td>
<td>608 (535)</td>
<td>Ultrasonography</td>
<td>0.75 vs 0.69 (P=0.20)</td>
<td>3 vs 0</td>
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<tr>
<td>France (Marfan Sartan trial)</td>
<td>Double-blind</td>
<td>Losartan vs placebo‡</td>
<td>42</td>
<td>30 (all &gt;10)</td>
<td>297 (292)</td>
<td>Ultrasonography</td>
<td>0.44 vs 0.51 (P=0.36)</td>
<td>1 vs 5</td>
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<tr>
<td>Belgium (Ghent Marfan Trial)</td>
<td>Double-blind</td>
<td>Losartan vs placebo</td>
<td>36</td>
<td>&gt;10</td>
<td>NA</td>
<td>Ultrasonography/MRI</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>UK (AIMS)</td>
<td>Double-blind</td>
<td>Irbesartan vs placebo</td>
<td>48</td>
<td>6–40</td>
<td>490</td>
<td>Ultrasonography</td>
<td>NA</td>
<td>NA</td>
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<tr>
<td>Italy¹</td>
<td>Open-label (blinded end points)</td>
<td>Losartan vs nebivolol vs both</td>
<td>48</td>
<td>1–55</td>
<td>291</td>
<td>Ultrasonography</td>
<td>NA</td>
<td>NA</td>
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<tr>
<td>Spain¹</td>
<td>Double-blind</td>
<td>Losartan vs atenolol</td>
<td>36</td>
<td>5–60</td>
<td>150</td>
<td>MRI/ultrasonography</td>
<td>NA</td>
<td>NA</td>
</tr>
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</table>

Franken et al> Nature Reviews Cardiology 2015
Inhibition of Marfan Syndrome Aortic Root Dilation by Losartan

Role of Angiotensin II Receptor Type 1—Independent Activation of Endothelial Function

Timely preventive aortic repair is the primary treatment!
Timing of preventive aortic repair
Timing of preventive aortic repair

High-risk features: FH or personal history of aortic dissection, rapid enlargement, or planned pregnancy
Selected issues relevant to practice in 2018

• The problem of the distal aorta.

• Clinically relevant biomarkers and tests of aortic function.

• The natural history of many genetic aortopathies is still being discovered.

• Quality of life problems – many are noncardiac.
Risk of type B dissection in MFS

Percent free from type B dissection

Follow up years

1. No risk factors
2. Aortic diameter ≥27mm or prior aortic surgery
3. Both risk factors

Den Hertog, et al.
JACC VOL. 65, NO. 3, 2015
Summary

• Genetic aortopathies are caused by mutations that affect aortic structure and function.

• The differential diagnosis includes syndromic disorders, vascular EDS, BAV aortopathy, and nonsyndromic familial TAA.

• In some genetic aortopathies the natural history is not fully known.

• Medical therapies are evolving.

• The primary treatment is preventive aortic repair.

• Care is individualized, interdisciplinary, and lifelong.
Thank you

bowen.juan@mayo.edu