I disclose the following financial relationships:

Data and Safety Monitoring Board for Jarvik Heart

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Major stockholder of Coolspine
Genetics in Thoracic Aneurysm

• Historical glimpse
• Discovery of Familial Patterns
• Mendelian Genetics
• Molecular Genetics (DNA)
• Molecular Genetics (RNA)
  – Investigational “RNA Signature” Test
Genetics in Thoracic Aneurysm

• **Historical glimpse**
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“The Nomads and Scythians have *lax joints* and easy bruising.”
Hippocrates 400 B.C.

Describing *Ehlers-Danlos Syndrome*
Antoine Marfan  
France  
1896

Edvard Ehlers  
Denmark  
1901

Henri-Alexandre Danlos  
France  
1908
Human genetics of the abdominal aortic aneurysm.

The results of recent studies suggest that genetic factors may be important in the pathogenesis of abdominal aortic aneurysms. In the present report, the apparent mechanisms of inheritance in 16 families with a total of 41 affected individuals are summarized. The results suggest that there may be both X-linked and autosomal dominant forms of the disease, with the X-linked variant as the more common type. A multifactorial mechanism cannot be ruled out from the results of the present data.
Bart Loeys
Belgium
2006

Hal Dietz
Johns Hopkins
2006

Diana Milewicz, University of Texas
“Quinckie’s Pulse: Exaggerated pulsation from large pulse pressure in severe aortic insufficiency”
Thoracic Aortic Aneurysm is a Genetic Disease: Marfan’s is just the Tip of the Genetic Iceberg
Genetics in Thoracic Aneurysm

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Three Generations of Type A Dissection in One Single Family

- 59 year old Female
  - Type A Dissection
    - Well
    - Well
  - Well
    - Well
Three Generations of Type A Dissection in One Single Family

- 78 year old Female
  - Type A Dissection

- 59 year old Female
  - Type A Dissection

- Well

- Well

- Well
Three Generations of Type A Dissection in One Single Family

78 year old Female
Type A Dissection

59 year old Female
Type A Dissection

Well

12 year old Female
Type A Dissection

Well

Well
Thumb-Palm Sign
Genetics in Thoracic Aneurysm

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• Molecular Genetics (RNA)
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Genetic Patterns in 300 Yale Family Pedigrees

- Autosomal dominant: 38.5%
- Autosomal dominant or X-linked: 23.1%
- Recessive: 26.9%
- Other: 11.5%
Familial Patterns of Thoracic Aortic Aneurysms

Michael A. Coady, MD, MPH; Ryan R. Davies, BA; Michele Roberts, MD, PhD; Lee J. Goldstein, BA; Matthew J. Rogalski, BS; John A. Rizzo, PhD; Graeme L. Hammond, MD; Gary S. Kopf, MD; John A. Elefteriades, MD

**Hypothesis:** To provide evidence that genetic factors contribute to the development of thoracic aortic aneurysms (TAA) by demonstrating familial patterns of the disease.

**Design:** Retrospective review.

**Settings:** University hospital.

**Patients and Methods:** We sought to identify familial patterns of TAA from a database of 598 patients evaluated or treated for TAA at the Yale Center for Thoracic Aortic Disease, New Haven, Conn, from January 1985 to August 1998. Of the 598 patients, 45 patients had a diagnosis of Marfan syndrome and 553 patients had no known history of any collagen vascular disorder. Of the 553 patients in the latter category, 398 patients had confirmed TAA, 66 had TAA with concomitant aortic dissections, and 89 had aortic dissections. From the group of 464 patients with TAA with or without concomitant aortic dissections, 2 interviewers attempted to contact 150 randomly selected patients for telephone screening to determine the presence of familial patterns of aortic disease. Fifteen of these patients were lost to follow-up. Complete medical and family histories of the remaining 135 patients (85 men, 50 women) were reviewed. Of the 135 individuals screened, 26 (18 men, 8 women) (19.3%) were found to belong to multiplex pedigrees. These 26 patients with familial nonsyndromic TAA were compared with the remaining 109 patients with sporadic TAA and the 45 patients with Marfan syndrome–associated TAA.

**Main Outcome Measures:** Groups were examined for statistical differences in age and aortic size at the time of diagnosis, growth rates of TAA, and rates of concomitant diseases. Nonsyndromic family pedigrees were analyzed and potential modes of inheritance were determined.

**Results:** The mean age at presentation for patients with familial nonsyndromic TAA (56.8 years) was significantly younger than the mean age of presentation in sporadic cases (64.3 years, \( P \leq .03 \)), and significantly older than that of patients with Marfan syndrome (24.8 years, \( P \leq .001 \)). Patients with a family history of aortic aneurysms had faster growth rates (0.22 cm/y) compared with patients with sporadic TAA (0.03 cm/y) \( (P \leq .001) \) and patients with Marfan syndrome (0.10 cm/y) \( (P \leq .04) \). Familial nonsyndromic TAA in patients with a concomitant aortic dissection had a growth rate of 0.33 cm/y, which was greater than that of patients with sporadic TAA (0.10 cm/y) and patients with Marfan syndrome (0.08 cm/y) with associated aortic dissection. This growth of 0.33 cm/y was significantly faster than the overall growth rate estimate of aneurysms in patients with aortic dissection (0.14 cm/y) \( (P \leq .05) \). Ten pedigrees (38.5%) showed direct father to son transmission, consistent with an autosomal dominant mode of inheritance. Six family pedigrees (23.1%) suggested an autosomal dominant or X-linked mode of inheritance. Seven pedigrees (26.9%) suggested a recessive mode of inheritance; 2 an autosomal recessive mode, and 5 an X-linked recessive or autosomal recessive mode. The remaining 3 pedigrees displayed more complex modes of inheritance.

**Conclusions:** This study supports the role of genetic factors influencing familial aggregation of TAA. Thoracic aortic aneurysms in association with multiplex pedigrees represent a new risk factor for aneurysm growth. Pedigree analysis suggests genetic heterogeneity. The primary mode of inheritance seems to be autosomal dominant, but X-linked dominant and recessive modes are also evident.

*Arch Surg. 1999;134:361-367*
Distribution of Arterial Aneurysms and Dissections Sites in Kindred of Familial Probands

<table>
<thead>
<tr>
<th>Kindred sites</th>
<th>Proband sites</th>
<th>asc</th>
<th>desc</th>
<th>AAA</th>
<th>other</th>
<th>Total paired sites</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>asc</td>
<td>106</td>
<td>90</td>
<td>9</td>
<td>34</td>
<td>148</td>
</tr>
<tr>
<td></td>
<td>desc</td>
<td>25</td>
<td>7</td>
<td>3</td>
<td>27</td>
<td>45</td>
</tr>
</tbody>
</table>

Ascending and Descending Thoracic aortic aneurysm are two different diseases.

Bicuspid Aortic Valve
Aortic Aneurysm in the setting of Bicuspid Aortic Valve

Mendelian and molecular genetics of bicuspid valve and aneurysm disease is incompletely understood.
## Likelihood of Aortic Dissection

<table>
<thead>
<tr>
<th></th>
<th>Incidence</th>
<th>Likelihood of aortic dissection</th>
</tr>
</thead>
<tbody>
<tr>
<td>Marfan’s Syndrome</td>
<td>0.01% (1 in 10,000)</td>
<td>40%</td>
</tr>
<tr>
<td>Bicuspid Aortic Valve</td>
<td>1 to 2%</td>
<td>5%</td>
</tr>
</tbody>
</table>

*Bicuspid aortic valve causes many more cases of aortic dissection than Marfan’s disease*

*Note: Dissection usually occurs long before onset of significant aortic stenosis*

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## Genetics of Thoracic Aortic Aneurysm

<table>
<thead>
<tr>
<th>Classification</th>
<th>Chromosome</th>
<th>Gene</th>
<th>Protein</th>
<th>Location</th>
<th>Frequency</th>
<th>Inheritance</th>
</tr>
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<tbody>
<tr>
<td><strong>Syndromic:</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Marfan</td>
<td>15q21.1</td>
<td>FBN1</td>
<td>Fibrillin 1</td>
<td>ECM</td>
<td>1:5000-10,000</td>
<td>Dominant</td>
</tr>
<tr>
<td>Loeys-Dietz</td>
<td>3p24-25</td>
<td>TGFBR2,</td>
<td>TGFβ-R2</td>
<td>Cell surface</td>
<td>Rare</td>
<td>Dominant</td>
</tr>
<tr>
<td></td>
<td>9q33-34</td>
<td>TGFBR1</td>
<td>TGFβ-R1</td>
<td>Cell surface</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ehlers-Danlos</td>
<td>2q24.3-31</td>
<td>COL3A1</td>
<td>Type III collagen</td>
<td>ECM</td>
<td>1:10,000-25,000</td>
<td>Dominant</td>
</tr>
<tr>
<td>ATS</td>
<td>20q13.1</td>
<td>SLC2A10</td>
<td>GLUT10</td>
<td>Intracellular</td>
<td>Rare</td>
<td>Recessive</td>
</tr>
<tr>
<td>AOS</td>
<td>15q22.2-24.3</td>
<td>SMAD3</td>
<td>SMAD3</td>
<td>Intracellular</td>
<td>Rare</td>
<td>Dominant</td>
</tr>
<tr>
<td>TGFβ2</td>
<td>1q41</td>
<td>TGFβ2</td>
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<tr>
<td>Cutis Laxa Syndrome</td>
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<td>10q23-24</td>
<td>ACTA2</td>
<td>Actin</td>
<td>Intracellular</td>
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<tr>
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<td>16p12-13</td>
<td>MYH11</td>
<td>β-MHC</td>
<td>Intracellular</td>
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<tr>
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<td>MYLK</td>
<td>MLCK</td>
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Schematic of Exome Sequencing

Genomic DNA → Construct shotgun library → Fragments → Hybridization → Pulldown → Wash → Captured DNA

Mapping, alignment, variant calling → DNA sequencing
Yale Experience with WES for Thoracic Aortic Disease

# Features of Specific Familial Etiologies of Thoracic Aortic Aneurysm

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>% of Familial Aortic Aneurysm Patients</th>
<th>Special considerations</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACTA 2</td>
<td>10-15%</td>
<td>Present with dissection Can dissect @ &lt;5cm Risk stroke, MI</td>
</tr>
<tr>
<td>MHY11</td>
<td>2%</td>
<td>Involved in SMC contraction</td>
</tr>
<tr>
<td>MYLK</td>
<td>1%</td>
<td>Involved in SMC contraction Exclusively involved with dissections (not aneurysms), so hard to counsel re best time for intervention</td>
</tr>
</tbody>
</table>
New “Dissection Genes”
Association of *FBN1* SNPs with Thoracic Aortic Dissection

*The Yale Study*

- FBN-1 variant rs2118181 was associated with TAD
- In contrast, rs10519177 was not associated with TAD


---

**FBN-1 Genotype**

- rs2118181
  - CC + CT
  - TT
  - OR = 1.87

- rs10519177
  - GG + AG
  - AA
  - OR = 1.21

*Odds Ratio (95% CI)*

* Adjusted for sex and study center

**“Dissection gene”**
Association of *KIF6* Trp719Arg with Thoracic Aortic Dissection

Including Coronary Heart Disease

- **OR = 2.14**
  - Arg/Arg + Arg/Trp
  - p = 0.013

- **OR = 2.39**
  - Arg/Trp
  - p = 0.0066

- **OR = 1.40**
  - Arg/Arg
  - p = 0.429

*Trp/Trp variant used as the reference group

**Adjusted for gender, age, smoking (current versus noncurrent), hypertension and participating center
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“RNA Signature”

- DNA is blueprint
- RNA tells us what rooms (systems) are actively being worked on
Figure 3

A.

B.

Accuracy
Sensitivity
Specificity

(7.7% variance)

(62.1% variance)

(5.4% variance)
Hierarchical Clustering Diagrams

Each vertical line represents a patient

Each horizontal line represents an RNA (One of 30,000 tested)
In patients with a thoracic aortic aneurysm, there is a 10% likelihood that they harbor an intracranial aneurysm.
Aneurysm Patients have Lower IMT and Lower Calcium Score Relative to Control Group

- MMPs are Pro-Aneurysmal
- MMPs are Anti-Atherogenic
Conclusion
Genetics of Thoracic Aortic Aneurysm

We are clearly headed toward a new era of:
1) Molecular identification of individuals at risk for TAA
2) Personalized strategic management of those individuals.