The Integration of Genetic Testing in the Work-Up of a Patient With Thoracic Aortic Aneurysm and Dissection

Bulat A. Ziganshin, MD, PhD and John A. Elefteriades, MD, PhD (hon)

Aortic Institute at Yale-New Haven, Yale University School of Medicine
New Haven, Connecticut, USA
Disclosures

• I do not have any potential conflicts of interest to disclose relevant to this presentation.
Thoracic Aortic Aneurysm and Dissection – Hereditary Disease

20% cases – Familial

Familial thoracic aortic dilatations and dissections: A case control study

Alan Biddinger, MSE, Marnie Rocklin, MS, Joseph Coselli, MD, and
Dianna M. Milewicz, MD, PhD, Houston, Texas.

Purpose: Evidence suggesting that genetic factors contribute to the development of common disorders can be obtained by demonstrating familial aggregation of the disease. Familial thoracic aortic dilatations and dissections aggregate in sporadic aortic aneurysms, thoracic aortic dissections of patients referred for thoracic aortic surgery. To study familial thoracic aortic dilatations and dissections, 158 nonsyndromic patients referred for aneurysms or dissections (probands) and their 147 first-degree relatives were derived from a Mayo Clinic cohort. Abdominal aortic aneurysms, sudden death, and myocardial infarction demonstrated a higher prevalence of thoracic aortic aneurysms compared with the control group. Relative risks of first-degree relatives compared with the control group were not significantly different. This study suggests that familial thoracic aortic aneurysms and dissections are less common than abdominal aortic aneurysms, which may be due to different genetic factors.

Familial Patterns of Thoracic Aortic Aneurysms

Michael A. Coady, MD, MPH, Ryan R. Davies, RA, Michele Roberts, MD, PhD;
Lee J. Goldstein, BA, Matthew J. Bolognesi, BS, John A. Ricco, 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.

Setting: University hospital.

Patients and Methods: We sought to identify familial patterns of TAA from a database of 308 patients evaluated or treated for TAA at the Mayo Clinic for Thoracic Aortic Aneurysm, New York, NY, from January 1985 to August 1998. Of the 308 patients, 45 patients had a diagnosis of Marfan syndrome and 353 patients had no known history of any collagen vascular disorder. Of the 353 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 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 < .001), and significantly older than that of patients with Marfan syndrome (24.8 years; P < .001). Patients with a family history of aortic aneurysms had faster growth rates (0.22 cm/year) compared with patients with sporadic TAA (0.03 cm/year; P < .001) and patients with Marfan syndrome (0.10 cm/year; P < .004). Familial nonsyndromic TAA in patients with a concomitant aortic dissection had a growth rate of 0.33 cm/year, which was greater than that of patients with sporadic TAA (0.10 cm/year) and patients with Marfan syndrome (0.08 cm/year) with associated aortic dissection. This growth of 0.33 cm/year was significantly faster than the overall growth rate estimate of aneurysms in patients with aortic dissection (0.14 cm/year; P < .001). 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 3 an X-linked recessive or autosomal recessive mode. The remaining 3 pedigrees displayed more complex modes of inheritance.

Conclusions: This study suggests 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.

### Genes Causative of Thoracic Aortic Aneurysm and Dissection

<table>
<thead>
<tr>
<th>Gene</th>
<th>Location</th>
<th>Protein</th>
<th>Syndromic TAAD</th>
<th>Nonsyndromic FTAAD</th>
<th>Associated Disease/Syndrome</th>
<th>Inheritance</th>
<th>OMIM No. (Phenotype)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACTA2</td>
<td>10q23.31</td>
<td>Smooth muscle α-actin</td>
<td>+</td>
<td>+</td>
<td>FTAA 6 + multisystemic smooth muscle dysfunction</td>
<td>AD</td>
<td>611788 + 613834</td>
</tr>
<tr>
<td>BGN</td>
<td>Xq28</td>
<td>Biglycan</td>
<td>+</td>
<td>-</td>
<td>Unidentified CTD</td>
<td>X-linked</td>
<td>301570 (gene)</td>
</tr>
<tr>
<td>COL1A1</td>
<td>17q21.33</td>
<td>Collagen 1 α1 chain</td>
<td>+</td>
<td>-</td>
<td>Ehlers-Danlos syndrome, arthrochasia type (VIIa)</td>
<td>AD</td>
<td>130050</td>
</tr>
<tr>
<td>COL1A2</td>
<td>7q21.3</td>
<td>Collagen 1 α2 chain</td>
<td>+</td>
<td>-</td>
<td>Ehlers-Danlos syndrome, arthrochasia type (VIIb)</td>
<td>AD</td>
<td>130060</td>
</tr>
<tr>
<td>COL3A1</td>
<td>2q23.2</td>
<td>Collagen 3 α1 chain</td>
<td>+</td>
<td>-</td>
<td>Ehlers-Danlos syndrome, vascular type (IV)</td>
<td>AD</td>
<td>130050</td>
</tr>
<tr>
<td>COL4A5</td>
<td>Xq22.3</td>
<td>Collagen 4 α5 chain</td>
<td>+</td>
<td>-</td>
<td>Alport syndrome</td>
<td>AD</td>
<td>301050</td>
</tr>
<tr>
<td>COL5A1</td>
<td>9q34.3</td>
<td>Collagen 5 α1 chain</td>
<td>+</td>
<td>-</td>
<td>Ehlers-Danlos syndrome, classic type (I)</td>
<td>AD</td>
<td>130000</td>
</tr>
<tr>
<td>COL5A2</td>
<td>2q23.2</td>
<td>Collagen 5 α2 chain</td>
<td>+</td>
<td>-</td>
<td>Ehlers-Danlos syndrome, classic type (II)</td>
<td>AD</td>
<td>130000</td>
</tr>
<tr>
<td>EFEMP2</td>
<td>11q13.1</td>
<td>Fibulin-4</td>
<td>+</td>
<td>-</td>
<td>Alport syndrome</td>
<td>AD</td>
<td>614437</td>
</tr>
<tr>
<td>ELN</td>
<td>7q11.23</td>
<td>Elastin</td>
<td>+</td>
<td>-</td>
<td>Ehlers-Danlos syndrome, classic type (II)</td>
<td>AD</td>
<td>123700</td>
</tr>
<tr>
<td>EMILN1</td>
<td>2p23.3</td>
<td>Elastin microfilibr interfer 1</td>
<td>+</td>
<td>-</td>
<td>Cuts laxa, AR type Ib</td>
<td>AR</td>
<td>614347</td>
</tr>
<tr>
<td>FBN1</td>
<td>15q21.1</td>
<td>Fibulin-1</td>
<td>+</td>
<td>+</td>
<td>Marfan syndrome</td>
<td>AD</td>
<td>154700</td>
</tr>
<tr>
<td>FBN2</td>
<td>5q33.3</td>
<td>Fibulin-2</td>
<td>+</td>
<td>+</td>
<td>Contractural arachnodactyly</td>
<td>AD</td>
<td>121050</td>
</tr>
<tr>
<td>FLNA</td>
<td>Xq28</td>
<td>Filamin A</td>
<td>+</td>
<td>-</td>
<td>Perventricular Heterotopia</td>
<td>XLD</td>
<td>300019</td>
</tr>
<tr>
<td>FOXE3</td>
<td>1p33</td>
<td>Forkhead box 3</td>
<td>-</td>
<td>+</td>
<td>FTAA</td>
<td>AD</td>
<td>601094 (gene)</td>
</tr>
<tr>
<td>LOX</td>
<td>5q23.1</td>
<td>Lysyl oxidase</td>
<td>-</td>
<td>+</td>
<td>FTAA</td>
<td>AD</td>
<td>153455 (gene)</td>
</tr>
<tr>
<td>MAT2A</td>
<td>2p11.2</td>
<td>Methionine adenosyltransferase II alpha</td>
<td>-</td>
<td>+</td>
<td>FTAA</td>
<td>AD</td>
<td>601468 (gene)</td>
</tr>
<tr>
<td>MFAP5</td>
<td>12p13.31</td>
<td>Microfibril-associated glycoprotein 2</td>
<td>-</td>
<td>+</td>
<td>FTAA 9</td>
<td>AD</td>
<td>611666</td>
</tr>
<tr>
<td>MYH11</td>
<td>16q13.11</td>
<td>Smooth muscle myosin heavy chain</td>
<td>-</td>
<td>+</td>
<td>FTAA 4</td>
<td>AD</td>
<td>132900</td>
</tr>
<tr>
<td>MYLK</td>
<td>9q34.3</td>
<td>Myosin light chain kinase</td>
<td>-</td>
<td>+</td>
<td>FTAA 7</td>
<td>AD</td>
<td>613780</td>
</tr>
<tr>
<td>NOTCH1</td>
<td>9q34.3</td>
<td>NOTCH1</td>
<td>-</td>
<td>+</td>
<td>FTAA with BAV</td>
<td>AD</td>
<td>109750</td>
</tr>
<tr>
<td>PRKGI</td>
<td>10q11.2-q21.1</td>
<td>Type 1 cGMP-dependent protein kinase</td>
<td>-</td>
<td>+</td>
<td>FTAA 8</td>
<td>AD</td>
<td>615436</td>
</tr>
<tr>
<td>SLC2A10</td>
<td>20q13.12</td>
<td>Glucose transporter 10</td>
<td>-</td>
<td>+</td>
<td>Shprintzen-Goldberg syndrome</td>
<td>AD</td>
<td>182212 (gene)</td>
</tr>
<tr>
<td>SMAD2</td>
<td>18q21.1</td>
<td>SMAD2</td>
<td>+</td>
<td>+</td>
<td>Unidentified CTD with arterial aneurysms/dissections</td>
<td>AD</td>
<td>601266 (gene)</td>
</tr>
<tr>
<td>SMAD3</td>
<td>15q22.33</td>
<td>SMAD3</td>
<td>+</td>
<td>+</td>
<td>Unidentified CTD with arterial aneurysms/dissections</td>
<td>AD</td>
<td>613795 (gene)</td>
</tr>
<tr>
<td>SMAD4</td>
<td>18q21.2</td>
<td>SMAD4</td>
<td>+</td>
<td>+</td>
<td>Unidentified CTD with arterial aneurysms/dissections</td>
<td>AD</td>
<td>175050 (gene)</td>
</tr>
<tr>
<td>TGFB2</td>
<td>1q41</td>
<td>TGF-β2</td>
<td>+</td>
<td>+</td>
<td>Unidentified CTD with arterial aneurysms/dissections</td>
<td>AD</td>
<td>614816 (gene)</td>
</tr>
<tr>
<td>TGFB3</td>
<td>1q24.3</td>
<td>TGF-β3</td>
<td>+</td>
<td>+</td>
<td>Unidentified CTD with arterial aneurysms/dissections</td>
<td>AD</td>
<td>615582 (gene)</td>
</tr>
<tr>
<td>TGFBR1</td>
<td>9q22.33</td>
<td>TGF-β receptor type 1</td>
<td>+</td>
<td>+</td>
<td>Unidentified CTD with arterial aneurysms/dissections</td>
<td>AD</td>
<td>609192 (gene)</td>
</tr>
<tr>
<td>TGFBR2</td>
<td>5p24.1</td>
<td>TGF-β receptor type 2</td>
<td>+</td>
<td>+</td>
<td>Unidentified CTD with arterial aneurysms/dissections</td>
<td>AD</td>
<td>610168 (gene)</td>
</tr>
</tbody>
</table>

Outline

• Routine molecular genetic testing for patients with thoracic aortic disease
• Special genetic considerations for patients with aortic dissection
• Novel screening tool to identify “at-risk” individuals
• Intervention recommendations for specific genetic mutations
Outline

• Routine molecular genetic testing for patients with thoracic aortic disease
  • Special genetic considerations for patients with aortic dissection
  • Novel screening tool to identify “at-risk” individuals
  • Intervention recommendations for specific genetic mutations
Schematic of Whole Exome Sequencing

Oragene Saliva Kits – Sample Collection for Whole Exome Sequencing

Images from: www.dnagenotek.com
Routine Genetic Testing for Thoracic Aortic Aneurysm and Dissection in a Clinical Setting

Bulat A. Ziganshin, MD, Allison E. Bailey, BS, Celinez Coons, Daniel Dykas, BS, Paris Charilaou, MD, Lokman H. Tanriverdi, Lucy Liu, BS, Maryann Tranquilli, RN, Allen E. Bale, MD, and John A. Elefteriades, MD

Aortic Institute at Yale-New Haven, and Department of Genetics, Yale University School of Medicine, New Haven, Connecticut

Background. Hereditary factors play an important etiologic role in thoracic aortic aneurysm and dissection (TAAD), with a number of genes proven to predispose to this condition. We initiated a clinical program for routine genetic testing of individuals for TAAD by whole exome sequencing (WES). Here we present our initial results.

Methods. The WES was performed in 102 patients (mean age 56.8 years; range 13 to 83; 70 males [68.6%]) with TAAD. The following 21-gene panel was tested by WES: ACTA2, ADAMTS10, COL1A1, COL1A2, COL3A1, COL5A1, COL5A2, ELN, FBN1, FBN2, MYH11, MYLK, NOTCH1, PRKG1, SL2A10, SMAD3, TGFBR2, TGFBR1, TGFBR2.

Results. Seventy-four patients (72.5%) had no medically important genetic alterations. Four patients (3.9%) had a deleterious mutation identified in the FBN1, COL5A1, MYLK, and FLNA genes. Twenty-two (21.6%) previously unreported suspicious variants of unknown significance were identified in 1 or more of the following genes: FBN1 (n = 5); MYH11 (n = 4); ACTA2 (n = 2); COL1A1 (n = 2); TGFBR1 (n = 2); COL3A1 (n = 1); COL5A1 (n = 1); COL5A2 (n = 1); FLNA (n = 1); NOTCH1 (n = 1); PRKG1 (n = 1); and TGFBR3 (n = 1). Identified mutations had implications for clinical management.

Conclusions. Routine genetic screening of patients with TAAD provides information that enables genetically personalized care and permits identification of novel mutations responsible for aortic pathology. Analysis of large data sets of variants of unknown significance that include associated clinical features will help define the mutational spectrum of known genes underlying this phenotype and potentially identify new candidate loci.

Results of Whole Exome Sequencing

247 Patients Tested with WES

75 Pts (30.4%) Positive Findings

86 Variants/Mutations

172 Pts (69.6%) No Findings

83 Variants in TAAD-related genes

3 Variants in Possibly TAAD-related genes

10 Variants PATHOGENIC or LIKELY PATHOGENIC

73 Variants VARIANTS OF UNCERTAIN SIGNIFICANCE
Advantages of Whole Exome Sequencing

• Comprehensive testing of all known aneurysm-causing genes simultaneously;

• Opportunity to reanalyze these data in the future if and when new TAD genes are discovered;

• Whole exome sequencing is becoming less expensive and more cost-effective;

• Opportunity to mine the data for potential new genes and variants.
Testing Family Members

• Can be conducted via single site (Sanger) testing
• Cost-effective
• Substantial benefit in identifying TAAD and preventing related deaths
• Non-mutation carrying family members can be spared from repeated imaging studies and emotional burden of the disease
MYLK Family

- 3 Family members suffered aortic dissection at 4.0 cm – all MYLK carriers

- 1 Family member (also MYLK carrier) operated on prophylactically at 3.9 cm to prevent aortic dissection
Outline

• Routine molecular genetic testing for patients with thoracic aortic disease

• **Special genetic considerations for patients with aortic dissection**

• Novel screening tool to identify “at-risk” individuals

• Intervention recommendations for specific genetic mutations
Do Familial Aortic Dissections Tend to Occur at the Same Age?

Alan S. Chou, BA, Wei-Guo Ma, MD, Salvior C. M. Mok, MD, Bulat A. Ziganshin, MD, Sven Peterss, MD, John A. Rizzo, PhD, Maryann Tranquilli, RN, and John A. Elefteriades, MD

Aortic Institute at Yale-New Haven Hospital, Yale University School of Medicine, New Haven, Connecticut; Department of Cardiovascular Surgery, Beijing Anzhen Hospital of Capital Medical University, Beijing Institute of Heart, Lung and Blood Vessel Diseases, Beijing, China; Department of Surgical Diseases #2, Kazan State Medical University, Kazan, Russia; Department of Cardiac Surgery, University Hospital Munich, Ludwig-Maximilians-University, Munich, Germany; and Department of Economics and Department of Preventive Medicine, Stony Brook University, Stony Brook, New York

Back for family clusters of patients with familial aortic dissection, we used 2 epidemiologic strategies to identify clusters. The first strategy was to screen all patients with familial aortic disease for familial clusters using the Family Health History Database of the Cardiac Surgery. The second strategy was to screen patients with familial aortic disease for familial clusters using the Family Health History Database of the Cardiac Surgery.

Results: Repeating familial clusters were identified in 51 patients (50%) from the families with familial aortic disease. The median age of the proband at dissection was 60.6 years (range, 40.5 to 79.2 years). The median age of the proband at dissection was 60.6 years (range, 40.5 to 79.2 years).

Correlation: The proband age at dissection and family age at dissection were both significant predictors. The proband age at dissection was 0.58 times the family age at dissection plus 21.4. The correlation coefficient was 0.33.

Aortic Dissection – Role of Positive Family History

Positive family history of aortic dissection dramatically increases dissection risk in family members☆

Wei-Guo Ma a,b, Alan S. Chou a, Salvior C.M. Mok a, Bulat A. Ziganshin a,c, Paris Charilaou a, Mohammad A. Zafar a, Richard S. Sieller a, Maryann Tranquilli a, John A. Rizzo a,d,e, John A. Elefteriades a,*

a Aortic Institute at Yale-New Haven Hospital, Yale University School of Medicine, New Haven, CT, United States
b Beijing Andhem Hospital of Capital Medical University and Beijing Institute of Heart, Lung and Blood Vessel Diseases, Beijing, China

Comparison: A positive FHAD family member significantly increases risk of developing aortic dissection in family members, with a higher annual probability of aortic dissection, a shorter duration of “exposure time” before dissection occurs and a lower mean age at time of dissection.

OR 2.7
Association of *KIF6* Trp719Arg and *FBN1* rs2118181 with Thoracic Aortic Dissection

**KIF6 Genotype:**

<table>
<thead>
<tr>
<th>Genotype</th>
<th>Odds Ratio</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arg/Arg+Arg/Trp</td>
<td>2.04</td>
<td>0.022</td>
</tr>
<tr>
<td>Arg/Trp</td>
<td>2.23</td>
<td>0.014</td>
</tr>
</tbody>
</table>

**FBN1 Genotype:**

<table>
<thead>
<tr>
<th>Genotype</th>
<th>Odds Ratio</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>rs2118181</td>
<td>2.36</td>
<td>0.344</td>
</tr>
<tr>
<td>rs10519177</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CC</td>
<td>1.84</td>
<td>0.031</td>
</tr>
<tr>
<td>CT</td>
<td>1.87</td>
<td>0.024</td>
</tr>
<tr>
<td>CC + CT</td>
<td></td>
<td></td>
</tr>
<tr>
<td>GG</td>
<td>1.47</td>
<td>0.409</td>
</tr>
<tr>
<td>AG</td>
<td>0.86</td>
<td>0.558</td>
</tr>
<tr>
<td>GG + AG</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>


Outline

• Routine molecular genetic testing for patients with thoracic aortic disease
• Special genetic considerations for patients with aortic dissection
• **Novel screening tool to identify “at-risk” individuals**
• Intervention recommendations for specific genetic mutations
Timeline

Biomarker Needed

Aortic Aneurysm

Pre-Aortic Dissection

Aortic Dissection

Type A

Post Aortic Dissection

Detectable Biomarkers:
- D-dimer
- Plasmin
- Fibrinogen
- MMPs
- Cytokines
- CD4+ CD28- T cells
- C-reactive protein
- Elastin peptide
“RNA Signature” Screening Test

Gene Expression Signature in Peripheral Blood Detects Thoracic Aortic Aneurysm

Yulei Wang, Catalin C. Barbactora, Dov Shiffman, Sriram Balasubramanian, Olga lakoubova, Maryann Tranquilli, Gonzalo Alborno, Julie Blake, Nedp N. Mehmet, Dewi Ngadino, Karen Poultet, Frances Chan, Raymond R. Samaha, and John A. Elefteriades

1 Applied Biosystems, Foster City, California, United States of America, 2Celera, Alameda, California, United States of America, 3Celera Genomics, South San Francisco, California, United States of America, 4Section of Cardiothoracic Surgery, Yale University School of Medicine, New Haven, Connecticut, United States of America

Background. Thoracic aortic aneurysm (TAA) is usually asymptomatic and associated with high mortality. Adverse clinical outcome of TAA is preventable by elective intervention. Identification of a reliable feature to identify patients at high risk is strongly needed. The objective of this study was to identify signature markers from gene expression profiling that gene expression patterns in peripheral blood are associated with a distinct gene expression signature in peripheral blood. Whole genome gene expression profiles (TAA patients and controls) were analyzed. Significance Analysis of Microarrays (SAM) and a 41-gene classifier were used to identify differentially expressed genes. Testing this classifier on an independent data set, a 41-gene classification model with 80% classification accuracy was achieved. Testing this classifier on an independent data set, a 41-gene classification model with 78% classification accuracy was achieved. Testing this classifier on an independent data set, a 41-gene classification model with 78% classification accuracy was achieved. Testing this classifier on an independent data set, a 41-gene classification model with 78% classification accuracy was achieved. Testing this classifier on an independent data set, a 41-gene classification model with 78% classification accuracy was achieved. Testing this classifier on an independent data set, a 41-gene classification model with 78% classification accuracy was achieved. Testing this classifier on an independent data set, a 41-gene classification model with 78% classification accuracy was achieved. Testing this classifier on an independent data set, a 41-gene classification model with 78% classification accuracy was achieved. Testing this classifier on an independent data set, a 41-gene classification model with 78% classification accuracy was achieved. Testing this classifier on an independent data set, a 41-gene classification model with 78% classification accuracy was achieved. Testing this classifier on an independent data set, a 41-gene classification model with 78% classification accuracy was achieved. Testing this classifier on an independent data set, a 41-gene classification model with 78% classification accuracy was achieved. Testing this classifier on an independent data set, a 41-gene classification model with 78% classification accuracy was achieved. Testing this classifier on an independent data set, a 41-gene classification model with 78% classification accuracy was achieved. Testing this classifier on an independent data set, a 41-gene classification model with 78% classification accuracy was achieved. Testing this classifier on an independent data set, a 41-gene classification model with 78% classification accuracy was achieved. Testing this classifier on an independent data set, a 41-gene classification model with 78% classification accuracy was achieved. Testing this classifier on an independent data set, a 41-gene classification model with 78% classification accuracy was achieved. Testing this classifier on an independent data set, a 41-gene classification model with 78% classification accuracy was achieved. Testing this classifier on an independent data set, a 41-gene classification model with 78% classification accuracy was achieved. Testing this classifier on an independent data set, a 41-gene classification model with 78% classification accuracy was achieved. Testing this classifier on an independent data set, a 41-gene classification model with 78% classification accuracy was achieved. Testing this classifier on an independent data set, a 41-gene classification model with 78% classification accuracy was achieved. Testing this classifier on an independent data set, a 41-gene classification model with 78% classification accuracy was achieved. Testing this classifier on an independent data set, a 41-gene classification model with 78% classification accuracy was achieved. Testing this classifier on an independent data set, a 41-gene classification model with 78% classification accuracy was achieved. Testing this classifier on an independent data set, a 41-gene classification model with 78% classification accuracy was achieved. Testing this classifier on an independent data set, a 41-gene classification model with 78% classification accuracy was achieved. Testing this classifier on an independent data set, a 41-gene classification model with 78% classification accuracy was achieved. Testing this classifier on an independent data set, a 41-gene classification model with 78% classification accuracy was achieved. Testing this classifier on an independent data set, a 41-gene classification model with 78% classification accuracy was achieved. Testing this classifier on an independent data set, a 41-gene classification model with 78% classification accuracy was achieved. Testing this classifier on an independent data set, a 41-gene classification model with 78% classification accuracy was achieved. Testing this classifier on an independent data set, a 41-gene classification model with 78% classification accuracy was achieved. Testing this classifier on an independent data set, a 41-gene classification model with 78% classification accuracy was achieved. Testing this classifier on an independent data set, a 41-gene classification model with 78% classification accuracy was achieved. Testing this classifier on an independent data set, a 41-gene classification model with 78% classification accuracy was achieved. Testing this classifier on an independent data set, a 41-gene classification model with 78% classification accuracy was achieved. Testing this classifier on an independent data set, a 41-gene classification model with 78% classification accuracy was achieved. Testing this classifier on an independent data set, a 41-gene classification model with 78% classification accuracy was achieved. Testing this classifier on an independent data set, a 41-gene classification model with 78% classification accuracy was achieved. Testing this classifier on an independent data set, a 41-gene classification model with 78% classification accuracy was achieved. Testing this classifier on an independent data set, a 41-gene classification model with 78% classification accuracy was achieved. Testing this classifier on an independent data set, a 41-gene classification model with 78% classification accuracy was achieved. Testing this classifier on an independent data set, a 41-gene classification model with 78% classification accuracy was achieved. Testing this classifier on an independent data set, a 41-gene classification model with 78% classification accuracy was achieved. Testing this classifier on an independent data set, a 41-gene classification model with 78% classification accuracy was achieved. Testing this classifier on an independent data set, a 41-gene classification model with 78% classification accuracy was achieved. Testing this classifier on an independent data set, a 41-gene classification model with 78% classification accuracy was achieved. Testing this classifier on an independent data set, a 41-gene classification model with 78% classification accuracy was achieved. Testing this classifier on an independent data set, a 41-gene classification model with 78% classification accuracy was achieved. Testing this classifier on an independent data set, a 41-gene classification model with 78% classification accuracy was achieved. Testing this classifier on an independent data set, a 41-gene classification model with 78% classification accuracy was achieved. Testing this classifier on an independent data set, a 41-gene classification model with 78% classification accuracy was achieved.

Conclusions. This study identified information on the status and subtypes of TAA. Moreover, a 41-gene classification model with 78% classification accuracy was achieved. The transcriptional programs in peripheral blood may play a role in the development of a classifier to identify patients at high risk for TAA. This classification model may provide a new tool for the early detection of TAA.
Hierarchical Clustering Diagrams

Ascending vs Descending

Familial vs Non-Familial

RNA Signature in Acute Aortic Dissection vs Non-Dissected Patients

Genes **IL-10** and **IL-18** were expressed 4-fold higher in patients with Acute Aortic Dissection, compared with patients without dissection.
Outline

• Routine molecular genetic testing for patients with thoracic aortic disease
• Special genetic considerations for patients with aortic dissection
• Novel screening tool to identify “at-risk” individuals

• Intervention recommendations for specific genetic mutations
Intervention recommendations with specific genetic mutations

Genes Associated with Thoracic Aortic Aneurysm and Dissection: 2018 Update and Clinical Implications

Adam J. Brownstein, BA1, Valentina Kostuk, BA1, Bulat A. Ziganshin, MD, PhD1,2, Mohammad A. Zafar, MD1, Helena Kuvanenmi, MD, PhD1, John A. Elefteriades, MD3

1 Department of Surgery, Section of Cardiac Surgery, Aortic Institute at Yale-New Haven Hospital, Yale University School of Medicine, New Haven, Connecticut, USA
2 Department of Cardiology, Kazzan State Medical University, Kazan, Russia
3 Division of Molecular Biology and Human Genetics, Department of Biomedical Sciences, and Department of Psychiatry, Faculty of Medicine and Health Sciences, Stellenbosch University, Tygerberg, South Africa

Address for correspondence John A. Elefteriades, MD, Aortic Institute at Yale-New Haven Hospital, Yale University School of Medicine, 789 Howard Avenue, Clinic Building – CB317 New Haven, CT 06519 (email: john.elefteriades@yale.edu).

Abstract
Thoracic aortic aneurysms, with an estimated prevalence in the general population of 1%, are potentially lethal, via rupture or dissection. Over the prior two decades, there has been an exponential increase in our understanding of the genetics of thoracic aortic aneurysm and/or dissection (TAAD). To date, 30 genes have been shown to be associated with the development of TAAD (~30% of individuals with nongenetic familial TAAD) have a pathogenic mutation in one of these genes. This review represents the authors’ yearly update summarizing the genes associated with TAAD, including implications for the surgical treatment of TAAD. Molecular genetics will continue to revolutionize the approach to patients afflicted with this devastating disease, permitting the application of genetically personalized aortic care.

Keywords
- genetics
- thoracic aortic aneurysm
- thoracic aortic dissection
Summary:
The Yale Genetic Work-up Algorithm

• Patients with a thoracic aortic aneurysm:
  – Whole Exome Sequencing during initial clinical visit

• Patients with an acute aortic dissection:
  – Whole Exome Sequencing at time of surgery
  – Follow-up testing of family members
  – Family members with an aorta greater than 4.0 cm are recommended prophylactic surgery

• Coming soon:
  – RNA-signature screening test to detect patients harboring an aneurysm or at risk of developing an aortic dissection