New Insights on Genetic Aspects of Thoracic Aortic Disease

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Liège, Belgium

September 15th, 2016
Genetics in Thoracic Aneurysm

• Historical glimpse
• Manifestation of Familial Patterns
• Mendelian Genetics
• Molecular Genetics (DNA)
• Molecular Genetics (RNA)
  – Investigational “RNA Signature” Test
• Whole Exome Sequencing
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“The Nomads and Scythians have *lax joints* and *easy bruising*.”
Hippocrates  400 B.C.

Describing *Ehlers-Danlos Syndrome*
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
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Three Generations of Type A Dissection in One Single Family

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  - Type A Dissection
  - Well
  - Well
  - Well
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- 78 year old Female
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- 59 year old Female
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- Well
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- Well
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78 year old Female
Type A Dissection

59 year old Female
Type A Dissection
Well

12 year old Female
Type A Dissection
Well

Well
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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%
Thoracic Aneurysm – Hereditary

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. Bigge, 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 396 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 396 patients, 45 patients had a diagnosis of Marfan syndrome and 533 patients had no known history of any collagen vascular disorder. Of the 533 patients in the latter category, 398 patients had confirmed TAA, 66 had TAA with concomitant aortic dissections, and 80 had aortic aneurysms. 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 49 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<.05), and significantly older than that of patients with Marfan syndrome (24.8 years, P<.001). Patients with a family history of aortic aneurysm had faster growth rates (0.22 cm/y) compared with patients with sporadic TAA (0.03 cm/y) (P<.001) and patients with Marfan syndrome (0.10 cm/y) (P=.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=.05). Ten pedigrees (38.5%) showed direct father–son transmission, consistent with an autosomal dominant mode of inheritance. In 7 family pedigrees (23.1%) an autosomal dominant or X-linked mode of inheritance was observed. 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.


Familial thoracic aortic dilatations and dissections: A case control study
Alan Biddinger, MSE; Marnie Rocklin, MS; Joseph Coselli, MD, and Dianna M. Milewics, MD, PhD, Houston, Tex.

Purpose: Evidence suggesting that genetic factors contribute to the development of common disorders can be obtained by demonstrating familial aggregation of the disease. This study investigated whether thoracic aortic dilatations and dissections aggregate in families by comparing the prevalence of thoracic aortic aneurysms, thoracic aortic dissections, and sudden death in first-degree relatives of patients referred for thoracic aortic surgery.

Methods: Families were ascertained through 158 nonsyndromic patients referred for surgical correction of either thoracic aortic aneurysms or dissections (proband) and their 343 first-degree relatives. A control group of 547 first-degree relatives was derived from 114 proband spouses. Groups were examined for statistical differences in the prevalence of thoracic aneurysms, thoracic aortic dissections, abdominal aortic aneurysms, sudden death, and myocardial infarctions.

Results: First-degree relatives of probands demonstrated a higher prevalence of thoracic aortic aneurysms and sudden death when compared with the control group. Relative risks of thoracic aortic aneurysm development in proband fathers, brothers, and sisters were 1.3, 1.9, and 1.8, respectively. A pattern of inheritance of the thoracic aortic aneurysms could not be determined.

Conclusions: This study indicates proband first-degree relatives are at higher risk of thoracic aortic aneurysms and sudden death compared with a control group. This study supports the role of genetic factors in the cause of thoracic aortic aneurysms and provides important information for identifying individuals at risk. (J Vasc Surg 1997;25:806-11.)

Aneurysms and dissections of the aorta are associated with a high degree of morbidity, mortality, and medical expenditure despite continued improvements in diagnostic and surgical techniques. Prevention of these disorders through the early identification of predisposed individuals and the modification of contributing environmental and genetic factors is a potential cost-effective method for addressing these diseases. Establishing familial aggregation and estimating relative risks of these disorders for family members is useful not only for identifying susceptible individuals but also for implicating a genetic contribution to these disorders. Although abdominal aortic aneurysms have been well characterized in regard to familial aggregation, risk factors, possible causes, and potential modes of inheritance less is known regarding thoracic aortic aneurysms (TAA) and thoracic aortic dissections. For this reason this study was primarily designed to compare first-degree relatives of patients referred for surgical
Distribution of Arterial Aneurysm and Dissection Sites in Kindred of Familial Probands

Distribution of Arterial Aneurysm and Dissection Sites in Kindred of Familial Probands

Ascending and Descending Thoracic aortic aneurysm are two different diseases.

Familial Age Clustering in Aortic Dissection

Chou AS, Ma WG, Mok SCM, Ziganshin BA, Peterss S, Rizzo JA, Tranquilli M, Elefteriades JA. Do Familial Aortic Dissections Tend to Occur at the Same Age? The Annals of Thoracic Surgery. 2016. [In Press]
Aortic Dissection – Role of Positive Family History

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# Genetics of Thoracic Aortic Aneurysm

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<th>Classification</th>
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<tr>
<td>Marfan</td>
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<tr>
<td>Loeys-Dietz</td>
<td>3p24-25</td>
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<td>TGFβ-R2, TGFβ-R1</td>
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<td>Ehlers-Danlos</td>
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### Features of Specific Familial Etiologies of Thoracic Aortic Aneurysm

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<th>Special considerations</th>
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<tr>
<td><strong>ACTA2</strong></td>
<td>10-15%</td>
<td>• Present with dissection&lt;br&gt;• Can dissect @ &lt;5cm&lt;br&gt;• Risk stroke, MI</td>
</tr>
<tr>
<td><strong>MYH11</strong></td>
<td>2%</td>
<td>• Involved in SMC contraction</td>
</tr>
<tr>
<td><strong>MYLK</strong></td>
<td>1%</td>
<td>• Involved in SMC contraction&lt;br&gt;• Exclusively involved with dissections (not aneurysms), so hard to counsel regarding best time for intervention</td>
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“RNA Signature”

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

A. Bar charts showing accuracy, sensitivity, and specificity with error bars.

B. PCA plot showing variance: 7.7% (red), 62.1% (blue), and 5.4% (green).
Hierarchical Clustering Diagrams

Each vertical line represents a patient

Each horizontal line represents an RNA (One of 30,000 tested)
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• Whole Exome Sequencing
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, FBLN4, FLNA, FBN1, FBN2, MYH11, MYLK, NOTCH1, PRKG1, SLC2A10, 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 potential identify new candidate loci.

Panel of 23 Tested Genes

### Genes Causative of Thoracic Aortic Disease:

**Syndromic Thoracic Aortic Aneurysm and Dissection:**

1. FBN1 → Marfan Syndrome
2. COL1A1
3. COL1A2
4. COL3A1 → Ehlers-Danlos Syndrome
5. COL5A1
6. COL5A2
7. TGFBR1 → Loeys-Dietz Syndrome
8. TGFBR2
9. TGFβ2 → TGFβ-related vasculopathy
10. SMAD3 → Aneurysm-Osteoarthritis Syndrome
11. EFEMP2
12. ELN → Cutis Laxa Syndrome
13. SLC2A10 → Arterial Tortuosity Syndrome
14. FLNA → Periventricular Heterotopia Syndrome
15. ADAMTS10 → Weill-Marchesani Syndrome
16. FBN2 → Contractural Arachnodactyly Syndrome
17. SKI

**Non-Syndromic Thoracic Aortic Aneurysm and Dissection:**

1. TGFB1
2. TGFB2
3. ACTA2
4. MYLK → Familial Thoracic Aortic Aneurysm
5. SMAD3
6. TGFβ2
7. PRKG1
8. MYH11 → Familial Thoracic Aortic Aneurysm with Patent Ductus Arteriosus
9. NOTCH1 → Familial Thoracic Aortic Aneurysm with Bicuspid Aortic Valve
10. MAT2A → Familial Thoracic Aortic Aneurysm

Future Directions

Methods for determining if a variant of unknown significance is Real

1. Extreme rarity in human genome (<1/10,000)

2. Animal model with knock-out replicates phenotype

3. Family studies: phenotype segregates with genotype
Use the family as a method to discover individuals at risk

- Image
  - Parents
  - Siblings
  - Children

Genetically test all family members by whole exome sequencing, once proband proves positive.
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
## Dictionary of Genetic Defects in TAA

| # | Age, Gender | Affected Gene | Chromosome Location | Variant (protein level) | Variant (DNA Sequence) | Variant Type | Variant Precisely Reported | Variant Allele Frequency | Variant related to Aortic Condition | Aortic Pathology | Aortic Valve Morphology | Proven Family History | Proven Etiology |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 67, M | COL5A1 | 19:12755928 | IVS19:1 | G>T | Splice Acceptor | No | < 0.0005% | Deleterious | Ascending and Descending Aortic Aneurysm | Trifurcet | No |
| 2 | 50, M | FBNI | 18:28980579 | c.1206A>G (p.S402R) | GAA_AA | Frameshift Deletion | No | < 0.0007% | Deleterious | Aneurysm of the Aortic Root and Ascending Aorta | Trifurcet | Yes |
| 3 | 54, F | MYLK | 3:123296947 | S1759P | TCC-CCC | Missense | Yes | < 0.0005% | Deleterious | Type A Aortic Dissection | Trifurcet | Yes |
| 4 | 60, M | ACTA2 | 19:90699954 | G170R | GOG-OAG | Missense | No | < 0.0008% | Unknown significance | Ascending Aortic Aneurysm | Trifurcet |
| 5 | 39, M | ACTA2 | 19:90697957 | E244N | ATC-AAC | Missense | Yes | < 0.0006% | Unknown significance | Ascending Aortic Aneurysm | Trifurcet |
| 6 | 72, M | COL5A1 | 17:42733959 | V149F | GTT-TTT | Missense | Yes | 0.0111% | Unknown significance | Unknown significance | | |
| 7 | 78, M | COL5A1 | 12:19653424 | P667T | CCT-CTT | Missense | Yes | 0.0167% | Unknown significance | Unknown significance | | |
| 8 | 60, M | COL5A1 | 9:13762272 | A372D | CCT-GAT | Missense | Yes | < 0.0005% | Unknown significance | Unknown significance | | |
| 9 | 48, F | COL5A2 | 2:189585028 | G1905S | GGC-GAC | Missense | No | < 0.001% | Unknown significance | Unknown significance | | |
| 10 | 63, M | FBNI | 15:48881643 | G341V | GGG-GTG | Missense | No | 0.016% | Unknown significance | Unknown significance | | |
| 11 | 58, M | FBNI | 15:48779375 | P1141L | CGG-CTG | Missense | Yes | 0.072% | Unknown significance | Unknown significance | | |
| 12 | 64, F | FBNI | 15:48828687 | C224R | TGT-CGT | Missense | No | < 0.0008% | Unknown significance | Unknown significance | | |
| 13 | 69, M | PBGDI | 19:5381450 | T280M | ACG-AGT | Missense | No | 0.006% | Unknown significance | Unknown significance | | |
| 14 | 56, M | FBNI | 15:48704843 | E771K | GAG-AAO | Missense | No | 0.016% | Unknown significance | Ascending Aortic Aneurysm | Trifurcet | No |
| 15 | 44, F | FLNA | X:153181070 | Y1324N | TAC-TAA | Nonsense | No | 0.002% | Unknown significance | Aortic Root Aneurysm | Trifurcet | No |
| 16 | 43, F | FLNA | X:153294009 | A36T | GCC-ACC | Missense | No | 0.001% | Unknown significance | Aortic Root Aneurysm | Trifurcet | No |
| 17 | 64, F | MYH11 | 16:13308013 | K186M | AA0-AT0 | Missense | No | < 0.0009% | Unknown significance | Ascending Aortic Aneurysm | Trifurcet | No |
| 18 | 61, F | MYH11 | 16:13314065 | D1066N | GAC-AAC | Missense | No | 0.069% | Unknown significance | Ascending Aortic Aneurysm | Trifurcet | Yes |
| 19 | 71, M | MYH11 | 16:13314848 | R1542Q | CGG-CAG | Missense | No | 0.23% | Unknown significance | Ascending Aortic Aneurysm | Trifurcet | No |
| 20 | 52, M | NOTCH1 | 19:13040911 | R917W | CGG-TSG | Missense | No | 0.19% | Unknown significance | Aortic Root Aneurysm | Bicuspid | No |
| 21 | 52, M | TGFBR1 | 9:1089590 | G185W | GGT-UTT | Missense | No | < 0.0008% | Unknown significance | Ascending Aortic Aneurysm Type B Aortic Dissection | Trifurcet | Yes |
| 22 | 53, F | TGFBR1 | 9:1089590 | G185W | GGT-UTT | Missense | No | < 0.0008% | Unknown significance | Ascending Aortic Aneurysm Type B Aortic Dissection | Trifurcet | Yes |
| 23 | 60, M | TGFBR3 | 1:92157605 | Q599R | CAS-OGG | Missense | No | 0.001% | Unknown significance | Aortic Root Aneurysm | Trifurcet | Yes |
| 24 | 30, M | MBD1 | 18:24374641 | R906X | CGA-TGA | Nonsense | No | 0.007% | Probable disease causing | Unknown | Aortic Root Aneurysm | No |
| 25 | 38, M | TGFBR3 | 14:76437087 | R145X | AGA-TGA | Nonsense | No | < 0.0008% | Probable disease causing | Unknown | Aortic Root Aneurysm | Yes |

**Table 5. Detailed list of identified variants in patients tested via whole exome sequencing.**

**Table 6. Detailed list of identified variants in patients tested via whole exome sequencing.**

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New “Dissection Genes”
The Yale Study

FBN-1 Genotype

- rs2118181: CC + CT (OR = 1.87)
- rs10519177: GG + AG (OR = 1.21)

FBN1 variant rs2118181 was associated with TAD
In contrast, rs10519177 was not associated with TAD

Association of \textit{KIF6} Trp719Arg with Thoracic Aortic Dissection


*Trp/Trp variant used as the reference group

**Adjusted for gender, age, smoking (current versus noncurrent), hypertension and participating center
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.