Familial Thoracic Aortic Aneurysms and Dissections
Identification of a Novel Locus for Stable Aneurysms With a Low Risk for Progression to Aortic Dissection
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Background—Thoracic aortic aneurysms leading to acute aortic dissections are the major diseases that affect the thoracic aorta. Approximately 20% of patients with thoracic aortic aneurysms and dissections (TAAD) have a family history of TAAD, and these patients present younger with more rapidly enlarging aneurysms than patients without a family history of aortic disease.

Methods and Results—A large family with multiple members with TAAD inherited in an autosomal-dominant manner was identified. The ascending aortic aneurysms were associated with slow enlargement, a low risk of dissection, and decreased penetrance in women. Genome-wide linkage analysis was performed, and a novel locus on chromosome 12 was identified for the mutant gene causing disease in this family. Of the 12 male members who carry the disease-linked microsatellite haplotype, 9 had ascending aortic aneurysms with an average diameter of 4.7 cm at an average age of 52.4 years (range, 32 to 76 years) at the time of diagnosis; only 1 individual had progressed to acute aortic dissection, and no other members with aortic dissections were identified. Women harboring the disease-linked haplotype did not have thoracic aortic disease, including 1 aged 84 years. Sequencing of 9 genes within the critical interval at the chromosome 12 locus did not identify the mutant gene.

Conclusions—Mapping a locus for ascending thoracic aortic aneurysms associated with a low risk of aortic dissection supports our hypothesis that genes leading to familial disease can be associated with less-aggressive thoracic aortic disease. (Circ Cardiovasc Genet. 2011;4:36-42.)

Key Words: aorta ■ dissection genes ■ aneurysm ■ genome-wide association analysis ■ mapping ■ risk

The natural history of ascending aortic aneurysms in the absence of surgical intervention is to progressively enlarge over time and ultimately lead to an aortic dissection (Stanford type A) or rupture. Type A aortic dissections are life-threatening events, causing sudden death in approximately 40% of affected individuals, and emergency repair of these dissections are associated with a high degree of morbidity and medical expenditure. In contrast, prophylactic repair of an ascending aortic aneurysm is associated with very low morbidity and mortality, leading to the current recommendation to repair an ascending aortic aneurysm before it dissects or ruptures.1 Although medical treatment can slow the enlargement of ascending aortic aneurysms, the mainstay of treatment to prevent an aortic dissection is surgical repair when the aortic diameter expands to 5.0 to 5.5 cm. However, aortic dissection can occur in some patients who have little or no aortic enlargement. In fact, data from the International Registry of Aortic Dissections indicate that nearly 60% of aneurysms dissect at aortic diameters <5.5 cm. Therefore, the optimal aortic diameter when the risk of aortic dissection exceeds that of surgical repair is still debated.

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Family studies indicate that up to 20% of patients with thoracic aortic aneurysms and dissections (TAAD) who do not have a known genetic syndrome have a first-degree relative with the disease.3,4 Familial TAAD (FTAAD) is primarily inherited in an autosomal-dominant manner with decreased penetrance and variable expression, including risk for dissection at a given aortic diameter. Although patients with FTAAD who experience aortic dissections with minimal or no aortic enlargement have been described,5 families with thoracic aneurysms associated with a low risk of dissection have not been reported. In fact, studies have determined that patients with TAAD with similarly affected first-degree relatives present younger with faster enlarging aneurysms.
than patients without a family history, suggesting familial disease is more clinically aggressive than sporadic disease. Genetic heterogeneity of FTAAD is established, and 4 genes causing the disease have been identified: TGFBR1, TGFBR2, MYH11, and ACTA2. Additionally, 2 disease loci have been mapped, but the causative genes have yet to be identified.

We describe here a large family (TAA254) with autosomal-dominant inheritance of TAAD. Interestingly, aortic imaging identified aortic root aneurysms in 9 family members and confirmed slow enlargement in at least 1 family member, but only 1 member had progressed to an acute aortic dissection. We hypothesize that the mutant gene at the novel chromosomal locus identified for TAAD in this family leads to stable ascending aneurysms with a slow rate of enlargement and a low risk of progression to an acute aortic dissection.

Methods

Subjects

This study was approved by the Institutional Review Board at the University of Texas Health Science Center at Houston, and all subjects gave informed consent to participate in the study. Relevant medical records were obtained from hospitals and healthcare providers, including imaging studies and cardiology and surgical reports. Measurement of the ascending aorta was performed using 2D echocardiography, and cross-sectional diameters were obtained at the following 4 levels: the aortic annulus, the sinuses of Valsalva, the sinotubular junction, and the ascending aorta. Subjects with aortic diameters ≥4.2 cm were scored as affected. First-degree relatives of affected individuals were imaged thoroughly for ascending aortic disease, whereas peripheral artery aneurysms detected incidentally were based on report or confirmed through review of imaging studies. Physical examinations were performed on available affected family members.

Linkage Analysis

Genomic DNA from 7 family members were analyzed using a 50K GeneChips Hind array from Affymetrix, Inc (Santa Clara, CA) following the manufacturer’s protocol. For the fine mapping, linkage analysis using DNA from 11 additional family members was performed using microsatellite markers. Primers and map locations were based on the MAP-O-MAT (http://compgen.rutgers.edu/mapomat/) and the National Center for Biotechnology Information UniSTS (http://www.ncbi.nlm.nih.gov/sites/entrez?db=unists) databases. Polymerase chain reaction (PCR) products were generated using a universal fluorescent-labeled primer set following published protocols. The amplified products were analyzed using the ABI Prism 3130xl Genetic Analyzer, and allele distribution was assigned using Genemapper 4.0 software (Applied Biosystems; Carlsbad, CA).

DNA Sequencing Protocol

Bidirectional exon sequencing of ACTA2, TGFBR1, TGFBR2, MYH11, and candidate genes in the TAAD5 locus were done using intron-based, exon-specific primers. PCR amplifications were carried out using HotStar Taq DNA polymerase (Qiagen Inc; Valencia, CA). PCR products were treated with EXOSAP-IT (Affymetrix, Inc) to digest the primers and followed with sequencing PCR using the BigDye sequencing reaction mix (Applied Biosystems). The sequencing PCR products were purified using the BigDye XTerminator kit (Applied Biosystems) and then loaded on an ABI 3730xl sequencing instrument using the Rapid36 run module. DNA sequencing results were analyzed using Mutation Surveyor (SoftGenetics, State College, PA) software.

Histology and Immunohistochemistry Analysis of Aortic Tissue

Hematoxylin and eosin staining and pentachrome Movat staining were carried out using standard procedures. Mouse monoclonal smooth muscle cell (SMC) ACTA2 antibody from Sigma (A5228; Sigma-Aldrich; St Louis, MO) was used for immunohistochemistry staining.

Statistical Analysis

Multipoint linkage analyses of the Affymetrix 50K single-nucleotide polymorphism (SNP) array data were performed with the Allegro version 2.0 program. An autosomal-dominant model for TAAD with a disease-gene frequency of 0.00006 was assumed. For men, 4 age-dependent liability classes described previously were used. Because the penetrance in women is extremely low, a separate liability class was constructed, and a penetrance value of 0.0001 for risk genotypes was used. Multipoint nonparametric linkage (NPL) and parametric logarithm of odds (LOD) scores were calculated by a sliding window of 180 to 200 SNPs within the Allegro program. Linkage analysis using microsatellite markers and an extended pedigree was performed as previously described.

Results

Clinical Data

A large family of Northern European descent with multiple members with thoracic aortic aneurysms was identified after the proband (III:10) (Figure 1) presented with an acute type A dissection at age 32. On presentation, MRI revealed an enlarged aorta with a maximum diameter of 6.6 cm involving the sinuses of Valsalva and a dissection of the ascending aorta. A paternal uncle (II:1) was reported to have received a diagnosis of aortic dilatation at age 47, and aortic imaging of at-risk relatives identified 7 additional family members with aortic root aneurysms involving the segment of the ascending aorta from the valvular annulus to the sinotubular junction. In this family, maximal aortic diameters ranged in size from 4.1 to 6.6 cm at the time of diagnosis, which on average was at age 52.4±15.6 years (range, 32 to 76 years) (Table 1). Of note, none of the affected individuals in generation II have had an acute dissection, but rather, these individuals appear to have slow enlarging and stable aneurysms measuring <5.0 cm at the time of diagnosis. In addition, individual III:5 has had serial aortic imaging studies over a period of 6 years that did not show a significant increase in the size of the aortic aneurysm. The proband (III:10) is the youngest family member to present with a thoracic aortic disease and the only member who had a dissection with no other risk factors for TAAD (eg, hypertension or bicuspid aortic valve). Interestingly, all of the affected family members are men. None of the women have been given a diagnosis of aortic disease despite aortic imaging, and reduced penetration is evident in individual II:10 who is 84 with no history of aortic disease but who has an affected son (III:5).

In addition to TAAD, some members of this family have early onset and bilateral peripheral artery aneurysms. Individual III:4 has an aortic root aneurysm (4.5 cm) as well as a bilateral dilatation of his iliac arteries that was detected incidentally on magnetic resonance angiogram at age 40. A paternal uncle (II:6) also was reported to have had repair of lower peripheral artery aneurysms in his 20s, although echocardiographic imaging before his death did not show ascending aortic dilatation. In addition, individual II:5 who died at age 55 from multiple myocardial infarctions had bilateral iliac aneurysms by report.
Examination of ascending aortic tissue from 1 affected family member (II:13) was remarkable for focal loss of SMCs and increased proteoglycan deposition but only minimal degradation of the elastic fibers (Figure 2). Sequencing of the \textit{ACTA2}, \textit{MYH11}, \textit{TGFBR1}, and \textit{TGFBR2} genes using DNA from the proband did not identify a mutation in any of these genes.

**Linkage of FTAAD to a Locus on Chromosome 12**

To map the gene causing TAAD in this family, a genome-wide linkage analysis was performed on 7 family members using the Affymetrix 50K SNP array (Figure 1). Assuming an age-dependent model of penetrance and reduced penetrance in women, parametric multipoint LOD score analysis for the TAAD phenotype yielded peaks at 1q32.1, 8p12-21, 12q13-14, and 17p12-13, with LOD\textsubscript{max} scores of >1.0 (Figure 3A). Fine mapping with microsatellite markers at these loci using DNA from 11 other members excluded 1q32.1, 8p12-21, and 17p12-13 as the location of the mutant gene causing TAAD (Table 2). Microsatellite genotyping, however, confirmed linkage to chromosome 12, designated as TAAD\textsubscript{5} locus. To define the critical interval of this locus, 40 microsatellite markers were genotyped and microsatellite haplotypes constructed. A chromosomal recombination in individual III:12 was observed between D12S1669 and D12S1057 that defined the proximal boundary of this interval. Additionally, a chromosomal recombination in individuals III:4, III:5, and III:10 were observed between D12S75 and D12S335, which defined the distal boundary of this interval. Therefore, the critical interval of TAAD\textsubscript{5} locus was defined between D12S1669 (19.5 Mb) and D12S335 (68.1 Mb) (Figure 3B). Pairwise and multipoint LOD score calculations based on the 5-liability class model gave a maximum parametric LOD score of 2.7 between markers D12S1691 and D12S1726. A maximum NPL LOD score of 3.6 also was obtained in the same marker region (exact NPL \(P=0.01\) ) (Figure 3B).

**Sequencing of Candidate Genes in the TAAD\textsubscript{5} Locus**

Based on current understanding of the molecular mechanisms of TAAD, we sequenced candidate genes in the TAAD\textsubscript{5} critical interval that are involved in maintaining the SMC contractile function, including the \textit{AVIL}, \textit{ITGA5}, \textit{ITGA7}, \textit{ITGB7}, \textit{LIMA1}, \textit{MYL6}, \textit{MYL6B}, \textit{MYO1A}, and \textit{TWF1} genes. No rare variants were identified in these genes that segregated with TAAD in this family.

**Discussion**

A large family was identified with autosomal-dominant inheritance of ascending aortic aneurysms involving the sinuses of Valsalva that is linked to a novel TAAD locus, termed TAAD\textsubscript{5}. Serial aortic imaging studies of at least 1 affected family member indicate a minimal rate of aortic enlargement of <0.1 cm per year, which is considerably slower than the 0.21 cm per year reported for patients with FTAAD.\textsuperscript{4} Only 1 out of 9 affected family members progressed to an acute aortic dissection despite the advanced age of many. Interestingly, none of the women in this family who carry the disease-linked microsatellite haplotype are affected with TAAD, including an 84-year-old woman, suggesting reduced penetrance in women. Among 12 men who carry the affected microsatellite haplotype, only 9 have aortic root
aneurysms, also indicating reduced penetrance in men. The average diameter of the root aneurysms is 4.7 cm at the age of diagnosis, which averaged 52.4 years.

The major risk factors for aortic dissections include the diameter of thoracic aortic aneurysm, rate of aneurysm enlargement, and hypertension.\textsuperscript{11,12} Despite a recommendation to repair thoracic aortic aneurysms with diameters $\geq 5.0$ cm, there is significant variability in the risk of dissection based on size, with a subset of aneurysms dissecting with no aortic enlargement and others not dissecting even at large aortic diameters of $>10$ cm.\textsuperscript{13} Another identified risk for dissection is a rapidly expanding aneurysm, defined as $>0.5$ cm increase in a year, particularly if the patient is young or is known to have inherited a genetic predisposition for the aneurysm.\textsuperscript{14} The low risk for aortic dissection associated with the aneurysms in the family reported here was most likely the

Table 1. Clinical Data of Affected Family Members

<table>
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<tr>
<th>Individual</th>
<th>Age</th>
<th>Sex</th>
<th>Asc Aneurysm, Age at Diagnosis, y</th>
<th>Type A Dissection, Age at Diagnosis, y</th>
<th>Aortic Measurements, cm$^2$</th>
<th>AN</th>
<th>SV</th>
<th>STJ</th>
<th>Asc</th>
<th>BSA, m$^2$</th>
<th>Age, y</th>
<th>CAD</th>
<th>HTN</th>
<th>HLD</th>
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<td></td>
<td></td>
<td>5.0$^\dagger$</td>
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<td>57</td>
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<td>M</td>
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<td>+, 32</td>
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<td>2.21</td>
<td>32</td>
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<td>2.5</td>
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The $+$ sign indicates present; the $-$ sign, absent; blank cells, not known. AN indicates aortic annulus; Asc, ascending aorta; BSA, body surface area; CAD, coronary artery disease; HLD, hyperlipidemia; HTN, hypertension; STJ, sinotubular junction; SV, sinuses of Valsalva.

*Aortic measurements were obtained by 2D echocardiography.

$t$Aortic measurements were obtained by MRI or CT scan.

Figure 2. Pathology of the aortic wall from an affected individual in the TAA254 family (II:13). H&E, SMC-specific $\alpha$-actin immunohistochemistry, and Movat staining of the patient’s aorta demonstrates medial degeneration of the aortic media characterized by increased proteoglycan deposition (blue on Movat stain, arrow) and focal loss of SMCs (SMC $\alpha$-actin staining, arrow). Elastic fibers appear to be relatively intact compared with the control, but there is widening between the elastic fibers (black on Movat staining, arrow). H&E indicates hematoxylin and eosin.
result of a slow rate of enlargement of the aneurysms and a low risk of dissection at diameters <5.0 cm.

Accumulating data suggest that the underlying gene predisposing an individual to thoracic aortic disease predicts the risk of aortic dissection at a given aortic diameter of an ascending thoracic aneurysm. For example, Marfan syndrome is an autosomal-dominant condition resulting from mutations in FBN1 and associated with TAAD, skeletal manifestations, and ocular complications. Loes-Dietz syndrome also predisposes individuals to TAAD and is caused by mutations in either TGFBR1 or TGFBR2.14 Although both syndromes cause aortic root aneurysms, patients with TGFBR2 mutation are at a high risk of aortic dissections at relatively small aortic diameters, with reported dissections occurring with minimal enlargements (4.2 cm). In contrast, patients with FBN1 mutations are at a low risk for dissection at aortic diameters <5.0 cm. Therefore, knowing the causative gene mutation makes it possible to not only identify family members who are at risk of developing aortic disease, but also predict the aortic diameter at which a dissection can occur, thereby optimizing the timing for surgical repair of a thoracic aortic aneurysm. Based on the limited information in family TAA254 reported here, the risk of dissection appears minimal until the aortic size is >6.0 cm.

Interestingly, 3 individuals in this family had bilateral peripheral artery aneurysms at relatively young ages, 1 of whom has the affected haplotype (III:4) and another who is an obligate carrier (II:6). Mutations in either TGFBR1 or TGFBR2 cause TAAD, along with aneurysms of other arteries, but do not specifically involve the iliac or lower peripheral arteries.14 Mutations in COL3A1 cause peripheral artery aneurysms often in the absence of aortic aneurysms, but bilateral peripheral aneurysms involving a specific artery have not been reported in these patients to our knowledge. We have identified a similar phenotype of thoracic aortic aneurysms and iliac aneurysms in other families in our cohort of families with 2 or more members with TAAD (unpublished data). Once the disease gene is identified, we will be able to assess whether this gene also causes iliac aneurysms.

The TAAD5 locus spans 49 Mb of chromosome 12 and encodes >600 genes or putative transcripts. To identify the gene mutation causing TAAD in this family, we sequenced candidate genes in this locus. Because mutations in ACTA2, MYH11, TGFBR1, and TGFBR2 result in FTAAD, we focused on genes involved in the maintenance of SMC contractile function. ITGA5, ITGA7, and ITGB7 were sequenced because they encode members of the integrin recep-
tor family, which are heterodimeric membrane glycoproteins that mediate a wide spectrum of cell-cell and cell-matrix interactions. In the arterial wall, integrins are the principal receptors for the extracellular matrix and serve as a transmembrane link between the matrix and the actin cytoskeleton and contractile units, therefore coupling the contractile force to the extracellular matrix.26 Because ACTA2 mutations are a known cause of FTAAD, TWF1 (actin-binding protein, homolog 1), LIMA1 (IM domain and actin binding 1), and AVIL (adillin) also were sequenced because they encode actin-binding proteins that are involved in the regulation of actin polymerization, stabilization, and function. In addition, MYL6, MYL6B, and MYO1A were sequenced because these genes encode proteins involved in myofibril structure and function. However, no disease-causing mutation was identified in the exons and intron-exon boundaries of these genes.

Characterization of this family with aortic root aneurysms with a slow rate of enlargement associated with a low risk for aortic dissection provides an example of further clinical heterogeneity associated with FTAAD. Mapping of a novel locus for the aortic disease in this family supports the conclusion that stable aneurysms can be due to a genetic variant at a single locus. We recommended that family members with the risk haplotype be imaged for aortic disease and the ascending aneurysms surgically repaired if the aortic root was >5.0 cm. At the same time, given the low risk for aortic dissection in this family, we are not certain that this recommendation is the optimal management of this family.

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Disclosures

None.

References


Thoracic aortic aneurysms and dissections (TAAD) are a common cause of premature death and have ranked as high as the 15th leading cause of death in the United States. The natural history of ascending thoracic aortic aneurysms is to progressively enlarge over time and, if not diagnosed and treated medically and surgically, ultimately lead to life-threatening acute aortic dissections or ruptures. Although medical treatments can slow the enlargement of an aneurysm, the mainstay of treatment to prevent dissections and premature deaths is surgical repair of the thoracic aortic artery. Surgery typically is recommended when the aneurysm reaches 5.0 to 5.5 cm in diameter; however, studies on patients presenting with acute type A dissections indicate that up to 60% present with aneurysms smaller than 5.5 cm. Family aggregation studies indicate that ~20% of patients with thoracic aortic disease have a family history of TAAD. Patients with familial TAAD tend to have an early age of onset of aortic disease and aneurysms that enlarge more rapidly than patients without a family history, suggesting familial disease is clinically more aggressive than sporadic disease. In the present study, we mapped a new locus for familial TAAD using a single, large family with TAAD. Aortic disease in this family was characterized by aneurysms in the sinuses of Valsalva with a slow rate of enlargement and a low risk of dissection along with decreased penetration in women. These data provide evidence that now all familial thoracic aortic disease is characterized by rapidly progressive disease.
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