

# Familial Patterns of Thoracic Aortic Aneurysms

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**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 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

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**T**HORACIC AORTIC aneurysms (TAA) of any cause involve a structural weakness in the aortic wall, resulting in progressive dilatation in accord with the relationships expressed in LaPlace's law. The manifestations of aneurysmal disease result in considerable morbidity and mortality for affected individuals. Understanding familial aggregation patterns and recognition of high-risk groups may lead to earlier detection and treatment and to the isolation of genetic factors contributing to

the development and growth of thoracic aortic aneurysms.

Although abdominal aortic aneurysms (AAA) have been well characterized in terms of familial clustering, risk factors, growth rates, and possible modes of inheritance, less is known about TAA. Aneurysms affecting the thoracic aorta in patients with Marfan syndrome behave more aggressively than TAA in patients without Marfan syndrome; however, the natural history of TAA in patients who do not have Marfan syndrome but who demon-

## PATIENTS AND METHODS

Several sources were used for identification of patients with TAA evaluated or treated at Yale University between January 1985 and August 1998. The computerized records of the Yale Center for Thoracic Aortic Disease were searched. This database stores longitudinal information (mean follow-up of 32 months) on 598 patients evaluated or treated for diseases of the thoracic aorta. In addition, the computerized database of the Department of Diagnostic Imaging at Yale University was searched for patients who underwent computed tomography, magnetic resonance imaging, angiography, and ultrasound studies of the thoracic aorta. Records of all patients undergoing operations of the thoracic aorta were reviewed. Autopsy records of all patients who died of aortic disease were examined. These sources identified 598 patients with TAA, and 1529 multiple imaging studies on most patients (computed tomography, magnetic resonance imaging, angiography, transesophageal echocardiography, and transthoracic echocardiography). Data recovered from hospital records and computer files were cross-checked with hospital discharge abstract data monitored by the Connecticut Hospital Association and Connecticut State Mortality Records, Wallingford, Conn.

Of the 598 patients, 45 patients had a diagnosis of Marfan syndrome, and 553 patients had no history of Marfan syndrome or any other collagen vascular disorder. From 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 (M.A.C. and M.J.R.) 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. All telephone screening was carried out consistently by 2 trained interviewers. Responses were recorded on standardized forms. Pedigree analysis was performed on families in which more than one member had an aortic aneurysm.

We defined familial nonsyndromic TAA as those occurring in patients having 1 or more first-generation relatives with an aortic aneurysm and no history of Marfan syndrome or any other collagen vascular disorder. Sporadic cases of thoracic aneurysms are defined as those with no family history of aneurysmal disease and no history of Marfan syndrome or any other collagen vascular disorder. Patients with a diagnosis of Marfan syndrome met the revised criteria for the diagnosis outlined by DePaeppe et al<sup>2</sup> in 1996.

Risk factors for vascular diseases were assessed (tobacco use, diabetes mellitus, hypertension, lipid profile, cardiac disease, and renal dysfunction), and were graded as mild, moderate, or severe according to the suggested standards for reports pertaining to lower extremity ischemia as formulated by the Ad Hoc Committee on Reporting

Standards of the Society of Vascular Surgery and the International Society of Cardiovascular Surgery North America.<sup>3</sup>

Statistical methods were used to compare 3 categories of TAA: familial nonsyndromic TAA, sporadic TAA, and Marfan syndrome-associated TAA. Univariate analyses were performed using a commercial software program (SAS, version 6.12; SAS Institute Inc, Cary, NC). Analysis of variance was performed to compare means between familial nonsyndromic patients, sporadic patients, and patients with Marfan syndrome. The Bonferroni technique was performed to test for differences between means in multiple groups.<sup>4</sup>

Dinsmore et al<sup>5</sup> reported an extremely high correlation among magnetic resonance imaging, computed tomography scans, and ultrasound studies in TAA measurement. In this study, these 3 modalities were used for growth rate measurement. Serial information on aneurysm size was available for 18 patients in the familial nonsyndromic group, 45 patients in the sporadic group, and 39 patients in the Marfan syndrome group. Mean follow-up time for the 3 categories of TAA was 52.9 months (range, 0.07-304 months) for patients with familial nonsyndromic TAA, 31.6 months (range, 0.3-174 months) for sporadic TAA, and 58.3 months (range, 0.03-220 months) for Marfan syndrome-associated TAA.

Once patients underwent surgical repair, their subsequent imaging measurements were excluded from growth rate estimates. Serial imaging studies for the 3 categories of TAA were performed at mean ( $\pm$ SD) intervals of  $9.75 \pm 14.5$  months for patients with familial nonsyndromic TAA,  $11.14 \pm 16.4$  months for sporadic TAA, and  $9.06 \pm 12.5$  months for Marfan syndrome-associated TAA.

Growth rate estimates were performed as we have reported previously, using multivariable regression analysis in which aneurysm growth follows an exponential path.<sup>1,6,7</sup> Specifically, an instrumental variables regression-based estimation technique was employed that is designed to mitigate measurement errors, yielding more stable and less biased estimates of aneurysm growth.<sup>7</sup> This approach correlates the change in aneurysm size with a variable, which, unlike aneurysm size, has little measurement error. The natural logarithm of the last measured size to the first measured size was related to the interval between the 2 tests and interactions between this time variable and risk factors.<sup>8,9</sup> This relationship is then estimated by ordinary least squares regression analysis, yielding an estimate that relates the interval between diagnostic imaging tests to aneurysm growth.<sup>7</sup> Importantly, the estimate will only be correlated with the true variation in aneurysm growth, not with the measurement error terms.

The overall growth rate estimates of aneurysms were calculated by examining all patients in our database for whom serial imaging measurements were available ( $n = 258$ ). Initial risk factors for aortic growth were analyzed and included chronic dissection, aneurysm location (ascending or arch vs descending or thoracoabdominal), age, smoking history, hypertension (diastolic blood pressure  $>95$  mm Hg), and sex.

strate a family history that is positive for aortic aneurysms has not been well-described.<sup>1</sup>

We sought to identify familial patterns of TAA from a database of 553 patients evaluated or treated for diseases of the thoracic aorta at the Yale Center for Thoracic

Aortic Disease, New Haven, Conn. One hundred thirty-five patients selected at random were interviewed, and both medical and family histories were obtained. Age and sex distributions, risk factors, and aneurysm growth rates are reported. These factors are compared for sporadic, famil-

**Table 1. Demographics and Clinical Characteristics of Patients With Familial Nonsyndromic Thoracic Aortic Aneurysms\***

Pedigree	Age, y/ Sex	Tobacco Use	DM	HTN	Lipid Status	Cardiac Disease	Renal Dysfunction	CT	MRI	TEE	AG	TTE	Initial Aortic Size, cm	Site	Dissection
P007	45/M	Mild	None	Moderate	Mild	Mild	None	+	-	+	-	+	4.2	Desc	-
P027	28/M	None	None	Mild	None	None	None	+	+	-	-	+	5.0	Asc	-
P042	58/M	Severe	None	Moderate	Severe	Mild	None	-	-	-	-	+	3.9	Arch	-
P141	52/M	Mild	None	Mild	Severe	Severe	None	+	+	-	-	-	4.7	Asc	-
P145	33/M	None	None	None	None	None	None	+	-	-	+	+	4.8	Asc	-
P167	57/F	Severe	Mild	Mild	None	None	Mild	+	+	-	-	+	9.8	TA	-
P184	74/F	Moderate	None	Moderate	Severe	Moderate	None	+	-	+	+	+	6.0	Asc	-
P188	59/M	None	None	Mild	None	Moderate	None	+	-	-	+	-	4.5	Asc	-
P271	74/M	Severe	None	None	None	None	None	-	-	-	-	+	4.0	Asc	-
P284	37/M	None	None	None	None	None	None	+	-	-	+	+	6.3	Asc	-
P286	65/F	Severe	Mild	Mild	None	Mild	None	+	-	-	-	+	3.3	TA	-
P330	14/F	None	None	None	None	None	None	-	+	-	-	+	6.0	Asc	-
P422	45/M	Mild	None	Moderate	None	None	None	-	+	-	+	+	4.5	Asc	-
P470	58/M	None	None	Severe	None	Mild	Mild	+	-	-	+	+	4.9	Desc	-
P511	64/M	None	None	None	None	None	None	+	+	+	-	-	3.3	Desc	Type B
P518	78/F	None	None	Mild	Mild	None	None	+	+	-	-	-	5.0	Asc	-
P546	69/M	None	None	Severe	None	None	None	+	-	-	+	-	4.0	Asc	Type A
P547	76/M	Mild	None	Mild	None	Mild	None	+	+	+	-	+	5.5	Asc	-
P557	79/M	None	None	Mild	None	Severe	None	+	+	+	-	+	4.2	Desc	Type B
P563	72/F	None	Mild	Mild	None	Moderate	None	+	-	-	-	-	7.0	Desc	Type B
P565	70/M	None	None	Severe	None	None	None	+	-	-	+	+	4.1	Asc	Type A
P571	75/M	Mild	Mild	Severe	Severe	Moderate	Mild	+	+	-	-	+	5.0	Asc	-
P572	61/M	Mild	None	Mild	None	Mild	None	-	+	-	-	-	3.3	Asc	Type A
P580	46/F	Moderate	None	Mild	None	Mild	None	+	-	-	-	-	4.0	Desc	-
P585	53/F	Moderate	None	None	None	None	Mild	+	-	-	-	-	4.1	Desc	-
P588	49/M	None	None	None	None	None	None	+	-	-	-	-	5.4	Asc	-

\*DM indicates diabetes mellitus; HTN, hypertension; CT, computed tomography; MRI, magnetic resonance imaging; TEE, transesophageal echocardiography; AG, angiography; TTE, transthoracic echocardiography; +, study was performed for either diagnosis or follow-up; -, study not performed; Desc, descending aorta; Asc, ascending aorta; and TA, thoracoabdominal aorta. Risk factors are graded as per the "Patients and Methods" section.

**Table 2. Comparison of Patients With Familial Nonsyndromic, Sporadic, and Marfan Syndrome–Associated Thoracic Aortic Aneurysms\***

Variable	Familial Nonsyndromic	Sporadic	Marfan Syndrome Associated
No. of patients (sex)	26 (18 M, 8 F)	109 (67 M, 42 F)	45 (29 M, 16 F)
Age, y	56.8 ± 18.2†‡	64.3 ± 14.0†‡	24.8 ± 17.1‡
Initial aortic diameter, cm	4.87 ± 1.3	5.25 ± 1.3‡	4.02 ± 1.1‡
Associated hypertension, %	73‡	75‡	16‡
Growth rate, cm/y	0.22 (0.14 to 0.31)§	0.03 (-0.04 to 0.10)§	0.10 (0.05 to 0.15)

\*Values are given as mean ± SD. The Bonferroni test for differences between means was used in the analysis of variance procedure.

†P ≤ .03.

‡P ≤ .001.

§P ≤ .0012.

||P ≤ .04.

ial nonsyndromic, and Marfan syndrome–associated TAA. The prevalence of aortic aneurysms among relatives of patients in our database is evaluated, and possible modes of inheritance are discussed.

## RESULTS

### DEMOGRAPHICS AND CLINICAL CHARACTERISTICS

One hundred thirty-five patients were interviewed, and information was collected regarding 1014 first-degree relatives, 510 of whom were men (50.3%) and 504 of whom were women (49.7%). Of the 135 patients interviewed,

26 patients (18 men, 8 women) (19.3%) with TAA were found to have at least 1 first-degree relative with an aortic aneurysm; the remaining 109 patients were considered sporadic cases. **Table 1** summarizes the demographic and clinical features of these 26 familial nonsyndromic patients. The mean age at presentation (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,  $P \leq .001$ ) (**Table 2**).

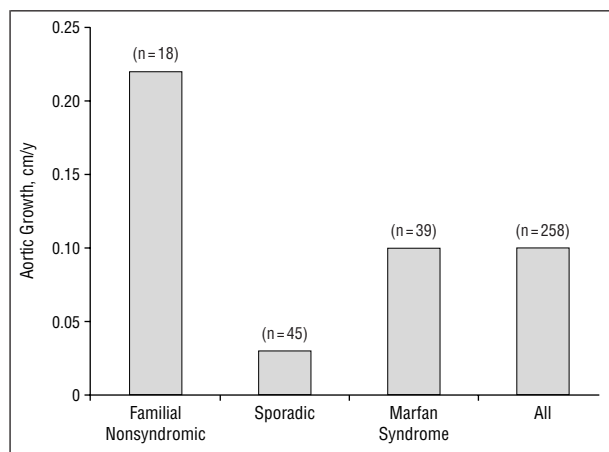
Sixteen (61.5%) of 26 patients with TAA and family history positive for nonsyndromic aortic aneurysms had an aneurysm located in the ascending aorta; the remaining 10 patients (38.5%) had an aneurysm located

**Table 3. Comparison of Aortic Growth Rate According to Dissection Status in Patients With Familial Nonsyndromic, Sporadic, and Marfan Syndrome–Associated Thoracic Aortic Aneurysms (TAA)\***

Type of TAA	Aortic Dissection, cm/y	No Dissection, cm/y
Familial nonsyndromic (n = 5)	0.33 (0.07 to 0.60)†	0.20 (0.10 to 0.30)
Sporadic (n = 18)	0.10 (0.00 to 0.20)	0.01 (-0.01 to -0.10)
Marfan syndrome associated (n = 39)	0.08 (-0.08 to 0.24)	0.09 (0.04 to 0.14)
Overall (n = 90)	0.14 (0.07 to 0.21)†	0.09 (0.06 to 0.13)

\*Values indicate aortic growth rate based on regression analysis for patients with serial imaging studies, both with and without aortic dissection. They are expressed as mean ( $\pm$ SD).

† $P < .05$ .

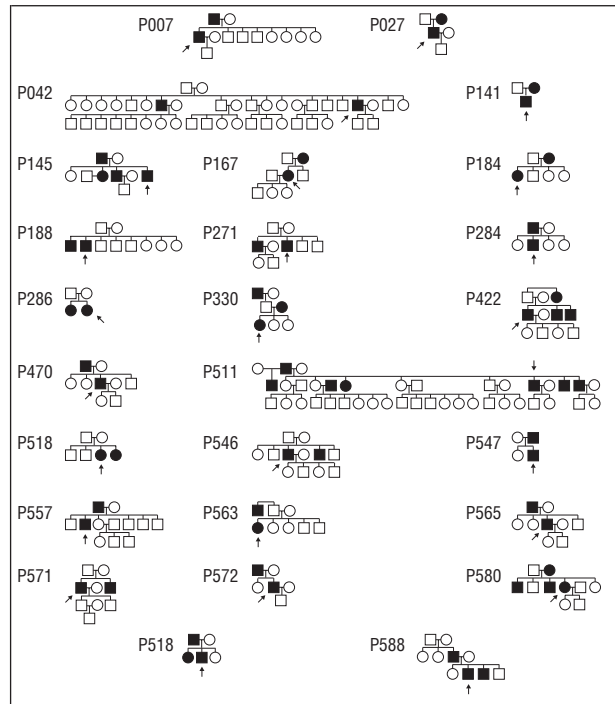


**Figure 1.** Mean growth rates for thoracic aortic aneurysms. For the familial nonsyndromic group,  $P \leq .04$ .

in the descending aorta (Table 1). Six patients (26.0%) had concomitant aortic dissections, 3 in the ascending aorta and 3 in the descending aorta.

Accompanying medical problems were common among the 26 patients (Table 1), particularly, tobacco use (13 patients, 50.0%), diabetes mellitus (4 patients, 15.4%), hypertension (19 patients, 73.1%), hypercholesterolemia (6 patients, 23.1%), cardiac disease (13 patients, 50.0%), and renal dysfunction (4 patients, 15.4%). Hypertension was associated more frequently with patients with familial nonsyndromic TAA and sporadic TAA (73% and 75%, respectively) than with Marfan syndrome–associated TAA (16%) ( $P \leq .001$ ) (Table 2).

Several different imaging studies were used in the diagnosis of TAA and in the follow-up of these patients (Table 1). One or more methods were used for every patient, and size measurements over time were used in growth rate calculations. Computed tomography, the most commonly used imaging modality, was used in 22 cases (84.6%). In addition, magnetic resonance imaging was performed in 11 patients (42.3%), angiography in 8 patients (30.7%), transesophageal echocardiography in 5 patients (19.2%), and transthoracic echocardiography in 16 patients (61.5%).



**Figure 2.** Nonsyndromic thoracic aortic aneurysm family pedigree. Squares represent the men and circles, the women. An arrow indicates the proband with a thoracic aortic aneurysm. Blackened squares or circles represent affected patients with aortic aneurysms.

## ANEURYSMAL GROWTH RATES

The initial aortic diameter at the time of diagnosis was similar for patients with familial nonsyndromic TAA and patients with sporadic TAA (means, 4.87 cm and 5.25 cm, respectively) (Table 2). Patients with Marfan syndrome–associated TAA tended to have smaller aortic aneurysm diameters at the time of diagnosis (mean  $\pm$  SD, 4.02 cm  $\pm$  1.1 cm) compared with familial cases (4.87 cm  $\pm$  1.3 cm), and a statistically significant difference compared with patients with sporadic TAA (5.25 cm  $\pm$  1.3 cm) ( $P \leq .001$ ).

Aortic aneurysm growth rates for familial nonsyndromic, sporadic, and Marfan syndrome–associated TAA are displayed in Table 2 and **Table 3**. 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–associated TAA (0.10 cm/y) ( $P \leq .04$ ). This is depicted graphically in **Figure 1**. The presence of a dissection also increased aortic growth. Familial nonsyndromic TAA in patients with a concomitant aortic dissection had a growth rate of 0.33 cm/y, which was greater than in patients with sporadic TAA (0.10 cm/y) and in patients with Marfan syndrome–associated TAA (0.08 cm/y). This growth of 0.33 cm/y was significantly faster than the overall growth rate estimate of aneurysms in patients with aortic dissection ( $P \leq .05$ ) (Table 3).

## PEDIGREE ANALYSIS

**Figure 2** displays the family pedigrees of the 26 patients and their first-order relatives.

Ten pedigrees (38.5%) display direct father to son transmission (P007, P145, P284, P470, P511, P547, P565,

P572, P585, and P588) consistent with an autosomal dominant mode of inheritance. Six family pedigrees (23.1%) suggest an autosomal dominant or X-linked mode of inheritance (P027, P141, P167, P184, P557, and P580). Seven pedigrees (26.9%) suggest a recessive mode of inheritance; 2 autosomal recessive (P286 and P518), and 5 X-linked recessive or autosomal recessive (P042, P188, P271, P546, and P571).

The final 3 pedigrees represent more complex modes of inheritance. In P330, the proband and her mother have an aortic aneurysm and her sister does not have an aneurysm. This situation may represent an autosomal dominant or X-linked dominant transmission. However, the paternal grandfather is also affected. The contribution of this on the proband is unclear.

In P422, the proband and his 2 brothers are affected. The paternal aunt is also affected. If the proband's father were affected and the gene was not penetrant, this might represent an autosomal transmission. Autosomal recessive transmission is less likely.

Finally, in P563 the proband and her paternal aunt are affected. Considerations include autosomal or X-linked dominant transmission with incomplete penetrance.

#### COMMENT

Most of what is known about the genetic factors involved in aortic aneurysms is derived from studies of patients with AAA. In 1977, Clifton<sup>10</sup> was the first to note a familial aggregation of AAA, describing a family of 3 male siblings who underwent surgery for ruptured aneurysms. Tilson and Seashore<sup>11</sup> later reported on 50 families with 1 or more first-degree relatives with AAA. Studies involving the familial nature of AAA have considered almost every possible genetic model (**Table 4**).<sup>11-14</sup> These studies confirm that AAA is one of the most common familial diseases, with at least 18% of patients with AAA having a first-degree relative with an aortic aneurysm.<sup>15</sup> For most patients, however, the cause of the aortic aneurysm remains unknown.

Although AAA has been studied extensively, less is known regarding TAA. Biddinger et al<sup>16</sup> in 1997 confirmed the familial aggregation of TAA. Similar to that study, our data support a genetic predisposition to the development of TAA in 19% of patients. We have demonstrated that patients with familial nonsyndromic TAA are younger at the time of diagnosis (56.8 years) than are patients with sporadic TAA (64.3 years) ( $P \leq .03$ ), but are older than patients with Marfan syndrome (24.8 years) (Table 2). Ascertainment bias may be a contributing factor in both familial nonsyndromic TAA and Marfan syndrome-associated TAA. Patients who have a close relative with an aneurysm may seek medical attention earlier than patients with sporadic TAA. Patients with Marfan syndrome are screened for asymptomatic aortic disease. The relative contribution of these factors remains to be elucidated.

Our data are similar to data presented by Biddinger et al<sup>16</sup>; hypertension is strongly associated with both familial nonsyndromic and sporadic cases (73% and 75%, respectively) (Table 2). Although it is well known that hypertension is associated with aortic aneurysms, aneurysm formation cannot simply be ascribed to elevated

**Table 4. Familial Studies of Abdominal Aortic Aneurysms**

Source, y	Proposed Genetic Models
Tilson and Seashore, <sup>11</sup> 1984	X-linked
Tilson and Seashore, <sup>11</sup> 1984	Autosomal dominant
Bowers and Cave, <sup>12</sup> 1985	Autosomal recessive
Tilson and Seashore, <sup>11</sup> 1984	Multifactorial
Powell and Greengalgh, <sup>13</sup> 1987	Multifactorial
Majumder et al, <sup>14</sup> 1991	Autosomal recessive, diallelic locus

blood pressure alone.<sup>16</sup> Interestingly, hypertension was found in only 16% of the patients with Marfan syndrome in our study. Thus, the inherent vessel weakness due to the genetic defect in the fibrillin gene may represent the greatest influence on aneurysm formation in these patients. In addition, patients may have different genetic predispositions to respond to hypertensive stresses imposed on their aortas. This may be reflected by our findings of an increased aneurysmal growth rate in the absence of a disparity in rates of hypertension between familial nonsyndromic and sporadic TAA.

We recently reported the overall growth rate for TAA to be 0.10 cm/y.<sup>6,7</sup> In this study, we have demonstrated that the growth rate of aortic aneurysms in familial nonsyndromic TAA is 0.22 cm/y (Table 2). Thus, the current study defines a new risk factor for aneurysm growth, namely, probands belonging to multiplex pedigrees. The aneurysmal growth rate of 0.22 cm/y is significantly faster than the growth rate of aneurysms in patients belonging to the sporadic (0.03 cm/y,  $P \leq .001$ ) or Marfan syndrome groups (0.10 cm/y,  $P \leq .04$ ) (Table 2, Figure 1).

We have also recently reported that the presence of an aortic dissection significantly increases the aneurysm growth rate.<sup>1</sup> This study demonstrates that patients with familial nonsyndromic aneurysms and superimposed aortic dissections also display a faster rate of aneurysmal growth (0.33 cm/y,  $P \leq .05$ ) when compared with the overall growth rate of aortic dissections alone. The reasons for faster growth rates in patients exhibiting familial patterns and with concomitant aortic dissections are not clear, but may reflect a compounded environmental insult on a genetically weakened aortic wall. There are likely to be additional contributing factors affecting aortic growth that have not been clarified.

Pedigree analysis (Figure 2) demonstrates more than 1 possible mode of transmission of aortic aneurysms. In this study, most seem to be autosomal dominant (38.5%), and an additional 23.1%, autosomal dominant or X-linked dominant. Twenty-seven percent represented a recessive mode of transmission. The current literature supports our findings that there may be more than 1 genetic model (Table 4).<sup>11-14</sup> This suggests that genetic heterogeneity (ie, more than 1 gene causing a single phenotype) may play an important role in aortic aneurysm formation.

One point that warrants discussion is the possibility of noninclusion of asymptomatic aneurysms in our pedigree analysis. It is possible that there are additional family members who have undetected TAA or AAA. Likewise, a relative may have died before an aneurysm developed. It is also possible that there may be undiagnosed familial clustering of aneurysms incorrectly placed

in the sporadic category. With the small number of pedigrees and the limited number of generations, our pedigree analysis may be affected by these potential pitfalls. It is also necessary to make a disclaimer for the incomplete accuracy of family history data acquired by interview. Errors including inaccurate or incomplete memory, lack of confirmation of diagnosis, and misinformation may have occurred. We made efforts to maximize consistency during data acquisition by maintaining 2 trained interviewers and confirming diagnoses whenever possible.

To avoid noninclusion of asymptomatic family members, we have begun to screen by ultrasound all first-generation family members of our 26 pedigrees to identify additional patients with previously undetected aneurysms and to confirm or refute absence of aortic disease in other family members. Screening the general population for TAA would not be cost effective. In a theoretical screening model for AAA of a population of 100 000 individuals, it has been proposed that 1500 lives could be saved at a cost of \$78 000 per life saved.<sup>17</sup> Most of the aneurysms detected by screening are small, with few aneurysms detected that were 6 cm in diameter or larger. Screening selective populations is far more cost effective. For instance, in 561 patients with peripheral vascular disease, almost all of whom were cigarette smokers, aneurysms 3 cm in diameter or larger were found in 14%.<sup>18</sup> Screening brothers of patients with aneurysms renders an incidence of aneurysms of 20% to 29%.<sup>19</sup> Therefore, we expect that ultrasound screening of the 26 families with familial nonsyndromic TAA will find additional affected patients and permit more accurate pedigree analysis.

The genetic basis of aortic aneurysms was reviewed by Kuivaniemi et al<sup>20</sup> in 1991. The major determining factor in the appearance of aortic aneurysms may be an in-born defect of collagen type III or of another component of the connective tissue matrix. In patients with Ehlers-Danlos syndrome, defects in the type III collagen gene (*COL3A1*) have been implicated.<sup>21</sup> The mutations associated with collagen diseases such as Ehlers-Danlos syndrome and osteogenesis imperfecta are heterogeneous, and a similar situation may exist for aortic aneurysms.<sup>20</sup> The gene for Marfan syndrome has recently been identified, and there is optimism that this will provide a basis for preventative medicine.<sup>22</sup> The gene has been linked to markers in or near the fibrillin-1 gene in chromosome band 15q21.1.<sup>23</sup> Interestingly, the Gly1127Ser mutation in an EGF domain of the fibrillin-1 gene has been shown to be a risk factor for ascending aortic aneurysms and dissections.<sup>24</sup> A mutation in the *COL3A1* gene resulting in an amino acid substitution was identified in a family with a strong history of AAA.<sup>25</sup> Although this mutation was not detected in any of 140 other patients with AAA, variants of the *COL3A1* gene are thought to predispose to aneurysm formation in the presence of other components of a multifactorial process.<sup>26</sup> Mutations of the *FBN1* and *COL3A1* genes may produce a spectrum of connective-tissue disorders responsible for abnormal or reduced matrix deposition in the aorta and subsequent aneurysm development.

As mentioned previously, we are supplementing the present pedigrees by ultrasound screening of families. Patients are examined and peripheral blood is drawn on both affected and unaffected family members. We are presently

employing mutation and linkage analysis in an effort to isolate candidate gene(s) causing TAA. The latter approach employs markers that have been mapped to a particular locus on the genome, and is used to test whether the marker is coinheritance with aortic aneurysms in families.<sup>27</sup>

In summary, clarifying the genetic basis for the development of TAA is a complex and challenging endeavor. We have confirmed that familial clustering of TAA does occur. The current study defines a new risk factor for aneurysm growth, namely, probands belonging to multiplex pedigrees. The aneurysmal growth rate of patients with familial nonsyndromic TAA is significantly faster than the growth rate of aneurysms in patients with sporadic or Marfan-associated TAA. In addition, the growth rate of familial TAA with concomitant aortic dissection exceeds both the growth rate for sporadic cases with aortic dissection as well as the overall growth rate for aortic dissection alone. Pedigree analysis demonstrates that the primary mode of inheritance seems to be autosomal dominant, but X-linked dominant and recessive modes are also evident.

*This work was funded by Grant-in-Aid CT-BP97-GR-45 from the American Heart Association, Dallas, Tex.*

*Presented at the 79th Annual Meeting of the New England Surgical Society, Toronto, Ontario, September 25, 1998.*

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## DISCUSSION

Richard Cambria, MD, Boston, Mass: Congratulations to Dr Coady on a very nice presentation and we've heard this afternoon the latest installment in a series of enlightening publications referable to thoracic aortic disease from Dr Elefteriades' group at Yale. The authors sought to establish the presence of familial clustering of thoracic aortic aneurysms. This information was previously available in only a single report in the literature for aneurysm disease north of the diaphragm, but as alluded to in the presentation, firmly established for the more commonly encountered AAA. Using telephone inquiry of 150 patients selected at random from their sizable registry, they recorded a 19.3% rate of familial clustering of thoracic aneurysms, that is, patients with a first-blood-order relative afflicted with the disease. In comparing familial with sporadic thoracic aneurysm patients, they noted younger age at treatment and significantly faster growth rates in familial cases. The latter discovery, of course, has potentially important clinical implications. They report a variety of inheritance modes and the frustration they note in attempting to clarify simple or uniform modes of inheritance is exactly paralleled in the literature referable to AAA.

My knowledge of genetics is limited to the fact that I know a fellow named Mendel who grew peas. We do, however, have complete demographic data on some 230 patients treated for thoracoabdominal aortic aneurysm with familial clustering noted in some 10% of these patients. I've recently had the opportunity to review the available data on the natural history of thoracic and thoracoabdominal aneurysms. I can assure you the information we heard today is a valuable addition to the literature.

Approximately 10 years ago, our group, under the leadership of Clem Darling, published a sizable series of 550 abdominal aneurysm repairs designed to answer many of the questions that Dr Coady asked today. Is there familial clustering; if so, are there characteristics of these familial aneurysms that are clinically important?

In this series we noted familial clustering in 15.1% of patients, a figure almost identical to that reported today. While AAA growth rates were not available from our studies since they were all operated cases, we did note that familial aneurysm patients were more likely in women and when such a familial aneurysm occurred in women, there was a significantly increased risk of presentation with rupture. Thus, our data is consistent with that from the Yale group, ie, familial cases seem to be more prone to expansion and rupture. Furthermore, in our vascular registry, the male-female sex ratio for abdominal aneurysms is the typically reported 5 to 6 to 1, but in our thoracoabdominal aneurysm cohort, the sex predilection is 1 to 1. This introduces my first question. Dr Coady, do you have information from your registry on sex distribution for degenerative vs chronic dissection aneurysms in the thoracic aorta?

My other questions relate to the issue of aneurysm growth rates, which the authors have emphasized as among their most

important findings. Apparently, part of the significance they've assigned to the growth rates of familial cases relates to the comparison to an extremely low, 0.03 cm/y, rate of expansion assigned to sporadic cases. This latter figure is approximately 10 times lower than my understanding of the available literature on this topic, and indeed lower than the information from your own registry. Could you comment on possible explanations for the apparent minuscule expansion rate in sporadic cases? Is it fair or logical to group growth rates in different regions of the thoracic aorta, namely ascending, arch, descending, and thoracoabdominal together, since the pathology may be different (dissection vs degenerative aneurysm) and it is well known that the lamellar architecture of the aorta is different in the ascending as opposed to the descending aorta.

Michael Coady, MD: Dr Cambria, thank you very much. I'll answer each of your questions in series. The first question addresses the interesting observation by Dr Darling made in 1989 (*J Vasc Surg*. 1989;10:39-43). Dr Darling, in a 9-year prospective study, noted an increased prevalence of female patients in a group of familial abdominal aortic aneurysms. He also studied the association between sex and the risk of aortic rupture. Dr Darling found that those families with AAA and a female member with an aneurysm had a strong correlation with aneurysm rupture. The term "black widow syndrome" was employed to describe the female member belonging to this group of familial AAA, as she served as a marker for families which were at significant risk for having at least 1 member of their family experience an aneurysm rupture. In our present series, we have not observed any sex predilection for aortic aneurysm rupture. Currently, the number of patients who had a ruptured aneurysm in these familial, sporadic, and Marfan groups is too small to make any meaningful observations regarding sex distribution. In our larger aneurysm registry, we have not identified any differences in the sex distribution for degenerative or chronic dissecting aneurysms of the thoracic aorta.

Regarding your second question on the growth rate, our sporadic group had a very small growth rate of 0.03 cm/y. While this is certainly much slower in comparison to the overall growth rate estimate of 0.12 cm/y that we published last year in a larger series, this is the first time we have attempted to segregate the groups of aneurysms into familial nonsyndromic, sporadic, and Marfan syndrome associated. While sample size may be affecting the growth rate estimates in all groups, I suspect that there may be true differences in growth that may directly relate to the genetic defect in the aortic wall. When segregated, familial and Marfan-associated aneurysms grow faster than sporadic aneurysms. Growth rate estimates for these groups have not been well studied. As we increase our sample size we hope to continue to achieve more accurate estimates.

Your last question addresses whether it is logical to analyze growth rates in different regions of the thoracic aorta. Our group has analyzed aneurysm growth rates at various aortic locations because it has been well documented that the growth rate varies by location. Descending and thoracoabdominal aortic aneurysms, for instance, may actually grow faster than ascending and arch aneurysms. Using regression techniques, we have previously shown that descending and thoracoabdominal aortic aneurysms grow 0.29 cm/y (*J Thorac Cardiovasc Surg*. 1997;113:476-491), which closely approximates the growth rate estimates reported by Dapunt et al (*J Thorac Cardiovasc Surg*. 1994;107:1323-1333) for aneurysms in this location. In this study, we have chosen to measure overall growth rates for the 3 groups primarily because the sample size did not permit more sophisticated analysis of aneurysm growth rates by location. As we continue to expand our database, we hope to refine further statistically-based growth rate estimates.