Original Article

Associations of Age and Sex With Marfan Phenotype

The National Heart, Lung, and Blood Institute GenTAC (Genetically Triggered Thoracic Aortic Aneurysms and Cardiovascular Conditions) Registry

Mary J. Roman, MD; Richard B. Devereux, MD; Liliana R. Preiss, MS; Federico M. Asch, MD; Kim A. Eagle, MD; Kathryn W. Holmes, MD, MPH; Scott A. LeMaire, MD; Cheryl L. Maslen, PhD; Dianna M. Milewicz, MD, PhD; Shaine A. Morris, MD, MPH; Siddharth K. Prakash, MD, PhD; Reed E. Pyeritz, MD, PhD; William J. Ravekes, MD; Ralph V. Shohet, MD; Howard K. Song, MD, PhD; Jonathan W. Weinsaft, MD; for the GenTAC Investigators*

Background—The associations of age and sex with phenotypic features of Marfan syndrome have not been systematically examined in a large cohort of both children and adults.

Methods and Results—We evaluated 789 Marfan patients enrolled in the National Heart, Lung, and Blood Institute GenTAC (Genetically Triggered Thoracic Aortic Aneurysms and Cardiovascular Conditions) Registry (53% male; mean age 31 [range: 1–86 years]). Females aged ≥15 and males aged ≥16 years were considered adults based on average age of skeletal maturity. Adults (n=606) were more likely than children (n=183) likely to have spontaneous pneumothorax, scoliosis, and striae but were comparable in revised Ghent systemic score, ectopia lentis, and most phenotypic features, including prevalence of aortic root dilatation. Prophylactic aortic root replacement and mitral valve surgery were rare during childhood versus adulthood (2% versus 35% and 1% versus 9%, respectively, both $P<0.0001$). Adult males were more likely than females to have aortic root dilatation (92% versus 84%), aortic regurgitation (55% versus 36%), and to have undergone prophylactic aortic root replacement (47% versus 24%), all $P<0.001$. Prevalence of previous aortic dissection tended to be higher in males than females (25% versus 18%, $P=0.06$); 44% of dissections were type B. Type B dissection was strongly associated with previous prophylactic aortic root replacement.

Conclusions—Pulmonary, skeletal, and aortic complications, but not other phenotypic features, are more prevalent in adults than children in Marfan syndrome. Aortic aneurysms and prophylactic aortic surgery are more common in men. Aortic dissection, commonly type B, occurs in an appreciable proportion of Marfan patients, especially in men and after previous prophylactic aortic root replacement. **(*Circ Cardiovasc Genet*. 2017;10:e001647. DOI: 10.1161/CIRCGENETICS.116.001647.)**

Key Words: adult ■ aneurysm ■ dilatation ■ Marfan syndrome ■ prevalence

Our understanding of the phenotypic features of the Marfan syndrome has evolved over the past several decades in the setting of increased availability of noninvasive imaging techniques, systematic evaluation of first-degree relatives, advances in genetic testing, and increased longevity. The 2010 revised Ghent diagnostic criteria[1] require the cardinal features of aortic root aneurysm and ectopia lentis. Lacking one of these features, the diagnosis can be made if an *FBN1* mutation is present, if the systemic score (composed of numerous other phenotypic features) is ≥7, or if a family member is definitely affected.

See Editorial by Jondeau et al
See Clinical Perspective

Much of the existing literature on the phenotypic features of patients with Marfan syndrome predates use of standardized diagnostic criteria, such as the Berlin nosology[2] and the original Ghent criteria.[3] Furthermore, studies have generally

Received July 26, 2016; accepted April 6, 2017.

From the Division of Cardiology, Weill Cornell Medicine, New York, NY (M.J.R., R.B.D., J.W.W.); Biostatistics and Epidemiology Division, RTI International, Rockville, MD (L.R.P.); MedStar Cardiovascular Research Network, Washington, DC (F.M.A.); Division of Cardiology, University of Michigan Health System, Ann Arbor (K.A.E.); Department of Pediatrics (K.W.H.), Division of Cardiothoracic Surgery (H.K.S.), and Knight Cardiovascular Institute (C.L.M.), Oregon Health & Science University, Portland; Division of Cardiothoracic Surgery (S.A.L.) and Division of Pediatric Cardiology, Department of Pediatrics (S.A.M.), Baylor College of Medicine, Houston, TX; Department of Cardiovascular Surgery, Texas Heart Institute, Houston (S.A.L.); Department of Internal Medicine, McGovern Medical School, University of Texas Health Science Center, San Antonio (D.M.M., S.K.P.); Department of Medicine, Perelman School of Medicine, University of Pennsylvania, Philadelphia (R.E.P.); Department of Pediatrics, Johns Hopkins University School of Medicine, Baltimore, MD (W.J.R.); and Department of Medicine, John A. Burns School of Medicine, Honolulu, HI (R.V.S.).

*The GenTac Investigators are listed in the appendix.

Correspondence to Mary J. Roman, MD, Division of Cardiology, Weill Cornell Medicine, 520 E 70th St, New York, NY 10021. E-mail mroman@med.cornell.edu

been small,[4–8] confined to either children[6,8–10] or adults[11], limited to cardiovascular manifestations,[4–6,9,11–13] or restricted to patients with *FBN1* mutations not all of whom fulfill Ghent diagnostic criteria for Marfan syndrome.[10,13,14]

Thus, the association of both age and sex with the entire spectrum of phenotypic manifestations of Marfan syndrome based on current diagnostic criteria has not been systematically examined. We have used the National Heart, Lung, and Blood Institute-sponsored National Registry of GenTAC (Genetically Triggered Thoracic Aortic Aneurysms and Cardiovascular Conditions) to provide comprehensive information on a large population of well-characterized patients with Marfan syndrome.

Methods

Study Population

The rationale and design of the GenTAC Registry have been previously described.[15] In brief, GenTAC was established as a longitudinal observational cohort study of individuals with genetically triggered thoracic aortic aneurysm, including Marfan syndrome and 12 other conditions. Between 2006 and 2014, 3700 participants were enrolled in the original 6 centers (Johns Hopkins University, Baylor College of Medicine, Oregon Health & Science University, University of Pennsylvania, University of Texas Health Science Center at Houston, and Weill Cornell Medicine) and 2 additional centers (National Institute of Aging-Harbor Hospital and Queen's Medical Center) added in the second phase.[16] Standardized data collection included clinical information related to phenotypic features and details of imaging studies, cardiovascular complications, and surgical interventions. Institutional Review Board approval was obtained for this study at each of the 8 participating GenTAC clinical centers. Individual informed consent was obtained from each GenTAC Registry patient.

At the conclusion of registry enrollment (December 31, 2013), 789 patients with a definite diagnosis of Marfan syndrome based on the revised Ghent diagnostic criteria[1] had been enrolled in the GenTAC database. Systemic score was calculated based on the presence and absence of specific phenotypic features. Ectopia lentis was diagnosed by slit lamp examination. The presence of cardiovascular features (aortic root dilatation, mitral valve prolapse, and aortic regurgitation) and cardiovascular complications (prophylactic aortic root replacement, mitral valve surgery, and aortic dissection) was determined from the Clinical Evaluation Form generated on each patient at the baseline evaluation. The presence of aortic root dilatation was confirmed by use of standardized age-appropriate criteria (*Z* scores and nomograms). Furthermore, agreement between echocardiographic sinuses of Valsalva diameter measurements made at clinical sites compared with the central Imaging Core (established during the second 5-year period of GenTAC) was quite high (intraclass correlation coefficient –0.93, mean of difference=0.05 cm).[17] The GenTAC Phenotyping Core Laboratory at Johns Hopkins University reviewed available data to assure that Marfan syndrome diagnoses met revised Ghent criteria; participants with mutations in genes other than *FBN1* were classified under the appropriate category and excluded from the present analyses. Females <15 and males <16 years of age were considered children based on mean age of skeletal maturity.[18]

Among the 789 Marfan patients, definite diagnosis in a first-degree relative was present in 393 (49.8%) and absent or unknown in 396. Although the presence of an *FBN1* mutation is not required for the diagnosis of Marfan syndrome in the revised Ghent criteria and genetic testing was not systematically performed in the GenTAC Registry, 28.4% of our 789 patients underwent genetic analysis that identified an *FBN1* mutation (135 [34.1%] of those without a family history and 89 [22.6%] of those with a family history of Marfan syndrome). Individuals with mutations identified in genes other than *FBN1* were categorized under the appropriate alternative diagnosis and thus were excluded from the present analysis of patients with Marfan syndrome. The basis for the diagnosis of Marfan syndrome is categorized in Table 1.

Table 1. Basis for Diagnosis of Marfan Syndrome

Family history absent or unknown (n)	396
AD+EL	80
AD+*FBN1* mutation	87
EL+*FBN1* mutation	7
AD+systemic score ≥7	87
AD+EL+*FBN1* mutation	19
AD+EL+systemic score ≥7	94
AD+systemic score ≥7+*FBN1* mutation	22
Family history present (n)	393
AD	148
EL	19
Systemic score ≥7	12
AD+EL	74
AD+systemic score ≥7	77
EL+systemic score ≥7	3
AD+EL+systemic score ≥7	60

AD indicates aortic disease (aortic root dilatation, aortic dissection, previous aortic surgery at time of GenTAC [Genetically Triggered Thoracic Aortic Aneurysms and Cardiovascular Conditions] enrollment); and EL, ectopia lentis.

Data Analyses

Demographic and phenotypic characteristics of children and adults and males and females with Marfan syndrome collected at the baseline evaluation were compared using independent samples *t* test or Mann–Whitney *U* test, as appropriate, for continuous variables and χ^2 test or Fisher exact test, as appropriate, for categorical variables. Unless otherwise indicated, the index of dispersion is the SD. To determine rates of cardiovascular complications (aortic and mitral surgeries and aortic dissection) in childhood and adulthood, the percentage of childhood surgeries was calculated using the entire population to include those adults whose surgery occurred during childhood. Such operations were then excluded from the adult population when rates of cardiovascular surgeries in adults were calculated. To explore further the age dependence of common skeletal, ocular, and cardiovascular features, children were divided into tertiles of age. For those conditions with a significant overall difference, prevalences were compared using pairwise analysis adjusted for multiple comparisons using Holm sequential Bonferroni test. *P* values <0.05 were considered significant.

Results

Comparison of Children and Adults With Marfan Syndrome

The 183 children and 606 adults with Marfan syndrome are compared in Table 2. The major diagnostic criteria (aortic root dilatation, ectopia lentis, and systemic score) were similar in children and adults. Components of the systemic score that occurred more commonly in adults included spontaneous pneumothorax, scoliosis, and skin striae. Aortic complications (prophylactic aortic root replacement and aortic dissection) were rare during childhood. Among the entire group, only 18 underwent prophylactic aortic root replacement during childhood (2% versus 35% during adulthood, *P*<0.0001). There was only 1 aortic dissection during childhood—a type B dissection in a 15-year-old male, whereas 130 adults (21%) experienced

Table 2. Comparison of Phenotypic Features in Children and Adults With Marfan Syndrome*

	Children	Adults	*P* Value
n	183	606	
Age at enrollment, y (range)	8.6±3.9 (1–15)	37.5±14.3 (15–86)	
% Male	56.8	52.2	0.3
Body mass index, kg/m^2	17.0±4.4	24.5±5.4	<0.0001
Aortic root dilatation (%)	89.6	88.0	0.54
Ectopia lentis (%)	48.1	47.9	0.96
Systemic score, median (IQR; range)	7 (3–9; 0–13)	7 (4–9; 0–15)	0.7
Arachnodactyly (%)	45.9	46.9	0.8
Pectus carinatum (%)	38.8	32.0	0.09
Pectus excavatum (%)	32.8	32.7	0.97
Spontaneous pneumothorax (%)	2.2	11.9	<0.0001
Scoliosis (%)	43.2	57.9	0.0004
Kyphosis (%)	10.9	16.2	0.09
Skin striae (%)	23.5	54.0	<0.0001
Mitral valve prolapse (%)	56.3	52.6	0.39

Categorical variables are expressed as percentage and compared using the χ^2 test.
*Continuous variables are expressed as mean±SD and were compared using unpaired *t* test with the exception of systemic score which is expressed as median and IQR and was compared using Mann–Whitney test. IQR indicates Interquartile range.

aortic dissection of any type (*P*<0.0001). Although prevalences of mitral prolapse were similar in adults and children, mitral valve surgery for severe mitral regurgitation was much more common during adulthood (9% versus 1%, *P*<0.0001).

A more detailed description of the age dependence of the presence of common phenotypic features over the span of childhood is depicted in Figures 1 and 2. Prevalence of aortic root dilatation was very similar across tertiles of childhood age. Although there were increases in ectopia lentis and pectus deformities between the first and second tertiles of age, the differences were not statistically significant. In contrast, prevalences of arachnodactyly, scoliosis, skin striae, and mitral valve prolapse steadily increased with significant differences between each tertile.

Comparison of Males and Females With Marfan Syndrome

The 420 males and 369 females with Marfan syndrome are compared in Table 3. Ages were similar, but all parameters of body size were larger in males. Average systemic score was higher in females because of higher prevalences of arachnodactyly and scoliosis. Although aortic root dilatation is exceedingly common in Marfan syndrome, it was present in a significantly higher percentage of males than females. In contrast, mitral valve prolapse, less common overall, was present more frequently in females. Results were comparable when the analyses were limited to adult men and women.

Cardiovascular Complications in Adult Males and Females With Marfan Syndrome

Ages were similar in the 316 adult males and 290 adult females (Table 4). Similar to the entire group, aortic root dilatation was more common in men than women as was aortic regurgitation. Previous prophylactic aortic root surgery was 2-fold more common in men than women (47% versus 24%; odds ratio, 2.8; 95% confidence interval, 2.0–4.0; *P*<0.001), and aortic dissection occurred more frequently in men than women. Of note, in both men and women, about 44% of dissections were type B. Prophylactic proximal aortic surgery had been performed in a higher proportion of patients who suffered type B dissection (60% versus 34% in those without type B dissection, *P*<0.0001). In 85% of cases, prophylactic proximal aortic surgery predated the distal dissection. Age at time of type B dissection was not significantly different in those with and without prophylactic proximal aortic surgery (35.7±11.8 versus 38.6±11.2 years, respectively, *P*=0.4). Although surgery and dissection occurred earlier in

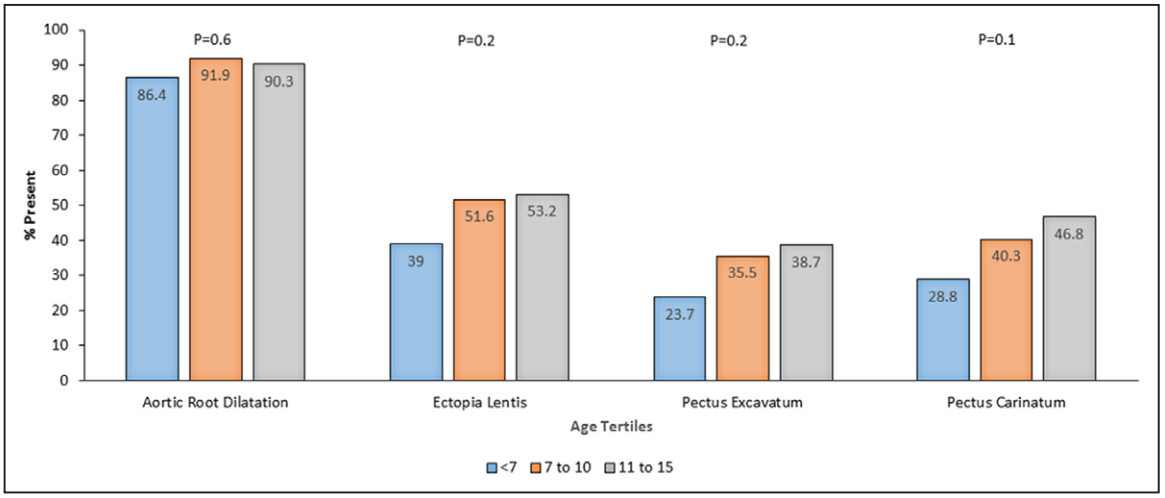

Figure 1. Prevalences of aortic root dilatation, ectopia lentis, and pectus deformities according to tertiles of childhood age.

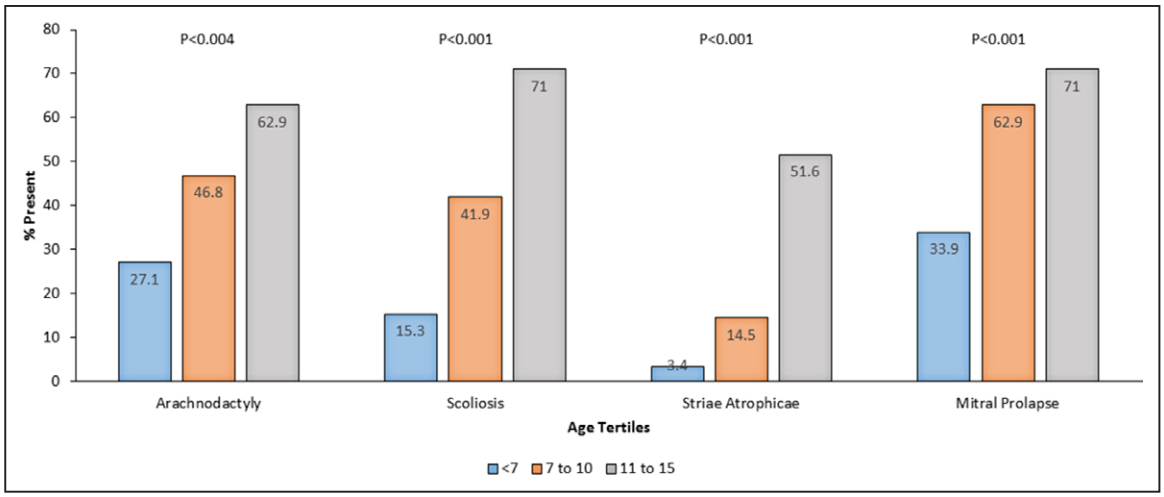

Figure 2. Prevalences of arachnodactyly, scoliosis, striae atrophicae, and mitral valve prolapse according to tertiles of childhood age.

men than women (32 versus 35 years for aortic surgery, 35 versus 36 years for type A dissection, and 35 versus 40 years for type B dissection, respectively), these differences did not reach statistical significance.

Although mitral valve prolapse was much less common in men (41% versus 65%; odds ratio, 0.4; 95% confidence interval, 0.3–0.5; $P<0.0001$), there was no sex difference in mitral valve surgery, performed, on average, 6 years earlier in women than men.

The distribution of prophylactic aortic surgery, mitral valve surgery, and aortic dissections is depicted in Figure 3. Mean and median ages were similar for all outcomes. Age at prophylactic aortic root surgery was younger than that at time of type A dissection, whereas average age at type A dissection was younger than at time of type B dissection. The overwhelming majority of aortic dissections and surgeries occurred before the sixth decade of life.

Discussion

Our study is the largest to date to describe phenotypic features of Marfan patients using current diagnostic criteria. In addition, our analyses include both cardiovascular and noncardiovascular manifestations, provide sex-related comparisons, and examine phenotypic features over a wide age range.

Our findings indicate that aortic root dilatation, arguably the most important prognostic feature, is present from an early age. Earlier studies containing adequate numbers of Marfan patients for meaningful analyses (>100) have varied with regard to the influence of age on the presence of aortic root dilatation. An early study from the Cornell population of 113 children (defined as <16 years in girls and <18 years in boys) and adults noted comparable prevalences of aortic root dilatation in children and adults (76 versus 81%).[18] Similarly, in a French population of 243 patient with *FBN1* mutations, aortic root dilatation was present in 76% of adults and 86% of children (defined as age <18 years).[14] In a subsequent publication from the same group,[13] expanded to include non-French cohorts, among 965 patients with *FBN1* mutations, 73% of whom fulfilled Ghent diagnostic criteria, ascending aortic dilatation increased with age. Only 53% of their population had aortic enlargement by the age of 30 compared with 96% by the age of 60. Other than differences between centers in the diagnosis of aortic dilatation, the explanation for the discrepant findings in the 2 studies is

Table 3. Comparison of Phenotypic Features in Males and Females With Marfan Syndrome*

	Males	Females	*P* Value
n	420	369	
Age at enrollment, y (range)	30.7±17.7 (1–86)	31.0±17.6 (1–76)	0.8
Height, cm	179.6±25.7	170.0±18.2	<0.0001
Weight, kg	79.5±31.5	65.3±22.7	<0.0001
Body surface area, m^2	1.97±0.52	1.74±0.37	<0.0001
Body mass index, kg/m^2	23.5±6.2	21.9±5.8	0.0003
Aortic root dilatation (%)	92.1	84.0	0.004
Ectopia lentis (%)	47.9	48.0	0.98
Systemic score, median (IQR; range)	6 (3–8; 0–14)	7 (4–9; 0–15)	0.02
Arachnodactyly (%)	40.0	54.2	<0.0001
Pectus carinatum (%)	35.2	31.7	0.3
Pectus excavatum (%)	34.0	31.2	0.4
Spontaneous pneumothorax (%)	9.3	10.0	0.8
Scoliosis (%)	49.3	60.4	0.002
Kyphosis (%)	13.3	16.8	0.19
Skin striae (%)	47.6	46.1	0.7
Mitral valve prolapse (%)	43.3	65.0	<0.0001

Categorical variables are expressed as percentage and compared using the χ^2 test.

*Continuous variables are expressed as mean±SD and were compared using unpaired *t* test with the exception of systemic score which is expressed as median and IQR and was compared using Mann–Whitney test.

Table 4. Comparison of Cardiovascular Complications in Adult Males and Females With Marfan Syndrome*

	Males	Females	Odds Ratio (95% CI)	*P* Value
n	316	290		
Age at enrollment, y (range)	37.9±14.1 (16–86)	37.1±14.7 (15–76)		0.5
Aortic root dilatation (%)	91.5	84.1	2.0 (1.2–3.3)	0.006
Aortic regurgitation ≥mild (%)	55.4	35.9	2.2 (1.6–3.1)	<0.0001
Prophylactic aortic surgery (%)	47.2	24.1	2.8 (2.0–4.0)	<0.001
Age at aortic surgery, y (range)	32.3±12.4 (10–71)	34.6±14.5 (8–70)		0.2
Any aortic dissection (%)	24.7	18.3	1.5 (1.0–2.2)	0.06
Type A aortic dissection (%)	13.9	10.0	1.4 (0.9–2.4)	0.14
Age at dissection, y (range)	34.9±10.5 (16–53)	36.1±10.8 (19–59)		0.6
Type B aortic dissection (%)	10.8	8.3	1.3 (0.8–2.3)	0.3
Age at dissection, y (range)	34.7±10.6 (15–53)	39.6±12.3 (20–65)		0.3
Mitral valve prolapse (%)	41.1	65.2	0.4 (0.3–0.5)	<0.0001
Mitral valve surgery (%)	9.5	10.0	0.9 (0.6–1.6)	0.8
Age at mitral surgery, y (range)	38.8±15.1 (10–70)	32.7±16.8 (8–70)		0.16

Categorical variables are expressed as percentage and compared using the χ^2 test. CI indicates confidence interval.

*Continuous variables are expressed as mean±SD and compared using unpaired *t* test.

not apparent because the authors state that the findings were similar when analyses were restricted to the 543 patients who fulfilled diagnostic criteria for Marfan syndrome. However, a separate study from France limited to children (<18 years of age) reported an 80% prevalence of aortic root dilatation with no differences between quartiles of increasing age.[10]

The male predominance of aortic aneurysms in Marfan syndrome noted in this study has been previously reported.[13,19] In the Cornell study, aortic root dilatation was present in 85% of males versus 73% of women.[19] In the multinational cohort of *FBN1*-positive patients, ascending aortic enlargement developed earlier in males (57% versus 50% by age 30 in females), although overall prevalences were not reported.[13] More importantly, our study documents the male predominance of complications of aortic aneurysm, including aortic regurgitation, need for prophylactic aortic surgery, and aortic dissection. Males underwent aortic root replacement at twice the rate of females and at a slightly earlier age. The recommendation for prophylactic aortic root replacement has traditionally been based on a single aortic dimension independent of body size and may partially account for the higher rate of surgery in males.

Aortic dissection was also more common among men and likewise occurred at a slightly younger age than in women. It is noteworthy that the average age at prophylactic aortic surgery or type A dissection (32–36 years) noted in our study approximates the average age of death (32 years) in the seminal report of Murdoch et al[20] from the presurgical era. In the multinational study, male sex was a predictor of a composite outcome of aortic surgery and aortic dissection.[13] The overall prevalence of type B dissection in our adult population (9.7%) is quite similar to a recent report from the Netherlands (9.0%).[21] Likewise, similar are the proportion of type B dissections in patients with previous prophylactic aortic root replacement (60% and 56%), mean age at time of dissection (36 years in both), and the male predominance of type B dissection (59% and 52%). Potential explanations for occurrence of type B dissection after prophylactic proximal aortic surgery include a more adverse phenotype or changes in flow dynamics and shear stress because of the rigid proximal conduit.

The presence of mitral valve prolapse was comparable in our children and adults with similar percentages of males and females; however, females were more likely to have mitral prolapse than males (65% versus 43%). Among 166 Marfan patients <22 years of age, Pyeritz et al[9] noted comparable prevalences of mitral prolapse (66% in males and 71% in females). However, in the Cornell study of children and adults,[18] mitral prolapse was more common in females (67% versus 48%), prevalences very similar to those in the large GenTAC population. The age dependence of the phenotypic expression of mitral prolapse in the non-Marfan population,[22] as well as the increase in mitral prolapse noted in tertiles of childhood age in this study, may account for differences in studies limited to pediatric patients. Although surgery for mitral valve prolapse was not more common in females in our study, it occurred, on average, 6 years earlier in females.

Ectopia lentis occurred with equal frequency in children and adults (48%) and in males and females (48%). This important phenotypic manifestation is unlikely to be underdiagnosed given its impact on visual acuity and is a common portal for diagnosis of underlying Marfan syndrome. Among 259 children meeting Ghent criteria and having an *FBN1* mutation, ectopia lentis was more common than in the GenTAC cohort (≈70%) but did not increase across quartiles of age.[10] Although the composite systemic score was likewise comparable in children and adults, important components differed. Those features that might be expected to develop or worsen over time, for example, spontaneous pneumothorax, scoliosis, and skin striae, were more common in adults. The time dependence of their occurrence is supported by progressive increases in prevalences over the span of childhood noted in Figure 2. These findings are very similar to the Marfan children described by Stheneur et al[10] in whom pectus deformity, arachnodactyly, scoliosis, and striae (but not aortic dilatation or ectopia lentis) all increased across quartiles of childhood (up to age 17).

Females in our study had higher systemic scores than males because of higher prevalences of arachnodactyly and scoliosis. The only previous sex-related comparison of noncardiovascular phenotypic features[19] likewise noted a significantly higher prevalence of scoliosis in females (72% versus 50%) with a trend for arachnodactyly likewise to be more common in females (78% versus 66%). A much smaller

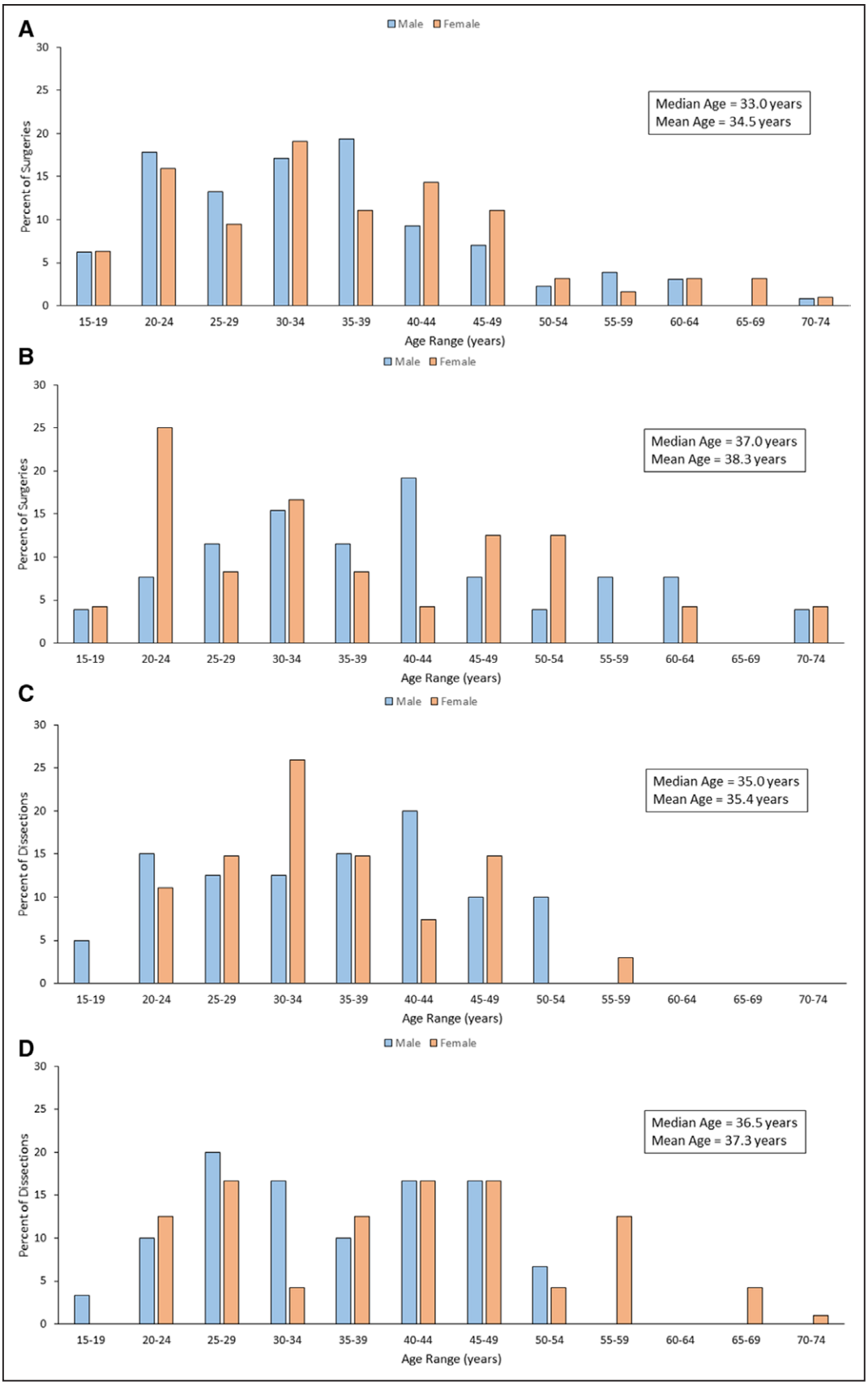

Figure 3. Age distributions of prophylactic aortic surgery (**A**), mitral valve surgery (**B**), type A dissection (**C**), and type B dissection (**D**).

sample size in the earlier study (n=113) may account for differences in overall prevalences (and statistical significance) compared with this study.

A potential limitation of our study is the lack of systematic genetic profiling of the cohort. Unfortunately, GenTAC did not include funding for genotyping; US health insurance often does not cover genetic testing. However, any participants whose clinical genetic testing identified mutations in genes other than *FBN1* had their diagnosis changed from Marfan syndrome to the appropriate alternative diagnosis. Furthermore, the GenTAC Phenotyping Core Laboratory at Johns Hopkins University provided standardization and validation of diagnoses. Additional validity of the accuracy of the revised clinical diagnostic criteria is provided by a recent study, wherein 96 of 100 patients meeting clinical diagnostic criteria for Marfan syndrome were subsequently found to have an underlying *FBN1* mutation or deletion using next-generation sequencing.[23] The presence of cardiovascular features such as aortic root dilatation and mitral prolapse was based on summary data provided by participating centers as opposed to systematic review by an imaging core. The sites involved in GenTAC were selected as referral centers for patients with genetically mediated thoracic aortic aneurysms with expertise in cardiovascular imaging, thereby substantially decreasing, if not eliminating, the likelihood of inaccurate measurements and diagnoses. As previously reported, agreement between echocardiographic sinuses of Valsalva diameter measurements made at clinical sites compared with the central Imaging Core (established during the second 5-year period of GenTAC) was quite high (r=0.93, mean difference=0.05 cm).[17] Although the potential for survivor bias is unavoidable, life expectancy now approaches that of the normal population in the current era of noninvasive detection of aortic disease, aggressive family screening, and effective aortic and mitral surgery.[24] At present, the major impediment to survival is failure to diagnose underlying Marfan syndrome and acute aortic dissection necessitating life-saving surgery.

In conclusion, our study describes the largest cohort to date of Marfan patients using current diagnostic criteria. We think our study provides a robust description of the disease spectrum and its complications that will help inform providers and patients in understanding the clinical history of Marfan syndrome in the current treatment era with its increased life expectancy.[24,25] Important observations include the lack of age dependence of the presence of aortic root dilatation (but not its severity), the higher rate of aortic complications in males, and the strong predilection for type B aortic dissections to occur in the setting of previous prophylactic aortic root replacement.

Sources of Funding

The GenTAC (Genetically Triggered Thoracic Aortic Aneurysms and Cardiovascular Conditions) Registry has been supported by US Federal Government contracts HHSN268200648199C and HHSN268201000048C from the National Heart Lung and Blood Institute and the National Institute of Arthritis and Musculoskeletal and Skin Diseases (Bethesda, MD).

Appendix

GenTAC Contributors. Johns Hopkins University: Williams Ravekes, MD, Harry C. Dietz, MD, PhD, Jennifer Habashi, MD; University of Texas: Dianna M. Milewicz, MD, PhD, Siddharth K. Prakash, MD, PhD; Baylor College of Medicine: Scott A. LeMaire, MD, Shaine A. Morris, MD; Oregon Health & Science University: Kathryn W. Holmes, MD, Cheryl L. Maslen, PhD, Howard K. Song, MD, PhD, G. Michael Silberbach, MD; University of Pennsylvania: Reed E. Pyeritz, MD, PhD, Joseph E. Bavaria, MD, Karianna Milewski, MD, PhD; Weill Cornell Medical College: Richard B. Devereux, MD, Mary J. Roman, MD, Jonathan W. Weinsaft, MD; The Queen's Medical Center: Ralph Shohet, MD; National Institute on Aging: Nazli McDonnell, MD; MedStar Health Research Institute: Federico M. Asch, MD; University of Michigan: Kim A. Eagle, MD; National Heart, Lung, and Blood Institute: H. Eser Tolunay, PhD, Patrice Desvigne-Nickens, MD; National Institute of Arthritis, Musculoskeletal and Skin Diseases: Hung Tseng, PhD; RTI International: Barbara L. Kroner, PhD.

Disclosures

None.

References

1. Loeys BL, Dietz HC, Braverman AC, Callewaert BL, De Backer J, Devereux RB, et al. The revised Ghent nosology for the Marfan syndrome. *J Med Genet*. 2010;47:476–485. doi: 10.1136/jmg.2009.072785.
2. Beighton P, de Paepe A, Danks D, Finidori G, Gedde-Dahl T, Goodman R, et al. International nosology of heritable disorders of connective tissue, Berlin, 1986. *Am J Med Genet*. 1988;29:581–594. doi: 10.1002/ajmg.1320290316.
3. De Paepe A, Devereux RB, Dietz HC, Hennekam RC, Pyeritz RE. Revised diagnostic criteria for the Marfan syndrome. *Am J Med Genet*. 1996;62:417–426. doi: 10.1002/(SICI)1096-8628(19960424)62:4<417::AID-AJMG15>3.0.CO;2-R.
4. Brown OR, DeMots H, Kloster FE, Roberts A, Menashe VD, Beals RK. Aortic root dilatation and mitral valve prolapse in Marfan's syndrome: an ECHOCARDIOgraphic study. *Circulation*. 1975;52:651–657.
5. Come PC, Fortuin NJ, White RI Jr, McKusick VA. Echocardiographic assessment of cardiovascular abnormalities in the Marfan syndrome. Comparison with clinical findings and with roentgenographic estimation of aortic root size. *Am J Med*. 1983;74:465–474.
6. Sisk HE, Zahka KG, Pyeritz RE. The Marfan syndrome in early childhood: analysis of 15 patients diagnosed at less than 4 years of age. *Am J Cardiol*. 1983;52:353–358.
7. Pan CW, Chen CC, Wang SP, Hsu TL, Chiang BN. Echocardiographic study of cardiac abnormalities in families of patients with Marfan's syndrome. *J Am Coll Cardiol*. 1985;6:1016–1020.
8. Geva T, Hegesh J, Frand M. The clinical course and echocardiographic features of Marfan's syndrome in childhood. *Am J Dis Child*. 1987;141:1179–1182.
9. Pyeritz RE, Wappel MA. Mitral valve dysfunction in the Marfan syndrome. Clinical and echocardiographic study of prevalence and natural history. *Am J Med*. 1983;74:797–807.
10. Stheneur C, Tubach F, Jouneaux M, Roy C, Benoist G, Chevallier B, et al. Study of phenotype evolution during childhood in Marfan syndrome to improve clinical recognition. *Genet Med*. 2014;16:246–250. doi: 10.1038/gim.2013.123.
11. Meijboom LJ, Timmermans J, Zwinderman AH, Engelfriet PM, Mulder BJ. Aortic root growth in men and women with the Marfan's syndrome. *Am J Cardiol*. 2005;96:1441–1444. doi: 10.1016/j.amjcard.2005.06.094.
12. Rybczynski M, Mir TS, Sheikhzadeh S, Bernhardt AM, Schad C, Treede H, et al. Frequency and age-related course of mitral valve dysfunction in the Marfan syndrome. *Am J Cardiol*. 2010;106:1048–1053. doi: 10.1016/j.amjcard.2010.05.038.
13. Détaint D, Faivre L, Collod-Beroud G, Child AH, Loeys BL, Binquet C, et al. Cardiovascular manifestations in men and women carrying a FBN1 mutation. *Eur Heart J*. 2010;31:2223–2229. doi: 10.1093/eurheartj/ehq258.
14. Attias D, Stheneur C, Roy C, Collod-Béroud G, Detaint D, Faivre L, et al. Comparison of clinical presentations and outcomes between patients with TGFBR2 and FBN1 mutations in Marfan syndrome and related disorders. *Circulation*. 2009;120:2541–2549. doi: 10.1161/CIRCULATIONAHA.109.887042.
15. Eagle KA; GenTAC Consortium. Rationale and design of the National Registry of Genetically Triggered Thoracic Aortic Aneurysms and Cardiovascular Conditions (GenTAC). *Am Heart J*. 2009;157:319–326. doi: 10.1016/j.ahj.2008.10.005.
16. Kroner BL, Tolunay HE, Basson CT, Pyeritz RE, Holmes KW, Maslen CL, et al. The National Registry of Genetically Triggered Thoracic Aortic

Aneurysms and Cardiovascular Conditions (GenTAC): results from phase I and scientific opportunities in phase II. *Am Heart J*. 2011;162:627.e1–632.e1. doi: 10.1016/j.ahj.2011.07.002.
17. Asch FM, Yuriditsky E, Prakash SK, Roman MJ, Weinsaft JW, Weissman G, et al; GenTAC Investigators. The need for standardized methods for measuring the aorta: multimodality core lab experience from the GenTAC Registry. *JACC Cardiovasc Imaging*. 2016;9:219–226. doi: 10.1016/j.jcmg.2015.06.023.
18. Erkula G, Jones KB, Sponseller PD, Dietz HC, Pyeritz RE. Growth and maturation in Marfan syndrome. *Am J Med Genet*. 2002;109:100–115. doi: 10.1002/ajmg.10312.
19. Roman MJ, Rosen SE, Kramer-Fox R, Devereux RB. Prognostic significance of the pattern of aortic root dilation in the Marfan syndrome. *J Am Coll Cardiol*. 1993;22:1470–1476.
20. Murdoch JL, Walker BA, Halpern BL, Kuzma JW, McKusick VA. Life expectancy and causes of death in the Marfan syndrome. *N Engl J Med*. 1972;286:804–808. doi: 10.1056/NEJM197204132861502.
21. den Hartog AW, Franken R, Zwinderman AH, Timmermans J, Scholte AJ, van den Berg MP, et al. The risk for type B aortic dissection in Marfan syndrome. *J Am Coll Cardiol*. 2015;65:246–254. doi: 10.1016/j.jacc.2014.10.050.
22. Devereux RB, Brown WT, Kramer-Fox R, Sachs I. Inheritance of mitral valve prolapse: effect of age and sex on gene expression. *Ann Intern Med*. 1982;97:826–832.
23. Proost D, Vandeweyer G, Meester JA, Salemink S, Kempers M, Ingram C, et al. Performant mutation identification using targeted next-generation sequencing of 14 thoracic aortic aneurysm genes. *Hum Mutat*. 2015;36:808–814. doi: 10.1002/humu.22802.
24. Silverman DI, Burton KJ, Gray J, Bosner MS, Kouchoukos NT, Roman MJ, et al. Life expectancy in the Marfan syndrome. *Am J Cardiol*. 1995;75:157–160.
25. Pyeritz RE. Recent progress in understanding the natural and clinical histories of the Marfan syndrome. *Trends Cardiovasc Med*. 2016;26:423–428. doi: 10.1016/j.tcm.2015.12.003.

CLINICAL PERSPECTIVE

Our understanding of the phenotypic features of the Marfan syndrome has evolved in the setting of increased availability of noninvasive imaging techniques, systematic evaluation of first-degree relatives, advances in genetic testing, and increased longevity. However, much of the literature on the phenotypic features of Marfan syndrome predates use of standardized diagnostic criteria, and the impact of both age and sex on the entire spectrum of phenotypic manifestations of Marfan syndrome using current diagnostic criteria has not been systematically examined. Among 789 Marfan patients (53% male; mean age 31 [range: 1–86 years]) enrolled in the National Heart, Lung, and Blood Institute-sponsored National Registry of GenTAC (Genetically Triggered Thoracic Aortic Aneurysms and Cardiovascular Conditions), we found that the cardinal phenotypic features (systemic score, ectopia lentis, and aortic root dilatation) were comparable in children and adults. However, adults were more likely to manifest disease complications, including spontaneous pneumothorax, need for prophylactic aortic root replacement, and aortic dissection. Furthermore, adult males were more likely than females to have aortic root dilatation and to have undergone prophylactic aortic root replacement. Forty-four percent of all aortic dissections were type B, and type B dissection was strongly associated with previous prophylactic aortic root replacement. In addition to providing a robust description of the disease spectrum and its complications, our findings have implications for screening strategies insofar because diagnosis should be apparent at an early age. The strong association of type B dissection with previous prophylactic proximal aortic surgery emphasizes the need for continued aortic surveillance, and the cause of this association requires further investigation.

Associations of Age and Sex With Marfan Phenotype: The National Heart, Lung, and Blood Institute GenTAC (Genetically Triggered Thoracic Aortic Aneurysms and Cardiovascular Conditions) Registry

Mary J. Roman, Richard B. Devereux, Liliana R. Preiss, Federico M. Asch, Kim A. Eagle, Kathryn W. Holmes, Scott A. LeMaire, Cheryl L. Maslen, Dianna M. Milewicz, Shaine A. Morris, Siddharth K. Prakash, Reed E. Pyeritz, William J. Ravekes, Ralph V. Shohet, Howard K. Song and Jonathan W. Weinsaft
for the GenTAC Investigators*

Circ Cardiovasc Genet. 2017;10:
doi: 10.1161/CIRCGENETICS.116.001647
Circulation: Cardiovascular Genetics is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231

Print ISSN: 1942-325X. Online ISSN: 1942-3268