Jpn J Radiol (2010) 28:273–277
DOI 10.1007/s11604-010-0420-6

ORIGINAL ARTICLE

High prevalence of vertebral artery tortuosity of Loeys-Dietz syndrome in comparison with Marfan syndrome

Atsushi K. Kono · Masahiro Higashi · Hiroko Morisaki Takayuki Morisaki · Yoshiaki Tsutsumi · Koichi Akutsu Hiroaki Naito · Kazuro Sugimura

Received: November 2, 2009 / Accepted: January 19, 2010

Abstract
Purpose. Loeys-Dietz syndrome (LDS) is a connective tissue disease caused by mutations in the genes encoding the transforming growth factor-β receptor (TGFBR). LDS is associated with aneurysms or dissections of the aorta similar to Marfan syndrome (MFS) as well as arterial tortuosity and aneurysms in the peripheral arteries. The purpose of this study was to evaluate the arterial diseases of LDS to differentiate it from MFS.
Materials and methods. A total of 10 LDS patients with an identified mutation in TGFBR (6 male, 4 female; mean age 36.3 years) and 20 MFS patients with an identified mutation in fibrilin-1 who were age- and sex-matched to the LDS subjects (12 male, 8 female; mean age 37.1 years) were reviewed. The prevalence of vertebral arterial tortuosity (VAT) and peripheral aneurysm (PAN) was studied using computed tomography angiography.
Results. In all, 9 of the 10 LDS patients had VAT, and five PANs were observed in 3 patients. In contrast, 8 (40%) of the MFS patients had VAT, and 1 patient had a PAN. LDS had a higher prevalence of VAT ($P = 0.017$) by Fisher's exact test.
Conclusion. The VAT was highly prevalent among LDS patients. Thus, the presence of VAT has the potential to differentiate LDS from MFS.

Key words Loeys-Dietz syndrome · Vertebral artery tortuosity · Peripheral aneurysm · Transforming growth factor-β receptor

A.K. Kono (✉) · M. Higashi · H. Naito
Department of Radiology and Nuclear Medicine, National Cardiovascular Center, 5-7-1 Fujishiro-dai, Suita 565-8565, Japan
Tel. +81-6-6833-5012; Fax +81-6-6872-7486
e-mail: ringonotegami@mac.com

A.K. Kono · K. Sugimura
Department of Radiology, Kobe University Graduate School of Medicine, Kobe, Japan

H. Morisaki · T. Morisaki
Department of Bioscience, National Cardiovascular Center Research Institute, Suita, Japan

Y. Tsutsumi · K. Akutsu
Division of Cardiology, Department of Medicine, National Cardiovascular Center, Suita, Japan

Introduction

Aortic dissection typically occurs in older patients with a peak incidence during the sixth decade, but 7.2% of cases occur in young subjects.[1] Aortic dissection in this subgroup is related to connective tissue diseases, such as Marfan syndrome (MFS), vascular Ehlers-Danlos syndrome, and Loeys-Dietz syndrome (LDS). LDS is a newly described phenotype caused by mutations in the genes encoding transforming growth factor-β receptor (TGFBR).[2–4] Clinical features of LDS include vascular disease, craniosynostosis, cleft palate/bifid uvula, hypertelorism, congenital heart defects, and mental retardation. Patients with LDS, similar to those with MFS, have an aneurysm or dissection of the ascending aorta and dilatation of the aortic root. In contrast to MFS, generalized arterial tortuosity and aneurysms of arteries have been noted in patients with LDS.[4] Aortic rupture and dissection can occur in LDS patients with aortic root diameters not considered at risk in MFS.[5]

The exact prevalence of LDS is unknown, and its characteristics are not familiar to radiologists. However, given the fact that LDS has recently been discovered,

many cases might not have been diagnosed yet. Because vascular pathology is more aggressive in LDS than in MFS, it is important to recognize the characteristics of this disorder and to diagnose it correctly.

The purpose of this study was to review radiological findings of the arterial diseases of LDS and to differentiate them from those found in MFS. Particular attention was given to computed tomography angiography (CTA), which is used quite frequently in the clinical setting.

Materials and methods

The study was approved by our institutional review board. Written informed consent to use the patients' clinical and imaging data was not required because it was a retrospective study.

A total of 10 LDS patients with an identified mutation in TGFBR (6 men, 4 women; mean age 36.3 years, range 20–54 years) were retrospectively reviewed. Causes of hospitalization were aortic root dilatation in four patients and aortic dissection in six. Among these 10 LDS patients, 9 (90%) were in a postoperative state (1 with aortic repair, 3 with valve replacement, 5 with both).

A group of 20 MFS patients with an identified mutation in fibrilin-1 (12 men, 8 women; mean age 37.1 years, range 20–56 years) were also reviewed. MFS patients who were age- and sex-matched to the LDS patients were selected randomly from our database. Causes of hospitalization were aortic root dilatation in 11 patients, aortic dissection in 8 patients, and mitral valve regurgitation in 1 patient. In all 17 MFS patients (85%) were in a postoperative state (3 with aortic repair, 7 with valve replacement, 7 with both).

All patients had had clinical examinations including a physical examination and laboratory data by a cardiovascular team. Initial and follow-up CTA was performed in a clinical setting as described below. All patients had undergone genetic analysis according to the method reported by Akutsu et al.[6]

CT protocol

The CT angiography was performed using a multislice CT scanner (16 or 64 slices) with an iodine contrast material injection of 1 ml/kg with an iodine content of 350 mg I/ml or 370 mg I/ml. Injection time varied from 30 to 40 s with a variable injection rate. A saline chaser of 25 ml with the same injection rate as the contrast material was applied with a dual-syringe power injector. The scan started when the density in the region of interest (ROI) positioned at the ascending artery increased 100 HU from a baseline value using an intermittent monitoring scan. The CT scan covered from the neck to the pubis. A field of view (FOV) of 320 or 400 mm was adopted according to the patient's body size. For three-dimensional (3D) reconstruction, a 1 or 2 mm slice thickness data set without slice gap was used. The data set was sent to a commercially available workstation and a CT image server.

Imaging analysis

All CT images were reviewed on a Picture Archiving and Communication System (PACS) viewer with an adjustable optimal widow setting and stack-view system. Reconstructed images, such as 3D volume rendering or multiplanar reconstruction, were also used if needed.

The prevalence of arterial diseases was studied in both LDS and MFS subjects. Peripheral aneurysm and peripheral idiopathic dissection in the abdominal aortic branches were evaluated. Tortuosity in the vertebral artery and the common carotid artery was also evaluated.

The presence of aneurysm and dissection was analyzed visually. The tortuosity was graded on a 3-point scale (Fig. 1): 0, the artery runs straight or with a mild curve; 1, the artery turns with multiple curves or a severe curve of 10 mm distance from the upper to the lower portion of a curve; and 2, the artery has a pigtail-like or corkscrew-like curve. After summing up each score for the right and left arteries, the score for patients varied from 0 to 4.

Statistical analysis

For the statistical analysis, JMP software (version 7.0; SAS Institute, Cary, NC, USA) was used. Continuous

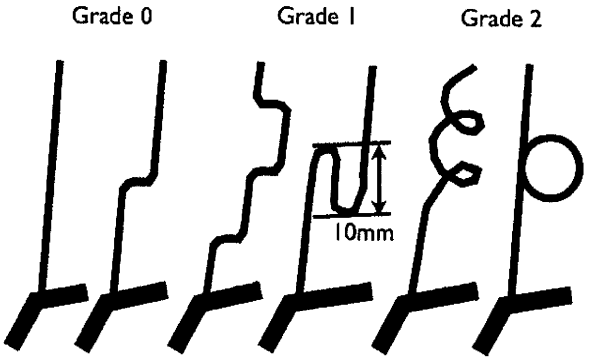

Fig. 1. Grading vertebral artery tortuosity. For grade 0, the artery runs straight or with a mild curve. For grade 1, the artery turns with multiple curves or has a severe curve, with 10 mm distance from the upper to the lower portion of a curve. For grade 2, the artery has a pigtail-like, or corkscrew-like, curve

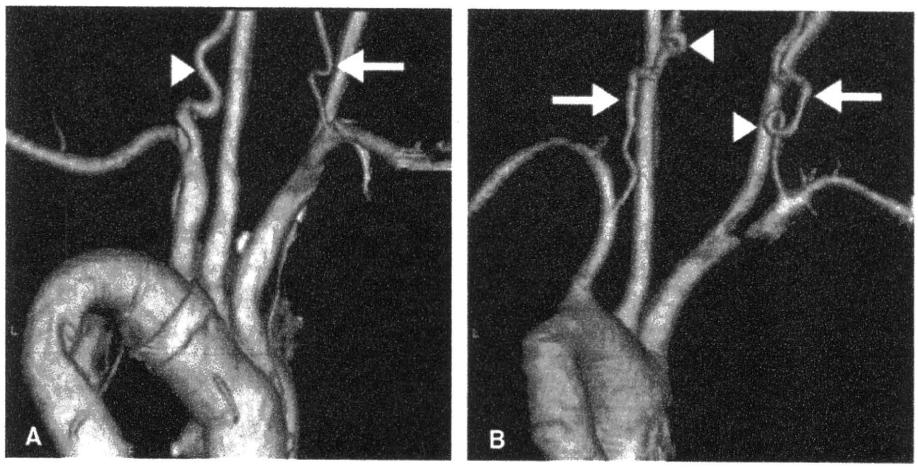

Fig. 2. **a** Computed tomography angiography (CTA) image, posterior view, of a 37-year-old patient with Loeys-Dietz syndrome (LDS). The patient is in a postoperative stage after aortic dissection. The right vertebral artery (*arrow*) is graded 0, and the left vertebral artery (*arrowhead*) as 1 because of its multiple curves. **b** CTA image from posterior view of a 19-year-old LDS patient. The patient underwent CT examination for preoperative evaluation of annuloaortic ectasia. Both vertebral arteries (*arrows*) are graded 2 owing to the pigtail-like curves (*arrowheads*). The right subclavian artery shows pseudostenosis owing to the artifact of contrast material in the vein

Table 1. Patient characteristics of Loeys-Dietz syndrome and Marfan syndrome

Characteristic	LDS	MFS	Difference
Gene mutation	TGFBR	FBN1	
No. of patients	10	20	
Age (years), mean ± SD	36.3 ± 12.6	37.1 ± 11.2	NS
Sex (M:F)	6:4	12:8	NS
Vascular disease:[a] (AAE/AD/other)	4/6/0	11/8/1	NS
Postoperative state	9 (90%)	17 (85%)	NS

AAE, annuloaortic ectasia; AD, aortic dissection; TGFBR, transforming growth factor-β receptor; FBN1, fibrilin-1; LDS, Loeys-Dietz syndrome; MFS, Marfan syndrome; NS, not significant using a significance level of $P < 0.05$

[a] Vascular disease that caused the patients' hospitalization

data were expressed as the mean ± SD. A two-tailed Student's *t*-test was used to compare continuous variables. The χ^2 test or Fisher's exact test was used for discrete variables. $P < 0.05$ was considered statistically significant.

Results

Patients' characteristics and vascular pathologies are summarized in Tables 1 and 2.

Arterial tortuosity

In all, nine (90%) of the LDS patients had vertebral arterial tortuosity (Fig. 2): two on the right side, three on the left, and four on both sides. Among the MFS patients,

Table 2. Vascular pathologies in Loeys-Dietz syndrome and Marfan syndrome

Characteristic	LDS	MFS	*P*
No. of patients	10	20	
Vertebral artery tortuosity			
Prevalence (no.)	9 (90%)	8 (40%)	0.017
Score[a]			
0	1	12	
1	3	4	
2	3	2	
3	1	2	
4	2	0	
Carotid artery tortuosity (no.)	0	0	NS
Peripheral aneurysm			
Abdominal branch	3 (30.0%)	1 (5.0%)	NS
Iliac artery	3 (33.3%)	3 (20.0%)	NS
Abdominal aortic aneurysm	1 (14.3%)	1 (8.3%)	NS

NS, not significant using a significance level of $P < 0.05$

[a] Score was calculated by the summation of both grades of vertebral arteries shown in Fig. 1

eight (40%) had vertebral artery tortuosity: two on the right side, two on the left, and four on both sides. The tortuosity scores are also noted in Table 2. The common carotid artery showed no tortuosity in any patients.

The LDS patients had a high prevalence of vertebral artery tortuosity ($P = 0.017$). The mean tortuosity score was 2.0 [95% confidence interval (CI) 1.26–2.73] for LDS patients and 0.7 (95% CI 0.18–1.22) for MFS patients.

Aortic and peripheral artery disease

A total of five peripheral aneurysms were observed in three LDS patients (30%). Three aneurysms presented in the hepatic artery, one in the superior mesenteric artery, and one in the pancreatic arcade. Three patients (33.3%) had common iliac artery aneurysms, and one (10%) had a common femoral artery aneurysm. Because one patient had iliac artery involvement secondary to aortic dissection, we excluded him from the analysis of iliac aneurysms. Among the seven patients without abdominal aortic dissection, an abdominal aortic aneurysm was observed in one patient (14.3%). No aneurysms were observed in the thoracic aorta and its branches. Because four patients had undergone thoracic aortic replacement, three of which were due to dissection, they were excluded from the analysis of the prevalence of aortic aneurysms.

Among the MFS patients, one (5%) had a hepatic artery aneurysm, and three (20%) had common iliac aneurysms. Among the 12 patients without abdominal aortic replacement, 1 (8.3%) had an abdominal aortic aneurysm. Because two patients had involvement of the celiac trunk and five of the iliac artery secondary to aortic dissection, such territories were excluded for evaluation of the prevalence of peripheral aneurysms. Because seven patients had thoracic aortic replacement and eight had abdominal aortic replacement, they were excluded from the analysis of the prevalence of aortic aneurysms.

The prevalence of peripheral aneurysms was not significantly different between LDS and MFS ($P = 0.057$).

Discussion

Our results showed that the high prevalence of vertebral artery tortuosity in LDS helps to differentiate LDS from MFS. Patients with LDS have aneurysms or dissection of the ascending aorta, similar to those observed in patients with MFS. In contrast to MFS, however, generalized arterial tortuosity and aneurysms of other arteries have been noted in patients with LDS.[4] On the other hand, there are some reports[7,8] that arterial tortuosity had not been found in their LDS groups although they had not been systematically evaluated in all patients. The exact prevalence of arterial tortuosity, especially in the vertebral artery, has not yet been reported. Our results showed that the vertebral arteries were highly affected in LDS patients.

Assessing the vertebral artery to help differentiate LDS from MFS is a superior method for a few reasons. First, the lower portion of the vertebral artery is easy to evaluate with thoracic or thoracoabdominal CTA. Second, the vertebral artery is rarely affected by aortic dissection, in contrast to the subclavian artery or carotid artery. Third, the vertebral artery is easy to evaluate because it runs straight, especially in young subjects. According to our unpublished data, among 10 subjects without either LDS or MFS (five men, five women; mean age 26.7 years), tortuosity was not observed in the vertebral artery. Arteries other than the vertebral artery (e.g., abdominal visceral arteries, iliac arteries) are difficult to evaluate because they sometimes display tortuosity even in normal populations. For these reasons, we recommend that the vertebral artery be evaluated.

An autosomal dominant genetic disorder, MFS has symptoms that include those of cardiovascular diseases (ascending aortic aneurysms, aortic dissections, mitral valve abnormalities), skeletal manifestations (pectus deformities, scoliosis, dolichostenomelia, arachnodactyly, joint laxity, highly arched palate), and ocular complications (ectopia lentis, retinal detachment, myopia). Diagnostic criteria for MFS, currently known as the Ghent criteria, emphasize the aortic aneurysms and dissections, a constellation of skeletal findings, ectopia lentis, dural ectasia, and the family history.[9] LDS has many similarities to MFS with regard to cardiovascular disorders or skeletal manifestations; therefore, if LDS patients did not show some characteristic manifestation, differentiation from MFS would be difficult without genetic analysis. Vertebral artery tortuosity may be the factor that can differentiate these disorders and so would be helpful in the clinical setting when genetic analysis is not immediately available.

Cardiovascular disease is more aggressive and widespread in LDS than MFS. Aortic rupture and dissection can occur in patients with aortic root diameters not considered at risk in MFS (<4.5 cm).[5] Recognition of LDS is important, especially for the management of these patients. The two major causes of death in LDS patients were reported to be aortic dissection and rupture in the thoracic (67%) and abdominal (22%) regions.[10] The third cause of mortality was intracranial hemorrhaging due to rupture of cranial arterial aneurysms (7%) because in LDS aneurysms are not confined to the aortic root, as with MFS, but occur throughout the entire arterial tree.

Our results indicated that peripheral aneurysms in LDS patients were present in the hepatic and mesenteric iliac arteries. These results were consistent with the fact that LDS has a high prevalence of peripheral aneurysms. The difference in the prevalence of peripheral aneurysms was not significant ($P = 0.057$), but it might be because the sample number was too small. It is important to know the prevalence of peripheral aneurysms for diagnosis and management.

Limitations

The number of patients in our sample was small, which was due to the requirement of genetic analysis to confirm the diagnosis of LDS and MFS in this study. Genetic analysis is not widely available in clinical settings. Also, bias may be present because our institution is a cardiovascular center. Hence, the patients referred to our hospital might have a higher prevalence of cardiovascular diseases than patients in other hospitals or institutions. Although the use of CT images for the initial diagnosis is preferred, because many of the LDS and MFS patients were referred to our hospital after the first operation we used the images obtained in the pre- or postoperative state. The mutation of TGFBR was classified as TGFBR-1 and TGFBR-2. Because both of these types have an aggressive vascular pathology, we did not mention the TGFBR types in this study. Further examination of a larger sample is needed to understand the relation between the gene type and the phenotype.

Conclusion

Vertebral artery tortuosity and peripheral aneurysms had a high prevalence among LDS patients. Identifying tortuosity in the vertebral artery has a potential to differentiate LDS from MFS. In the diagnosis of patients suspected of connective tissue disease, we should pay attention to peripheral artery diseases as well as aortic pathologies.

References

1. Januzzi JL, Isselbacher EM, Fattori R, Cooper JV, Smith DE, Fang J, et al. Characterizing the young patient with aortic dissection: results from the International Registry of Aortic Dissection (IRAD). J Am Coll Cardiol 2004;43:665–9.
2. Mizuguchi T, Collod-Beroud G, Akiyama T, Abifadel M, Harada N, Morisaki T, et al. Heterozygous TGFBR2 mutations in Marfan syndrome. Nat Genet 2004;36:855–60.
3. Loeys BL, Chen J, Neptune ER, Judge DP, Podowski M, Holm T, et al. A syndrome of altered cardiovascular, craniofacial, neurocognitive and skeletal development caused by mutations in TGFBR1 or TGFBR2. Nat Genet 2005;37: 275–81.
4. Loeys BL, Schwarze U, Holm T, Callewaert BL, Thomas GH, Pannu H, et al. Aneurysm syndromes caused by mutations in the TGF-beta receptor. N Engl J Med 2006;355:788–98.
5. Williams JA, Loeys BL, Nwakanma LU, Dietz HC, Spevak PJ, Patel ND, et al. Early surgical experience with Loeys-Dietz: a new syndrome of aggressive thoracic aortic aneurysm disease. Ann Thorac Surg 2007;83:S757–63; discussion S85–90.
6. Akutsu K, Morisaki H, Takeshita S, Sakamoto S, Tamori Y, Yoshimuta T, et al. Phenotypic heterogeneity of Marfan-like connective tissue disorders associated with mutations in the transforming growth factor-beta receptor genes. Circ J 2007; 71:1305–9.
7. Alberts JJ, van den Berg MP, Bergman JE, du Marchie Sarvaas GJ, Post JG, van Unen H, et al. The many faces of aggressive aortic pathology: Loeys-Dietz syndrome. Neth Heart J 2008;16:299–304.
8. Singh KK, Rommel K, Mishra A, Karck M, Haverich A, Schmidtke J, et al. TGFBR1 and TGFBR2 mutations in patients with features of Marfan syndrome and Loeys-Dietz syndrome. Hum Mutat 2006;27:770–7.
9. De Paepe A, Devereux RB, Dietz HC, Hennekam RC, Pyeritz RE. Revised diagnostic criteria for the Marfan syndrome. Am J Med Genet 1996;62:417–26.
10. Johnson PT, Chen JK, Loeys BL, Dietz HC, Fishman EK. Loeys-Dietz syndrome: MDCT angiography findings. AJR Am J Roentgenol 2007;189:W29–35.

Circulation Journal
Official Journal of the Japanese Circulation Society
http://www.j-circ.or.jp

ORIGINAL ARTICLE
Molecular Cardiology

Genetic Analysis of Young Adult Patients With Aortic Disease Not Fulfilling the Diagnostic Criteria for Marfan Syndrome

Koichi Akutsu, MD*,‡; Hiroko Morisaki, MD**; Toshiya Okajima, MD*; Tsuyoshi Yoshimuta, MD*; Yoshiaki Tsutsumi, MD*; Satoshi Takeshita, MD*; Hiroshi Nonogi, MD*; Hitoshi Ogino, MD†; Masahiro Higashi, MD††; Takayuki Morisaki, MD**

Background: Although the existence of the young patients with aortic disease not fulfilling the diagnostic criteria for Marfan syndrome (MFS) has been known, the etiology of their disease has not yet been elucidated. The purpose of the present study was to elucidate the genetic and clinical features of the young patients with aortic disease not having MFS.

Methods and Results: Eighty young adult patients with aortic disease were examined. They were divided into a definite MFS (n=51) and a non-definite MFS group (n=29) according to the Ghent nosology. Clinical and genetic characteristics were compared between the 2 groups. Among 29 non-definite MFS probands, 1 (3%) *FBN1*, 2 (7%) *TGFBR1*, and 3 (10%) *TGFBR2* mutations were found, and 4 *ACTA2* mutations were found in the 23 probands examined without *FBN1*, *TGFBR1*, or *TGFBR2* mutations. In total, more than 10 out of 29 (34%) probands in the non-definite MFS group were associated with genetic mutations. Skeletal involvement was less frequent in the non-definite than in the definite MFS group (7% vs 82%, P<0.01).

Conclusions: In the probands with aortic diseases in young who cannot be diagnosed with MFS, mutations other than *FBN1* mutations accounted for at least one-third of all causes of aortic disease. (*Circ J* 2010; **74:** 990–997)

Key Words: *ACTA2*; Aortic disease; Marfan syndrome; *TGFBR1*; *TGFBR2*

Aortic dissection or annulo-aortic ectasia (AAE) often develops in young patients with Marfan syndrome (MFS), which is caused by mutations in the *FBN1*.[1] Recently, progress in genetic analysis has revealed genetic disorders other than *FBN1* mutations, such as mutations of *TGFBR1* or *TGFBR2*, *ACTA2*, *MYH11*, and *SLC2A10*, which also cause aortic disease in young patients.[2–7] It is often believed that the cause of aortic disease in young patients is MFS. However, these patients cannot always be diagnosed as MFS.

Although the existence of the young patients with aortic disease not fulfilling the diagnostic criteria for MFS has been known, the details of their disease have not yet been elucidated. The purpose of the present study was to elucidate the genetic and clinical features of young patients with aortic disease not fulfilling the diagnostic criteria for MFS.

Methods

Patients who were suspected of connective tissue disorders and who consented to undergo genetic analysis (n=129) were initially enrolled for the present study to investigate the characteristics of young patients with aortic disease, such as, aortic dissection, AAE and other forms of aortic aneurysm. Then, patients with the following characteristics were excluded: age <15 years (n=5), patients with relatives diagnosed with MFS (n=21), patients who did not have aortic disease (n=11), patients whose aortic dissection developed at age ≥50 years or whose aneurysms were found at age ≥50 years (n=9), and patients with aortitis that was regarded as having other etiologies (n=3). In total, 80 young adult patients (probands) with aortic disease who were suspected of connective tissue disorders were included in the present study.

Received October 5, 2009; revised manuscript received January 19, 2010; accepted January 27, 2010; released online March 30, 2010
Time for primary review: 14 days

*Department of Cardiovascular Medicine, **Department of Bioscience, †Department of Cardiovascular Surgery, ††Department of Radiology, National Cardiovascular Center, Suita and ‡Department of Intensive and Cardiac Care Unit, Nippon Medical School, Tokyo, Japan

Mailing address: Takayuki Morisaki, MD, Department of Bioscience, National Cardiovascular Center, 5-7-1 Fujishirodai, Suita 565-8565, Japan. E-mail: morisaki@ri.ncvc.go.jp

ISSN-1346-9843 doi:10.1253/circj.CJ-09-0757

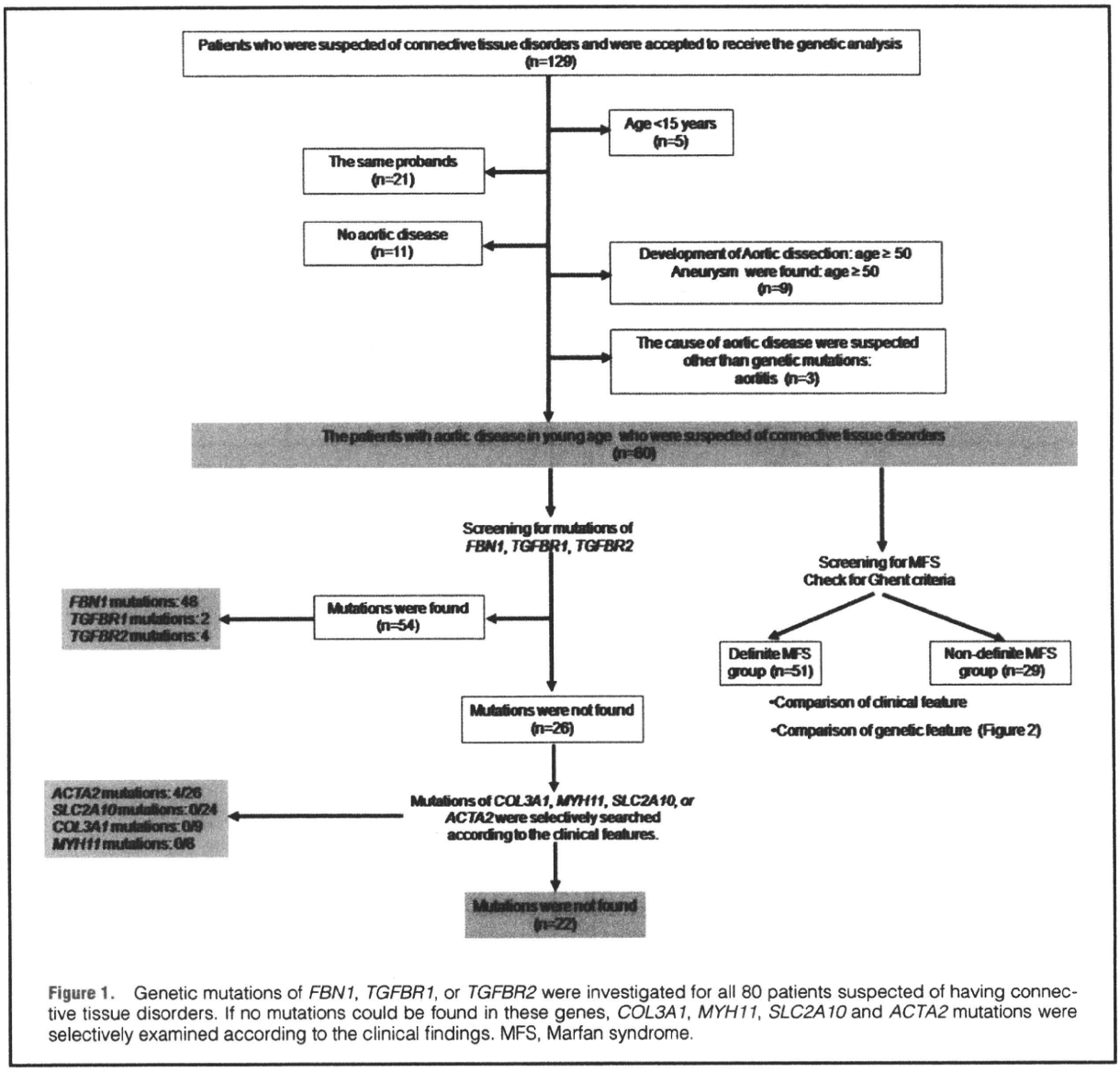

Figure 1. Genetic mutations of *FBN1*, *TGFBR1*, or *TGFBR2* were investigated for all 80 patients suspected of having connective tissue disorders. If no mutations could be found in these genes, *COL3A1*, *MYH11*, *SLC2A10* and *ACTA2* mutations were selectively examined according to the clinical findings. MFS, Marfan syndrome.

Genetic Features

The probands of all 80 probands were investigated for *FBN1*, *TGFBR1*, or *TGFBR2* mutations. If we could find no mutations in these genes, *COL3A1*, *MYH11*, *SLC2A10* and *ACTA2* mutations were selectively examined according to the clinical findings of each patient. A flow diagram of the investigations is shown in Figure 1.

FBN1, *TGFBR1*, *TGFBR2*, *ACTA2*, and *SLC2A10* mutations were examined using genomic DNA, which was isolated from the peripheral blood leukocytes of patients and amplified using polymerase chain reaction as described previously.[5] Genetic variants were screened with a denaturing high performance liquid chromatography method and the detected variations were further confirmed using direct sequencing as described previously.[1,2,5,8] *COL3A1* and *MYH11* mutations were examined using mRNA, which was obtained from surgical tissue specimens. Therefore, we could not determine the existence of *COL3A1* and *MYH11* mutations if the surgical specimen could not be obtained.

Clinical Features Related to the Ghent Nosology

In order to determine whether the patients fulfilled the diagnostic criteria of MFS using the Ghent nosology, all patients received careful assessments, including physical examination, computed tomography scanning or magnetic resonance imaging, echocardiography, and slit-lamp examination for ocular lesion, which covered all criteria listed in the Ghent nosology.[8] We defined the patients who fulfilled the Ghent nosology as the "definite MFS group", and the rest as "non-definite MFS group". According to the results of these examinations, all 80 probands were divided into definite MFS group (n=51) and non-definite MFS group (n=29).

Comparison of Probands in the Definite MFS Group and the Non-Definite MFS Group

First, clinical features were compared between the definite and non-definite MFS groups with respect to: (1) age, gender, height; (2) family history of aortic dissection or sudden death at age <50 years, or family history of suspected MFS; (3)

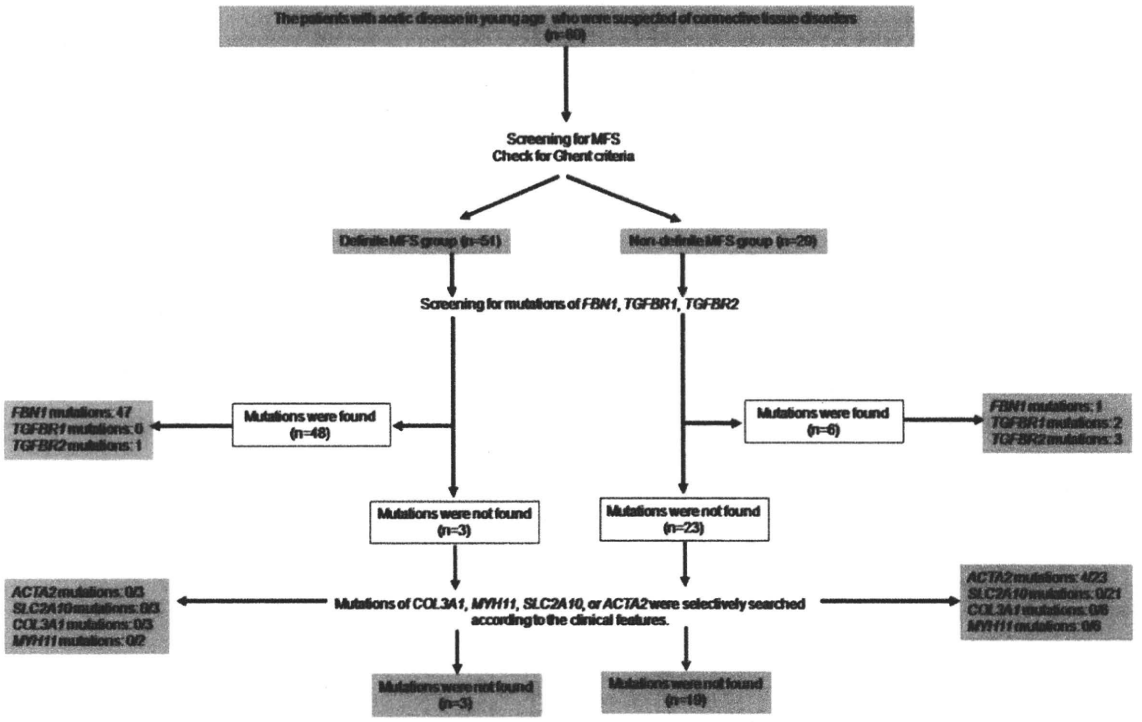

Figure 2. Genetic mutations of *FBN1*, *TGFBR1*, or *TGFBR2* were investigated for each of the 51 probands with definite MFS and 29 probands with non-definite MFS. If no mutations could be found in those genes, *COL3A1*, *MYH11*, *SLC2A10*, and *ACTA2* mutations were selectively examined according to the clinical findings. MFS, Marfan syndrome.

Ghent nosology. Ghent nosology included: involvement of skeletal system such as arm-span-to-height ratio, thumb and wrist signs, and joint hypermobility; involvements of the cardiovascular system, such as AAE, aortic dissection or mitral valve prolapse; ectopia lentis; dural ectasia; involvement of the pulmonary system, such as pneumothorax and apical blebs in the apex; and involvement of skin system, such as atrophic striae and recurrent hernia. Second, the genetic features were compared between the 2 groups (Figure 2).

Specific Clinical Features in the Non-Definite MFS Group

We divided the non-definite MFS group into 2 groups, the patients with some mutations in *FBN1*, *TGFBR1* or *TGFBR2*, *ACTA2*, *MYH11*, *SLC2A10*, or *COL3A1* (Mutation (+) group) and the patients without these mutations (Mutation (–) group). Then, we investigated specific clinical features in each group, which were the characteristics of connective tissue disorders other than MFS, such as Loeys-Dietz syndrome (LDS), Ehlers-Danlos syndrome type IV, arterial tortuosity syndrome (ATS), and thoracic aortic aneurysm and/or aortic dissection (TAAD). The following specific features of each disease were examined: hyperterolism; bifid uvula; aortic branch aneurysms; squint (which were often seen in LDS); easy bruising; thin and visible veins, (which were often seen in Ehelers-Danlos syndrome type IV); arterial tortuosity (which were often seen in LDS or ATS); livedo reticularis; iris flocculi (which were often seen in patients with *ACTA2* mutation); and patent ductus arteriosus (LDS and patients with *MYH11* mutations).[4,6,9–12] In addition to comparing the phenotypes of patients with non-definite MFS with the definite MFS group, we examined how the patients in non-definite MFS group fulfilled each feature of Ghent criteria.

Ethical Considerations

The present study was conducted according to the articles of the Declaration of Helsinki regarding the participation of human subjects in clinical studies and was approved by the Ethics Committee of the National Cardiovascular Center (Suita, Japan). All patients gave written informed consent to participate in the present study.

Statistical Analysis

Continuous variables were expressed as mean±standard deviation (SD). The Student t-test was used to analyze significant differences in factors between the 2 groups. Differences in percentages between the 2 groups were evaluated using Fisher's exact test. SPSS (11.0) software (SPSS Inc, Chicago, IL, USA) was used for all statistical analyses. A P value<0.05 was considered statistically significant.

Results

Genetic Features of Patients

For all 80 probands, mutations of *FBN1*, *TGFBR1*, and *TGFBR2* were investigated. Mutations of *FBN1*, *TGFBR1*, and *TGFBR2* were found in 48 (60%), 2 (3%), and 4 (5%) of the probands, respectively. At the next step, *COL3A1*, *MYH11*, *SLC2A10*, and *ACTA2* mutations were selectively examined according to the clinical features among the 26 probands who did not have any mutations in *FBN1*, *TGFBR1*,

Table 1. Genotypic Manifestations

Mutations	Definite MFS group (n=51)	Non-definite MFS group (n=29)
FBN1 (n, %)	47/51 (92%)**	1/29 (3%)
TGFBR1 (n, %)	0/51 (0%)	2/29 (7%)
TGFBR2 (n, %)	1/51 (2%)	3/29 (10%)
TGFBR1 or *TGFBR2* (n, %)	1/51 (2%)	5/29 (17%)*
ACTA2 (n, %)	0/3 (0%)	4/23 (17%)
SLC2A10 (n, %)	0/3 (0%)	0/21 (0%)
MYH11 (n, %)	0/2 (0%)	0/6 (0%)
COL3A1 (n, %)	0/3 (0%)	0/6 (0%)
Undetermined (n, %)	3/51 (6%)	19/29 (66%)**

Data were expressed as mean±SD. *P<0.05, **P<0.01.

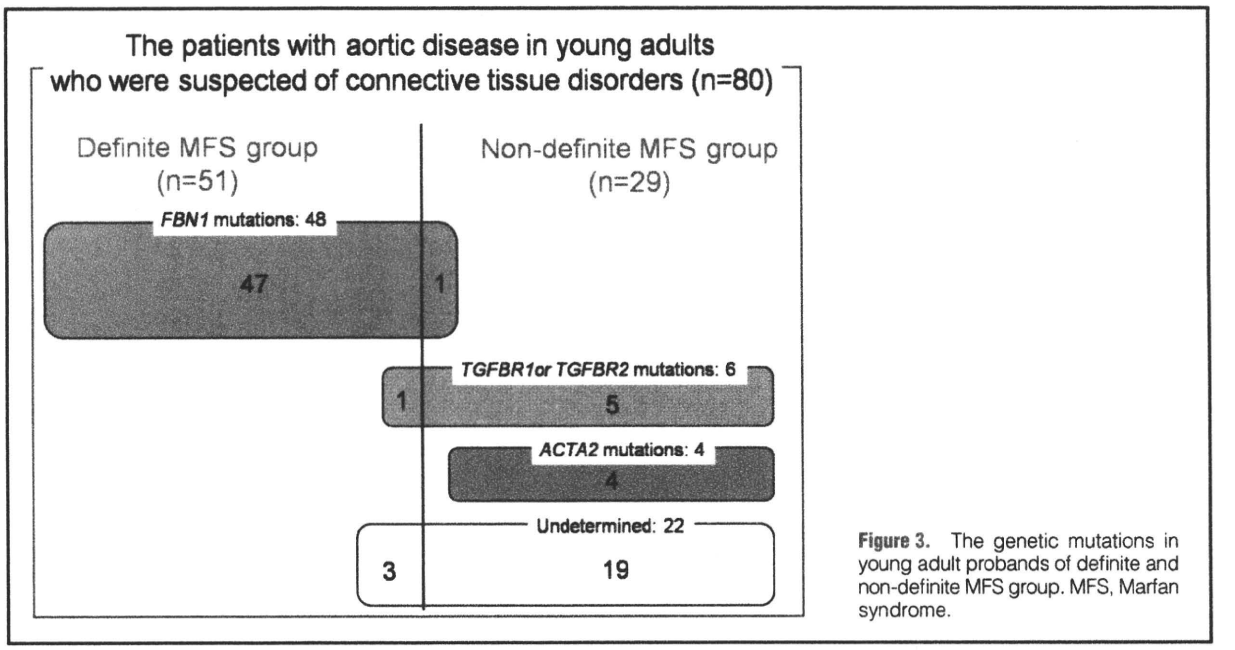

Figure 3. The genetic mutations in young adult probands of definite and non-definite MFS group. MFS, Marfan syndrome.

and *TGFBR2*. Mutations of *ACTA2* were examined in all of these 26 probands and 4 mutations were found. Mutations of *SLC2A10* were not found in 24 probands examined, and there were no *COL3A1* mutations out of 9 examined, and no *MYH11* mutations out of 8 examined. As a result, at least 58 (73%) mutations among all 80 probands were associated with aortic disease in young adults. The investigation flow chart is shown in Figure 1.

The results of genetic analysis of *FBN1* did not indicate any apparent phonotype–genotype correlation. All mutations of *TGFBR1* or *TGFBR2* were found in the exons corresponding to the kinase domain (data not shown). Also, all of these *TGFBR1* or *TGFBR2* mutations but one were a missense mutations, while the nonsense mutations found were not suggested to be a mutation causing nonsense mediated mRNA decay (data not shown).

Comparison of the Probands in Definite and Non-Definite MFS Groups

Genotypic Manifestations Genotypic manifestations in each group are shown in Table 1. Among 51 probands in the definite MFS group, 47 (92%) *FBN1* mutations and 1 (2%) *TGFBR2* mutations were found. *ACTA2* and *SLC2A10* mutations were investigated in the remaining 3 probands in the definite MFS group and no mutations were found.

Among 29 probands in the non-definite MFS group, 1 (3%) *FBN1*, 2 (7%) *TGFBR1*, and 3 (10%) *TGFBR2* mutations were found. In the remaining 23 probands, 4 *ACTA2* mutations were found. In total, at least 10 out of 29 (34%) probands in the non-definite MFS group had genetic mutations. Genetic mutations of both groups are summarized in Figure 3.

Comparing the probands in the definite and non-definite MFS groups, *FBN1* mutations were found more frequently in the definite MFS group than in non-definite MFS group (92% vs 3%, P<0.01). In contrast, *TGFBR1* or *TGFBR2* mutations were found more frequently in the non-definite than in the definite MFS group (17% vs 2%, P<0.05). *ACTA2* mutations were only found in the non-definite MFS group.

Phenotypic Manifestations The baseline clinical features are shown in Table 2. Comparing the probands in the definite and non-definite MFS groups, shorter height was observed more frequently in the non-definite MFS group (male; 176±6cm vs 184±6cm, P<0.01, female; 159±3cm vs 174±8cm,

Table 2. Baseline Clinical Features

	Definite MFS group (n=51)	Non-definite MFS group (n=29)
Age (years)	37±10	39±11
Male sex (n, %)	28 (38%)	20 (63%)
Height (cm)		
Male	184±6**	176±6
Female	174±8**	159±3
Obstructive sleep apnea	2/47 (4%)	3/24 (13%) (*ACTA2*:1)
Aortic dissection during pregnancy	2/23 female	1/9 female (*ACTA2*:1)
Family history (n, %)	25 (49%)	11 (40%)
Among Mutations (+) in each group	25/48 (52%)	7/10 (70%)
Among Mutations (–) in each group	0/3	4/19 (21%)

Data were expressed as mean±SD. **P<0.01.
Family history: family history of aortic dissection and/or sudden death at age <50 years or suspected.
Marfan syndrome: *ACTA2*:1, one patient was associated with *ACTA2* mutations.
Mutation (+): some mutations such as *FBN1*, *TGFBR1*, *TGFBR2*, *ACTA2*, were found.
Mutation (–): no mutations were found in *FBN1*, *TGFBR1*, *TGFBR2*, *ACTA2*, *SLC2A10*, *MYH11*, and *COL3A1* in the present study.

Table 3. Clinical Features Related to Ghent Nosology

	Definite MFS group (n=51)	Non-definite MFS group (n=29)
Skeletal system (n, %)		
Skeletal involvement	42/51 (82%)**	2/29 (7%) *TGFBR2*:1
Arm-span-to-height ratio >1.05	10/51 (20%)	1/27 (3%) *TGFBR2*:1
Thumb sign and wrist sign	33/51 (65%)**	2/28 (7%) *TGFBR2*:1
Joint hypermobility	26/50 (52%)**	3/25 (12%) *TGFBR2*:1
Cardiovascular system (n, %)		
Annulo-aortic ectasia	49/49 (100%)**	14/27 (52%)
Type A aortic dissection	11/51 (22%)	10/29 (34%)
Type B aortic dissection	18/51 (35%)	12/29 (41%)
Mitral valve prolapse	6/50 (52%)**	5/29 (17%)
Ectopia lentis (n, %)	13/50 (26%)**	0/26 (0%)
Dural ectasia (n, %)	35/51 (69%)**	4/29 (14%)
Lung involvement (n, %)	24/51 (47%)	7/29 (24%)
Skin involvement (n, %)	44/51 (24%)**	4/25 (7%)

Data were expressed as mean±SD. **P<0.01
Skeletal involvement: fulfilling 2 major criteria of Ghent nosology or one major and 2 minor criteria.

P<0.01). In the non-definite MFS group, the height of the patients with genetic mutations (n=10) was not significantly different from those without genetic mutations (n=19) (male; 177±6cm vs 176±6cm, female; 158±2cm vs 159±3cm). Obstructive sleep apnea was observed in 2 probands (2%) in the definite MFS group and 3 probands (13%) in the non-definite MFS group. Out of 3 probands with obstructive sleep apnea in the non-definite MFS group, one was associated with *ACTA2* mutations. Two probands in the definite MFS group and 1 proband in the non-definite MFS group presented with aortic diseases during pregnancy, and the latter proband had *ACTA2* mutations. Probands with hypertension from young age, and steroid use were not observed in either group. Although the number of the patients with family history of MFS or aortic disease did not differ between the definite and non-definite MFS group, some patients in the non-definite MFS group with no genetic mutations identified had a family history of MFS (4 out of 19; 21%).

Clinical features related to Ghent nosology are shown in Table 3. The following manifestations of Ghent nosology were less frequent in the non-definite than in the definite MFS group: skeletal system involvement (7% vs 82%, P< 0.01); thumb sign and wrist sign (3% vs 20%, P<0.01); joint hypermobility (12% vs 52%, P<0.01); AAE (52% vs 100%, P<0.01); mitral valve prolapse (17% vs 52%, P<0.01); ectopia lentis (0% vs 26%, P<0.01); dural ectasia (14% vs 69%, P<0.01); and skin involvement (7% vs 24%, P<0.01). The genetic background of each skeletal manifestation is also shown in Table 3. In the non-definite MFS group, Ghent skeletal manifestations were seen in some probands. However, one particular proband with mutations in *TGFBR2* gene fulfilled the criteria of "skeletal involvement", which means fulfilling 4 major skeletal manifestations, "arm-span-to-height ratio >1.05", "thumb sign and wrist sign", and "joint hypermobility", while the other probands of this group who fulfilled the skeletal criterion were not found to have any genetic mutations.

Clinical Features in Non-Definite MFS Group

The specific clinical features of the patients in the non-defi-

Table 4. Clinical Feature of Non-Definite MFS Group

	Mutations (+) (n=10)	Mutations (–) (n=19)
Features often found in the patients with genetic mutations other than *FBN1*		
Hyperterolism (n, %)	1 (*TGRBR1*)	0
Bifid uvula (n, %)	1 (*TGRBR2*)	0
Aortic branch aneurysm (n, %)	1 (*TGRBR1*)	0
Squint (n, %)	3 (*TGRBR2*:2) (*ACTA2*:1)	1 (FH–)
Arterial tortuosity (n, %)	2 (*TGRBR2*)	2 (FH–)
Livedo reticularis (n, %)	1 (*ACTA2*)	0
Iris flocculi (n, %)	1 (*ACTA2*)	0
Features listed in Ghent nosology		
Fulfilling 2 major criteria		
Cardiovascular+skeletal	1 (*TGFBR2*)	0
Cardiovascular+dural ectasia	0	1 (FH–)
Fulfilling 1 major criteria+2 involvement		
Dural ectasia+skin and cardiovascular involvement	0	1 (FH–)
Dural ectasia+skin and pulmonary involvement	0	1 (FH–)
Fulfilling 1 major criteria+1 involvement		
Cardiovascular+skeletal involvement	0	1 (FH–)
Cardiovascular+pulmonary involvement	1 (*TGFBR1*)	4 (FH+:1/FH–:3)
Cardiovascular+skin involvement	4 (*TGFBR1*:1) (*TGFBR2*:2) (*ACTA2*:1)	1 (FH+)

Mutation (+): some mutations such as *FBN1*, *TGFBR1*, *TGFBR2*, *ACTA2*, were found.
Mutation (–): no mutations were found in *FBN1*, *TGFBR1*, *TGFBR2*, *ACTA2*, *SLC2A10*, *MYH11* and *COL3A1* in the present study.
FH–: having no family history of aortic dissection and/or sudden death at age <50 years or suspected Marfan syndrome.
FH+: having a family history of aortic dissection and/or sudden death at age <50 years or suspected Marfan syndrome.

nite MFS group are shown in Table 4. Since easy bruising and thin and visible veins were not observed in the patients in the present study, no patient was strongly suspected of having Ehlers-Danlos syndrome. Patent ductus arteriosus was also not observed. Few specific skeletal features were observed in the patients with *ACTA2* mutations. In the Mutation (–) group, only 2 patients with tortuous aorta and one patient with squint, both without family history of MFS or aortic disease, were observed.

In addition, the extent of fulfilling the Ghent nosology in the non-definite MFS group is shown in Table 4. In the Mutation (+) group, some patients with *TGFBR1* or *TGFBR2* mutations fulfilled some criteria. In contrast, only one patient with *ACTA2* mutations fulfilled the criterion of skin involvement in addition to major criteria of cardiovascular system. In the Mutation (–) group, few patients fulfilled the Ghent criteria, even though some had a family history of MFS or aortic disease

Discussion

The results of the present study demonstrated that genetic mutations account for at least three-fourths of all causes of aortic disease in young adults. Especially in the non-definite MFS group, the genetic examination elucidated mutations of *TGFBR1* or *TGFBR2* and *ACTA2* in some probands, and genetic mutations accounted for at least one-third of all causes of aortic disease in the probands of the non-definite MFS group.

Among young patients with aortic disease, MFS associated with *FBN1* mutations was the most frequent cause of aortic disease. Recently, genetic mutations other than *FBN1* mutations were found in aortic disease. *TGFBR1* or *TGFBR2* mutations are known to cause LDS, Furlong syndrome and Shprintzen-Goldberg syndrome.[9,13,14] Among these diseases, phenotypic data of LDS are well documentd.[9] LDS is characterized by widely spaced eyes (hypertelorism), bifid uvula and/or cleft palate, and generalized arterial tortuosity with ascending aortic aneurysm and dissection. Although LDS was reported as MFS II initially, the phenotypic manifestations are often different from MFS.[2] In addition, the patients with *TGFBR1* or *TGFBR2* mutations do not always show the typical phenotype of LDS.[15] Therefore, we could not easily discriminate LDS from normal individuals only by clinical features.

ACTA2 mutations are reportedly the most common cause of TAAD without syndromatic characteristics, and they are responsible for 14% of TAAD, as compared with 5% and <2% for *TGFBR2* and *MYH11*, respectively.[4,16,17] The clinical features of the patients with *ACTA2* mutations were reported to be livedo reticularis and iris flocculi, but they are not always found in these patients, as we recently reported for a number of probands with *ACTA2* mutations.[4,5] *SLC2A10* mutations cause ATS, which is characterized by tortuousity and elongation of the large and medium-sized arteries, pulmonary arteries stenosis and aneurysm formation, often resulting in death at young age.[11] *MYH11* mutations are known as a cause of TAAD with patent ductus arteriosus.[6] Although patients

with mutations of *ACTA2*, *SLC2A10* or *MYH11* will develop characteristic abnormality in the aorta, their characteristic MFS-like features have not been described; therefore, we could not recognize their genetic disease by their readily observable physical features.

In the present study, *FBN1* mutations were found in 48 of 80 (60%) probands from patients with suspected connective tissue disorders, who had aortic diseases at a young age, and *TGFBR1* or *TGFBR2* mutations were found in 6 (8%) probands. *ACTA2* mutations were detected in 4 of the 26 probands examined. In total, more than 58 (73%) young probands with aortic disease had genetic mutations. Among 29 probands in the non-definite MFS group, there was 1 (3%) *FBN1* mutations and 5 (17%) *TGFBR1* or *TGFBR2* mutations. *ACTA2* mutations were found in 4 of the 22 probands examined. In total, more than 10 probands in the non-definite MFS group had genetic mutations. The remainder of the patients may have unknown genetic mutations, acquired factors or both. Indeed, some patients in the non-definite MFS group with no genetic mutations identified in the present study had a family history of MFS or aortic disease.

Acquired factors causing aortic diseases have not been fully elucidated. The causes of aortic dissection and those of aortic aneurysm should be different, and the causes of aortic disease in young individuals and those in old individuals should be also different. In elder individuals, aortic diseases were often associated with hypertension, smoking, atherosclerosis, and sleep apnea syndrome.[18–21] In contrast, in young individuals, the acquired factors causing aortic diseases are slightly different, including hypertension from young age, sleep apnea syndrome, pregnancy, steroid use, aortitis, etc.[22–27] In the present study, 3 cases of aortitis were observed among the first 129 patients before exclusion of some patients. Among the 29 probands in the non-definite MFS group, 3 obstructive sleep apnea cases including 1 with *ACTA2* mutations, and 1 pregnancy with *ACTA2* mutations, were found. Therefore, among the 29 probands in the non-definite MFS group, there are only 2 probands with aortic disease in young age whose aortic disease might be caused by acquired factors alone. Therefore, 12 probands had genetic mutations and/or acquired factors, and aortic disease in young age in 17 probands was still inexplicable through consideration of either genetic mutations or acquired factors.

Patients with MFS often develop aortic disease such as aortic dissection or AAE in young age. MFS is characterized by phenotypic abnormalities of the skeletal, ocular, and cardiovascular systems. Especially, skeletal abnormalities such as tall stature with long extremities are indicative of MFS. However, if young patients with aortic disease did not have MFS, we could not determine the cause of their aortic disease, because the characteristic features were often not observed in the patients with disorders other than MFS. The present study clearly showed that not only physical examination but also genetic study is needed to give a proper diagnosis, especially in young patients with aortic disease without MFS.

Some limitations of the present study must be taken into account. First, *COL3A1*, *MYH11*, *SLC2A10*, and *ACTA2* mutations were not examined for all 80 probands. We studied these mutations only in a maximum of 26 probands without *FBN1*, *TGFBR1*, and *TGFBR2* mutations. We have identified simultaneous two-gene mutations of *FBN1* and *TGFBR2* in one proband, although such double mutations seem to be rather rare. Therefore, we suspect the incidence of *ACTA2* mutations may be close to 4 out of 80 in the present study. Although we could not determine the exact incidence of the mutations, it is important to note that some patients with *ACTA2* mutations can be found in the patient population with aortic disease in young age. Second, we only showed the general characteristics in young patients with aortic disease without MFS. The presentation of the non-definite MFS could be heterogeneous. They may consist of various patients including patients with unknown genetic mutations, those with unknown acquired factors, etc. However, the present study showed that the non-definite MFS patients with aortic disease at a young age possess only a few obvious characteristic features, and it is difficult for us to discriminate them from normal individuals. Third, the method used to search genetic mutations in the present study might not capture all the causative mutations.

In conclusion, genetic mutations other than *FBN1* mutations were found in the non-definite MFS group with aortic disease in young age, and they accounted for one-third of all causes of aortic disease. If the etiology of aortic disease is not clear, we recommend genetic analysis with ethical considerations because these patients do not often exhibit characteristic features of MFS.

References

1. Dietz HC, Cutting GR, Pyeritz RE, Maslen CL, Sakai LY, Corson GM, et al. Marfan syndrome caused by a recurrent de novo missense mutation in the fibrillin gene. *Nature* 1991; **2352:** 279–281.
2. Mizuguchi T, Collod-Beroud G, Akiyama T, Abifadel M, Harada N, Morisaki T, et al. Heterozygous TGFBR2 mutations in Marfan syndrome. *Nat Genet* 2004; **36:** 855–860.
3. Loeys BL, Chen J, Neptune ER, Judge DP, Podowski M, Holm T, et al. A syndrome of altered cardiovascular, craniofacial, neurocognitive and skeletal development caused by mutations in TGFBR1 or TGFBR2. *Nat Genet* 2005; **37:** 275–281.
4. Guo DC, Pannu H, Tran-Fadulu V, Papke CL, Yu RK, Avidan N, et al. Mutations in smooth muscle alpha-actin (ACTA2) lead to thoracic aortic aneurysms and dissections. *Nat Genet* 2007; **39:** 1488–1493.
5. Morisaki H, Akutsu K, Ogino H, Kondo N, Yamanaka I, Tsutsumi Y, et al. Mutation of *ACTA2* gene as an important cause of familial and non-familial non-syndromatic thoracic aortic aneurysm and/or dissection. *Hum Mutat* 2009; **30:** 1406–1411.
6. Zhu L, Vranckx R, Khau Van Kien P, Lalande A, Boisset N, Mathieu F, et al. Mutations in myosin heavy chain 11 cause a syndrome associating thoracic aortic aneurysm/aortic dissection and patent ductus arteriosus. *Nat Genet* 2006; **38:** 343–349.
7. Coucke PJ, Willaert A, Wessels MW, Callewaert B, Zoppi N, De Backer J, et al. Mutations in the facilitative glucose transporter SLC2A10 alter angiogenesis and cause arterial tortuosity syndrome. *Nat Genet* 2006; **38:** 452–457.
8. 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.
9. Loeys BL, Schwarze U, Holm T, Callewaert BL, Thomas GH, Pannu H, et al. Aneurysm syndromes caused by mutations in the TGF-beta receptor. *N Engl J Med* 2006; **355:** 788–798.
10. Beighton P, De Paepe A, Steinmann B, Tsipouras P, Wenstrup RJ. Ehlers-Danlos syndromes: Revised nosology, Villefranche, Ehelers-Danlos National Foundation (USA) and Ehlers-Danlos Support Group (UK). *Am J Med Genet* 1998; **77:** 31–37.
11. Wessels MW, Catsman-Berrevoets CE, Mancini GM, Breuning MH, Hoogeboom JJ, Stroink H, et al. Three new families with arterial tortuosity syndrome. *Am J Med Genet A* 2004; **131A:** 134–143.
12. D'Aloia A, Vizzardi E, Zanini G, Antonioli E, Faggiano P, Dei Cas L. Young woman affected by a rare form of familial connective tissue disorder associated with multiple arterial pulmonary stenosis and severe pulmonary hypertension. *Circ J* 2008; **72:** 164–167.
13. Ades LC, Sullivan K, Biggin A, Haan EA, Brett M, Holman KJ, et al. FBN1, TGFBR1, and the Marfan-craniosynostosis/mental retardation disorders revisited. *Am J Med Genet A* 2006; **140:** 1047–1058.
14. Kosaki K, Takahashi D, Udaka T, Kosaki R, Matsumoto M, Ibe S, et al. Correspondence: Molecular pathology of Shprintzen-Goldberg syndrome. *Am J Med Genet A* 2006; **140:** 104–108.
15. Akutsu K, Morisaki H, Takeshita S, Sakamoto S, Tamori Y,

Yoshimuta T, et al. Phenotypic heterogeneity of Marfan-like connective tissue disorders associated with mutations of the transforming growth factor-β receptor gene. *Circ J* 2007; **71:** 1305–1309.
16. Pannu H, Fadulu VT, Chang J, Lafont A, Hasham SN, Sparks E, et al. Mutations in transforming growth factor-beta receptor type II cause familial thoracic aortic aneurysms and dissections. *Circulation* 2005; **112:** 513–520.
17. Pannu H, Tran-Fadulu V, Papke CL, Scherer S, Liu Y, Presley C, et al. MYH11 mutations result in a distinct vascular pathology driven by insulin-like growth factor 1 and angiotensin II. *Hum Mol Genet* 2007; **16:** 3453–3462.
18. Hagan PG, Nienaber CA, Isselbacher EM, Bruckman D, Karavite DJ, Russman PL, et al. The International Registry of Acute Aortic Dissection (IRAD): New insights into an old disease. *JAMA* 2000; **283:** 897–903.
19. Kakafika AI, Mikhailidis DP. Smoking and aortic diseases. *Circ J* 2007; **71:** 1173–1180.
20. Barbetseas J, Alexopoulos N, Brili S, Aggeli C, Chrysohoou C, Frogoudaki A, et al. Atherosclerosis of the aorta in patients with acute thoracic aortic dissection. *Circ J* 2008; **72:** 1773–1776.
21. Sampol G, Romero O, Salas A, Tovar JL, Lloberes P, Sagales T, et al. Obstructive sleep apnea and thoracic aorta dissection. *Am J Respir Crit Care Med* 2003; **168:** 1528–1531.
22. Vogt BA, Birk PE, Panzarino V, Hite SH, Kashtan CE. Aortic dissection in young patients with chronic hypertension. *Am J Kidney Dis* 1999; **33:** 374–378.
23. Kohler M, Blair E, Risby P, Nickol AH, Wordsworth P, Forfar C, et al. The prevalence of obstructive sleep apnoea and its association with aortic dilatation in Marfan's syndrome. *Thorax* 2009; **64:** 162–166.
24. Elkayam U, Ostrzega E, Shotan A, Mehra A. Cardiovascular problems in pregnant women with the Marfan syndrome. *Ann Intern Med* 1995; **123:** 117–122.
25. Hussain KM, Chandna H, Santhanam V, Sehgal S, Jain A, Denes P. Aortic dissection in a young corticosteroid-treated patient with systemic lupus erythematosus: A case report. *Angiology* 1998; **49:** 649–652.
26. Suzuki A, Amano J, Tanaka H, Sakamoto T, Sunamori M. Surgical consideration of aortitis involving the aortic root. *Circulation* 1989; **80:** I222– I232.
27. Shiono M, Hata M, Sezai A, Iida M, Negishi N, Sezai Y. Reoperation for ascending aortic aneurysm, coronary ostial aneurysm and patent Cabrol trick after bentall operation for aortitis syndrome. *Circ J* 2005; **69:** 861–864.