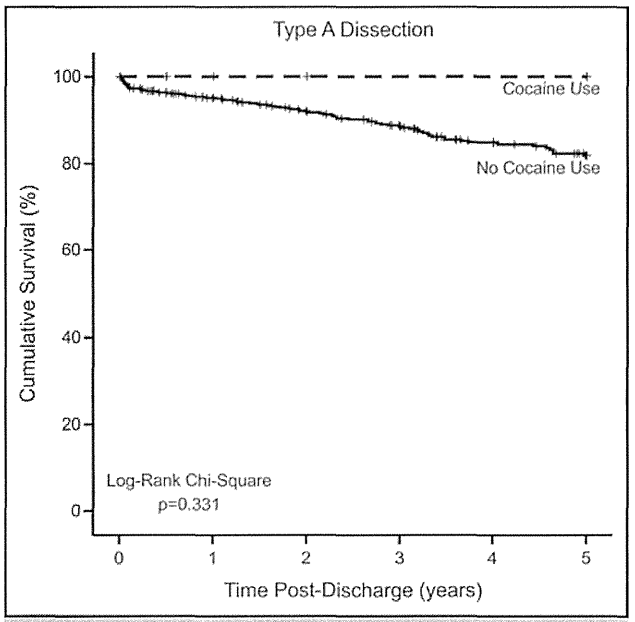

Figure 3 Postdischarge survival: type A.

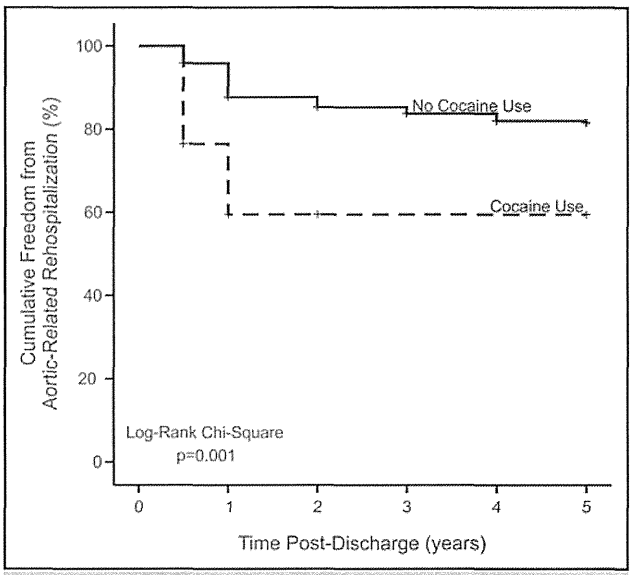

Figure 5 Freedom from aortic-related rehospitalization.

cohorts, cocaine users were more likely to have smaller ascending aortic diameters. Furthermore, our finding on all cause long-term mortality contrasted the observation by Singh et al.[2] It is possible that this is due to selection bias with recalcitrant cocaine-users having poor outcomes and not being found during attempts at follow-up.

Patients using cocaine were more likely to present to a US IRAD center than to a European site. This could be due to an increased prevalence of cocaine use within the United States compared with European countries.[10] In addition, registry hospitals in the United States cover more urban areas per capita compared with IRAD European centers (**Figure 2**). Cocaine is used more frequently in urban areas.[1]

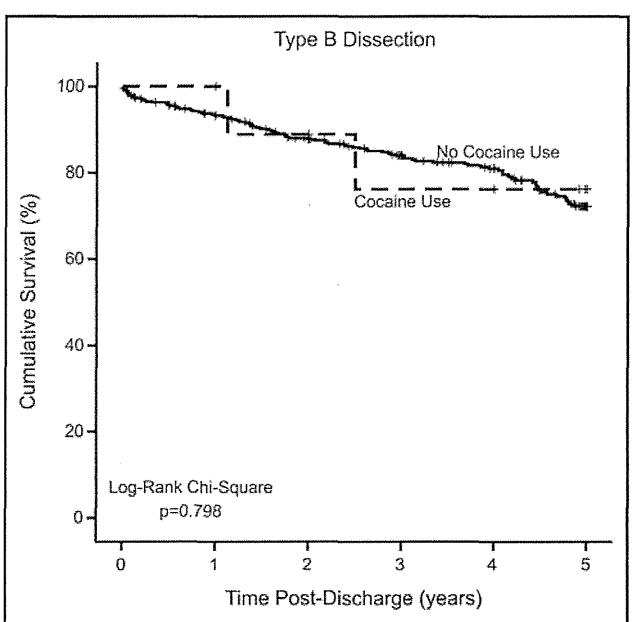

Figure 4 Postdischarge survival: type B.

The combination of cocaine and tobacco use is thought to have a serious physiologic effect on the aorta, creating a harmful synergistic effect for the user. Such effects may contribute to the early development of a dissection in a young patient. Cocaine use inhibits the reuptake of catecholamine neurotransmitters and increases neuron receptor sensitivity to norepinephrine.[3,6,15] This results in a dramatic increase in heart rate and blood pressure, inducing a hypertensive state for the user.[3,6,15] In addition, this results in a larger myocardial oxygen demand while simultaneously decreasing oxygen supply because of coronary vasoconstriction.[6,15] Cocaine use also can lead to the premature development of aortic atherosclerosis.[3] Tobacco enhances cocaine's physiologic effects by acting as a vasoconstrictor.[2] In addition, its use also promotes the development of hypertension.[3] These facets collectively place increased stress on the aorta, decreasing its elasticity and leading to increased susceptibility of a dissection at an age when there would normally be a lower risk. These findings reveal that cocaine and tobacco use, along with hypertension, collectively increase an individual's risk of developing an aortic dissection.

Study Limitations

Although the IRAD database provides the largest report of cocaine-related aortic dissections to date, there were limitations to our study. The IRAD definition of cocaine use and location of IRAD centers might not accurately comprise the cocaine-using population. Cocaine users who have not experienced detriment to their health and social functioning were left out of the cocaine user group. The IRAD

abstractors relied on patients to self-report cocaine use. No distinction was made between cocaine and crack cocaine. Furthermore, details of acute or chronic cocaine exposure relative to an acute aortic dissection were not recorded. The IRAD represents patients treated at centers specialized in aortic diseases. As a result, these findings may not be applicable to the general population. The IRAD is an observational, nonrandomized study. Furthermore, the IRAD does not have a standard protocol for the diagnosis, management, or imaging of dissections. Treatments reflect individual approaches. Another limitation is the lower rate of follow-up among cocaine users after the aortic dissection. This may have biased our long-term outcome results.

CONCLUSIONS

Cocaine-related acute aortic dissection is rare, comprising 1.8% of patients enrolled in the IRAD. This study provides a tool for clinicians to properly identify and treat an aortic dissection in this specific patient cohort. When a clinician encounters a young survivor of dissection with elevated blood pressure, it is critical to investigate his/her history of cocaine use. Identifying cocaine users and providing addiction counseling may help prevent re-dissections and aortic ruptures in these patients.

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Review Article

Pathophysiology and Japanese clinical characteristics in Marfan syndrome

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Abstract Marfan syndrome is an autosomal dominant heritable disorder of the connective tissue, caused by mutations of the gene *FBN1*, which encodes fibrillin-1, a major component of the microfibrils of the extracellular matrix. Fibrillin-1 interacts with transforming growth factor-β (TGF-β), and dysregulated TGF-β signaling plays a major role in the development of connective tissue disease and familial aortic aneurysm and dissection, including Marfan syndrome. Losartan, an angiotensin II blocker, has the potential to reduce TGF-β signaling and is expected to be an additional therapeutic option. Clinical diagnosis is made using the Ghent nosology, which requires comprehensive patient assessment and has been proven to work well, but evaluation of some of the diagnostic criteria by a single physician is difficult and time-consuming. A Marfan clinic was established at the University of Tokyo Hospital in 2005, together with cardiologists, cardiac surgeons, pediatricians, orthopedists, and ophthalmologists in one place, for the purpose of speedy and accurate evaluation and diagnosis of Marfan syndrome. In this review, we discuss the recent progress in diagnosis and treatment of Marfan syndrome, and the characteristics of Japanese patients with Marfan syndrome.

Key words connective tissue disease, fibrillin-1, losartan, transforming growth factor-β.

Marfan syndrome (MFS) is an autosomal dominant heritable disorder that affects the body's connective tissue, with prominent involvement of the cardiovascular, ocular, and skeletal systems. The estimated prevalence of MFS ranges from 1 in 5000 to 10 000 individuals, and this number does not appear to vary with ethnicity or geography.[1] Mutations in the fibrillin-1 gene (*FBN1*) that encodes the cysteine-rich, extracellular matrix glycoprotein, cause MFS, and approximately 75% of MFS cases are inherited and 25% involve *de novo* mutations for *FBN1*. Fibrillin-1 microfibrils serve as the regulator of transforming growth factor-β (TGF-β) signaling, and the understanding of dysregulated TGF-β signaling in MFS and treatment have been widely explored over the last few years.[2]

Clinical criteria for diagnosing MFS (Ghent criteria) were developed and revised on the basis of data from European and US patients,[3,4] but the validity of the Ghent nosology for the Japanese population has not been fully elucidated. In this review, we discuss recent progress in the diagnosis and treatment of Marfan syndrome, and the characteristics of Japanese MFS patients, who visited the Marfan clinic at the University of Tokyo Hospital.

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Pathophysiology in Marfan syndrome; involvement of fibrillin-1 and TGF-β signaling

In 1896, Antoine Bernard-Jean Marfan first described a little girl with long limbs, digital and joint contractures and kyphoscoliosis.[5] Since then, different features such as mitral valve disease, dislocation of the ocular lens, ruptured aortic aneurysm, aortic root dilatation and dissection, and autosomal dominant inheritance, have been added to the description of this disease we now call MFS. In 1991, mutations of *FBN1* were reported to be causative for MFS.[6] Fibrillin-1 is a major component of the microfibrils of the extracellular matrix, and thus MFS has traditionally been considered to result from structural weakness of connective tissue, explaining the progressive dilatation of the aorta. Certainly, affected vascular disease in MFS patients is characterized by elastic matrix abnormalities in the medial layer of the aortic wall, including fragmentation and disorganization of elastic fibers, a generalized loss of elastin content, and the accumulation of amorphous matrix components.[7] This hypothesis, however, cannot explain some phenotypic features, such as the disproportionate growth of the long bones or myxoid changes in the valves. Since mutations in TGF-β receptor 2 (*TGFBR2*) on chromosome 3p24.1 were reported to cause classic MFS type 2,[8] with prominent aortic/arterial phenotypes but without ectopia lentis,[9] the traditional idea of the pathogenesis of MFS has dramatically changed. Now, a dysregulated relationship between fibrillin-1 and TGF-β signaling is considered a major cause of MFS (Fig. 1).

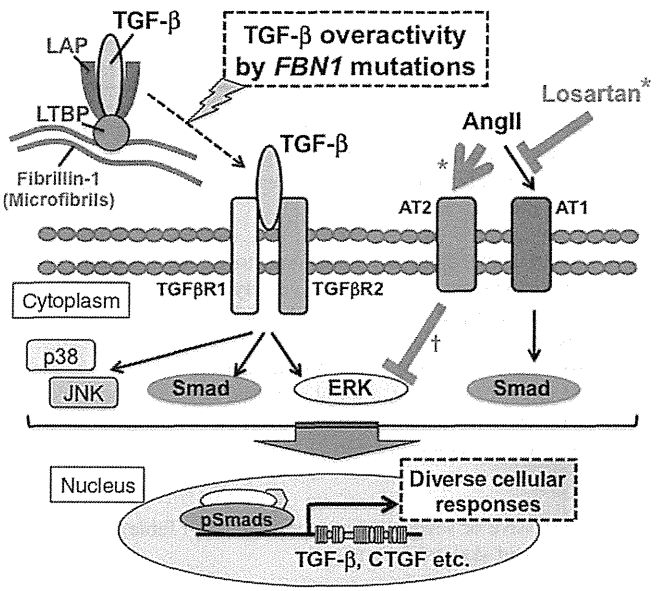

Fig. 1 Involvement of altered fibrillin-1 and transforming growth factor (TGF)-β signaling in the pathogenesis of Marfan syndrome (MFS). A TGF-β large latent complex, consisting of TGF-β, latency-associated peptide (LAP) and latent TGF-β-binding protein (LTBP), is anchored to the extracellular matrix that includes fibrillin-1. Mutated fibrillin-1 in MFS patients binds poorly to TGF-β, and this defective binding leads to increased TGF-β activity, which plays a critical role in the pathogenesis of MFS. Diverse intracellular signaling pathways are activated, including Smad and mitogen-activated protein kinase (MAPK) pathways, p42/44 (EAK), JNK and p38, which interact with angiotensin II signaling. Selective angiotensin II receptor 1 (AT1) blocker (e.g. losartan) can potentially inhibit TGF-β-mediated EAK activation, by continued signaling through AT2 (†),[10] and has favorable effects in MFS. CTGF, connective tissue growth factor.

The TGF cytokines are secreted as large latent complexes and anchored to the extracellular matrix that includes fibrillin-1. Degradation of microfibrils by inflammatory proteolytic enzymes (e.g. elastase) and certain physiological stimuli releases fragments of fibrillin-1, which contribute to local TGF-β activation.[11] In most MFS patients and animal models, deficient or abnormal fibrillin-1 leads to failed sequestration of TGF-β and causes overactivity of the TGF-β signaling cascades, and thus TGF-β-neutralizing antibody affords relative but significant protection against dilatation of aortic aneurysm and impaired pulmonary alveolar septation in a mouse model of MFS.[12] TGF-β plays a pivotal role in diverse cellular processes, and the canonical SMAD pathway also plays a central role in the pathogenesis of MFS. Until recently, mutations in *TGFB2*,[13,14] *TGFBR1*,[15] *TGFBR2*,[15] and *SMAD3*[16] were reported to be associated with diseases that resemble MFS, such as Loeys–Dietz syndrome and aneurysm–osteoarthritis syndrome. Phenotypes in patients with mutations of *FBN1*, *TGFBR1*, *TGFBR2*, *SMAD3* or *TGFB2*, are summarized in Table 1.

Mitogen-activated protein kinase p42/44 (EAK) is also downstream of TGF-β signaling, and is activated in MFS aorta. Recently, a selective angiotensin II type I receptor (AT1) blocker, losartan, has been shown to inhibit TGF-β-mediated activation of EAK, by continued signaling through AT2.[10,17] Efficacy of losartan in prevention of aortic dilatation is of current interest, and this point is discussed later in this review.

Ghent nosology and revised Ghent nosology

The diagnosis of Marfan syndrome can be made according to the criteria of the Ghent nosology, which was established in 1996 and requires evaluation of the family history, *FBN1* mutations and six organ systems, including the skeletal, ocular, cardiovascular, and pulmonary systems, and the skin and dura (Fig. 2; Table 2).[3] The Ghent criteria consist of major and minor criteria, and the major criteria set in four systems (skeletal, cardiovascular and ocular systems and dura) are considered to be clinical manifestations that are specific in patients with MFS and rare in people who do not have it. In the absence of a family history of MFS, affected patients must meet major criteria in two systems, with involvement of the third system. In patients with a family history, only one major criterion needs to be met, along with involvement of a second system. This nosology enables physicians to make a comprehensive assessment of the patient and has been proven to work well, but the diagnosis requires the evaluation of multiple systems, and thus some of the diagnostic criteria have not been sufficiently validated, and are not applicable in children. A patient must visit orthopedists, ophthalmologists, cardiologists or pediatricians, and undergo several expensive examinations.

Given that there has been considerable research on the underlying pathophysiology of MFS and related connective tissue disorders, the diagnostic criteria were revised in 2010 (revised Ghent nosology), which place more weight on aortic root aneurysm/dissection, ectopia lentis and the presence of causative *FBN1* mutations (Table 3).[4] The other most selective systemic features in the original Ghent nosology were included in the systemic score. Higher points are assigned to more specific features, such as the combination of wrist and thumb sign, pectus carinatum, hindfoot deformity, pneumothorax, dural ectasia and acetabular protrusion. A systemic score of ≥7 points is used as a cut-off for systemic involvement. In addition, aortic root dilatation is corrected for age and body size and interpreted as a Z-score, which is applicable for children. Further, the revised nosology also requires the exclusion of other disorders that mimic MFS, such as Shprintzen–Goldberg syndrome, congenital contractural arachnodactyly, Loeys–Dietz syndrome, and the vascular form of Ehlers–Danlos syndrome, each of which has discriminating clinical features, some causative gene mutations and management guidelines. Incomplete forms of MFS might be classified into familial ectopia lentis; mitral valve prolapse (MVP) syndrome; and MVP, aortic dilatation, skin, and skeletal (MASS) phenotype.

Finally, the revised Ghent nosology helps to allay concerns regarding delayed or ambiguous diagnosis by providing context-specific recommendations for patient counseling and follow up. Special consideration is given to children who are clinically suspected, but who do not fulfill the diagnostic criteria. For

Table 1 Differential diagnosis for Marfan-like connective tissue diseases

Differential diagnosis	Gene	Discriminating features
Congenital contractural arachnodactyly	*FBN2*	Contractures, crumpled ears
Ehlers–Danlos syndrome (vascular type)	*COL3A1*	Translucent skin, middle sized artery aneurysm, dystrophic scars, facial characteristics, organ rupture (uterus in pregnancy, intestines)
Loeys–Dietz syndrome	*TGFBR1/2*	Bifid uvula/cleft palate, hypertelorism, arterial tortuosity and aneurysm (early dissection): Triad
	TGFB2	
	SMAD3	Lack of ectopia lentis, clubfoot, craniosynostosis, cervical spine instability, translucent skin, thin and velvety skin, easy bruising, osteoarthritis, bicuspid aortic valve, blue sclerae
Shprintzen–Goldberg syndrome	*FBN1* and other	Craniosynostosis, mental retardation
		Lack of progressive or severe aortic root dilatation
Arterial tortuosity syndrome	*SLC2A10*	Generalized arterial tortuosity, arterial stenosis, facial dysmorphism, autosomal recessive inheritance
Ectopia lentis syndrome	*FBN1*	Lack of aortic root dilatation (Table 2)
	LTBP2	
	ADAMTSL4	
MASS phenotype		Lack of progressive or severe aortic root dilatation (Table 2)
FTAA		Lack of Marfanoid skeletal features
FTAA with stroke, Moyamoya disease, coronary artery disease	*ACTA2*	
FTAA with patent ductus arteriosus	*MYH11*	
FTAA with bicuspid aortic valve	*NOTCH1*	Affected without aortic valve stenosis
	KCNJ2	
Homocystinuria	*CBS*	Thrombosis, mental retardation
Multiple endocrine neoplasia, type 2b		Multiple mucosal neuromas in early life

FTAA, familial thoracic aneurysm syndrome.

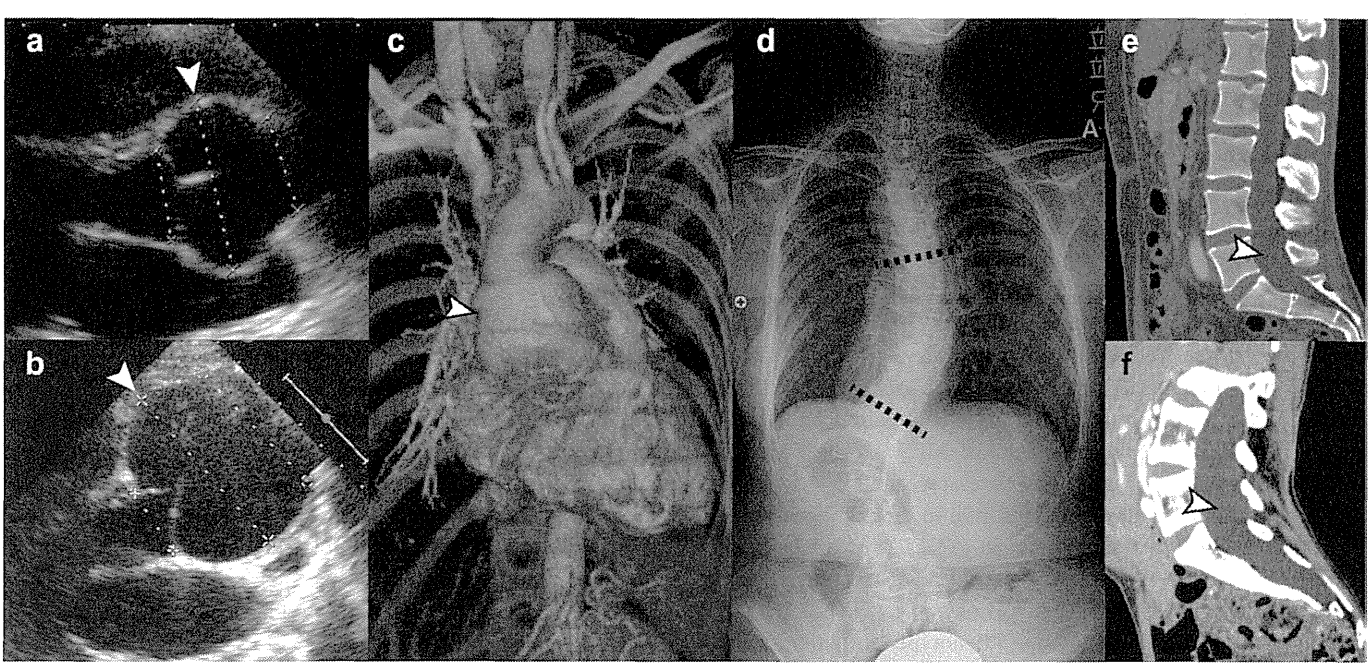

Fig. 2 Clinical features of Marfan syndrome. (a–c) Aortic root dilatation at the sinuses of Valsalva in (a) a 14-year-old child (41 mm, Z score = 5.9; echocardiography), and (b,c) a 30-year-old woman (68 mm, Z score = 15.0; b, echocardiography; c, computed tomography [CT] angiography). Arrowhead, dilated aortic root. (d) Scoliosis with a Cobb's angle >20° (two dotted lines), in a 36-year-old woman with lumbago. (e,f) Dural ectasia with an elevated dural sac ratio (dural sac diameter/vertebral body diameter)[18] in the lumbosacral spine (L1–S1) in (e) a 32-year-old man (CT) and (f) a 13-year-old child (CT). Arrowhead, dilated dural sac.

Table 2 Ghent nosology for Marfan syndrome[3]

System	Major criteria	Criterion for involvement
Skeletal	Requires four of the eight manifestations listed below	Requires two of the eight manifestations in the left column or one manifestation plus two minor criteria
	Pectus carinatum	
	Pectus excavatum requiring surgery	
	Reduced upper to lower segment ratio <0.86 or arm span/height ratio >1.05	Pectus excavatum of moderate severity
		Joint hypermobility (Beignton score ≥4)
	Wrist and thumb signs	Highly arched palate with crowding of teeth
	Scoliosis >20° or spondylolisthesis	Facial appearance (dolichocephaly, malar hypoplasia, enophthalmos, retrognathia, down-slanting palpebral fissures)
	Reduced extension at the elbows (<170°)	
	Medial displacement of the medial malleolus causing pes planus	
	Protrusio acetabuli of any degree	
Ocular	Ectopia lentis	Requires two of the following three minor criteria
		Abnormally flat cornea (<41.5 diopters)
		Increased axial length of the ocular globe (>23.5 mm)
		Hypoplastic iris or hypoplastic ciliary muscle causing decreased miosis
Cardiovascular	Dilatation of the ascending aorta with or without aortic regurgitation and involving at least the sinuses of Valsalva	Requires the presence of at least one major criterion or one minor criterion
	Dissection of the ascending aorta	
		Mitral valve prolapse with or without mitral valve regurgitation
		Dilatation of the main pulmonary artery in the absence of valvular or peripheral pulmonic stenosis or any other obvious cause below the age of 40 years
		Calcification of the mitral annulus below the age of 40 years
		Dilatation or dissection of the descending thoracic or abdominal aorta below the age of 50 years
Pulmonary	None	Requires at least one minor criterion listed below
		Spontaneous pneumothorax
		Apical blebs
Skin and integument	None	Striae atrophicae (stretch marks) not associated with marked weight changes, pregnancy or repetitive stress
		Recurrent or incisional herniae
Dura mater	Lumbosacral dural ectasia	None
Family history/ genetics	Having a parent, child or sibling who meets these diagnostic criteria independently	
	Presence of a mutation in *FBN1* known to cause the Marfan syndrome	None
	Presence of an *FBN1* haplotype around FBN1, inherited by descent, known to be associated with unequivocally diagnosed Marfan syndrome in the family	

Confirmation of the diagnosis requires the presence of at least two major criteria in two different organ systems and involvement of a third organ system. Family history/genetics is counted as an organ system. *FBN1*, fibrillin-1.

example, in sporadic cases in children, if insufficient systemic features (<7) and/or borderline aortic root measurements ($Z < 3$) are present without *FBN1* mutation, they should be carefully followed up as "non-specific connective tissue disorder" until serial echocardiography shows aortic root dilation ($Z \geq 3$). If an *FBN1* mutation is identified in sporadic or familial cases but aortic root is not dilated ($Z < 3$), they must be followed up as "potential MFS".[4]

FBN1 mutations and related ethics issues

FBN1 spans a 230 kb genomic region with 65 exons on chromosome 15q21.1. Fibrillin-1 contains seven TGF-β binding protein-like (TB) domains and 47 epidermal growth factor (EGF)-like domains characterized by six conserved cysteine residues that form three intramodule disulfide bonds. Of the 47 EGF domains, 43 contain a consensus sequence for calcium binding (cb-EGF),

Table 3 Revised Ghent nosology for Marfan syndrome and related conditions[4]

In the absence of family history:
(1) Aortic aneurysm (Z ≥ 2) AND ectopia lentis[†]
(2) Aortic aneurysm (Z ≥ 2) AND *FBN1* mutation
(3) Aortic aneurysm (Z ≥ 2) AND systemic score (≥7 pts)[†]
(4) Ectopia lentis AND *FBN1* mutation with known aortic aneurysm
Ectopia lentis syndrome (ELS): ectopia lentis with or without systemic score AND with an *FBN1* mutation not known with aortic aneurysm or no *FBN1* mutation
MASS: aortic aneurysm (Z < 2) AND systemic score (5 ≥ with at least one skeletal feature) without ectopia lentis
MVPS: mitral valve prolapse AND aortic aneurysm (Z < 2) AND systemic score (<5) without ectopia lentis
In the presence of family history:
(5) Ectopia lentis AND family history of MFS (as defined above)
(6) Systemic score (≥7 pts) AND family history of MFS (as defined above)
(7) Aortic aneurysm (Z ≥ 2 above 20 years old, ≥ 3 below 20 years) AND family history of MFS (as defined above)
Scoring of systemic features:
Maximum total: 20 points; score ≥7 indicates systemic involvement
Wrist AND thumb sign – 3 (wrist OR thumb sign – 1)
Pectus carinatum deformity – 2 (pectus excavatum or chest asymmetry – 1)
Hindfoot deformity – 2 (plain pes planus – 1)
Pneumothorax – 2
Dural ectasia – 2
Protrusio acetabuli – 2
Reduced US/LS AND increased arm/height AND no severe scoliosis – 1
Scoliosis or thoracolumbar kyphosis – 1
Reduced elbow extension – 1
Facial features (3/5) – 1 (dolichocephaly, enophthalmos, down-slanting palpebral fissures, malar hypoplasia, retrognathia)
Skin striae – 1
Myopia > 3 diopters – 1
Mitral valve prolapse (all types) – 1

[†]Caveat: without discriminating features of Shprintzen–Goldberg syndrome, Loeys–Dietz syndrome and vascular form of Ehlers–Danlos syndrome AND after *TGFBR1/2*, collagen biochemistry, *COL3A1* testing if indicated. Other conditions/genes will emerge with time. *FBN1*, fibrillin-1; MFS, Marfan syndrome; MASS, myopia, mitral valve prolapse, borderline (Z < 2) aortic root dilatation, striae, skeletal findings phenotype; MVPS, mitral valve prolapse syndrome; US/LS, upper segment/lower segment ratio.

which plays a crucial role in microfibril stability and assembly.[19] More than 1000 reported *FBN1* mutations are spread throughout the gene, and are mostly unique in each affected family. According to the data for 1013 probands with known *FBN1* mutations, the majority of mutations are missense mutations (56%), in which a base change alters the codon so as to produce a different amino acid, usually in the EGF-like domains of protein and affecting cysteine residues or amino acids implicated in calcium binding. Other mutations are frameshift (17%), nonsense (14%) and splicing (11%) mutations.[20,21] Although there is no robust correlation between the *FBN1* genotype and the nature and severity of the clinical phenotype, mutations in exons 24–32 tend to predict a severe phenotype at all ages, including neonatal MFS (the most severe form). A higher probability of ectopia lentis is found in patients with a missense mutation substituting or producing a cysteine,[21] although these underlying mechanisms remain to be elucidated.

In the revised Ghent nosology, *FBN1* genetic testing has greater weight in the diagnostic assessment, although it is not mandatory. In such a setting, we developed a microarray-based high-throughput resequencing system for the efficient and accurate diagnosis of MFS.[22] In an analysis of 53 probands, 35 kinds of possible *FBN1* mutations were found in 36 probands, including 23 new mutations, which were all verified on direct sequencing with 100% accuracy. There were 18 missense, nine nonsense and eight possible splicing mutations. Deletion or insertion mutations make it difficult, however, for the probes to hybridize those alleles, therefore supplemental Sanger direct sequence analysis for probands in whom mutations were not detected in the microarray-based system, was performed, identifying five such deletion mutations. Ultimately, *FBN1* mutations were detected in 71% of patients who fulfilled the original Ghent criteria. We now combine conventional direct sequencing and microarray-based resequencing on a case-by-case basis. In the near future, the application of next-generation sequencing (NGS) will enable better understanding of connective tissue disease and familial aortic aneurysm and dissection, including MFS. Single-nucleotide polymorphisms, however, are the most frequent sequence variation encountered in a genome, which makes it difficult to identify a causative *FBN1* mutation in the absence of family history. Although the revised nosology provides useful criteria for causative *FBN1* mutations, emphasizing the significance of altered conserved residues of cysteine and EGF consensus sequence, the relationship between genotype–phenotype correlation and altered TGF-β signaling needs to be better elucidated.

Genetic test, however, is not necessarily required, and it does not have 100% sensitivity and 100% specificity. Among Marfan patients who have a firm clinical diagnosis, it is possible to detect *FBN1* mutations in between 60% and 90%.[22] Even if available,

caution is needed in handling genetic information, because it might cause a social disadvantage to the examinees and their relatives. Physicians and medical staff involved in the genetic test should not order it only to satisfy their curiosity, and are requested to pursue appropriate medical practices, based on the global strategy for the diagnosis and management, and general principles of the ethics issues.[23] Genetic testing may be of benefit in sporadic cases in which MFS is clinically suspected, but in which sufficient clinical features to fulfill the diagnostic criteria are lacking. Genetic testing may not be immediately necessary for children of an MFS patient, or those with isolated ectopia lentis or clinical features sufficient for diagnosis, because clinical features may emerge gradually as they grow to adulthood, and they eventually need to be carefully followed up, even if they do not have any *FBN1* mutations.

New markers for Marfan syndrome

There is a strong clinical imperative to identify reliable molecular biomarkers and assessment methods to inform the diagnosis and management of MFS. Elevated plasma total TGF-β1 was reported in MFS patients, and was lowered by losartan or beta-blocker.[24] Accurate measurement of plasma TGF-β1, however, is complicated, partially because of *ex vivo* release of TGF-β1 from platelet stores upon platelet activation. In Japanese MFS patients at the Marfan clinic, circulating TGF-β1 was not elevated compared to healthy volunteers, with equivalent plasma platelet factor 4 (PF4), an indicator of platelet activation.[25] Recently, circulating fibrillin-1 fragments was reported as a potential biomarker for thoracic aortic aneurysm and acute aortic dissection.[26] Further studies are necessary to validate these biomarkers for clinical and commercial use.

Several markers of vascular function have been examined as potential predictors of cardiovascular events in MFS. Impaired aortic distensibility (stiffness) on magnetic resonance imaging, was an independent predictor of progressive aortic dilatation.[27] We measured flow-mediated dilation (FMD), an ultrasound-guided non-invasive measurement of endothelial function evaluated in the brachial artery, in 39 patients with MFS. Impairment of FMD was significantly correlated with diameter of ascending thoracic aorta.[28] FMD could be a useful non-invasive tool for optimal risk assessment and monitoring.

Prevention and therapy

The most life-threatening complication of MFS is thoracic aortic aneurysm, leading to aortic dissection and rupture. All patients with MFS, including suspected/ambiguous cases, should have an echocardiogram every 6–12 months. Surgical replacement of the aorta is recommended if the aortic diameter is ≥45 mm (less well defined in children) or shows rapid change (5 mm/year) or there are concerns regarding heart or valve function.[4] The typical localization of dilation is the aortic root, not the tubular portion of the ascending aorta, and recent advances in the surgical managements of MFS make it possible to replace the aortic root with preservation of the aortic valve, which eliminates the need for lifetime anti-coagulation therapy. Even after successful aortic root replacement, however, other aortic segments remain a source of late aortic aneurysm/dissection formation. According to the Japan Cardiovascular Surgery Database (JCVSD), the 30 day operative mortality rate in MFS patients was 4.4% (37/845), and renal insufficiency and respiratory disorder had great impact.[29] Stent-graft repair is not indicated, because stent deployment imposes high stresses and vascular injury on the aortic wall.

The current gold standard for prevention and treatment is beta-blocker in all MFS patients, including children.[2] Beta-blocker should be titrated to effect, aiming for a heart rate after submaximum exercise <100 beats/min in patients aged >5 years.[4] Recently, angiotensin II receptor blocker (ARB; e.g. losartan) have been shown to prevent and possibly reverse aortic root dilation in some animal models of MFS and small cohort studies.[12,30] Several large randomized clinical trials are currently under way, and one such trial, the multi-center randomized controlled COMPARE trial, found that losartan was associated with a significantly reduced rate of aortic enlargement after 3 years, compared to patients who did not receive the treatment.[31] The timing of ARB initiation and dose escalation, especially in children with MFS, remain to be fully elucidated, and other drugs that can potentially reduce TGF-β signaling are currently being studied, as an additional therapeutic option.

Prevention or cure of dental and periodontal disease, is also important for MFS patients with valve disease, who have a high risk of developing infective endocarditis. The dental problems are related to the development of the facial bones, and patients may have a high-arched palate with crowded teeth. In addition, fibrillin-1 is expressed in periodontal tissue, and it must play a pivotal role in supporting teeth and controlling peripheral blood flow. We found that MFS patients had more severe periodontitis and fewer remaining teeth, and thus careful intraoral observation and monitoring is advised in MFS patients.[32]

Characteristics of Ghent nosology-positive patients in Japan

Since we started the Marfan clinic at the University of Tokyo Hospital in 2005, 339 patients were satisfactorily evaluated using the original Ghent criteria, and 157 (46%) were diagnosed as having MFS. We previously reported the clinical features of 45 Japanese Ghent-positive patients in 2011,[22] and described the characteristics of Japanese MFS patients. The percentages of MFS patients who met the criteria for major skeletal, cardiovascular and ocular systems were 29%, 98% and 56%, respectively. Compared with the *FBN1* Universal Mutation Database, the data in which are derived mainly from Western patients (n = 1013),[21] involvement of the dura (83% vs 53%) and of pulmonary systems (30% vs 7% for pneumothorax) were more frequent in Japanese MFS patients. The frequencies of marfanoid habitus characterized by dolichostenomelia (long limbs; arm/height > 1.05: 20% vs 55%) and arachnodactyly (spider finger; positive wrist and thumb signs: 74% vs 78%) and reduced elbow extension (<170 degrees: 5% vs 15%), were lower than in Western MFS patients. The lower frequency of enlarged arm span/height ratio in the present Japanese MFS patients (1.018 ± 0.03), was consistent with a previous report by the National Cardiovascular Center (Japan),[33] indicating that the cut-off should be corrected for Asian

patients. Preliminary data from our larger study of Japanese MFS patients also support these findings that there are more pulmonary phenotypes and fewer skeletal phenotypes in Japanese MFS patients. Therefore, the original Ghent criteria may not be entirely applicable to Japanese patients, and further epidemiologic and genetic studies are needed to generate useful Japanese diagnostic criteria.

Comparison of the Ghent and revised Ghent nosologies

Verification and comparison of the revised and the original Ghent nosologies is important for clinical follow up of patients with MFS-related disorders. Aalberts *et al.* and Yang *et al.* compared the nosologies in Dutch and South Korean patients, respectively, and the agreement rates were approximately 95%.[34,35] A small percentage of patients were newly diagnosed with MFS according to the revised Ghent criteria, and similar numbers of the original Ghent-positive MFS patients were more precisely diagnosed as having Loeys-Dietz syndrome, MASS phenotype and familial mitral valve prolapse. The change in diagnosis did not lead to a difference in clinical follow up. In the revised criteria, dura ectasia and some minor manifestations (e.g. pulmonary phenotypes) defined by the original Ghent criteria, both of which Japanese MFS patients tend to present, can become influential factors. Preliminary data show that the diagnosis is the same in 94% (320/339) of the present Japanese patients on two criteria, and the cut-off for systemic score (≥7 points) seems appropriate also in Japanese MFS patients (D. Fujita, Y. Imai, unpubl. data 2014).

Conclusion

Recent advances in molecular and genetic analysis have led to greater understanding of the pathophysiology of MFS and related disorders. Interactions between fibrillin-1 and TGF-β signaling play a major role in the pathogenesis of MFS. Development of new treatments that modify dysregulated TGF-β signaling can be expected in the future, and several large clinical randomized control trials using such possible candidate ARB (e.g. losartan) are currently under way. In Japanese MFS patients, clinical features are somewhat different from Western MFS, but the revised Ghent criteria, which give weight to cardiovascular and ocular systems and *FBN1* mutations, might work favorably also in the Japanese population.

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