Chapter 5
Genetics of Marfan Syndrome, Related Disorders, and Bicuspid Aortic Valve

Takayuki Morisaki and Hiroko Morisaki

Abstract Recently, the genetic study of aortic diseases such as Marfan syndrome has been advanced, leading to not only identifying responsible genes but also providing better understanding of the pathophysiology and possible new therapeutic targets. Genes identified for aortic diseases include *FBN1*, *TGFBR1*, *TGFBR2*, *SMAD3*, *TGFB2*, *TGFB3*, *SKI*, *EFEMP2*, *COL3A1*, *FLNA*, *ACTA2*, *MYH11*, *MYLK*, *SLC2A10*, and *NOTCH1* as well as others. Their dysfunction is mainly connected with altered function of transforming growth factor-β (TGF-β) signaling pathways, as well as that of the extracellular matrix and smooth muscle contractile apparatus, resulting in progression of structural damage to aorta and great vessels including aortic aneurysms and dissections. Furthermore, it has been shown that the TGF-β signaling pathway plays a key role in the pathogenesis of Marfan syndrome and related disorders, which may be important for development of strategies for medical and surgical treatment of thoracic aortic aneurysms and dissections.

Keywords Aortic aneurysm • Aortic dissection • Valve diseases • Transforming growth factor-β (TGF-β) • Extracellular matrix • Smooth muscle

5.1 Introduction

Aortic diseases including aortic aneurysms and dissections account for 1–2 % of all deaths in Western countries [1]. There are two types of aortic aneurysms based on their location: thoracic aortic aneurysm (TAA) and abdominal aortic aneurysm (AAA). It was reported that the incidence of TAA and dissection (TAAD) is about 10 per 100,000 person-years [2]. In TAA, approximately 20 % of patients have a

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K. Niwa, H. Kaemmerer (eds.), *Aortopathy*, DOI 10.1007/978-4-431-56071-5_5

positive family history, while 10–20 % of patients with AAA also have such a positive history. However, most patients with AAA also have various risk factors for cardiovascular events, such as smoking, hyperlipidemia, hypertension, sex, and age [3]. Therefore, AAA is thought to be a multifactorial disease with several genes and loci identified to have a positive association with the disease.

In this chapter, we especially focus on Marfan syndrome, related disorders, and bicuspid aortic valve in TAAD [4]. It is thought that excessive matrix degradation is involved in the development of TAAD, though the exact pathological mechanisms are not yet fully understood. An imbalance between matrix metalloproteinases (MMPs) and their inhibitors is thought to induce medial degeneration and aneurysm development. In addition, some other conditions including hypertension can lead to thickening and fibrosis of the intimal layer, and degradation and apoptosis of smooth muscle cells, resulting in wall weakness and eventually development of aneurysms, dissections, and ruptures.

Over the past more than two decades after discovery of the *FBN1* gene as a causative factor for Marfan syndrome (MFS), it has become clear that genetic factors are also at the basis of TAAD formation. Studies of the human syndromic form of TAAD including MFS and its counterparts in mice have provided a better understanding of the cause of the disease condition, including the finding that the transforming growth factor-β (TGF-β) signaling pathway plays a key role in the pathogenesis of TAAD. Since the genes for Marfan related to other syndromic aneurysmal conditions (Loeys-Dietz syndrome, arterial tortuosity syndrome, autosomal recessive cutis laxa, aortic osteoarthritis syndrome, others) have been identified, it is now considered that there is ample evidence showing that dysregulation of TGF-β signaling is the common pathogenic process in aortic diseases. In addition, recent findings have led to new therapeutic strategies for patients with Marfan and related diseases.

5.2 Marfan Syndrome (MFS)

5.2.1 MFS: Syndromic TAAD and TGF-β Signaling

MFS (OMIM #154700) is an autosomal dominant connective tissue disorder first described by Antoine Marfan [5] and with a prevalence of about 1 per 5000 individuals [6]. It was found to be caused by mutations in the *FBN1* gene encoding fibrillin-1, a large glycoprotein and component of extracellular matrix microfibrils. MFS is a systemic disorder affecting skeletal (increased height, disproportionately long limbs and digits, anterior chest deformity, joint laxity, vertebral column deformity, narrow highly arched palate with crowding of teeth), ocular (myopia, increased axial globe length, corneal flatness, ectopia lentis), and cardiovascular (dilatation of aorta, especially aortic root, aortic regurgitation, mitral valve prolapse, mitral regurgitation) systems. Other phenotypes of MFS are dural ectasia,

striae distensae, inguinal hernias, pneumothorax, and pulmonary emphysema, though cardiovascular phenotypes, especially TAA, are the most important causes of morbidity and mortality in MFS patients. In most cases, the primary dilatation occurs at the aortic root, especially at the level of the sinus of Valsalva.

For clinical diagnosis of MFS, first the Berlin [7], later the Ghent [8], and most recently the revised Ghent nosology [9] (Table 5.1) were proposed. The revised Ghent nosology is thought to facilitate accurate recognition of MFS and differential diagnosis from other related but distinct disorders, thereby improving patient management as well as counseling. Four possible sets of findings can lead to a diagnosis of MFS in a patient: aortic root dilatation (Z-score >2) and ectopia lentis, aortic root dilatation with an FBN1 mutation, aortic root dilatation with sufficient systemic findings (score of ≥7 on systemic scale), and ectopia lentis with an *FBN1* mutation that has been previously associated with aortic root dilatation. As compared with the previous nosology, the revised Ghent nosology adds more weight to genetic information, especially the relevant *FBN1* mutation.

Scoring of systemic features

Systemic features	Score
Wrist and thumb sign (wrist or thumb sign)	3 (1)
Pectus carinatum deformity – (pectus excavatum or chest asymmetry)	3 (1)
Hindfoot deformity (plain pes planus)	2 (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) (dolichocephaly, enophthalmos, downslanting palpebral fissures, malar hypoplasia, retrognathia)	1
Skin striae	1
Myopia >3 diopters	1
Mitral valve prolapse (all types)	1

Maximum total, 20 points; score ≥7 indicates systemic involvement

Criteria for causal FBN1 mutation

Mutation	Conditions
Segregation	Mutation previously shown to segregate in Marfan family
De novo	De novo (with proven paternity and absence of disease in parents) mutation (one of the five following categories)
Nonsense	Nonsense mutation
Deletion/ Insertion	In-frame and out-of-frame deletion/insertion
Splice site mutation	Splice site mutations affecting canonical splice sequence or shown to alter splicing on mRNA/cDNA level

(continued)

Mutation	Conditions
Missense	Missense affecting/creating cysteine residues
	Missense affecting conserved residues of the EGF consensus sequence ((D/N)X(D/N)(E/Q)Xm(D/N)Xn(Y/F) with m and n representing variable number of residues; D aspartic acid, N asparagine, E glutamic acid, Q glutamine, Y tyrosine, F phenylalanine)
	Other missense mutations: segregation in family if possible + absence in 400 ethnically matched control chromosomes, if no family history absence in 400 ethnically matched control chromosomes
Linkage	Linkage of haplotype for n ≥ 6 meioses to the FBN1 locus

Table 5.1 Revised Ghent nosology [9]

General criteria	
	Condition
In the absence of family history	(1) Ao (Z≥2) and EL = MFS
	(2) Ao (Z≥2) and *FBN1* = MFS
	(3) Ao (Z≥2) and Syst (≥7pts) = MFS[a]
	(4) EL and *FBN1* with known Ao = MFS
In the presence of family history	(5) EL and FH of MFS (as defined above) = MFS
	(6) Syst (≥7 pts) and FH of MFS (as defined above) = MFS*
	(7) Ao (Z≥2 above 20 years old, ≥3 below 20 years old) + FH of MFS (as defined above) = MFS*
Others	EL with or without Syst and with an *FBN1* not known with Ao or no *FBN1*= ELS
	Ao (Z< 2) and Syst (≥5) without EL = MASS
	MVP and Ao (Z<2) and Syst (<5) without EL = MVPS

Ao aortic diameter at the sinuses of Valsalva above indicated Z-score or aortic root dissection, *Z* Z-score, *EL* ectopia lentis, *Syst* systemic score (see below), *FBN1* fibrillin-1 mutation, *FBN1 with known Ao FBN1* mutation that has been identified in an individual with aortic aneurysm; *FBN1 not known with Ao FBN1* mutation that has not previously been associated with aortic root aneurysm/dissection; *ELS* ectopia lentis syndrome, *MASS* myopia, mitral valve prolapse, aortic root dilatation, striae, skeletal findings, aortic aneurysm syndrome, *MVPS* mitral valve prolapse syndrome, *MFS* Marfan syndrome
and after *TGFBR1/2*, collagen biochemistry, and *COL3A1* testing if indicated, other conditions/genes will emerge with time
[a]Caveat: without discriminating features of SGS, LDS, or vEDS

5.2.2 MFS: FBN1 and TGF-β Signaling Pathways (Fig. 5.1)

Fibrillin-1 regulates the TGF-β signaling pathway by interacting with latency-associated peptide (LAP), which is a protein derived from the N-terminal region of the TGF-β gene product and latent TGF-β-binding protein (LTBP) [10]. TGF-β interacts with LAP to form a complex termed small latent complex (SLC), which is bound by LTBP to form a larger complex called large latent complex (LLC) and then secreted to the extracellular matrix. Then, TGF-β remains in the extracellular

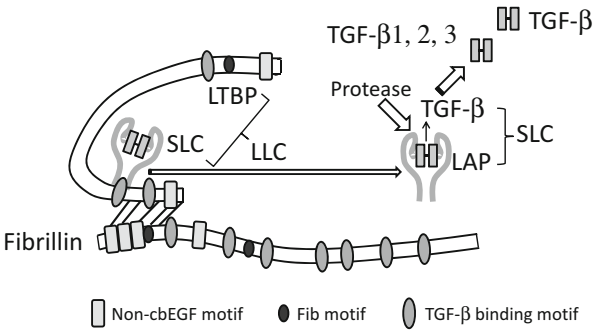

Fig. 5.1 FBN1 and TGF-β signaling pathways. Fibrillin-1 regulates the TGF-β signaling pathway by associating with LLC, consisting of LTBP and SLC. Active, free TGF-β molecules (TGF-β1, TGF-β2, TGF-β3) will be released by protease cleavage of inactive SLC molecules bound to LAP. *LLC* large latent complex, *SLC* small latent complex, *LAP* latency-associated peptide, *LTBP* latent TGF-β-binding protein

matrix in an inactivated complex with LTBP and LAP, and this inactive complex regulates mediation of TGF-β signaling. Since fibrillin-1 interacts with LTBP and LAP to regulate the active level of TGF-β, its dysfunction results in activation of TGF-β signaling [11]. Therefore, it was initially thought that upregulation of TGF-β signaling occurred in canonical (SMAD-dependent) pathways. However, recent findings have shown changes in noncanonical (SMAD-independent) TGF-β pathways involving mitogen-activated protein kinases (MAPK), including extracellular signal-regulated kinase (ERK)1/2, p38, and Jun N-terminal kinase (JNK). As a result, increased TGF-β signaling via both canonical and noncanonical pathways contributes to aortic lesion formation. As shown in the following sections, increased TGF-β signaling is also critical for pathogenic changes in other related genetic aortopathies.

5.2.3 FBN1 Mutations in MFS

In 1990, the genetic locus for MFS was mapped to chromosome 15 by linkage analysis [12]. Thereafter, the first fibrillin gene mutation was found in an MFS patient in 1991, and it was confirmed that mutations in the *FBN1* gene on chromosome 15 are responsible for MFS [13]. Since then, more than 1500 *FBN1* mutations have been identified in MFS patients. Several lines of evidence were also shown that many *FBN1* mutant alleles cause MFS phenotypes through a dominant-negative effect [14], though there is a considerable number of patients with mutations resulting in haploinsufficiency due to gene deletion, splicing mutations, or nonsense mutations causing nonsense-mediated mRNA decay (NMD) [15] (Fig. 5.2). Therefore, decreased protein synthesis as well as the dominant-negative effect by the mutant protein is thought to be a pathogenic mechanism for MFS

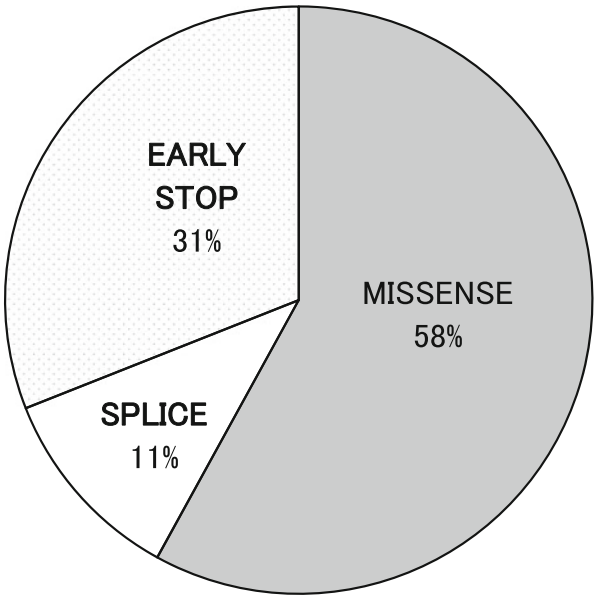

Fig. 5.2 NMD and haploinsufficiency. About 30 % of FBN1 mutations resulted in haploinsufficiency, while about 60 % of mutations resulted in qualitative changes of fibrillin-1 molecules and about 10 % of mutations resulted in splicing defect [4]

[16]. In addition, the function of fibrillin-1 was shown to be closely related to regulation of TGF-β signaling pathways, as noted in the previous section.

5.3 Loeys-Dietz Syndrome (LDS)

5.3.1 LDS and Related Disorders

Loeys-Dietz syndrome (LDS: OMIM #609192, #610168) is an autosomal dominant disorder with an aortic disease and widespread systemic involvement that shows both similarities and differences as compared with MFS [17]. LDS was originally described as a disorder with the triad of arterial tortuosity and aneurysms, hypertelorism, and bifid uvula or cleft palate, though a wide range of variable phenotypes associated with this disorder were recognized [18]. The syndrome was originally reported as that caused by mutations in the TGF-β receptor 1 and 2 genes (*TGFBR1, TGFBR2*), and diagnosis is confirmed by genotyping. Some patients have craniofacial involvement consisting of cleft palate, craniosynostosis, or hypertelorism, though those features do not appear in all. Bifid uvula may also be present in some, but not in all patients. Some reports have indicated that the natural history is characterized by aggressive arterial aneurysms, while some patients show milder aortic phenotypes.

Mutations in the *TGFBR2* gene in patients with the type 2 variant of MFS, MFS without ocular involvement, were also reported [19]. Most LDS patients develop

aortic root aneurysms, while a previous study showed that the mean age at death was 26 years old (range 0.5–47 years) and caused by such factors as thoracic aortic dissection, abdominal aortic dissection, and intracerebral bleeding [17]. Based on this, it is recognized that LDS patients tend to experience more aggressive vascular events. However, it is also known that LDS has a large variability of phenotypes including vascular lesions, since some affected patients show severe and rapid aortic events with typical craniofacial features, while others show mild aortic lesions without craniofacial or skeletal features.

5.3.2 *LDS and Related Disorders: TGF-β Signalopathies (Fig. 5.3)*

Most LDS patients demonstrate missense mutations in the serine/threonine kinase domain of the TGF-β receptors, suggesting loss of function in these molecules as the pathogenic mechanism. Also, there were several reports of dysregulation of TGF-β signaling. In histochemical studies, increased TGF-β and MAPK signaling in aortic lesions of affected patients as well as in *Tgfbr2* knockout mice was found [20].

Recently, three additional genes were identified as responsible for LDS-like syndromic aortopathy: *SMAD3*, *TGFB2*, and *TGFB3*. *SMAD3* mutations were initially described in relation to aneurysm-osteoarthritis syndrome [21], though some patients with an *SMAD3* mutation do not show such prominent osteoarthritis. *TGFB2* mutations have also been described in patients with mild systemic features of MFS or LDS [22, 23]. Very recently, *TGFB3* mutations were also reported in patients with syndromic types of thoracic aortic aneurysms similar to those seen in MFS and LDS [24], though one patient with a de novo *TGFB3* mutation showed MFS and LDS features with no evidence of vascular disease [25].

In most of these gene mutations, immunohistochemical staining reveals an increase of phosphorylated SMAD2 in aortic tissues, indicating that TGF-β signaling has been changed to increase the downstream molecules. Therefore, in addition to the receptors, intracellular signaling molecules as well as their ligands are now considered to be responsible for the common pathogenic changes toward MFS- or LDS-related phenotypic features. Nevertheless, it remains unknown how dysfunction or haploinsufficiency status of these molecules results in increased TGF-β signaling even if such a change causes loss of function. Although the precise mechanisms involved in these changes are uncertain, it is considered that negative feedback and noncanonical stimulus may lead to the increase in TGF-β signaling. Indeed, previous results showed that haploinsufficient *Tgfbr2* mice as well as cranial neural crest cell-specific *Tgfbr2*-deficient mice recapitulate human phenotypes, such as aortic dilatations or craniofacial deformities, along with increased noncanonical (phosphorylated extracellular signal-regulated kinase) TGF-β signaling pathways [20, 26].

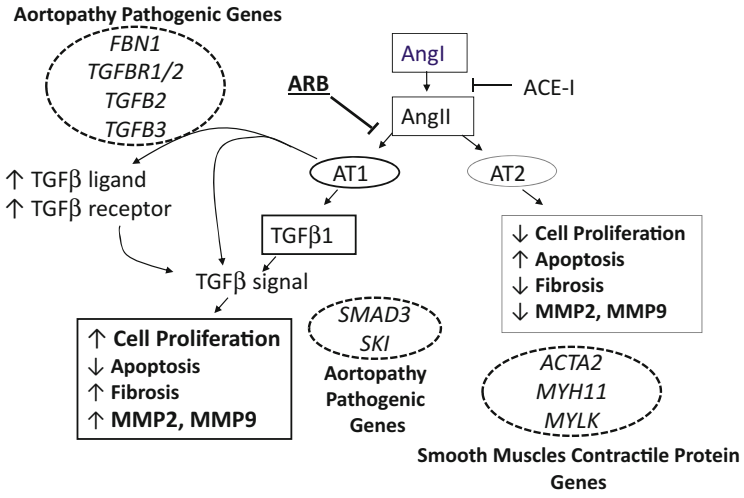

Fig. 5.3 TGF-β signalopathies. Several genes (*FBN1*, *TGFBR1*, *TGFBR2*, *TGFB2*, *TGFB3*, *SMAD3*, and *SKI*) associated with Marfan and related disorders are indeed closely connected with the TGF-β signaling pathways. Changes in the signal regulatory function promote pathological progress of vessels. Also, genes for smooth muscle contractile proteins (*ACTA2*, *MYH11*, *MYLK*) were depicted

Shprintzen-Goldberg syndrome (SGS: OMIM 182212), which results in craniosynostosis, skeletal changes (arachnodactyly, camptodactyly, scoliosis, joint hypermobility), and aortic aneurysms, shows considerable phenotypic overlap with MFS and LDS, and affected patients have been found to have mutations in the v-ski avian sarcoma viral oncogene homolog gene, SKI [27]. The oncogene *SKI* encodes a protein that plays important roles in the negative feedback loop of the TGF-β signaling pathway. Therefore, not only signaling molecules but also molecules affecting the TGF-β signaling pathway, as well as possibly others, may play additional key roles in MFS- or LDS-like phenotypes including aortopathy.

Autosomal recessive cutis laxa type 1B and arterial tortuosity syndrome, two other rare recessive connective tissue disorders, were shown to have autosomal recessive gene mutations in *EFEMP2* [28], which codes FBLN4 proteins. FBLN4 binds to LTBP1 and regulates the latency of TGF-β cytokine. Indeed, upregulated TGF-β signaling has been found in both fibroblasts of patients with *FBLN4* mutations and of the aortic walls in *Fbln-4* hypomorphic mice [28, 29].

5.4 Vascular Ehlers-Danlos Syndrome (vEDS)

5.4.1 vEDS and Gene

The vascular type of Ehlers-Danlos syndrome (vascular EDS, vEDS, type 4 EDS: OMIM #130050), caused by a defect of type III collagen (*COL3A1*) [30], is a disorder featuring cutaneous, skeletal, and vascular abnormalities, including vascular rupture and easy bruising, though affected individuals usually do not show skin hyperextensibility. Clinical features include rupture of the middle-sized arteries, the bowels, or the uterus. Therefore, general care and follow-up examinations are critical for management of vEDS patients upon the diagnosis, and determination of the *COL3A1* mutation is critical for affected individuals and their family members. There is no evidence indicating that *COL3A1* mutations change TGF-β pathway regulation, while it was reported that celiprolol can reduce the risk for vascular events in patients with vEDS [31].

5.4.2 EDS-Like Features and FLNA

It was also reported that EDS-like phenotypes are associated with *FLNA* mutations [32]. The *FLNA* gene encodes filamin A, an intermediate filament connecting the contractile apparatus of vascular smooth muscle cells to the cell membrane [33]. Also, filamin A has numerous interaction partners, including membrane receptors, signaling proteins, and transcription factors. *FLNA* mutations are well known to be associated with periventricular nodular heterotopias (OMIM #300049), though patients with those mutations may also exhibit aortic root dilatation, mitral valve disease, and joint hypermobility even without demonstrating periventricular nodular heterotopias.

5.5 TAAD with Bicuspid Aortic Valves

In 1–2 % of the population, a bicuspid aortic valve (BAV) is present, frequently associated with aortic valve stenosis, insufficiency, and dilatation of ascending aorta which may cause aortic dissection. The valve calcification was also often observed in BAV. Mutations in the signaling and transcription regulator NOTCH1 were reported to cause a spectrum of developmental aortic valve anomalies and severe valve calcification in nonsyndromic aortopathy pedigrees [34]. In 2008, two heterozygous missense variants of *NOTCH1* in six probands among 91 unrelated patients with congenital aortic valve stenosis, bicuspid aortic valve, coarctation of the aorta, and/or hypoplastic left heart syndrome were reported [35]. Since the NOTCH1 variant was also present in an unaffected parent, the report suggested that

these variants represent susceptibility alleles but are not the direct cause to perturb cardiac development. About the BAV, it was also reported that a genome-wide screen in 353 BAV individuals with or without associated cardiovascular malformation from 38 families obtained significant linkage peaks in 18q22, 5q15-21, and 13q33-qter [36] besides 9q34 and 17q24.

5.6 Other Types of Syndromic TAAD

In addition to syndromic TAAD described above, aortic aneurysms and/or dissection have also been found in other rare genetic syndromes. Sometimes, patients were not recognized to have distinct syndromic features but showed TAAD events as the main clinical features. In these cases, other signaling pathways besides the TGF-β pathway seem to be involved. For example, aortic aneurysms have been described to sporadically occur in association with mutations involving the rat sarcoma (RAS)-ERK signaling pathway, including Noonan syndrome pathogenic genes such as *PTPN11* [37] and the neurofibromatosis gene, *NF1* [38]. The fact that these genes play roles in TAAD indicates that the RAS and noncanonical TGF-β signaling pathways are involved in aortic aneurysms, as shown in MFS and LDS.

Also, the Notch signaling pathway, which is involved in Alagille syndrome [39] as well as in BAV as indicated above, and genes encoding collagens or enzymes involved in collagen maturation (*COL1A1*/*A2*, *COL4A1*, *COL4A3*/*4*/*5*, *PLOD3*) have been shown to be associated with aortic aneurysm development. In addition, aortic aneurysm has been implicated to have an association with autosomal dominant polycystic kidney disease (ADPKD) [40], and aortic aneurysms and/or dissections of the thoracic aorta occur more frequently in patients with ADPKD.

5.7 Nonsyndromic TAAD

In addition to the genes involved in syndromic types of TAAD, several other genes have been identified in nonsyndromic familial TAAD (FTAAD), while *ACTA2* mutations have been found to be responsible for approximately 15 % of patients with FTAAD [41]. The *ACTA2* gene encodes a smooth muscle-specific isoform of the α-actin protein and is involved in contractile function of vascular smooth muscles. Patients with an *ACTA2* mutation also show other vascular diseases, such as coronary artery disease and stroke, as well as several functional disorders of smooth muscles including vasculopathy, congenital mydriasis, patent ductus arteriosus, and thoracic aortic aneurysm. In addition, some specific *ACTA2* missense mutations (p.Arg179His, p.Arg258His, p.Arg258Cys) have been reported to be accompanied with a moyamoya-like cerebral arterial disorder [42, 43]. Livedo reticularis and iris flocculi were also found in patients with the p.Arg149Cys *ACTA2* missense mutation [33].

Mutations in *MYH11* were also found in patients with FTAAD and patent ductus arteriosus [44]. *MYH11* encodes a myosin heavy chain involved in the contractile function of vascular smooth muscles. In addition, *MYLK* mutations were found in a minority of FTAAD patients [45]. The *MYLK* gene encodes myosin light-chain kinase, which regulates the calcium-calmodulin-binding capacity of vascular smooth muscles by phosphorylating myosin.

Interestingly, upregulation of TGF-β signaling in the aortic walls of TAAD patients with *ACTA2* or *MYH11* mutations was reported [46]. This phenomenon suggests interactions between the smooth muscle contractile apparatus and cell surface integrins that regulate TGF-β activity. However, aortic events in patients with a dysfunction of smooth muscle contractile proteins seem somewhat different as compared to those in patients with a dysfunction of the TGF-β pathway, such as MFS or LDS, since FTAAD patients with an *ACTA*2 or *MYH11* mutation demonstrate enlargement of the entire ascending aorta, not restricted to the sinus of Valsalva. Therefore, there may be some differences regarding the pathophysiological processes involved in dysfunction of the smooth muscle contractile apparatus and those of the TGF-β pathway.

5.8 Therapy for TAAD

After identification of the genes causing TAAD as shown above, clinical management stratification is based on the phenotypes related to the underlying genetic mutation. For example, LDS patients with a *TGFBR1* or *TGFBR2* mutation have greater risk for aortic and arterial aneurysms than other TAAD patients and are thought to need more extensive imaging follow-up examinations to prevent vascular events. As for patients with *ACTA2* mutations, the risk of coronary artery disease or stroke should be evaluated to prevent those events. The current guidelines of the American College of Cardiology [47] recommend prophylactic surgery based on different scenarios according to the underlying gene since the different clinical courses are expected in patients with different gene mutations.

Medical management strategy for TAAD patients aims to control blood pressure and reduce aortic wall stress, generally by β-blocker treatment. In addition, calcium channel blockers and angiotensin-converting enzyme inhibitors or angiotensin receptor blockers may be considered. In a study of MFS and related disorders, the discovery of the key role of TGF-β signaling pathway in the pathogenesis of Marfan syndrome mice prompted investigation of the effects of anti-TGF-β treatment by a TGF-β-neutralizing antibody and losartan, an angiotensin II type I receptor antagonist, in a mouse model [48]. Results showed beneficial effects of losartan on aortic root dilatation and elastic fiber fragmentation by reduction of TGF-β signaling [44]. Since losartan is an established drug for treatment of hypertension, investigations of its usefulness in MFS patients have begun. An initial preliminary study showed improved effectiveness for reducing progressive aortic root dilatation by losartan added to β-blocker therapy as compared with β-blocker therapy alone

[49]. However, the largest clinical trial to date to assess the efficacy of losartan as compared with a β-blocker found no better outcome in MFS patients who received losartan therapy [50]. However, there are several lines of evidence showing involvement of the TGF-β pathway in MFS, LDS, and related disorders. Therefore, treatments aimed to block noncanonical components of the TGF-β signaling pathway are anticipated and proposed. In addition, changes in the VSMC contractile apparatus or MMP proteins are thought to have other important pathogenic roles in genetic aortic diseases. Based on these mechanisms, other alternative therapeutic targets will also have to be considered. Further delineation of the genes and pathways responsible for aortopathies with unknown mechanisms is also needed.

5.9 Conclusion

Since the discovery of *FBN1* and *COL3A1* mutations in patients with MFS or vEDS in the late twentieth century, several genes responsible for genetic aortic diseases have been identified, and understanding of the related pathophysiological mechanisms has progressed very much. However, progress for developing new strategies to cure these diseases remains rather slow, despite the rapid understanding of the physiological roles of genes involved in these aortic diseases. Therefore, additional studies are needed for development of novel therapeutic strategies for these aortic diseases.

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