

The fibrillinopathies: New insights with focus on the paradigm of opposing phenotypes for both *FBN1* and *FBN2*

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Abstract

Different pathogenic variants in the fibrillin-1 gene (*FBN1*) cause Marfan syndrome and acromelic dysplasias. Whereas the musculoskeletal features of Marfan syndrome involve tall stature, arachnodactyly, joint hypermobility, and muscle hypoplasia, acromelic dysplasia patients present with short stature, brachydactyly, stiff joints, and hypermuscularity. Similarly, pathogenic variants in the fibrillin-2 gene (*FBN2*) cause either a Marfanoid congenital contractual arachnodactyly or a *FBN2*-related acromelic dysplasia that most prominently presents with brachydactyly. The phenotypic and molecular resemblances between both the *FBN1* and *FBN2*-related disorders suggest that reciprocal pathomechanistic lessons can be learned. In this review, we provide an updated overview and comparison of the phenotypic and mutational spectra of both the “tall” and “short” fibrillinopathies. The future parallel functional study of both *FBN1/2*-related disorders will reveal new insights into how pathogenic fibrillin variants differently affect the fibrillin microfibril network and/or growth factor homeostasis in clinically opposite syndromes. This knowledge may eventually be translated into new therapeutic approaches by targeting or modulating the fibrillin microfibril network and/or the signaling pathways under its control.

KEY WORDS

fibrillin-1, fibrillin-2, fibrillinopathies, pathophysiology, skeletal dysplasia

1 | INTRODUCTION

Fibrillin microfibrils provide mechanical and functional support to human cells, tissues, and organs. The fibrillinopathies, a diverse group of connective tissue disorders, are caused by pathogenic variants in the fibrillin-1 (*FBN1*) and fibrillin-2 (*FBN2*) genes, respectively, encoding *FBN1* and *FBN2*. A spectrum of disorders with opposite phenotypic features has been linked to pathogenic variants in *FBN1*,

for which the divergent pathophysiological mechanisms remain largely elusive. Recent evidence suggests that this paradigm of opposing phenotypes is recapitulated in *FBN2*. In this review, we provide an updated overview of the structure, expression, and function of the different fibrillins, compare the phenotypic and mutational spectra of *FBN1*- and *FBN2*-related disorders and discuss the state-of-the-art and challenges of current fundamental mechanistic research. In this way, we aim to provide more insights into the

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underlying mechanisms of the phenotypically distinct fibrillinopathies and guide future research.

2 | THE FIBRILLINOPATHIES: A SPECTRUM OF DISORDERS WITH OPPOSING PHENOTYPES

Different pathogenic variants in the *FBN1* cause Marfan syndrome (MFS, MIM# 154700) and the acromelic dysplasias, respectively. Remarkably, both disorders present with opposing skeletal ("tall" vs. "short") and cardiovascular phenotypes. Interestingly, pathogenic variants in *FBN2* can cause either a Beals-Hecht syndrome/Marfanoid congenital contractual arachnodactyly (CCA, MIM# 121050) or an acromelic dysplasia that most prominently presents with brachydactyly, suggesting that this paradigm of opposing skeletal phenotypes is recapitulated in *FBN2* (Figure 1, Table 1). In the next section, we will explore the phenotypic state-of-the-art of the "tall" and "short" fibrillin-1/2-opathies.

2.1 | Phenotypic comparison of the "tall" fibrillinopathies

MFS is an autosomal dominant disorder caused by heterozygous variants in *FBN1*. It is characterized by thoracic aortic aneurysm and dissection (most commonly at the level of the sinus of valsalva), mitral valve defects, tall stature, arachnodactyly, scoliosis, muscle hypoplasia, and ectopia lentis (Keane & Pyeritz, 2008; Sakai et al., 2016). The revised Ghent nosology stipulates that one of the following four criteria needs to be fulfilled to formally establish a diagnosis of MFS: (1) the presence of ectopia lentis and aortic root dilatation, (2) the presence of aortic root dilatation and a pathogenic *FBN1* variant, (3) the presence of aortic root dilatation and a high "systemic" score (≥ 7), which is based on the presence of other cardiovascular and ocular manifestations of MFS and findings in other organs (skeleton, dura, lungs, skin), or (4) the presence of ectopia lentis and a *FBN1* variant that previously has been associated with aortic disease (Loeys, Dietz, et al., 2010).

CCA or Beals-Hecht syndrome (now called Distal Arthrogryposis type 9 or DA9) is an autosomal dominant disorder that has similar phenotypic features as MFS but is caused by heterozygous pathogenic

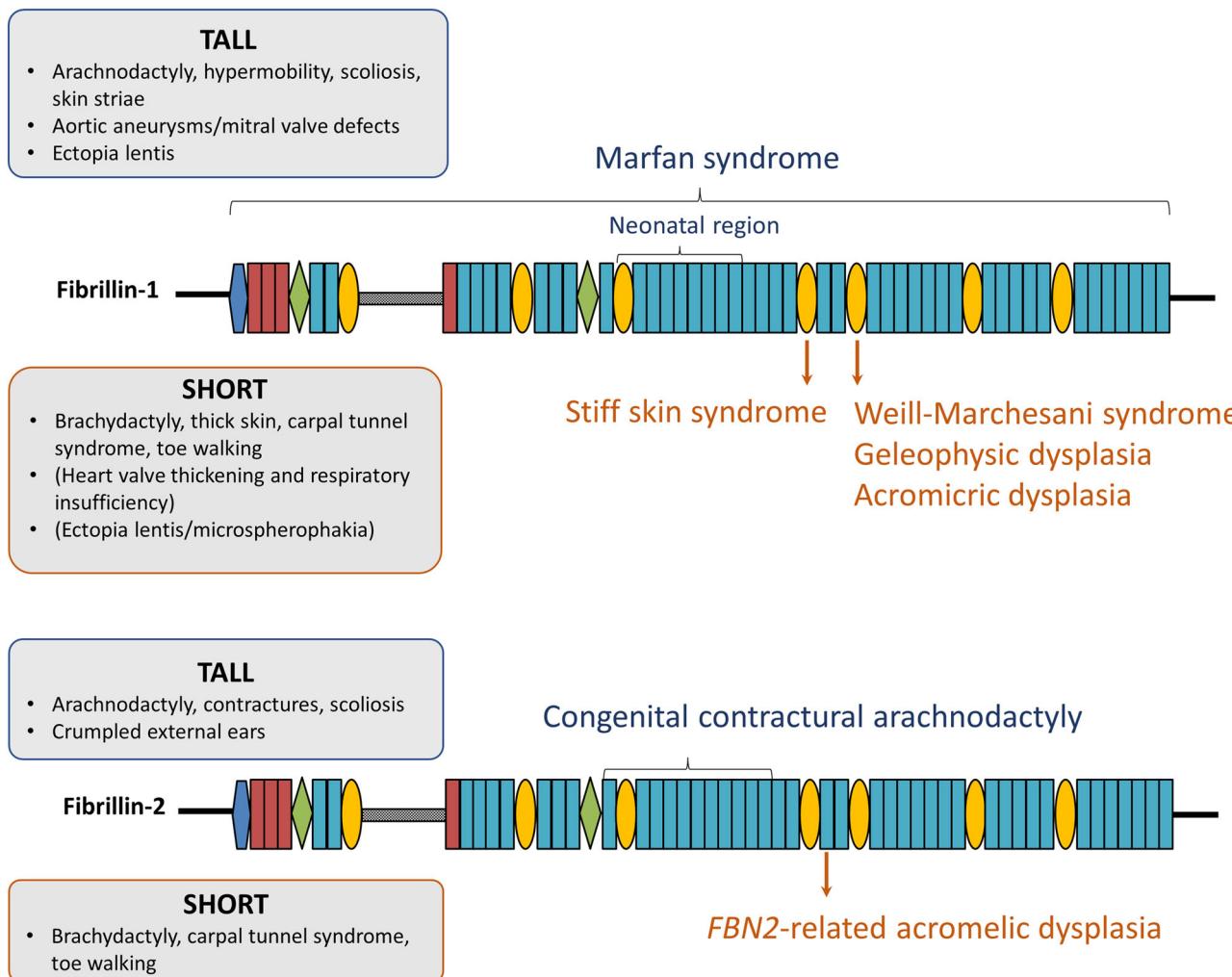


FIGURE 1 Pathogenic variants in *fibrillin-1* (*FBN1*) and *fibrillin-2* (*FBN2*) can cause "tall" and "short" fibrillinopathies.

TABLE 1 Overview of the “tall” and “short” fibrillinopathies.

Disorder	Inheritance (gene)	Skeletal features	Cardiovascular features	Ophthalmological features	Other features	Location variant in <i>FBN1/FBN2</i>
“Tall” fibrillinopathies						
Marfan syndrome	Autosomal dominant (<i>FBN1</i>)	Tall stature, arachnodactyly, scoliosis, pectus deformities, contractures, hypermobility of joints, muscle hypoplasia, pes planus	Thoracic aortic aneurysms and dissections, mitral/tricuspid valve prolapse	Ectopia lentis	Pneumothorax, skin striae, long narrow face, malar hypoplasia, micrognathia, retrognathia	All over gene, “neonatal region”. TB3-cbEGF18
Congenital contractual arachnodactyly (Beals–Hecht syndrome; distal arthrogryposis type 9)	Autosomal dominant (<i>FBN2</i>)	Tall stature, arachnodactyly, (kypho)scoliosis, pectus deformities, contractures, muscle hypoplasia	Mild cardiovascular involvement		Long, narrow face, highly arched palate, micrognathia, crumpled external ears	cbEGF10–cbEGF20
“Short” fibrillinopathies						
Weill–Marchesani syndrome	Autosomal dominant (<i>FBN1</i>) and autosomal recessive (<i>ADAMTS10</i> , <i>ADAMTS17</i> , <i>LTPB2</i>)	Short stature, brachydactyly, joint stiffness and contractures, toe walking, muscular build, early-onset carpal tunnel syndrome		Ectopia lentis, microspherophakia	Thick skin, maxillary hypoplasia	TB5 domain, TB1-EGF4 domain
Geleophysic dysplasia	Autosomal dominant (<i>FBN1</i> , <i>LTPB3</i>), autosomal recessive (<i>ADAMTS12</i>)	Short stature, brachydactyly, joint stiffness and contractures, toe walking, early onset carpal tunnel syndrome	Progressive thickening of cardiac valves		Thick skin, tracheal stenosis, respiratory insufficiency, full cheeks, a short nose, hypertelorism, a thin upper lip (“happy face”)	TB5 domain
Acromicric dysplasia	Autosomal dominant (<i>FBN1</i> , <i>LTPB3</i>)	Short stature, brachydactyly, joint stiffness and contractures, pseudomuscular build, notch femoral head, early onset carpal tunnel syndrome			Thick skin, round face, a bulbous nose, thick lips, short palpebral fissures, hoarse voice	TB5 domain
Stiff skin syndrome	Autosomal dominant (<i>FBN1</i>)	Relative short stature, brachydactyly, joint stiffness and contractures, diffuse entrapment neuropathy including carpal tunnel syndrome			Thick skin, cutaneous nodules	TB4 domain
<i>FBN2</i> -related acromelic dysplasia	Autosomal dominant (<i>FBN2</i>)	Relative short stature, brachydactyly, toe walking, early onset carpal tunnel syndrome			Short palpebral fissures	cbEGF23

variants in *FBN2*. It is characterized by tall stature, arachnodactyly, progressive scoliosis, contractures, and crumpled ears (Hecht & Beals, 1972; Viljoen, 1994). In a fraction of CCA patients, cardiovascular abnormalities such as aortic root dilatation and mitral valve prolapse have been reported (Callewaert et al., 2009; Carmical et al., 1999; Gupta et al., 2002; Takeda et al., 2015). Although extremely rare, a few CCA patients with aortic dissection have been reported (Takeda et al., 2015). A clinical scoring system for the diagnosis of CCA has recently been described (Meerschaut et al., 2020).

2.2 | Phenotypic comparison of the “short” fibrillinopathies

Interestingly, heterozygous pathogenic variants in *FBN1* and *FBN2* can either result in conditions presenting with tall stature and arachnodactyly or disorders displaying short stature and brachydactyly. Weill-Marchesani syndrome (WMS), geleophysic dysplasia (GD), and acromicric dysplasia (AD) are classified under the group of acromelic dysplasias in the latest nosology of genetic skeletal disorders (Mortier et al., 2019). These skeletal dysplasias are characterized by short stature and shortening of the limbs, mainly in the acromelic segments (brachydactyly). Although pathogenic variants in other genes (ADAMTS10, ADAMTS17, ADAMTSL2, LTBP2, LTBP3, see Table 1) have also been linked to these disorders, all three phenotypes can be caused by pathogenic variants in the *FBN1* gene. The *FBN1*-related acromelic dysplasias share short stature, brachydactyly, joint stiffness, contractures, and thick skin as common features. However, some disorder-specific clinical features have been suggested. In WMS, severe eye abnormalities such as microspherophakia and ectopia lentis are present (Faivre, Dollfus, et al., 2003). Distinguishing GD features are progressive thickening of the cardiac valves, tracheal stenosis, respiratory insufficiency, toe walking, and a “happy” face characterized by full cheeks, a short nose, hypertelorism, and a thin upper lip (Faivre, Dollfus, et al., 2003; Sakai & Keene, 2019). A round face, a bulbous nose and thick lips, a hoarse voice, and some specific radiological features such as a notch of the femoral head are rather typical for AD (Kochhar et al., 2013; Sakai & Keene, 2019). Interestingly, in all three acromelic dysplasias, early-onset carpal tunnel syndrome (CTS) has been reported. The frequency of CTS in acromelic dysplasia patients seems to range between 25% and 66% (Faivre, Gorlin, et al., 2003; Globa et al., 2018; Klein et al., 2014; Marzin et al., 2020). Another *FBN1*-related disorder that is distinct from the acromelic disorders but in which relative short stature has been described is stiff skin syndrome (SSKS, MIM# 184900), an autosomal dominant congenital form of scleroderma. The fibrotic skin of SSKS patients limits joint mobility and causes flexion contractures (Esterly & McKusick, 1971). Additional features of SSKS include cutaneous nodules, relative short stature and again, diffuse entrapment neuropathies (including CTS) due to local compression. In one patient, also ectopia lentis was seen (Loeys, Gerber, et al., 2010).

We recently identified a new fibrillin-2-opathy characterized by brachydactyly, early-onset CTS and a peculiar facial appearance with rather short palpebral fissures (Peeters et al., 2020). Relative short stature

(mean height SDS = -1.17) and short Achilles' tendons resulting in toe walking during childhood was seen in a proportion of the affected individuals. Interestingly, these features resemble the phenotypic characteristics of the *FBN1*-related acromelic dysplasias. However, CTS was more common, and presented earlier in life in the new fibrillin-2-opathy. Although only one family has been reported so far, this new *FBN2*-related disorder seems to complement the spectrum of fibrillin-2-opathies with an acromelic dysplasia-like phenotype.

3 | THE FIBRILLIN FAMILY OF PROTEINS

3.1 | Fibrillin protein structure

Fibrillins are large (350 kDa), cysteine-rich glycoproteins that assemble into beaded structures in the extracellular matrix (ECM) of connective tissues, called microfibrils (Sakai et al., 1986). The fibrillin proteins are encoded by three genes, that is, *FBN1* (chromosome 15q15-21.3), *FBN2* (chromosome 5q23-31), and *FBN3* (chromosome 19p13.3-13.2), and have a highly conserved domain architecture (Piha-Gossack et al., 2012). At the amino acid level, a sequence homology of 61%–69% is seen between the three human fibrillins, with the highest homology between *FBN1* and *FBN2* (Sakai & Keene, 2019). Fibrillins are organized in highly repetitive domains (Figure 2). The most prominent domain is the epidermal growth factor (EGF) domain, which is present 47 times in *FBN1* and *FBN2* and 46 times in *FBN3*. Most of the EGF domains (43 out of 46–47) contain a EGF consensus sequence for calcium binding (Asp/Asn-X-Asp/Asn-Glu/Gln-X-Asp/Asn-X-Tyr/Phe) and are referred to as calcium-binding EGF (cbEGF) domains, where X indicates a variable number of amino acid residues (Handford et al., 1991). Furthermore, fibrillins contain seven 8-cystein or transforming growth factor beta (TGF- β) binding-like (TB) domains and two hybrid domains. These domains are quite unique to the human proteome and are only seen in fibrillins and latent TGF- β binding proteins (LTBPs) (Robertson et al., 2011). The three fibrillins also contain a characteristic domain immediately following the first TB domain, which is proline-rich in *FBN1*, glycine-rich in *FBN2*, and proline/glycine-rich in *FBN3*. The proline-rich region in *FBN1* is suggested to be a hinge region, enabling folding of the proteins into microfibrils (Baldock et al., 2001). The N-terminal and the C-terminal parts of fibrillins contain a 4-cysteine motif and a 2-cysteine motif, respectively. Both the N- and C-terminal domains of the fibrillins also contain tribasic consensus sequences (Arg-X-Lys/Arg-Arg) for furin cleavage, which are important for processing profibulin to fibrillin. The N-terminal consensus sequences of *FBN1* and *FBN2* are located between amino acid positions 41–45 and 74–77, respectively, whereas the C-terminal sequences are located between amino acid positions 2728–2731 and 2776–2779, respectively.

Cysteine residues within the different domain types are well conserved between the three fibrillin proteins. The sulphydryl groups present in cysteines are known to form disulfide bonds with one another. Most of these disulfide bridges are formed within domains and are important to maintain intradomain stability and folding. The (cb)EGF domains contain six highly conserved cysteine residues that

form three disulfide bridges in a 1–3, 2–4, 5–6 arrangement (Campbell & Bork, 1993; Downing et al., 1996). The TB domains on the other hand have four intramolecular disulfide bonds in a 1–3, 2–6, 4–7, 5–8 pattern (Lee et al., 2004; Yuan et al., 1997). Similar to the latter domains, the two hybrid domains contain four disulfide bridges but in a 1–3, 2–5, 4–6, 7–8 arrangement. Finally, the N-terminal part contains two disulfide bridges in a 1–3, 2–4 pattern (Bork et al., 1996; Yadin et al., 2013).

Even though the different fibrillins are very similar with respect to protein domain organization, they differ in other structural aspects. Besides having the characteristic proline-, glycine-, or proline/glycine-rich region after the first TB domain, they also differ in the number and the position of N-glycosylation sites; FBN1 has 15 N-glycosylation sites, FBN2 12, and FBN3 10 (Sakai & Keene, 2019). N-glycosylation sites play key roles in protein folding, stability, and protein–protein interaction (Hart, 1992). Furthermore, the fibrillins have discrete numbers of Arg-Gly-Asp (RGD) motifs for integrin binding, which are important for cell adhesion and normal ECM production (Jovanovic et al., 2008). While all fibrillins contain an RGD-site in the TB4 domain, only FBN2 and FBN3 have a second RGD-site in the TB3 and cbEGF18 domain, respectively.

3.2 | Fibrillin microfibril assembly

Although the vast majority of studies investigating fibrillin processing have been focusing on FBN1, all fibrillins are predicted to be

processed in a similar manner. After secretion, pro-fibrillins multimerize at the cell surface to assemble into microfibrils, a process that is mediated by cell surface heparan sulfate proteoglycans (HSPG) (Tiedemann et al., 2001). Further multimerization is initiated by cleavage of the C- and N-terminal propeptides by furin (Milewicz et al., 1995). Next, fibrillins form head-to-tail and lateral disulfide-mediated interactions (Ashworth et al., 1999; Trask et al., 1999). In addition, nonreducing lateral cross-links between glutamines and lysines are formed to provide extra strength to the microfibrillar network (Qian & Glanville, 1997; Thurmond & Trotter, 1996). All these interactions eventually lead to the formation of mature microfibrils. Immunolocalization studies in fetal tissues showed that FBN1 either coassembles with other FBN1 molecules to form a homopolymeric microfibril or coassembles with FBN2 into a heteropolymeric microfibril (Charbonneau et al., 2003; Lin et al., 2002). Interestingly, homopolymeric interactions of FBN2 proteins were not seen (Charbonneau et al., 2003; Corson et al., 2004). Immunolocalization studies showed that FBN3 is localized to microfibrils but it remains unknown whether FBN3 interacts with other fibrillins (Corson et al., 2004).

3.3 | Fibrillin expression

A partially overlapping spatiotemporal expression pattern has been reported for the three fibrillins. It has been shown that *FBN1* expression persists during life, while the expression of *FBN2* and

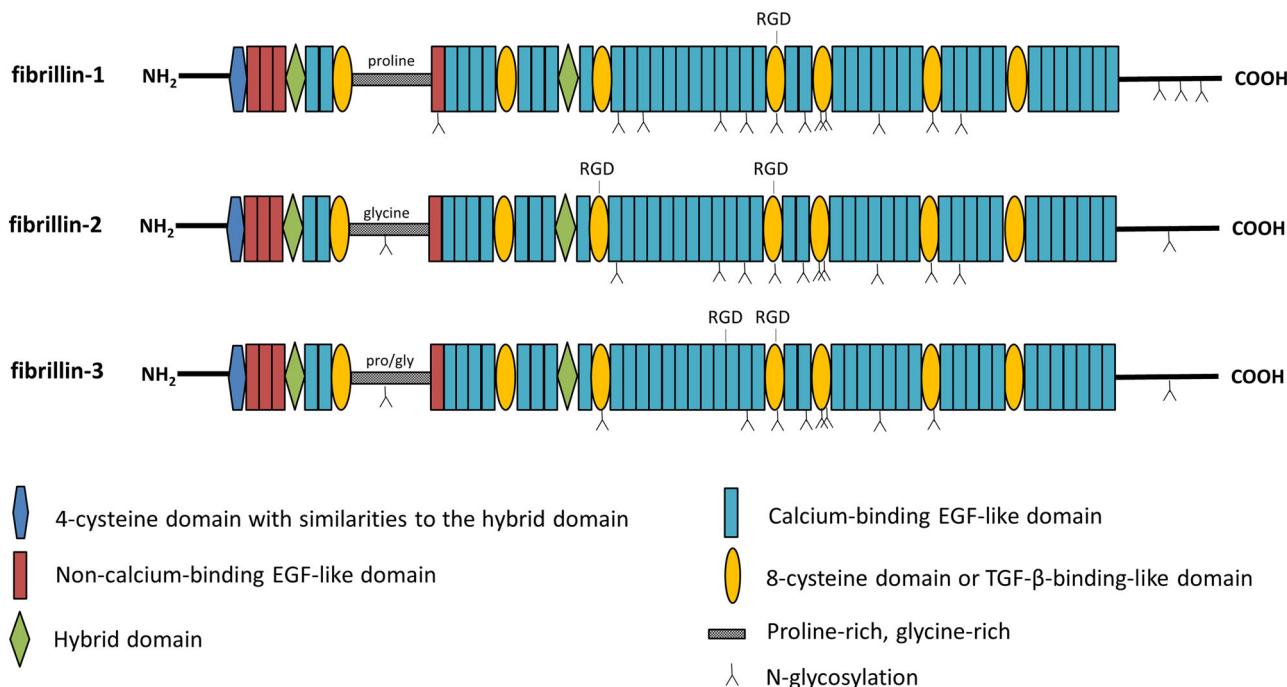


FIGURE 2 Domain organization of fibrillin-1 (FBN1), fibrillin-2 (FBN2), and fibrillin-3 (FBN3). The fibrillin domain organization consists of a 4-cysteine motif with similarities to the hybrid domain, four non-calcium-binding epidermal growth factor (EGF)-like domains, 43 calcium-binding EGF-like domains, seven 8-cysteine or transforming growth factor beta (TGF- β) binding-like (TB) domains, and two hybrid domains. N-glycosylation sites and Arg-Gly-Asp (RGD) motifs for integrin binding are depicted.

FBN3 seems to drop significantly after birth (Corson et al., 2004; H. Zhang et al., 1995). The observation that *FBN2* is mainly expressed during early development has led to the assumption that it is less important after birth. However, since *FBN2* makes up the inner core of microfibrils in postnatal life, its role after birth may be underestimated (Charbonneau et al., 2010). Protein expression studies may fail in detecting *FBN2* after birth because the protein is hidden in the core of the postnatal microfibrils. Caution is therefore warranted when performing, comparing, and/or interpreting immunohistochemical analyses.

In general, the three fibrillins are expressed in the same organs during development, including the skin, lungs, heart, aorta, kidneys, and nerves (Quondamatteo et al., 2002; Sabatier et al., 2011). Exceptions are the ciliary zonules in the eyes, where primarily *FBN1* is found and the liver, in which no expression of *FBN3* is seen (Sabatier et al., 2011). However, differences in the distribution of fibrillins have been observed in specific organs. For example, whereas expression of *FBN1* and *FBN2* proteins is seen in the outer fibrous layer of the perichondrium, *FBN3* is primarily found in the inner chondrogenic layer. Furthermore, while *FBN1* and *FBN3* are both present in the hypertrophic zone of hyaline cartilage, *FBN2* is absent in this part of the growth plate. Apart from the perichondrium and hyaline cartilage, differences in fibrillin distribution have been reported in the developing lungs and kidneys (Sabatier et al., 2011).

Interestingly, a few species-specific differences in expression of *FBN1* and *FBN2* have been reported. While murine ciliary zonules are composed of both *Fbn1* and *Fbn2* (Beene et al., 2013), only *FBN1* is seen in human zonules (Hubmacher et al., 2014). Furthermore, *FBN3* does not exist in rodents (Corson et al., 2004), suggesting that this protein is not essential for all mammalian life. Therefore, and because no disease in humans is unequivocally associated with *FBN3* mutations, we will focus this review on *FBN1* and *FBN2*.

3.4 | Fibrillin microfibril function and its associated protein network

In elastic tissues such as lungs, blood vessels, skin, and ligaments, microfibrils serve as a scaffold for elastin deposition and modification during elastic fiber formation (Jones et al., 1980; Kewley et al., 1978; Ross & Bornstein, 1969). In nonelastic tissues such as the ciliary zonule and cornea, tendon, perichondrium, and renal glomerulus, microfibrils provide tensile strength (Kumaratilake et al., 1989; Sakai et al., 1986; Sterzel et al., 2000). These discrete architectural roles are reflected by the microfibrils' tissue-specific properties. It has been shown that both the microfibril bead morphology as well as the proteolytic susceptibility of microfibrils differ between tissues (Eckersley et al., 2018).

Besides exerting a structural role, microfibrils are involved in the control of cell signaling pathways through storage and activation of growth factors, including TGF- β , bone morphogenic proteins (BMPs), and growth differentiating factors (GDFs) (Sengle et al., 2008). Most fibrillin-related studies that have been done so far focused on their

role in the regulation of the TGF- β signaling pathway. The TGF- β cytokines (TGF- β 1, TGF- β 2, and TGF- β 3) are encoded by three genes (*TGFB1*, *TGFB2*, and *TGFB3*). These cytokines are involved in numerous cellular processes such as growth, differentiation, and apoptosis, as well as in immune system regulation and tissue homeostasis. Mature TGF- β forms a complex with latency associated proteins (LAPs), called the small latent TGF- β complex (SLC) (Gentry et al., 1988; Lawrence et al., 1984). In turn, these LAPs covalently bind LTBPs (LTBP1, LTBP3, LTBP4) to form a large latent complex (LLC). LTBPs are members of the fibrillin superfamily and, although much smaller, have similar structural properties as fibrillins. Through binding of the SLC with LTBPs, TGF- β is held in an inactive state (Annes et al., 2003; Koli et al., 2001; Miyazono et al., 1988) (Figure 3). The LLC interacts with ECM components, mostly fibrillins (Isogai et al., 2003), to sequester TGF- β ligands into the ECM and, as such, controls their biological availability. Activation of the TGF- β pathway through release of TGF- β from the LLC is initiated by different mechanisms, including proteolytic cleavage by plasmin or matrix metalloproteinases (MMP2 and MMP9) (Sato & Rifkin, 1989; Yu & Stamenkovic, 2000), activation by thrombospondin (which is upregulated during wound healing) (Schultz-Cherry & Murphy-Ullrich, 1993) or conformational alterations of the LLC-mediated by integrin binding ($\alpha v \beta 6$, upregulated during wounding/inflammation), and the ensuing force-depending activation (Annes et al., 2003; Hinz, 2013; Shi et al., 2011). Binding of active TGF- β to TGFBRII receptors initiates phosphorylation of the TGFBR1 receptors. Further downstream signaling either involves the canonical or noncanonical pathway. In the canonical pathway, receptor-regulated SMADs (R-SMADs; SMAD2 or SMAD3) are phosphorylated after which a complex with SMAD4 is formed. This complex is then translocated into the nucleus and activates transcription of TGF- β target genes. The noncanonical TGF- β signaling pathway activates ERK, JNK, and p38 via mitogen-activated protein (MAPK) kinases, eventually also stimulating transcription of TGF- β target genes.

Fibrillins do not only control TGF- β signaling via their interaction with LTBPs. As previously mentioned, they also interact with cells via RGD-binding integrin receptors. For FBN, it has been shown that this interaction inhibits TGF- β signaling through the regulation of miRNA expression. MiR-503, one of the miRNAs that is upregulated upon fibrillin-1 RGD-integrin interaction, has been shown to downregulate TGF- β 2 and reduce pSMAD2 activity (Zeyer et al., 2019). Furthermore, recent evidence suggests that fibrillin-1 RGD-integrin interaction inhibits miR-1208 expression, an inhibitor of noncanonical TGF- β signaling (R. M. Zhang et al., 2021).

Apart from LTBPs, fibrillin microfibrils interact with several other ECM proteins. These molecules are known to mediate the assembly of microfibrils and/or contribute to their (tissue-specific) functionality, both structurally and functionally. Key binding proteins of *FBN1* include *FBN2*, MAGPs, MFAPs, ADAMTS(L)s, fibulins, fibronectin, chondroitin/HSPG, integrins, aggrecan, versican, hyaluronan, perlecan, syndecan-4, tropoelastin, lysyl oxidase (Thomson et al., 2019). Limited studies focused on interaction partners of *FBN2* so far, although interactions with *FBN1*, MFAP5, MFAP2, and ADAMTS17

have been reported (Hubmacher et al., 2017). To date, however, most interaction studies use recombinant FBN1/FBN2 protein fragments because of the propensity of full-length fibrillin to aggregate. Since the affinity for certain proteins and polysaccharides (including heparan sulfate) tend to change upon multimerization of fibrillins (Sabatier et al., 2014), caution is warranted when interpreting protein-interaction studies using recombinant fragments.

4 | MOLECULAR COMPARISON OF THE “TALL” AND “SHORT” FIBRILLIN-1/2-OPTHIES

4.1 | Mutational spectrum and genotype–phenotype correlations of the “tall” fibrillinopathies

Zooming in on the mutation spectrum underlying MFS and CCA, both commonalities and discordances can be observed. In both disorders, pathogenic variants have been described that introduce or replace a cysteine residue in the cbEGF domains. Cysteine-affecting variants have been shown to interfere with normal intradomain or

interdomain disulfide bridging, thereby affecting normal protein folding. Fibrillin misfolding affects protein secretion and/or causes an increased proteolytic susceptibility by anomalous exposure of cryptic cleavage sites and/or decreased calcium binding (Reinhardt et al., 1997; Suk et al., 2004; Vollbrandt et al., 2004), ultimately leading to a weakened microfibril scaffold. Other pathogenic missense variants in *FBN1* or *FBN2*, respectively causing MFS or CCA, have been shown to change critical residues in the cbEGF consensus sequence for calcium binding, thereby again affecting normal calcium binding (Rao et al., 1995). In MFS, missense variants that do not affect cysteine or calcium binding residues as well as nonsense variants, splice site variants, (partial) *FBN1* deletions, duplications, and small insertions have been described (Booms et al., 2000; Caputi et al., 2002; Collod-Beroud et al., 2003; Dietz et al., 1991; Hilhorst-Hofstee et al., 2011; Liu et al., 2001). Similar to MFS (partial) deletions of *FBN2* and splice site variants have also been reported in CCA patients (Gupta et al., 2002). In addition, a pathogenic variant that introduces an additional glycosylation site in cbEGF9 has been identified in one CCA patient (Gupta et al., 2002). A missense variant that creates an additional N-glycosylation site in *FBN1* has also been reported in a patient with severe MFS (Lonnqvist et al., 1996). Excessive

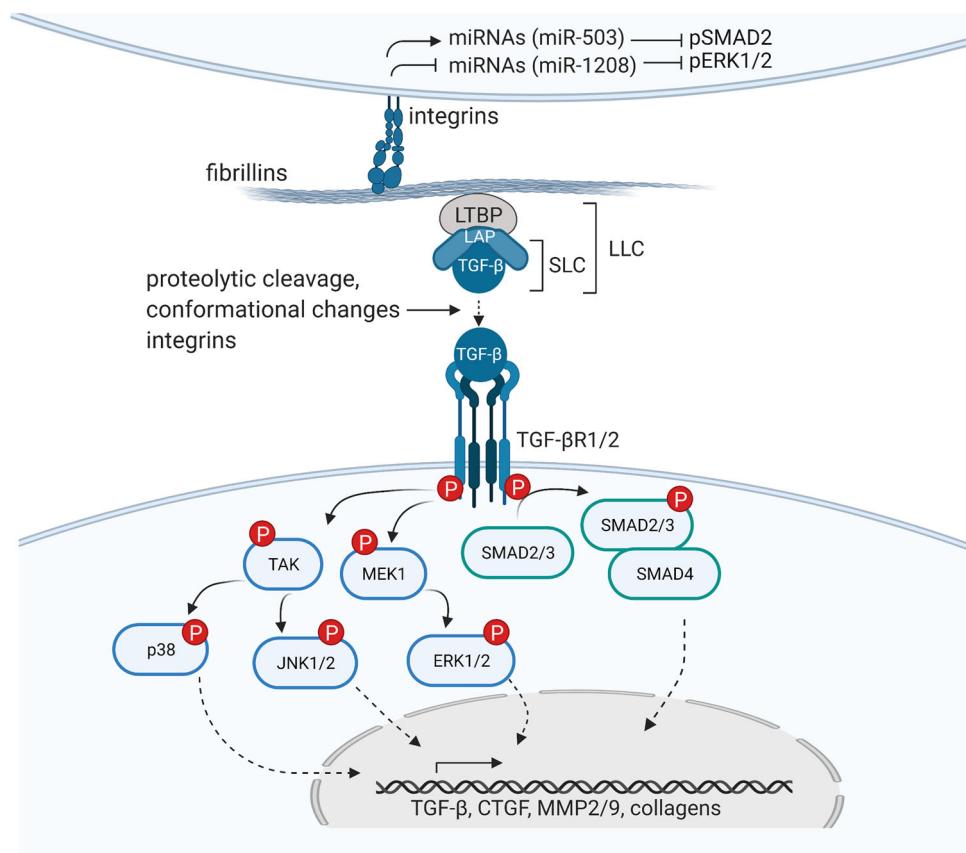


FIGURE 3 Fibrillins control transforming growth factor beta (TGF- β) signaling. Through the sequestration of the large latent complex (LLC), consisting of the small latent complex (SLC) and TGF- β ligands, and the interactions with integrins on the cell surface, fibrillins control TGF- β signaling. Both the noncanonical (or SMAD-independent) pathway (blue) and the canonical (SMAD-dependent) pathway (green) are depicted. Figure created with BioRender.com.

N-glycosylation has been shown to severely affect microfibril formation (Lonnqvist et al., 1996).

Few strong genotype–phenotype correlations have been described for both MFS and CCA. Pathogenic variants in the so-called “neonatal” region of *FBN1* (exons 25–33 encoding TB3-cbEGF18), have been shown to cause a more severe form of MFS that often results in neonatal death, referred to as neonatal MFS (nMFS) (Maeda et al., 2016). However, the use of the term “nMFS” is discouraged as this term does not adequately represent a specific subset of individuals with truly distinguishing characteristics (Dietz, 2001 [Updated February 17, 2022]). Furthermore, there are exceptions and some cases of this “early onset” and “rapidly progressive” MFS are caused by pathogenic variants outside this particular region (Universal Mutation Database (UMD)-*FBN1*) (Collod-Beroud et al., 2003). Pathogenic variants causing this more severe type of MFS have been shown to drastically alter proteolytic sensitivity, protein secretion, and heparin/heparan sulfate binding (Kirschner et al., 2011; Maeda et al., 2016). In addition, multiple studies report a strong link between cysteine creating or replacing variants and ectopia lentis (Loeys et al., 2001; Rommel et al., 2005; Schrijver et al., 2002). Furthermore, some studies suggest that MFS patients with haploinsufficient *FBN1* variants generally have a higher aortic risk than MFS patients with dominant negative *FBN1* variants (Arnaud et al., 2021; Baudhuin et al., 2015; Franken et al., 2015, 2016). However, these findings are contradicted by a recent study in a pediatric MFS cohort showing that dominant negative variants in exons 26–49 result in a more severe aortic phenotype than patients with haploinsufficient variants or dominant negative variants in other exons (Meester et al., 2021). This study also noticed a clear gradient in the proportion of ectopia lentis according to the location of the dominant negative *FBN1* variant, with the highest prevalence of lens dislocation in the N-terminal region (Meester et al., 2021). In contrast to the findings on aortic risk, skeletal features including pectus excavatum and tall stature are more pronounced in patients carrying haploinsufficient variants (Meester et al., 2021). Similarly, another study in adult MFS patients reported an association between premature stop codon variants and a higher risk of severe scoliosis and tall stature (Arnaud et al., 2021). Finally, it has been shown that pathogenic variants in exon 64 of *FBN1* can cause a specific subtype of MFS called marfanoid–progeroid–lipodystrophy syndrome (MFLS, MIM# 616914), a disorder mainly characterized by congenital lipodystrophy, tall stature, arachnodactyly, and progeroid appearance (Romere et al., 2016). MFLS variants are clustered around the C-terminal furin cleavage site of profibrillin (amino acids 2728–2731), leading to a mutant, truncated profibrillin protein and reduced levels of the 140-amino-acid long C-terminal cleavage product of profibrillin, called asprosin. Reduced levels of the asprosin hormone affect normal adiposity and cause metabolic dysregulation in patients (Duerrschnid et al., 2017; Romere et al., 2016).

Unlike MFS-causing variants, which are spread across the *FBN1* gene, most CCA-causing variants cluster between exon 23 and exon 34 (cbEGF10–cbEGF20) of *FBN2* (Gupta et al., 2002). This specific region of *FBN2* roughly corresponds to the “neonatal” region of

FBN1. Though less common, pathogenic CCA variants outside this region (e.g., in exon 17 and exon 21) have also been described (Callewaert et al., 2009; Meerschaut et al., 2020). For CCA, a few reports suggest that intragenic deletions (Lavillaureix et al., 2017) and splice-site alterations in the central region of *FBN2* that result in in-frame exon skipping (Wang et al., 1996), cause a more severe form of CCA (Callewaert et al., 2009), but further confirmation is warranted. Although most CCA patients carry dominant negative variants, also a few haploinsufficient *FBN2* variants, including whole gene deletions and a nonsense variant, have been described (Courtens et al., 1998; Inbar-Feigenberg et al., 2014; Kloth et al., 2021).

In both disorders, an extensive inter- and intrafamilial variability in age at onset and phenotypic severity is seen. The mechanisms underlying this variability are largely unknown. For *FBN1* this most likely involves the variable expression level of the other normal allele (Aoyama et al., 1995; Aubart et al., 2015; Hutchinson et al., 2003) or other genetic modifiers (Aubart et al., 2018).

4.2 | Mutational spectrum and genotype–phenotype correlations of the “short” fibrillinopathies

The short fibrillin-1-opathies, WMS, AD, and GD, are all caused by pathogenic variants in the heparin-binding TB5 domain of *FBN1*. A deletion of exons 9–11 (coding for TB1-EGF4), which abolishes a binding site for ADAMTSL proteins, has been described in one family with WMS (Sengle et al., 2012). SSKS, on the other hand, is caused by pathogenic cysteine-replacing or introducing variants in the TB4 domain of *FBN1*. The pathogenic variant causing the *FBN2*-related acromelic dysplasia (NM_001999.4: c.5009T>G; p.(Phe1670Cys)) is located in the cbEGF23 of *FBN2*, a domain adjacent to TB4.

Apart from the observation that nearly all these “acromelic” variants cluster within the TB4-TB5 region of *FBN1*/*FBN2*, one additional genotype–phenotype correlation has been described for the “short” fibrillin-1-opathies. A recent study on variants causing AD/GD phenotypes showed that variants involving a cysteine in *FBN1*-TB5 were more often associated with a severe phenotype with life-threatening heart valve disease compared to other *FBN1*-TB5 variants (Marzin et al., 2020).

5 | THE MECHANISMS UNDERLYING THE OPPOSING PHENOTYPES

The observation that opposing phenotypes may result from heterozygous pathogenic variants in the same gene (either *FBN1* or *FBN2*) is intriguing and deserves further discussion. Different (and sometimes conflicting) disease mechanisms have been proposed to underlie this phenomenon. Whereas loss of the structural integrity or stability of microfibrils (both due to haplo-insufficiency or dominant negative mechanisms) is suggested to underlie MFS, altered cell–matrix interactions to the TB4–TB5 region are thought to be

the primary defect driving the acromelic phenotypes (Jensen et al., 2015; Peeters et al., 2020). However, to date, there is still no consensus on the precise pathophysiology, suggesting that it is more complex and may involve more than one mechanism.

5.1 | Cell-matrix interactions

Only a few studies have investigated cell-matrix interactions. Cain et al. showed that *FBN1*-TB5 variants causing WMS, AD, and GD (often cysteine-replacing or -creating variants) disrupt pericellular interactions with heparin/heparan sulfate (Cain et al., 2012). These interactions have been shown to be important for microfibril assembly and cell adhesion. Interestingly, pathogenic variants, including cysteine-affecting missense variants in the TB5 domain of *FBN1* have also been identified in at least about a dozen MFS patients without features of acromelic dysplasia. It remains to be determined whether these variants affect heparan sulfate interactions to the TB5 domain. However, pathogenic variants in the so-called “neonatal” middle region of *FBN1* (exons 24–32), causing a severe form of MFS, have also been shown to affect heparan sulfate-*FBN1* interactions (Kirschner et al., 2011). These findings suggest that impaired heparin/heparan sulfate binding to TB5 on itself fails to explain the paradox of opposing phenotypes and that other mechanisms may be involved.

Another mechanism related to disturbed cellular sensing involve alterations in integrin-binding. The SSKS variant (p.(Trp1570Cys)) in the TB4 domain of *FBN1*, a domain containing the RGD site for integrin binding, has been shown to inhibit the *FBN1*-integrin (i.e., $\alpha 5\beta 1$, $\alpha v\beta 5$, and $\alpha v\beta 6$) interaction, affecting normal cell adhesion and cell spreading (Del Cid et al., 2019). Similarly, the pathogenic variant (NM_001999.4: c.5009T>G; p.(Phe1670Cys)) causing the “short” fibrillin-2-opathy is located in the cbEGF23 of *FBN2*, a domain adjacent to the TB4 domain that also contains an RGD site. Altered cell adhesion and cell spreading to mutant *FBN2* protein fragments was shown for this variant (Peeters et al., 2020). Although SSKS and the “short” fibrillin-2-opathy present with milder skeletal phenotypes, these findings may suggest that proper integrin-binding is required for normal growth. It remains to be determined whether integrin-binding is affected in the “tall” fibrillinopathies and/or whether more complex mechanisms, such as the ratio of normal microfibrils versus integrin content, have an impact on the overall growth phenotype.

5.2 | Clues from the fibrillin protein network: The LTBPs and ADAMTS(L)s

More insights into the pathomechanisms for the acromelic disorders have been obtained by the identification of pathogenic variants in other genes coding for ECM proteins that bind to fibrillin microfibrils.

The LTBP protein family is evolutionarily related to the fibrillins and is characterized by a highly similar domain organization. Most LTBPs, including LTBP1, LTBP3, and LTBP4, have been shown to

sequester latent TGF- β in the ECM (Robertson et al., 2015). Pathogenic variants in the LTBPs have been associated with skeletal dysplasias that have similar—or even identical—clinical features to the *FBN1*- and *FBN2*-related phenotypes. Heterozygous pathogenic variants in *LTBP3* cause GD (GPHYSD2, MIM# 614185) with an indistinguishable phenotype from *FBN1*-related GD. A diminished and disorganized microfibril network was found in tissues of GD patients with pathogenic variants in *LTBP3*, suggesting that this protein is important for the proper formation of microfibrils (McInerney-Leo et al., 2016). Although it has been shown that LTBP3 does not bind to the C-terminal of *FBN1*, it remains unknown whether it interacts with other parts of *FBN1* (or *FBN2*), including the N-terminal part. Autosomal recessive variants in *LTBP3* cause Short Stature syndrome (DASS, MIM# 601216). Patients with DASS syndrome have amelogenesis imperfecta, brachydactyly, and a short trunk due to platyspondyly (Verloes et al., 1996). Furthermore, some DASS patients also exhibit mitral valve prolapse and aortic (root) dilation (Guo et al., 2018). The pathomechanisms underlying both *LTBP3*-related disorders remain largely unknown. Based on the nature of the described variants, it is suggested that gain-of-function (missense) variants give rise to acromelic phenotypes while truncating and loss-of-function variants give rise to aortic phenotypes (Verstraeten et al., 2020). However, more research is required to confirm this statement.

Bi-allelic pathogenic variants in the *FBN1*-binding region of *LTBP2* cause an autosomal recessive form of WMS (WMS3, MIM# 614819). Pathogenic variants in *LTBP2* have been shown to affect normal *LTBP2* secretion and/or the ability to bind *FBN1* (Inoue et al., 2014). Again, disruption of the stability of fibrillin microfibrils was shown (Haji-Seyed-Javadi et al., 2012). These findings suggests that, in addition to *LTBP3*, also *LTBP2* is involved in normal microfibril functioning in the ECM.

Another *LTBP*-related disorder includes cutis laxa type IIE syndrome (ARCL2E, MIM# 619451). Patients with cutis laxa type IIE syndrome have generalized cutis laxa, inguinal hernias, craniofacial dysmorphology, short stature, brachydactyly, and mild cardiac defects (Pottie et al., 2021). Cutis laxa type IIE is caused by autosomal recessive truncating variants in *LTBP1*.

The ADAMTS(L) family consists of proteins that function in normal tissue development and homeostasis. Some of them, including ADAMTS10, have a catalytic domain and perform proteolytic activities in the ECM (Mead & Apte, 2018). Interaction studies showed that the deletion of exons 9–11 of *FBN1* (coding for TB1-EGF4 and found in a WMS family) abolishes the binding site for several ECM proteins including ADAMTS2, -3, and -6 (Sengle et al., 2012). Furthermore, pathogenic variants in ADAMTS10 and ADAMTS17 have been shown to cause autosomal recessive WMS (WMS1, MIM# 277600 and WMS4, MIM# 613195). In cultured fibroblasts derived from WMS patients with pathogenic variants in ADAMTS10, reduced *FBN1* microfibril formation was seen (Kutz et al., 2011). In the eye of a homozygous mouse model in which the Adams10 protein is truncated, excessive fibrillin microfibrils were observed that were primarily composed of Fbn2 (Mularczyk

et al., 2018). Also, in patient-derived fibroblasts of WMS patients with pathogenic variants in ADAMTS17, decreased FBN1 microfibrils and collagen type 1 deposition was observed (Karoulias et al., 2020). Furthermore, mutant ADAMTS17 suppresses FBN2 incorporation in microfibrils by transcriptional downregulation of *Fbn2* mRNA expression in cultured fibroblasts (Hubmacher et al., 2017). In contrast to pathogenic variants in ADAMTS10 and ADAMTS17, ADAMTSL2 mutations cause an autosomal recessive form of GD (GPHYSD1, MIM# 231050). Increased *Fbn2* staining was also found in the lungs of *Adamtsl2* knock-out mice but, in contrast to what has been shown for ADAMTS17, transcriptional regulation of *Fbn2* was not altered in these mice (Hubmacher et al., 2015). These findings suggest that ADAMTS(L) proteins regulate the ratio of FBN1 and FBN2 incorporation into microfibrils, and that an imbalance towards (or gain-of-function of) FBN2 may contribute to the development of WMS and GD (Hubmacher et al., 2015; Sakai & Keene, 2019). However, more research is required to further test this hypothesis.

Based on the functional characterization of several Cre-specific *Adamtsl2* knockout mice, several hypotheses have emerged as to which cell types or tissues are implicated in decreased longitudinal bone growth in GD. In the growth plates of chondrocyte-specific (*Col2a1-Cre*) knockout *Adamtsl2* mice, an impaired microfibrillar network, increased chondrocyte proliferation and impaired chondrocyte differentiation was observed, suggesting that chondrocyte dysfunction is the main driver of short stature in GD (Delhon et al., 2019). However, these chondrocyte-specific growth plate abnormalities could not be confirmed in a limb-specific (*Prx1-Cre*) *Adamtsl2* knockout mouse model (Hubmacher et al., 2019). Surprisingly, however, impaired skeletal growth was also observed in a tendon- and ligament-specific (*Scx-Cre*) *Adamtsl2* knockout mouse, suggesting that the growth impairment may arise secondary to shortened tendons/ligaments rather than intrinsically by chondrocyte- or growth plate abnormalities. Supporting this hypothesis, two reports state that tendon- and ligament-specific (*Scx-Cre*) *Fbn1* deletion, as a model for MFS, results in increased longitudinal growth in mice (Hubmacher et al., 2019; Smaldone et al., 2018). However, more research is required to support this hypothesis.

To date, only a few pathogenic ADAMTS(L) variants have been associated with thoracic aortic aneurysms in humans. One patient with GD and a compound heterozygous variant in ADAMTSL2 developed several arterial aneurysms including a thoracic aortic aneurysm (Legare et al., 2018). In addition, it was recently shown that heterozygous variants in *THSD4*, which encodes the ADAMTSL6, predispose to hereditary thoracic aortic aneurysms (Elbitar et al., 2021). Skeletal involvement was limited in these patients. Introducing the *THSD4* variants in transfected HEK293 cells led to haploinsufficiency or reduced assembly of FBN1 microfibrils. *Thsd4^{+/−}* mice showed progressive thoracic aortic aneurysm formation. Medial degeneration and disruption of ECM was seen upon histological examination of aortic samples from a *THSD4* patient and from *Thsd4^{+/−}* mice. Furthermore, increased TGF-β signaling was observed in patient samples (Elbitar et al., 2021).

In conclusion, FBN1, FBN2, the LTBPs, and the ADAMTS(L)s seem to interact in a common network to establish normal tissue homeostasis and growth. Alterations in this fibrillin protein network may cause acromelic disorders. It remains to be determined to what extent intrinsic growth plate abnormalities and/or extrinsic factors such as soft tissue defects affect normal bone growth in the fibrillinopathies. The growth phenotypes of the FBN2-related disorders are milder compared to the fibrillin-1-opathies, suggesting that FBN2 has a less important role in longitudinal bone growth. One possible explanation could be that FBN1 takes over the function of FBN2 postnatally, which could explain the less severe FBN2-related growth phenotypes. However, more research is required to confirm this statement. Despite the number of cases described so far being limited, there is also evidence for a role of the ADAMTS(L)/LTBP/FBN1/FBN2 network in thoracic aortic aneurysms.

5.3 | Effects on cell signaling pathways

The effects of pathogenic variants causing the “tall” and “short” fibrillinopathies on cell signaling pathways are not fully understood. Studies in MFS mouse models that recapitulate the human MFS phenotype, demonstrated that increased TGF-β signaling plays a key role in the progression of aortic aneurysm (Habashi et al., 2006). However, other studies have suggested that TGF-β can also be protective in specific stages of aortic development (Li et al., 2014; Wei et al., 2017). Elevated TGF-β signaling has also been found in the mitral valves of MFS mice (Ng et al., 2004). Furthermore, studies of induced pluripotent stem cell (iPSC)-derived chondrocyte pellets of MFS patients suggest that increased TGF-β signaling promotes linear growth in the growth plates of the tubular bones in MFS patients (Quarto et al., 2012). In contrast to MFS mouse models, no *Fbn2* animal model fully recapitulates the clinical characteristics of CCA (Table S1) (Chaudhry et al., 2001; Miller et al., 2010; Nistala et al., 2010). Syndactyly, muscle weakness, and transient contractures are the main findings in *Fbn2* knockout mice (Miller et al., 2010). Furthermore, also reduced bone mass and a reduced length of bones have been reported in *Fbn2^{−/−}* mice (Nistala et al., 2010). Although *Fbn2* knockout mice do not exhibit the full CCA phenotype, results from these mouse models suggest tissue-specific roles of FBN2 in growth factor regulation. While the weakened muscles may be caused by altered BMP signaling (Arteaga-Solis et al., 2001; Sengle et al., 2015), the low bone mass in *Fbn2^{−/−}* mice was attributed to elevated TGF-β signaling (Nistala et al., 2010).

Similar to what has been observed in MFS, elevated TGF-β signaling has been reported in the “short” fibrillinopathies, including in the skin and/or fibroblasts of patients with FBN1-related AD and GD (McInerney-Leo et al., 2016), ADAMTSL2-related AD (Le Goff et al., 2008), SSKS (Loeys, Gerber, et al., 2010), and in the carpal tissues of patients with the recently reported “short” fibrillin-2-opathy (Peeters et al., 2020). In contrast, normal TGF-β signaling was reported in fibroblasts of WMS patients and a WMS mouse model (*Fbn1^{WMdelta}*, Table S1), both carrying the exon 9–11 deletion (or in

mice exon 8–10) in *FBN1* (Sengle et al., 2012), and in AD/GD patients with pathogenic variants in *LTPB3* (McInerney-Leo et al., 2016).

The observation that elevated TGF- β signaling has been reported in tissues of both “tall” and “short” fibrillinopathies suggests that altered TGF- β signaling may not fully explain the paradigm of opposing phenotypes either. It remains unknown whether the functional outcome of dysregulation of the TGF- β pathway is dependent on its contextual (i.e., time-dependent and/or tissue-specific) microenvironment and/or other cell-signaling pathways, and what its effect may be in the pathogenesis of the tall and short fibrillinopathies.

Apart from TGF- β , fibrillin microfibrils sequester other growth factors, including BMPs and GDFs (Sengle et al., 2008). An important role of these growth factors in abnormal skeletal growth is illustrated by the fact that autosomal recessive variants in *GDF5* and its receptor gene *BMPR1B* cause acromesomelic chondrodysplasias, a particular form of short stature known as short-limb dwarfism (Demirhan et al., 2005; Thomas et al., 1997). In addition, heterozygous variants in *GDF5*, *BMPR1B*, and *BMP2* cause different types of isolated brachydactylies (BDC, MIM# 113100 and BDA2, MIM# 112600). Furthermore, the fact that pathogenic variants in *SMAD4* cause Myhre syndrome (MYHRS, MIM# 139210), another acromelic dysplasia, further suggests involvement of TGF- β and BMP signaling in the acromelic dysplasias as the *SMAD4* protein is a central player in both pathways. However, as most studies to date have mainly focused on the TGF- β pathway, the exact role of the BMP/GDF pathway in the pathophysiology of the fibrillinopathies remains largely unknown.

6 | CONCLUDING REMARKS AND FUTURE PERSPECTIVES

Although differences in protein structure and spatio-temporal expression have been reported, *FBN1* and *FBN2* seem to cooperate to provide mechanical and functional support to cells, tissues, and organs, especially during development. Consistent with their important and divergent role in the ECM, an increasing number of connective tissue disorders has been linked to pathogenic variants in the *FBN1* and *FBN2* genes. For *FBN1*, a paradigm of opposing phenotypes has been described (MFS vs. AD, GD, WMS), which seems to be recapitulated in *FBN2* (CCA vs. the *FBN2*-related acromelic dysplasia). To date, the pathophysiological mechanisms underlying these contrasting clinical syndromes remain largely unknown. The current phenotypic and molecular analogy between both “tall” and “short” *FBN1* and *FBN2*-related disorders are highly suggestive for the existence of shared pathomechanisms. Although it remains unclear which cell types are primarily involved, the few functional studies that have focused on *FBN2* (or ADAMTS(L)s) to date point mainly towards the involvement of disturbed fibrillin-cell interactions, changes in the *FBN1*/*FBN2* ratio (gain-of-function of *FBN2*?) and changes in TGF- β signaling in the pathophysiology of the acromelic phenotypes. More research is required to further prove

this model and to determine whether these (or a combination of these) mechanisms are also underlying the “tall” fibrillinino-1/2-pathies.

The identification of additional patients and the subsequent reporting of variants with a precise description of the patient's phenotypes in databases (UMD-*FBN1*, UMD-*FBN2*, LOVD, HGMD) are important to unveil additional genotype-phenotype correlations in the future. Furthermore, the creation of additional specific knock-in *Fbn1* (for AD) and knock-in *Fbn2* mouse models (for CCA and AD) will be necessary to achieve more insights in the involved pathomechanisms underlying the opposing phenotypes. Additionally, since some differences in spatiotemporal expression of *Fbn1* and *Fbn2* have been reported in mice compared to humans, the parallel study of the disease mechanisms in human cellular models of relevant cell types, such as iPSC-derived chondrocytes/tenocytes and iPSC-vascular smooth muscle cells, will be essential. More specifically, a multiomics approach (transcriptomic, proteomic and, especially, interactomics) in murine and human cellular models may reveal further insights into how the different *FBN1* or *FBN2* mutations affect cell-matrix interactions, the fibrillin protein network (*FBN1*, *FBN2*, ADAMTS(L)s, LTBPs) as well as growth factors switches between phenotypically opposite fibrillinopathies. This knowledge may eventually be translated into new therapeutic approaches by targeting or modulating the fibrillin microfibril network and/or the signaling pathways over which it exerts control.

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DATA AVAILABILITY STATEMENT

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