Supplemental Material 1. Peptidic sequences used for the protein structure predictions.

Sequence WT: cbEGF14-TB5-cbEGF15

DIDECEVFPGVCKNGLCVNTRGSFKCQCPSGMTLDATGRICL
ETCFLRYEDEECTLPIAGRHRMDACCCSVGAAWGTEECEECPMRNTPEYEELC
DINECKMIPSLCTHGKCRNTIGSFKCRCDSGFALDSEERNCT

Sequence MFS: cbEGF14-TB5-cbEGF15

DIDECEVFPGVCKNGLCVNTRGSFKCQCPSGMTLDATGRICL
ETCFLRYEDEECTLPIAGRHRMDA**Y**CCSVGAAWGTEECEECPMRNTPEYEELC
DINECKMIPSLCTHGKCRNTIGSFKCRCDSGFALDSEERNCT

Sequence GPHYSD-1: cbEGF14-TB5-cbEGF15

DIDECEVFPGVCKNGLCVNTRGSFKCQCPSGMTLDATGRICL
ETCFLRYEDEECTLPIAGRHRMDA**W**CCSVGAAWGTEECEECPMRNTPEYEELC
DINECKMIPSLCTHGKCRNTIGSFKCRCDSGFALDSEERNCT

Sequence GPHYSD-2: cbEGF14-TB5-cbEGF15

DIDECEVFPGVCKNGLCVNTRGSFKCQCPSGMTLDATGRICL
ETCFLRYEDEECTLPIAGRHRMDACC**G**SVGAAWGTEECEECPMRNTPEYEELC
DINECKMIPSLCTHGKCRNTIGSFKCRCDSGFALDSEERNCT

Sequence WSM: cbEGF14-TB5-cbEGF15

DIDECEVFPGVCKNGLCVNTRGSFKCQCPSGMTLDATGRICL
ETCFLRYEDEECTLPIAGRHRMDACC**S**SVGAAWGTEECEECPMRNTPEYEELC
DINECKMIPSLCTHGKCRNTIGSFKCRCDSGFALDSEERNCT

		Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7	Patient 8	Patient 9	Patient 10	Patient 11	Patient 12	Total / mean
	***FBN1* pathogenic variant**	**c.5076_5078del p.(Arg1692del)**		**c.5079_5084del p.(Leu1694_Cys1695del)**				**c.5123G>A p.(Gly1708Glu)**		**c.5156G>A p.(Cys1719Tyr)**	**c.5159G>A p.(Cys1720Tyr)**			**2 small indel and 3 missense variations**
	Gender	**F**	M	**F**	F	F	M	**M**	F	**F**	**M**	F	F	**8 F and 4 M**
	Family relationship	**Proband**	Son	**Proband**	Mother	Sister	Nephew	**Proband**	Mother	**Proband**	**Proband**	Mother	Sister	**5 probands and 7 relatives**
	Age range at diagnosis (y.o.)	**40-45**	5-10	**10-15**	50-55	25-30	0-5	**10-15**	30-35	**5-10**	**20-25**	60-65	15-20	**Mean age 24.3**
	Age range at consultation (y.o.)	**40-45**	5-10	**15-20**	55-60	25-30	0-5	**25-30**	NA	**15-20**	**30-35**	65-70	15-20	**Mean age 29.3**
	Height at last physical examination (cm)	**171.5**	136.5 (+3SD)	**176**	158	171	72	**175**	157	**183**	**198**	167	178	**-**
Cardiovascular	**Thoracic aortic aneurysm**	**NA**	Y	**Y**	Y	Y	N	**NA**	NA	**N**	**Y**	Y	N	**6/9**
	Valsalva diameter [z-score (Campens *et al.*, 2014)[23]]	**NA**	NA	**31mm (+2.8SD)**	40mm (+3SD)	37mm (+3SD)	NA	**NA**	NA	**30mm (+0.9SD)**	**NA**	44mm (+3SD)	34mm (+1SD)	**-**
	Ascending aortic dissection	**N**	N	**N**	N	N	N	**N**	N	**N**	**N**	N	N	**0/12**
	aortic surgery	**N**	N	**N**	N	N	N	**Mitral valve replacement**	N	**N**	**Y**	N	N	**2/12**
	age/type/indication of surgery	**-**	-	**-**	-	-	-	**10-15 yo/ mitral valve replacement / severe endocarditis**	-	**-**	**20-25 yo/ Tirone-David/ TAA**	-	-	
	Mitral valve prolapse (MVP)	**N**	N	**Y**	N	Y	N	**NA**	NA	**N**	**Y**	Y	Y	**5/10**
	Ascending aortic dilatation or dissection before 40 years old	**N**	N	**N**	N	N	N	**N**	N	**N**	**N**	N	N	**0/12**
Ocular	**Ectopia lentis (EL)**	**Y**	Y	**Y**	Y	Y	N	**N**	NA	**Y**	**Y**	Y	N	**8/11**
	Myopia (> 3 dioptries)	**N**	N	**Y**	N	Y	N	**N**	NA	**Y**	**N**	N	N	**3/11**
	Flat cornea	**N**	N	**Y**	N	Y	N	**N**	NA	**Y**	**N**	Y	N	**4/11**
Musculoskeletal	**Pectus carinatum**	**N**	Y	**N**	N	N	N	**Y**	NA	**N**	**N**	Y	Y	**4/11**
	Severe pectus excavatum	**Y**	N	**N**	N	N	N	**N**	NA	**N**	**Y**	N	N	**2/11**
	Dolichostenomelia = Reduced US/LS AND increased arm/height AND no severe scoliosis	**N**	N	**N**	Y	Y	NA	**Y**	NA	**Y**	**N**	N	N	**4/10**

	Positive wrist and thumb signs (arachnodactyly)	**N**	N	**N**	N	Y	NA	**Y**	NA	**Y**	**N**	N	Y	**4/10**
	Positive wrist or thumb signs	**N**	N	**Y**	Y	N	NA	**N**	NA	**N**	**Y**	N	N	**3/10**
	Scoliosis >20° or spondylolisthésis	**N**	N	**Y**	N	NA	N	**Y**	NA	**Y**	**Y**	Y	N	**5/10**
	Limited elbow extension < 170°	**Y**	N	**N**	N	N	NA	**N**	NA	**N**	**N**	N	Y	**2/10**
	Joint hypermobility	**Y**	Y	**N**	N	N	NA	**Y**	NA	**Y**	**N**	N	N	**4/10**
	Protrusio acetabulae	**NA**	N	**N**	Y	NA	NA	**N**	NA	**NA**	**N**	Y	N	**2/6**
	Hindfoot deformity	**N**	N	**N**	N	N	NA	**N**	NA	**N**	**N**	N	N	**0/10**
	Plain pes planus	**N**	Y	**Y**	Y	N	NA	**N**	NA	**N**	**N**	N	N	**3/10**
	Typical facial appearance (3/5 : dolichocephaly, enophtalmos, downslanting palpebral fissures, malar hypoplasia, retrognathia)	**N**	N	**N**	N	N	N	**Y**	NA	**Y**	**N**	N	N	**2/11**
	Highly arched palate with crowding	**Y**	N	**Y**	N	N	N	**Y**	NA	**N**	**N**	N	N	**3/11**
Other	**Pneumothorax**	**N**	N	**N**	N	N	NA	**NA**	NA	**N**	**N**	N	N	**0/9**
	Striae	**N**	N	**Y**	Y	Y	NA	**NA**	NA	**N**	**Y**	Y	Y	**6/9**
	Recurrent herniae	**N**	N	**Y**	N	Y	NA	**NA**	NA	**N**	**N**	N	N	**2/9**
	Dural ectasia	**NA**	NA	**N**	N	NA	NA	**NA**	NA	**NA**	**N**	Y	N	**1/5**
	Systemic score	**2**	**3**	**6**	**6**	**7**	**NA**	**8**	**NA**	**7**	**5**	**9**	**8**	**Mean SS = 6.1**
	Diagnosis	**EL + SK-m**	**MFS**	**MFS**	**MFS**	**MFS**	**NA (Presymptomatic diagnosis)**	**Mitral valve replacement + SK-M**	**NA**	**EL + SK-M**	**MFS**	**MFS**	**MVP + SK-M**	

Supplemental Material 2 (related to Table 2). Clinical features according to the revised Ghent nosology for MFS[1] for the twelve patients (five probands and their relatives) carrying a *FBN1* pathogenic variant in the TGFBP#5 domain. The grey columns correspond to the clinical features of the five probands. Y=yes; N=no; NA=not available; F=female; M=male; SK-m: minor skeletal involvement; SK-M: major skeletal involvement.