

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

Sequence WT: **cbEGF14-TB5-cbEGF15**

DIDCEVFPVCKNGLCVNTRGSFKCQCPSGMTLDATGRICL
ETCFLRYEDEECTLPIAGRHRMDACCCSVGAAWGTEEECECPMRNTPEYEELC
DINECKMIPSLCTHGKCRNTIGSFKCRCDSGFALDSEERNCT

Sequence MFS: **cbEGF14-TB5-cbEGF15**

DIDCEVFPVCKNGLCVNTRGSFKCQCPSGMTLDATGRICL
ETCFLRYEDEECTLPIAGRHRMDA**Y**CCSVGAAWGTEEECECPMRNTPEYEELC
DINECKMIPSLCTHGKCRNTIGSFKCRCDSGFALDSEERNCT

Sequence GPHYS-1: **cbEGF14-TB5-cbEGF15**

DIDCEVFPVCKNGLCVNTRGSFKCQCPSGMTLDATGRICL
ETCFLRYEDEECTLPIAGRHRMDA**W**CCSVGAAWGTEEECECPMRNTPEYEELC
DINECKMIPSLCTHGKCRNTIGSFKCRCDSGFALDSEERNCT

Sequence GPHYS-2: **cbEGF14-TB5-cbEGF15**

DIDCEVFPVCKNGLCVNTRGSFKCQCPSGMTLDATGRICL
ETCFLRYEDEECTLPIAGRHRMDACC**G**SVGAAWGTEEECECPMRNTPEYEELC
DINECKMIPSLCTHGKCRNTIGSFKCRCDSGFALDSEERNCT

Sequence WSM: **cbEGF14-TB5-cbEGF15**

DIDCEVFPVCKNGLCVNTRGSFKCQCPSGMTLDATGRICL
ETCFLRYEDEECTLPIAGRHRMDACC**S**SVGAAWGTEEECECPMRNTPEYEELC
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 <i>et al.</i> , 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 replaceme nt	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 spondylolisthesis	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, enophthalmos, 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 MFS¹ for the twelve patients (five probands and their relatives) carrying a *FBN1* pathogenic variant in the TGF β P5 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.