Supplementary tables

Supplementary table 1

Nt. change	Protein change	n total	n CD	Height (SD)	Height p-value	Severe TAA*	MVP*	CLM*	Reported	Classification	Variation ID
c.8405G>T	p.Gly2802Val	1		2,183645					No	**Likely pathogenic**	
c.8249A>G	p.Asn2750Ser	1		-1,41332					No	VUS	
c.8185A>C	p.Lys2729Gln	3		-2,492					Clinvar	Benign	199954
c.8149G>A	p.Glu2717Lys	3		0,231					(1)	VUS	
c.8072G>A	p.Gly2691Asp	1		-1,581438					No	VUS	
c.8038C>T	**p.Arg2680Cys**	**21**	**10**	**1,463**	**5,65E-08**	**23,278**	**29,773**	**78,783**	**(2-4)**	**Pathogenic**	**200127**
c.7906G>A	p.Gly2636Ser	1		NA					Clinvar	VUS	393275
c.7852 G>A	p.Gly2618Arg	3		0,368					(5)	VUS	42434
c.7727 G>A	p.Arg2576His	2		-0,769					Clinvar	VUS	927828
c.7699+2T>C	**p.IVS62+2**	**2**		**1,244039**					**This study**	**Pathogenic**	
c.7516G>A	p.Gly2506Ser	1		-1,24					(5)	Likely benign	457262
c.6744-6746delGGA	**p.Glu2248del**	**2**	**2**	**1,787**		**95,202**	**88,606**		**This study**	**Pathogenic**	
c.6724C>T	p.Arg2242Cys	13		0,274					(6)	Likely benign	384344
c.6577G>A	p.Glu2193Lys	1		NA					(2)	Likely benign	255306
c.6496+7A>G	p.IVS53+7	1		0,113					No	VUS	
c.6446A>G	**p.Tyr2149Cys**	**1**	**1**	**NA**					**(7, 8)**	**Pathogenic**	**42402**
c.5788+5G>A	**p.IVS47+5**	2	**2**	**NA**					**(9-13)**	**Pathogenic**	**42394**
c.5753A>G	p.His1918Arg	1		-2,274146					No	VUS	
c.5738A>G	p.Asn1913Ser	1		0,788290					Clinvar	VUS	912763
c.5512G>A	p.Gly1838Ser	2		0,106993					Clinvar	VUS	457232
c.5267T>C	p.Val1756Ala	3		0,317					No	VUS	
c.4921G>A	p.Glu1641Lys	3		-0,624					No	VUS	
c.4915C>G	p.Leu1639Val	1		NA					No	VUS	
c.4727T>C	p.Met1576Thr	1		0,303					(14, 15)	VUS	
c.4704A>T	p.Lys1568Asn	1		NA					No	VUS	
c.4444G>A	p.Gly1482Ser	1		0,343343					Clinvar	VUS	373256
c.4211A>G	**p.Asp1404Gly**	**2**	**1**	**NA**					**This study**	**Pathogenic**	
c.4130A>G	p.His1377Arg	2		NA					No	VUS	
c.4106A>G	p.Asn1369Ser	1		NA					Clinvar	VUS	42348
c.4087+6T>C	p.IVS33+6	2		1,518	0,026258				No	**Likely pathogenic**	
c.4085C>G	p.Thr1362Ser	1		NA					No	**Likely pathogenic**	
c.3965-8T>C	p.IVS32-8	2		-1,069					Clinvar	Benign	36072
c.3740A>G	p.Asn1247Ser	1		0,448814					No	VUS	
c.3688A>C	p.Met1230Leu	2		0,602					Clinvar	VUS	928219

c.3610A>G	p.Met1204Val	6		-0,051					Clinvar	VUS	527204
c.3590-8T>C	p.IVS29-8	3		-0,0187					Clinvar	VUS	137306
c.3547A>G	p.Asn1183Asp	2		-0,307372					No	VUS	
c.3463+3A>G	p.IVS28+3	3		2,188	0,018977				Clinvar	Benign	42337
c.3454G>A	p.Ala1152Thr	3		0,129					Clinvar	VUS	255292
c.3431A>G	p.His1144Arg	1		-0,206343					No	VUS	
c.3394A>G	p.Thr1132Ala	1		0,293138					No	VUS	
c.3290G>A	**p.C1097Y**	**1**	**1**	**NA**					**This study**	**Pathogenic**	
c.3226A>T	p.Ile1076Leu	2		-0,551455					Clinvar	VUS	406367
c.3082+6A>G	p.IVS25+6	1		0,655347					Clinvar	Benign	137304
c.3061A>G	p.Asn1021Asp	2		0,326					No	VUS	
c.3026C>T	p.Pro1009Leu	1		-0,151					Clinvar	VUS	925193
c.3018G>C	p.Glu1006Asp	1		0,254					No	VUS	
c.3016G>A	p.Glu1006Lys	1		NA					Clinvar	VUS	921753
c.2931G>A	p.Met977Ile	3		-0.926					Clinvar	VUS	200007
c.2893G>A	p.Glu965Lys	2		0,77					Clinvar	VUS	449603
c.2860C>T	p.Arg954Cys	**4**		0,149175					(14, 16-18)	**Pathogenic**	495582
c.2855-2A>G	**p.IVS24-2**	1	**1**	**NA**					**This study**	**Pathogenic**	
c.2813C>T	p.Pro938Leu	2		0,12					Clinvar	VUS	549115
c.2729-8C>T	p.IVS23-8	2		0,380913					Clinvar	Likely benign	527226
c.2434G>A	p.Glu812Lys	1		NA					Clinvar	VUS	199997
c.1972C>T	p.Arg658Trp	2		0,300701					Clinvar	VUS	919151
c.1850G>A	**p.Cys617Tyr**	**1**	**1**	**1,902062**					**Clinvar**	**Pathogenic**	**495563**
c.1743G>A	p.Met581Ile	1		0,29					No	VUS	
c.1616G>A	p.Arg539Gln	4		0,663	0,011541	29,776			No	**Likely pathogenic**	
c.1529C>T	p.Ser510Leu	**1**		-1,521974					Clinvar	VUS	923073
c.1464dupT	**p.Ile489TyrfsTer2**	1		**NA**					**This study**	**Pathogenic**	
c.1216C>G	p.Leu406Val	1		-0,929350					Clinvar	VUS	922145
c.1201T>A	p.Tyr401Asn	1		NA					No	VUS	
c.1169C>T	p.Ser390Phe	3		0,23					Clinvar	VUS	549007
c.1148-8T>G	p.IVS10-8	2		0,102					No	VUS	
c.1057A>G	p.Ile353Val	12		-0,0217					No	VUS	
c.902G>T	p.Gly301Val	1		0,17					Clinvar	VUS	199960
c.863A>G	p.Asp288Gly	1		NA					Clinvar	VUS	519791
c.206C>G	p.Pro69Arg	3		0,884					No	VUS	
c.59A>G	p.Tyr20Cys	1		NA					(9)	VUS	

Supplementary Table 1: All *FBN1* variants detected in the study, from case-series and deCODE database combined, in addition we present the nMFS case. Total of 70 variants in 163 individuals. 31 individuals are deceased and therefore not used to calculate final prevalence.

Significance was predicted using the AMCG guidelines. Variants in individuals with a clinical diagnosis are bolded. *Height is adjusted for year of birth.

n total=Number of individuals in the deCODE database+case-series, n CD= Number of individuals in the case-series, MVP= Mitral valve prolapse, CLM= Congenital lens malformation, NA=Not available, CVS=Cardio vascular system, EL=Ectopia lentis, sc=Skeletal, DCM=Dilated cardiomyopathy, abao=abdominal aneurysm, MVD=Mitral valve disease, CM= Cardiomyopathy, AoV ins.=Aorta valve deficiency, Ao=Aorta dilation, AD=Aorta dissection, SP=Spontaneous pneumothorax.

*Odds ratio (OR), values with p-value <0,05.

Variant	**Qty**	Significance	Height SD mean	Thoracic aneurysm	AoV surgery	MV disease/surgery	PE	Glaucoma	Reported
p.Arg2680Cys	**21**	**Classical MFS**	**1,463**	**3**	**1**	**2**	**1**	**1**	**(2-4)**
p.Tyr2149Cys	**1**	**Classical MFS**	**NA**	**1**	**NA**	**1**	**NA**	**0**	**(7, 8)**
p.IVS47+5	**2**	**Classical MFS**	**NA**	**0**	**0**	**0**	**0**	**0**	**(9-13)**
p.Arg954Cys	4	Classical MFS	0,149175	0	0	0	0	0	(14, 16-18)

Supplementary Table 2: Previously reported pathogenic or likely pathogenic variants observed in the Icelandic cohort and data from deCODE phenotype lists. Qty=Quantity; SD=Standard deviation; AoV=Aortic Valve; MV=Mitral Valve; PE=Pectus excavatum; VUS= Variant of uncertain significance; MFS=Marfan syndrome; Skeletal=Isolated skeletal symptoms; CVS=Isolated involvement of the Cardiovascular system; EL=Isolated ectopia lentis.

Variants from the case series are bolded.

1. Ziganshin BA, Bailey AE, Coons C, Dykas D, Charilaou P, Tanriverdi LH, et al. Routine Genetic Testing for Thoracic Aortic Aneurysm and Dissection in a Clinical Setting. The Annals of Thoracic Surgery. 2015;100(5):1604-11.
2. Arnaud P, Hanna N, Aubart M, Leheup B, Dupuis-Girod S, Naudion S, et al. Homozygous and compound heterozygous mutations in the FBN1 gene: unexpected findings in molecular diagnosis of Marfan syndrome. Journal of Medical Genetics. 2016.
3. Palz M, Tiecke F, Booms P, Göldner B, Rosenberg T, Fuchs J, et al. Clustering of mutations associated with mild Marfan-like phenotypes in the 3′ region of FBN1 suggests a potential genotype–phenotype correlation. American Journal of Medical Genetics. 2000;91(3):212-21.
4. Grossfield J CS, Milewics DM. Mutations in the carboxy terminus of FBN1 suggest a potential genotype-phenotype correlation in the Marfan syndrome. American Journal of Human Genetics. 1993;53:1167.
5. Baudhuin LM, Kotzer KE, Lagerstedt SA. Decreased frequency of FBN1 missense variants in Ghent criteria-positive Marfan syndrome and characterization of novel FBN1 variants. J Hum Genet. 2015.
6. Wooderchak-Donahue W, VanSant-Webb C, Tvrdik T, Plant P, Lewis T, Stocks J, et al. Clinical utility of a next generation sequencing panel assay for Marfan and Marfan-like syndromes featuring aortopathy. Am J Med Genet A. 2015;167a(8):1747-57.
7. Yang H, Luo M, Fu Y, Cao Y, Yin K, Li W, et al. Genetic testing of 248 Chinese aortopathy patients using a panel assay. Sci Rep. 2016;6:33002-.
8. Lerner-Ellis JP, Aldubayan SH, Hernandez AL, Kelly MA, Stuenkel AJ, Walsh J, et al. The spectrum of FBN1, TGFβR1, TGFβR2 and ACTA2 variants in 594 individuals with suspected Marfan Syndrome, Loeys–Dietz Syndrome or Thoracic Aortic Aneurysms and Dissections (TAAD). Molecular Genetics and Metabolism. 2014;112(2):171-6.
9. Arbustini E, Grasso M, Ansaldi S, Malattia C, Pilotto A, Porcu E, et al. Identification of sixty-two novel and twelve known FBN1 mutations in eighty-one unrelated probands with Marfan syndrome and other fibrillinopathies. Hum Mutat. 2005;26(5):494.
10. Nijbroek G, Sood S, McIntosh I, Francomano CA, Bull E, Pereira L, et al. Fifteen novel FBN1 mutations causing Marfan syndrome detected by heteroduplex analysis of genomic amplicons. American Journal of Human Genetics. 1995;57(1):8-21.
11. Youil R, Toner TJ, Bull E, Bailey AL, Earl CD, Dietz HC, et al. Enzymatic mutation detection (EMD) of novel mutations (R565X and R1523X) in the FBN1 gene of patients with Marfan syndrome using T4 endonuclease VII. Hum Mutat. 2000;16(1):92-3.
12. Rommel K, Karck M, Haverich A, Schmidtke J, Arslan-Kirchner M. Mutation screening of the fibrillin-1 (FBN1) gene in 76 unrelated patients with Marfan syndrome or Marfanoid features leads to the identification of 11 novel and three previously reported mutations. Hum Mutat. 2002;20(5):406-7.
13. Stheneur C, Collod-Beroud G, Faivre L, Buyck JF, Gouya L, Le Parc JM, et al. Identification of the minimal combination of clinical features in probands for efficient mutation detection in the FBN1 gene. Eur J Hum Genet. 2009;17(9):1121-8.
14. Sheikhzadeh S, Kade C, Keyser B, Stuhrmann M, Arslan-Kirchner M, Rybczynski M, et al. Analysis of phenotype and genotype information for the diagnosis of Marfan syndrome. Clin Genet. 2012;82(3):240-7.

15. Rommel K, Karck M, Haverich A, von Kodolitsch Y, Rybczynski M, Muller G, et al. Identification of 29 novel and nine recurrent fibrillin-1 (FBN1) mutations and genotype-phenotype correlations in 76 patients with Marfan syndrome. Hum Mutat. 2005;26(6):529-39.
16. Comeglio P, Johnson P, Arno G, Brice G, Evans A, Aragon-Martin J, et al. The importance of mutation detection in Marfan syndrome and Marfan-related disorders: report of 193 FBN1 mutations. Hum Mutat. 2007;28(9):928.
17. Deng T, Dong B, Zhang X, Dai H, Li Y. Late-onset bilateral lens dislocation and glaucoma associated with a novel mutation in FBN1. Molecular Vision. 2008;14:1229-33.
18. Hung CC, Lin SY, Lee CN, Cheng HY, Lin SP, Chen MR, et al. Mutation spectrum of the fibrillin-1 (FBN1) gene in Taiwanese patients with Marfan syndrome. Ann Hum Genet. 2009;73(Pt 6):559-67.