

Supplementary Materials

Table S1 Missense/ in-frame vs. splicing mutation (SV, sinus of Valsalva; MVP, mitral valve prolapse; TVP, tricuspid valve prolapse, PA dilatation, pulmonary artery dilatation; David, David surgery; Facial features (>3 of enophthalmus, dolichocephaly, downslanting palpebral fissures, malar hypoplasia, retrognathia), foot deformity (pes planus or hindfoot deformity).

	Prevalence			Age of onset		
	Missense/ in-frame	Splicing	p-value	Missense/ in-frame	Splicing	p-value
SV dilatation	35/62 (56.5%)	7/14 (50.0%)	ns	7.4 ± 0.5	9.4 ± 6.9	ns
MVP	31/62 (50.0%)	9/14 (64.3%)	ns	7.8 ± 5.7	10.0 ± 5.9	ns
TVP	38/62 (61.3%)	11/14 (78.6%)	ns	6.9 ± 5.6	10.0 ± 6.1	ns
PA dilatation	6/61 (9.8%)	2/14 (14.3%)	ns	4.3 ± 5.1	10.5 ± 9.1	ns
David	5/62 (8.1%)	0/14 (0.0%)	ns	13.1 ± 5.5	-	-
Medication	35/62 (56.5%)	8/14 (57.1%)	ns	7.6 ± 5.1	11.5 ± 4.1	ns
Dural ectasia	21/61 (34.4%)	7/14 (50.0%)	ns	11.1 ± 4.9	14.7 ± 3.4	ns
High arched palate	33/62 (53.2%)	9/14 (64.3%)	ns	9.0 ± 5.1	11.4 ± 4.8	ns
Facial feature	24/62 (38.7%)	3/14 (21.4%)	ns	5.9 ± 5.8	5.5 ± 3.3	ns
Arm-span-to-height ratio > 1.05	15/62 (24.2%)	5/14 (35.7%)	ns	11.0 ± 4.7	10.2 ± 5.9	ns
Pectus excavatum	6/62 (9.7%)	6/14 (42.9%)	0.0067	7.5 ± 6.7	7.7 ± 4.4	ns
Pectus carinatum	15/62 (24.2%)	2/14 (14.3%)	ns	10.4 ± 4.9	14.7 ± 2.6	ns
scoliosis	22/62 (35.5%)	5/14 (35.7%)	ns	10.0 ± 4.7	10.9 ± 5.2	ns
Wrist and thumb sign	7/62 (11.3%)	3/14 (21.4%)	ns	10.5 ± 4.6	9.2 ± 6.7	ns
Foot deformity	35/62 (56.5%)	7/14 (50.0%)	ns	7.6 ± 5.5	8.8 ± 4.7	ns
Reduced elbow-extension	9/62 (14.5%)	0/14 (0.0%)	ns	10.5 ± 6.8	-	ns
Ectopia lentis	23/62 (37.1%)	4/14 (28.6%)	ns	7.4 ± 5.5	10.1 ± 6.4	ns
Myopia	14/61 (23.0%)	3/14 (21.4%)	ns	6.3 ± 4.4	7.5 ± 7.2	ns
Skin striae	14/62 (22.6%)	4/14 (28.6%)	ns	13.4 ± 3.4	13.1 ± 4.1	ns
Hernia	3/62 (4.8%)	1/14 (7.1%)	ns	5.3 ± 1.4	12.9 ± 0.0	0.0416
pneumothorax	4/62 (6.5%)	0/14 (0%)	ns	15.1 ± 0.6	-	ns
Systemic score ≥ 7	21/59 (35.6%)	4/14 (28.6%)	ns	11.1 ± 5.5	14.1 ± 2.1	ns

Table S2 Missense/ in-frame vs. nonsense/ frameshift mutations (SV, sinus of Valsalva; MVP, mitral valve prolapse; TVP, tricuspid valve prolapse, PA dilatation, pulmonary artery dilatation; David, David surgery; Facial features (>3 of enophthalmus, dolichocephaly, downslanting palpebral fissures, malar hypoplasia, retrognathia), foot deformity (pes planus or hindfoot deformity).

	Prevalence			Age of onset		
	Missense/ in-frame	Nonsense/ frameshift	p-value	Missense/ in-frame	Nonsense/ frameshift	p-value
SV dilatation	35/62 (56.5%)	18/29 (62.1%)	ns	7.4 ± 0.5	8.5 ± 4.5	ns
MVP	31/62 (50.0%)	18/29 (62.1%)	ns	7.8 ± 5.7	9.1 ± 4.0	ns

TVP	38/62 (61.3%)	21/28 (75.0%)	ns	6.9 ± 5.6	7.6 ± 4.6	ns
PA dilatation	6/61 (9.8%)	2/29 (6.9%)	ns	4.3 ± 5.1	15.4 ± 4.1	0.0334
David	5/62 (8.1%)	1/29 (3.4%)	ns	13.1 ± 5.5	13.5 ± 0.0	ns
Medication	35/62 (56.5%)	21/29 (72.4%)	ns	7.6 ± 5.1	8.7 ± 4.9	ns
Dural ectasia	21/61 (34.4%)	19/28 (67.8%)	0.0054	11.1 ± 4.9	11.1 ± 3.8	ns
High arched palate	33/62 (53.2%)	19/29 (65.5%)	ns	9.0 ± 5.1	8.9 ± 4.7	ns
Facial feature	24/62 (38.7%)	6/29 (20.7%)	ns	5.9 ± 5.8	7.2 ± 2.3	ns
Arm-span-to-height ratio > 1.05	15/62 (24.2%)	13/29 (44.8%)	ns	11.0 ± 4.7	11.4 ± 4.0	ns
Pectus excavatum	6/62 (9.7%)	7/29 (24.1%)	ns	7.5 ± 6.7	9.9 ± 4.1	ns
Pectus carinatum	15/62 (24.2%)	7/29 (24.1%)	ns	10.4 ± 4.9	9.9 ± 3.4	ns
scoliosis	22/62 (35.5%)	11/29 (37.9%)	ns	10.0 ± 4.7	9.7 ± 5.3	ns
Wrist and thumb sign	7/62 (11.3%)	7/29 (24.1%)	ns	10.5 ± 4.6	11.9 ± 3.2	ns
Foot deformity	35/62 (56.5%)	17/29 (58.6%)	ns	7.6 ± 5.5	8.1 ± 4.0	ns
Reduced elbow-extension	9/62 (14.5%)	3/28 (10.7%)	ns	10.5 ± 6.8	11.8 ± 4.8	ns
Ectopia lentis	23/62 (37.1%)	2/29 (6.9%)	0.0023	7.4 ± 5.5	9.1 ± 4.9	ns
Myopia	14/61 (23.0%)	5/29 (17.2%)	ns	6.3 ± 4.4	5.5 ± 4.1	ns
Skin striae	14/62 (22.6%)	6/29 (20.7%)	ns	13.4 ± 3.4	14.1 ± 2.1	ns
Hernia	3/62 (4.8%)	4/29 (13.8%)	ns	5.3 ± 1.4	7.3 ± 3.5	ns
pneumothorax	4/62 (6.5%)	1/29 (3.4%)	ns	15.1 ± 0.6	14.5 ± 0.0	ns
Systemic score ≥ 7	21/59 (35.6%)	13/29 (44.8%)	ns	11.1 ± 5.5	11.3 ± 4.1	ns

Table S3 Nonsense/ frameshift mutations vs. Splicing mutations (SV, sinus of Valsalva; MVP, mitral valve prolapse; TVP, tricuspid valve prolapse, PA dilatation, pulmonary artery dilatation; David, David surgery; Facial features (>3 of enophthalmus, dolichocephaly, downslanting palpebral fissures, malar hypoplasia, retrognathia), foot deformity (pes planus or hindfoot deformity).

	Prevalence			Age of onset (years)		
	Nonsense/ frameshift	Splicing	p- value	Nonsense / frameshift	Splicing	p- value
SV dilatation	18/29 (62.1%)	7/14 (50.0%)	ns	8.5 ± 4.5	9.4 ± 6.9	ns
MVP	18/29 (62.1%)	9/14 (64.3%)	ns	9.1 ± 4.0	10.0 ± 5.9	ns
TVP	21/28 (75.0%)	11/14 (78.6%)	ns	7.6 ± 4.6	10.0 ± 6.1	ns
PA dilatation	2/29 (6.9%)	2/14 (14.3%)	ns	15.4 ± 4.1	10.5 ± 9.1	ns
BAV	1/28 (3.5%)	0/14 (0%)	ns	17.7 ± 0.0	-	-
Medication	21/29 (72.4%)	8/14 (57.1%)	ns	8.7 ± 4.9	11.5 ± 4.1	ns
Dural ectasia	19/28 (67.8%)	7/14 (50.0%)	ns	11.1 ± 3.8	14.7 ± 3.4	ns
High arched palate	19/29 (65.5%)	9/14 (64.3%)	ns	8.9 ± 4.7	11.4 ± 4.8	ns
Facial feature	6/29 (20.7%)	3/14 (21.4%)	ns	7.2 ± 2.3	5.5 ± 3.3	ns
Arm-span-to-height ratio > 1.05	13/29 (44.8%)	5/14 (35.7%)	ns	11.4 ± 4.0	10.2 ± 5.9	ns
Pectus excavatum	7/29 (24.1%)	6/14 (42.9%)	ns	9.9 ± 4.1	7.7 ± 4.4	ns

Pectus carinatum	7/29 (24.1%)	2/14 (14.3%)	ns	9.9 ± 3.4	14.7 ± 2.6	ns
scoliosis	11/29 (37.9%)	5/14 (35.7%)	ns	9.7 ± 5.3	10.9 ± 5.2	ns
Wrist and thumb sign	7/29 (24.1%)	3/14 (21.4%)	ns	11.9 ± 3.2	9.2 ± 6.7	ns
Foot deformity	17/29 (58.6%)	7/14 (50.0%)	ns	8.1 ± 4.0	8.8 ± 4.7	ns
Reduced elbow-extension	3/28 (10.7%)	0/14 (0%)	ns	11.8 ± 4.8	-	ns
Ectopia lentis	2/29 (6.9%)	4/14 (28.6%)	ns	9.1 ± 4.9	10.1 ± 6.4	ns
Myopia	5/29 (17.2%)	3/14 (21.4%)	ns	5.5 ± 4.1	7.5 ± 7.2	ns
Skin striae	6/29 (20.7%)	4/14 (28.6%)	ns	14.1 ± 2.1	13.1 ± 4.1	ns
Hernia	4/29 (13.8%)	1/14 (7.1%)	ns	7.3 ± 3.5	12.9 ± 0.0	ns
pneumothorax	1/29 (3.4%)	0/14 (0%)	ns	14.6 ± 0.0	-	ns
Systemic score ≥ 7	13/29 (44.8%)	4/14 (28.6%)	ns	11.3 ± 4.1	14.1 ± 2.1	ns

Table S4 Missense mutations involving a cysteine (cys-missense) vs. Missense mutations not involving a cysteine (non-cys-missense) (SV, sinus of Valsalva; MVP, mitral valve prolapse; TVP, tricuspid valve prolapse, PA dilatation, pulmonary artery dilatation; David, David surgery; Facial features (>3 of enophthalmus, dolichocephaly, downslanting palpebral fissures, malar hypoplasia, retrognathia), foot deformity (pes planus or hindfoot deformity).

	Prevalence			Age of onset		
	cys-missense	non-cys-missense	p-value	cys-missense	non-cys-missense	p-value
SV dilatation	23/34 (67.6%)	9/24 (37.5%)	0.0327	6.3 ± 5.6	8.6 ± 6.3	ns
MVP	18/34 (52.9%)	11/24 (45.8%)	ns	6.5 ± 5.6	10.5 ± 5.8	ns
TVP	25/34 (73.5%)	10/24 (41.7%)	0.0281	6.3 ± 4.9	8.2 ± 7.6	ns
PA dilatation	2/34 (5.9%)	4/23 (17.4%)	ns	2.1 ± 1.7	5.4 ± 6.2	ns
David	4/34 (11.8%)	1/24 (4.2%)	ns	13.6 ± 6.2	10.9 ± 0.0	ns
Medication	24/34 (70.6%)	7/24 (29.2%)	0.003	7.5 ± 5.3	7.7 ± 5.2	ns
Dural ectasia	13/34 (38.2%)	7/24 (29.2%)	ns	10.5 ± 5.7	11.8 ± 3.7	ns
High arched palate	18/34 (52.9%)	13/24 (54.2%)	ns	7.9 ± 5.0	10.6 ± 4.9	ns
Facial feature	13/34 (38.2%)	9/24 (37.5%)	ns	5.1 ± 5.6	7.6 ± 6.6	ns
Arm-span-to-height ratio > 1.05	5/34 (14.7%)	9/24 (37.5%)	ns	10.1 ± 5.3	11.9 ± 4.6	ns
Pectus excavatum	3/34 (8.8%)	3/24 (12.5%)	ns	6.9 ± 6.2	8.4 ± 10.0	ns
Pectus carinatum	9/34 (26.5%)	5/24 (20.8%)	ns	8.4 ± 4.0	12.7 ± 4.8	ns
scoliosis	11/34 (32.4%)	10/24 (41.7%)	ns	8.4 ± 4.9	11.3 ± 4.2	ns
Wrist and thumb sign	3/34 (8.8%)	3/24 (12.5%)	ns	8.5 ± 3.8	11.7 ± 5.4	ns
Foot deformity	22/34 (64.7%)	11/24 (45.8%)	ns	6.6 ± 5.0	9.8 ± 5.8	ns
Reduced elbow-extension	5/34 (14.7%)	4/24 (16.7%)	ns	12.9 ± 7.1	6.5 ± 5.0	ns
Ectopia lentis	15/34 (44.1%)	6/24 (25.0%)	ns	5.8 ± 5.3	9.8 ± 5.7	ns
Myopia	7/34 (20.6%)	4/23 (17.4%)	ns	3.7 ± 2.2	9.6 ± 4.8	0.0245
Skin striae	5/34 (14.7%)	8/24 (33.3%)	ns	13.2 ± 5.2	13.3 ± 2.1	ns
Hernia	2/34 (5.9%)	1/24 (4.2%)	ns	5.7 ± 1.6	4.4 ± 0	ns
pneumothorax	2/34 (5.9%)	1/24 (4.2%)	ns	15.6 ± 0.0	14.8 ± 0	0.025

Systemic score ≥ 7	10/32 (31.3%)	9/23 (39.1%)	ns	10.6 \pm 5.9	9.7 \pm 4.8	ns
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Table S5 Cardiovascular genotype-phenotype correlations (YOP, year of publication; cys-missense, missense mutations involving a cysteine; non-cys, missense mutations not involving a cysteine; PTC, premature termination codon; HI, haploinsufficiency; DN, dominant-negative; cardiovasc, cardiovascular; SV-Dil, sinus of Valsalva dilatation; PA-Dil, pulmonary artery dilatation; TVP, tricuspid valve prolapse; MVP, mitral valve prolapse).

Authors	YOP	Results
Loeys et al.	2004	No difference of cardiovasc. involvement (cys-miss/PTC)
Waldmüller et al.	2007	No difference of cardiovasc. involvement (cys-miss/PTC)
Detaint et al.	2010	More aortic dilatation, aortic events, and MVP in cys-missense
Baudhuin et al.	2014	More+earlier aortic events in in truncating+splicing variants than missense
Aubart et al.	2015	More aortic dilatation if low level of Wild-type <i>FBN1</i> mRNA
Yang et al.	2016	More aortic involvement in truncating or splicing variants than missense
Franken et al.	2017	More aortic phenotype in HI (larger, more rapid dilatation, increased risk of death and dissections) than in DN
Salvi et al. [53]	2017	Same aortic stiffness in HI and DN
Seo et al.	2018	More aortic dilatation in cys-missense than in non-cys-missense
Becerra-Munoz et al.	2018	More aortic events in truncating (nonsense, frameshift) than in missense
Takeda et al.	2018	More SV-Dil, aortic events in HI than DN More SV-Dil, aortic events in DN-cys than DN-non-cys Same risk aortic events in HI and DN-cys
Li et al.	2019	More aortic dissection in HI than DN
Gao et al.	2019	More cardiovasc. involvement in PTC than in non-PTC More cardiovasc. involvement in cys-missense More cardiovasc. involvement in exons 43–65
Xu et al.	2020	More aortic dissection in HI (frameshift + nonsense) than in missense
Stark et al.	2020	More SV-Dil, TVP, medication in cys-missense than in non-cys-missense Earlier PA-Dil in missense/in-frame than in nonsense/frameshift

Table S6 Ocular genotype-phenotype correlations (YOP, year of publication; EL, ectopia lentis, cys-missense, missense mutations involving a cysteine; non-cys, missense mutations not involving a cysteine; PTC, premature termination codon; HI, haploinsufficiency; DN, dominant-negative)

Authors	YOP	Results
Schriever et al.	1999 2002	More EL in cys-missense than in PTC
Comeglio et al.	2002	More EL in missense exons 1–15

Biggin et al. [54]	2004	More EL in cys-missense than in PTC
Loeys et al.	2004 2007	More EL in cys-missense than in PTC
Comeglio et al.	2007	More EL in cys-missense than nonsense/frameshift
Rommel et al.	2005	More EL in cys-missense than PTC or non-cys missense
Faivre et al.	2007	More EL in cys-missense than in other missense
Aubart et al.	2015	More EL if low level of wild-type <i>FBN1</i> mRNA
Baudhuin et al.	2015	More EL in cys-missense than in other missense
Seo et al.	2018	More EL in missense than in other mutations
Becerra-Munoz et al.	2018	More EL in missense than nonsense, frameshift
Li et al.	2019	More EL in DN than in HI More EL in cys-missense than in PTC
Gao et al.	2019	More EL in cys-missense More EL in non-PTC than PTC More EL in missense than frameshift
Stark et al.	2020	More EL in missense than in nonsense/frameshift Earlier myopia in cys-missense than in non-cys-missense

Table S7 Skeleton, skin, lung and dural genotype-phenotype correlations (YOP, year of publication; cys-missense, missense mutations involving a cysteine; non-cys, missense mutations not involving a cysteine; PTC, premature termination codon; HI, haploinsufficiency; DN, dominant-negative)

Authors	YOP	Results
Schrijver et al.	2002	More skeletal involvement in PTC than in cys-missense
Loeys et al.	2004	More skeletal in PTC than in cys-missense
Rommel et al.	2005	More skeletal in splice than PTC
Faivre et al.	2007	More skeletal involvement in PTC than in in-frame More skin involvement in PTC than in in-frame
Comeglio et al.	2007	More skeletal involvement in nonsense/frameshift than cys-missense
Haine et al.	2015	More musculoskeletal in PTC than in in-frame
Aubart et al.	2015	More pectus abnormality if low level of wild-type <i>FBN1</i> mRNA
Franken et al.	2015	More pectus carinatum in HI than DN More dural ectasia in HI than DN More skin striae in HI than DN
Seo et al.	2018	Less dural ectasia in missense mutations than other variants
Becerra-Munoz et al.	2018	More positive systemic score in truncating (nonsense, frameshift) than in missense
Stark et al.	2020	More pectus excavatum in splicing than missense/in-frame Earlier hernias in missense/ in-frame than splicing More dural ectasia in nonsense/frameshift than missense