

Additional file 1 Table S1. – Variants in FBN-1 and phenotypic characteristics of the carrier patients.

| Genetic variant | | | | | | | | Phenotypic characteristics | | | | | | | MFS |
|-----------------|------|---------------|-------------------|------------------|-----------------------|-------------|---------------------|----------------------------|-----|-----|------------------|-------------|--------|----------------|-----|
| Meaning | Type | Exon / Intron | Nucleotide change | Protein change | Domain | Inheritance | Described | N° family members | Sex | Age | Vascular | Systemic ≥7 | Ocular | Family history | |
| Missense | Sub | Exon 1 | c.3G>A | p.Met1Lle | Signal peptide | Mother | No | 1 | F | 48 | MVP | Yes | EL, SM | | No |
| Missense | Sub | Exon 2 | c.175T>C | p.Cys59Arg | 4-cys motif LTBP-like | Father | Yes ⁶ ★ | 1 | M | 39 | MAD, MVP | Yes | EL | SD (M 40y) | Yes |
| Missense | Sub | Exon 2 | c.185G>A | p.Arg62His | 4-cys motif LTBP-like | ND | Yes ¹⁴ ★ | 1 | M | 68 | TA | No | No | | No |
| Missense | Sub | Exon 2 | c.213G>C | p.Trp71Cys | 4-cys motif LTBP-like | De novo | No | 1 | F | 8 | No | No | EL | | No |
| Nonsense | Sub | Exon 4 | c.349C>T | p.Gln117* | EGF-like #02 | ND | No | 2 | M | 31 | TA (BB 20y) | Yes | No | | Yes |
| | | | | | | | | | M | 30 | TA (Yacoub 30y) | Yes | No | | Yes |
| Nonsense | Sub | Exon 5 | c.493C>T | p. Arg165* | EGF-like#03 | ND | Yes ¹² | 1 | F | 33 | MAD, MVP | No | No | TAAD (F 42y) | Yes |
| Nonsense | Sub | Exon 6 | c.643C>T | p.Arg215* | Hybrid module #01 | ND | Yes ¹ | 2 | F | 42 | TA (David 40 y) | Yes | EL, SM | | Yes |
| | | | | | | | | | M | 15 | MAD, MVP | Yes | No | | Yes |
| Frameshift | Ins | Exon 8 | c.950insC | p.Pro317ProfsX30 | cb EGF-like #02 | Father | No | 1 | M | 45 | TA (David 39 y) | No | SM | TAAD (M 50y) | Yes |
| Missense | Sub | Exon 9 | c.1027G>A | p.Gly343Arg | TGFBP#01 | Mother | Yes ² | 2 | M | 45 | TA (BB 38y), MVP | Yes | No | | Yes |
| | | | | | | | | | M | 41 | TA, MVP | Yes | EL | | Yes |
| Missense | Sub | Exon 9 | c.1097G>C | p.Trp366Ser | TGFBP#01 | Father | No | 2 | M | 17 | MAD | Yes | No | SD (M 46y) | Yes |
| | | | | | | | | | F | 11 | MVP | No | No | SD (M 46y) | Yes |
| Intronic | Sub | Exon 9-10 | c.1148-1G>A | | TGFBP#01 | ND | No | 2 | F | 45 | MAD | Yes | EL | SD (M 42y) | Yes |
| | | | | | | | | | F | 22 | MAD, MVP | Yes | No | SD (M 42y) | Yes |

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|----------|-----|---------|------------|-------------|------------------|---------|-------------------|---|---|----|----------------------|-----|----|---------------------------------|-----|
| Nonsense | Sub | Exon 13 | c.1533C>G | p.Tyr511* | cb EGF-like #03 | ND | No | 1 | F | 43 | TA (Yacoub 40y) | Yes | No | | Yes |
| Missense | Sub | Exon 14 | c.1792T>C | p.Cys598Arg | cb EGF-like #05 | Mother | No | 1 | M | 15 | No | No | EL | TA (F 40y) | Yes |
| Missense | Sub | Exon 16 | c.1849T>C | p.Cys617Arg | cb EGF-like #06 | ND | No | 1 | F | 19 | MAD, MVP, osAID | Yes | EL | | Yes |
| Missense | Sub | Exon 18 | c.2177A>C | p.Glu726Ala | cb EGF-like #07 | ND | No | 1 | M | 51 | MAD | Yes | EL | | Yes |
| Missense | Sub | Exon 18 | c.2223A>G | p.Asn741Ser | cb EGF-like #07 | ND | No | 2 | M | 43 | MAD | No | EL | | Yes |
| | | | | | | | | | M | 18 | MAD, BAV, MVP | No | EL | | Yes |
| Missense | Sub | Exon 18 | c.2242T>C | p.Cys748Arg | cb EGF-like #07 | Mother | No | 1 | F | 45 | TA (Yacoub 43y), MVP | Yes | EL | TAAD (F 21y, M 24y), SD (M 50y) | Yes |
| Missense | Sub | Exon 18 | c.2258G>T | p.Gly753Val | cb EGF-like #07 | De novo | No | 1 | M | 14 | MAD | Yes | EL | | Yes |
| Missense | Sub | Exon 19 | c.2375G>A | p.Cys792Tyr | cb EGF-like #08 | Father | Yes ¹³ | 1 | F | 41 | MAD, MVP | Yes | EL | TAAD (M 52y), SD (M 7y) | Yes |
| Nonsense | Sub | Exon 20 | c.2438C>G | p.Ser813* | cb EGF-like #09 | De novo | Yes ¹ | 1 | F | 9 | MAD | Yes | No | | Yes |
| Missense | Sub | Exon 20 | c.2495G>A | p.Cys832Tyr | cb EGF-like #09 | ND | Yes ⁴ | 2 | M | 41 | MAD | Yes | EL | | Yes |
| | | | | | | | | | F | 1 | MAD | No | EL | | Yes |
| Nonsense | Sub | Exon 21 | c.2581C>T | p.Arg861* | Hybrid motif #02 | | Yes ⁴ | 1 | F | 50 | TAAD (David 48 y) | Yes | No | | Yes |
| Missense | Sub | Exon 23 | c.2740 T>A | p.Cys914Ser | cb EGF-like #10 | ND | Yes ⁷ | 9 | F | 65 | MAD | No | SM | | Yes |
| | | | | | | | | | M | 63 | MAD | No | No | | Yes |
| | | | | | | | | | F | 57 | No | No | SM | | Yes |
| | | | | | | | | | F | 38 | MAD | No | EL | | Yes |
| | | | | | | | | | M | 31 | MAD | No | No | | Yes |
| | | | | | | | | | M | 27 | MAD | No | EL | | Yes |
| | | | | | | | | | M | 10 | MAD | No | EL | | Yes |
| | | | | | | | | | M | 8 | MAD | No | EL | | Yes |
| F | 7 | MAD | No | EL | | Yes | | | | | | | | | |

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|------------|--------|------------|-------------------|-------------------|-----------------|---------|------------------|---|---|----|------------------------------|-----|--------|------------------------|-----|
| Missense | Sub | Exon 26 | c.3290G>A | p.Cys1097Tyr | cb EGF-like #12 | ND | No | 1 | F | 46 | TA (BB 38y) | Yes | EL | | Yes |
| Nonsense | Sub | Exon 27 | c.3373 C>T | p.Arg1125* | cb EGF-like #13 | ND | Yes ³ | 3 | F | 48 | TA (BB 25y) | Yes | SM | SD (M 33y) | Yes |
| | | | | | | | | | M | 21 | MAD | Yes | EL | SD (M 33y) | Yes |
| | | | | | | | | | F | 17 | MAD | Yes | EL, SM | SD (M 33y) | Yes |
| Nonsense | Sub | Exon 27 | c.3397G>T | p.Glu1133* | cb EGF-like #13 | ND | No | 1 | F | 43 | TAAD (BB 43 y) | Yes | SM | | Yes |
| Frameshift | Del | Exon 27 | c.3439delT | p.Ser1147fs*1161 | cb EGF-like #13 | Father | No | 1 | F | 42 | TA (David 36 y), MVP | Yes | No | SD (M 24y), SD (F 45y) | Yes |
| Frameshift | Del | Exon 31 | c.3848_3849delAG | Glu1283fs*1284 | cb EGF-like #17 | ND | No | 2 | F | 46 | MAD, MVP (PMVR 33 y) | Yes | | | Yes |
| | | | | | | | | | M | 25 | MAD | Yes | SM | | Yes |
| Missense | Sub | Exon 32 | c.3977G>C | p.Cys1326Ser | cb EGF-like #18 | De novo | No | 1 | M | 3 | MAD, MVP | Yes | EL | | Yes |
| Intronic | Sub | Exon 33-34 | c.4210+1 G>A | | cb EGF-like #20 | ND | No | 1 | M | 45 | TA (Yacoub 43y) | Yes | EL | | Yes |
| Nonsense | Sub | Exon 34 | c.4255C>T | p.Gln1419* | cb EGF-like #20 | Mother | No | 2 | M | 57 | TA (BB 50y) | Yes | No | | Yes |
| | | | | | | | | | F | 31 | MAD | Yes | No | | Yes |
| Missense | Sub | Exon 34 | c.4283G>C | p.Arg1428Pro | cb EGF-like #20 | De novo | No | 1 | M | 7 | MAD | No | EL | | Yes |
| Missense | Sub | Exon 37 | c.4588C>T | p.Arg1530Cys | TGFBP#04 | ND | Yes ⁸ | 2 | F | 61 | MAD MVP (MVrep + Yacoub 55y) | No | No | | Yes |
| | | | | | | | | | F | 27 | MAD, MVP | Yes | EL | | Yes |
| Frameshift | InsDel | Exon 37 | c.4595_6delGAinsT | p.Gly1532Valfs*49 | TGFBP#04 | ND | No | 3 | M | 32 | TA (David 27 y) | Yes | No | | Yes |
| | | | | | | | | | M | 7 | MAD | Yes | No | | Yes |
| | | | | | | | | | M | 4 | MAD | Yes | No | | Yes |
| Frameshift | Del | Exon 42 | c.5266_5278del | p.Val1756*fs169 | TGFBP#05 | ND | No | 2 | M | 53 | TAAD (BB 31 y) | No | No | | Yes |
| | | | | | | | | | M | 25 | MAD, MVP | Yes | No | | Yes |
| Missense | Sub | Exon 43 | c.5345G>T | p.Cys1782Phe | cb EGF-like #25 | De novo | No | 1 | M | 8 | MAD | Yes | EL | | Yes |
| Missense | Sub | Exon 44 | c.5518C>T | p.Arg1840Cys | cb EGF-like #26 | Father | No | 1 | F | 34 | SCAD | No | No | | No |

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|------------|-----|------------|-------------------|-------------------------------|-----------------|-----------------|-------------------|----|---|----|-------------------------------|-----|--------|--------------|-----|
| Frameshift | Ins | Exon 45 | c.5581insA | p.Ser1861fs*1866 | cb EGF-like #26 | ND | No | 1 | M | 39 | TA (David 33 y) | Yes | No | | Yes |
| Missense | Sub | Exon 46 | c.5683T>C | p.Cys1895Arg | cb EGF-like #28 | ND | Yes ⁵ | 1 | M | 23 | MAD | Yes | EL | | Yes |
| Intronic | Sub | Exon 46-47 | c.5788+1G>T | | cb EGF-like #29 | ND | Yes ¹⁷ | 1 | F | 32 | TA, MVP (Yacoub + MVrep 24 y) | Yes | EL | | Yes |
| Missense | Sub | Exon 47 | c.5788G>A | p.Asp1930Asn | cb EGF-like #29 | ND | Yes ⁴ | 1 | F | 14 | MAD, MVP | Yes | EL | | Yes |
| Missense | Sub | Exon 47 | c.5834G>A | p.Gly1945Asp | cb EGF-like #29 | Mother | No | 2 | F | 34 | MAD | No | No | SD (M 50y) | Yes |
| | | | | | | | | | M | 27 | MAD, MVP | Yes | SM | SD (M 50y) | Yes |
| Missense | Sub | Exon 52 | c.6392G>A | p.Cys2131Tyr | cb EGF-like #32 | De novo | No | 1 | M | 10 | MAD, MVP | Yes | No | | Yes |
| Nonsense | Sub | Exon 54 | c.6658C>T | p.Arg2220* | cb EGF-like #34 | Mother | Yes ¹ | 1 | F | 51 | TA (David 43 y) BTD (45y) | No | No | SD (F 40y) | Yes |
| Nonsense | Sub | Exon 54 | c.6658C>T | p.Arg2220* | cb EGF-like #34 | ND | Yes ¹ | 1 | F | 37 | BTD (31 y) TA (David 34y) | Yes | No | | Yes |
| Nonsense | Sub | Exon 54 | c.6658C>T | p.Arg2220* | cb EGF-like #34 | De novo | Yes ¹ | 1 | M | 9 | MAD | Yes | SM | | Yes |
| Missense | Sub | Exon 54 | c.6661T>C | p.Cys2221Arg | cb EGF-like #34 | ND | Yes ¹¹ | 2✦ | M | 40 | TA | Yes | No | SD (M 32y) | Yes |
| | | | | | | | | | F | 37 | MAD, MVP | Yes | No | SD (M 32y) | Yes |
| Missense | Sub | Exon 55 | c.6797C>G | p.Cys2265Trp | cb EGF-like #35 | ND | No | 1 | M | 43 | MAD | Yes | No | | Yes |
| Missense | Sub | Exon 57 | c.7003C>T | p.Arg2335Trp (homocigosis) | TGFBP #07 | Father & Mother | Yes ⁹ | 1 | M | 8 | MVP | No | EL | | No |
| Frameshift | Del | Exon 57 | c.7039_7040delAT | p.Met2347Valfs*19 | TGFBP #07 | Father | Yes ¹⁶ | 1 | M | 50 | TAAD (Yacoub 50y) | Yes | No | TAAD (M 64y) | Yes |
| Intronic | Sub | Exon 57-58 | c.7204+01 G>A | | TGFBP #07 | Father | No | 1 | M | 36 | MAD, MVP | Yes | EL, SM | | Yes |
| Frameshift | Del | Exon 58 | c.7276_7278delCAT | p.His2426del | cb EGF-like #37 | ND | No | 3 | M | 58 | TA (Yacoub 55y) | No | No | | Yes |
| | | | | | | | | | M | 58 | MAD, DCM | Yes | No | | Yes |
| | | | | | | | | | M | 24 | MAD, MVP | No | No | | Yes |

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|----------|-----|---------|-----------|--------------|-----------------------|---------|-------------------|---|---|----|--|-----|----|--------------|-----|
| Missense | Sub | Exon 62 | c.7754T>C | p.Ile2585Thr | cb EGF-like #41 | De novo | Yes ⁴ | 1 | M | 30 | MVP | Yes | No | | No |
| Missense | Sub | Exon 65 | c.8176C>T | p.Arg2726Trp | FibuCTDIII-like motif | De novo | Yes ¹⁵ | | | | | | | | |
| Missense | Sub | Exon 63 | c.7828G>A | p.Glu2610Lys | cb EGF-like #42 | De novo | Yes ⁴ | 1 | M | 23 | MAD | Yes | EL | | Yes |
| Nonsense | Sub | Exon 63 | c.7977C>A | p.Cys2659* | cb EGF-like #43 | ND | Yes ¹⁰ | 4 | M | 55 | TAAD (BB 40 y), MVP | Yes | No | | Yes |
| | | | | | | | | | M | 53 | TAAD (BB 43 y), BTD (48y) | Yes | No | | Yes |
| | | | | | | | | | M | 48 | TAAD, (BB 23y), BTD (31y), MVP (PMVR 40 y) | Yes | No | | Yes |
| | | | | | | | | | F | 44 | MAD, MVP | Yes | No | | Yes |
| Missense | Sub | Exon 65 | c.8609T>G | p.Leu2870Arg | FibuCTDIII-like motif | Mother | No | 5 | F | 59 | MAD | No | No | TAAD (F 72y) | Yes |
| | | | | | | | | | F | 55 | TAAD (BB 48 y), MVP | Yes | No | TAAD (F 72y) | Yes |
| | | | | | | | | | F | 52 | MAD | Yes | SM | TAAD (F 72y) | Yes |
| | | | | | | | | | F | 28 | No | No | SM | TAAD (F 72y) | Yes |
| | | | | | | | | | M | 19 | MAD | No | No | TAAD (F 72y) | Yes |

BAV= Bicuspid aortic valve; **BB** = Bono-Bentall; **DCM** = Dilated cardiomyopathy; **Del** = Deletion; **EL** = Ectopia lentis; **F** = Female; **Ins** = Insertion; **InsDel** = Insertion + deletion; **M** = Male; **MAD** = Mild aortic dilatation; **MFS** = Diagnosis of Marfan Syndrome according to the Ghent Criteria of 2010; **MVP** = Mitral valve prolapse; **MVrep** = Mitral valve repair; **osASD** = Ostium secundum atrial septal defect; **PMVR** = Prosthetic mitral valve replacement; **SCAD** = Spontaneous coronary artery dissection; **SM** = Severe myopia; **Sub** = Substitution; **TA** = Thoracic aorta aneurysm; **TAAD** = Type A dissection; **TBAD** = Type B dissection; **y** = years.

★ Previously described variants, but not proven to cause MFS.

✦ Both patients, siblings with a common family history of early SD (father at 32 years), present a mutation in COL5A1, p.Gln126His, of unknown pathogenicity.

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