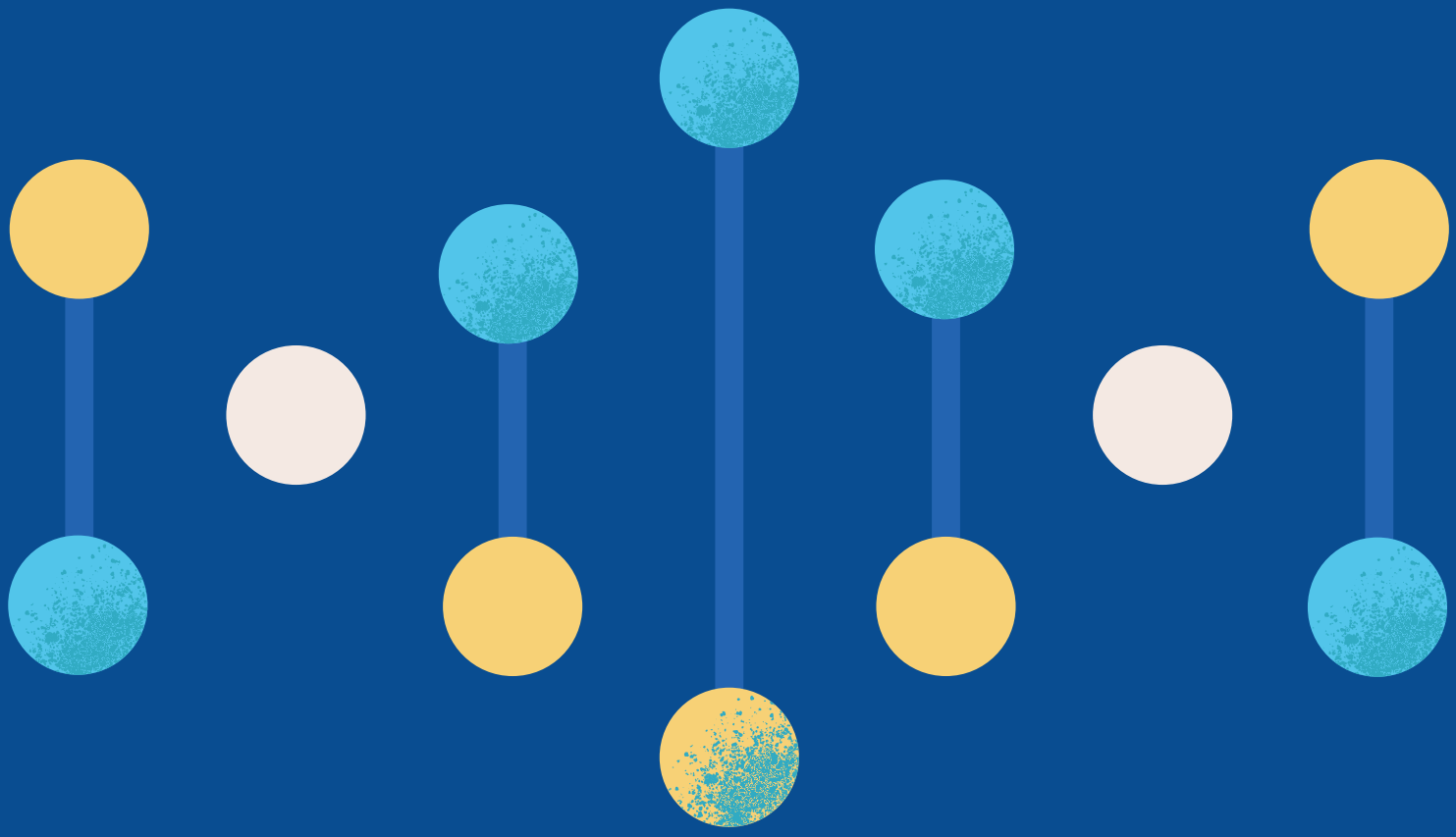
FBN1 GENE COMPENDIUM

A Curated Reference for Thoracic Aortic Aneurysm and Dissection (TAAD)



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This compendium is provided as an educational resource.
Medical and genetic knowledge evolves rapidly, and users are advised to consult up-to-date literature and clinical guidance when interpreting genetic variants.

Curators have made every effort to ensure accuracy but bear no liability for clinical or diagnostic outcomes based on this document. All variant classifications and recommendations should be considered in context and with professional clinical judgment.

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1. Basic Information for TAAD Gene

1.1 Gene Identifiers

Gene MIM Number	134797
Phenotype MIM Number	154700
Orphanet code	FTAAD: ORPHA 91387 Marfan syndrome (MFS): ORPHA 558 Neonatal MFS: ORPHA 284979
Chromosomal Position (hg19/GRCh37)	Chr 15: 48,700,510-48,937,918
Chromosomal Position (hg38/GRCh38)	Chr 15: 48,408,313-48,645,721
Total Number of Amino Acids	2871
MANE Transcript	ENST00000316623.10, NM_000138.5, NP_000129.3
Are there pseudogenes?	No
Other pitfalls (e.g. retrocopy insertion polymorphisms)?	

1.2 Other phenotypes associated with FBN1 with no or lower prevalence of TAAD

- Progeroid and marfanoid aspect-lipodystrophy syndrome: ORPHA 300382; variants clustering in the last exon (exon 64) of FBN1 (Passarge et al. 2016).
- Stiff skin syndrome: ORPHA 2833; Missense variants in the RGD sequence in the TFGβ binding protein like domain 4 have been associated with stiff skin syndrome (Jensen et al., 2015; Loeys et al. 2010).
- Weill-Marchesani syndrome: ORPHA 3449.
- Isolated ectopia lentis: ORPHA 1885; variants throughout the gene.
- Acromicric dysplasia: ORPHA 969 & Geleophysic dysplasia: ORPHA 2623; Missense variants in the TGF-β binding protein like domain 5 have been associated with acromicric and geleophysic dysplasia (Jensen et al., 2015; Le Goff et al., 2011).

2. Protein Structure Overview

The FBN1 gene encodes the propeptide, profibrillin-1 which is then proteolytically processed into two proteins, the multidomain glycoprotein fibrillin-1 and the protein hormone asprosin.

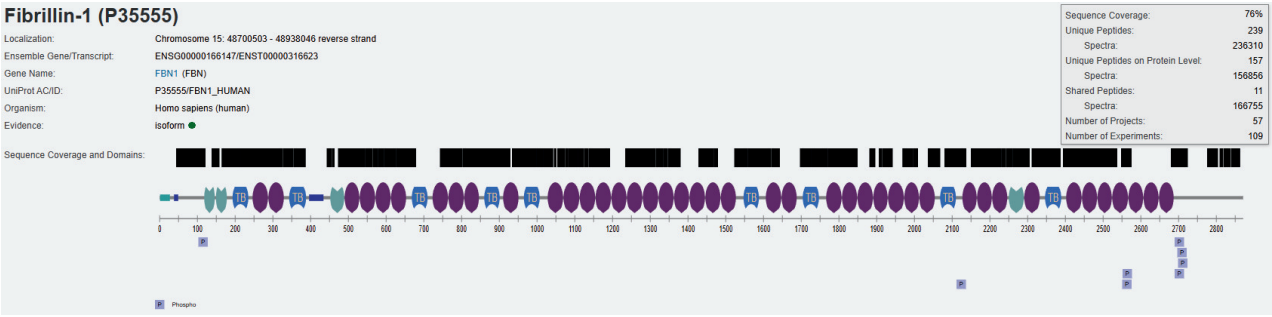
Profibrillin-1 consists of 2871 amino-acids which are arranged into multiple domains. The largest part of the protein is composed of 47 Epidermal Growth Factor (EGF)-like domains of which 43 are calcium-binding (cb-EGF). Each cb-EGF domain contains 6 cysteines, which are pairwise connected through disulphide bonds. Disruption of these bonds has been shown to make the protein more vulnerable to proteolysis.

Next to the cysteine sequences, the cb-EGF domains contain a consensus sequence for calcium binding ((D/N) X (D/N) (E/Q) Xm (D/N) Xn (Y/F) where m and n are variable number of residues and D: Aspartic acid, N: Asparagine E: Glutamic acid, Q: Glutamine, Y: Tyrosine and F: Phenylalanine). These cb-sites confer structural stability to the protein, provide protection against degradation and control interaction with other components of the extracellular matrix.

Interposed between the cb-EGF domains are 2 other types of domains: 7 TGFβ-binding (Transforming Growth factor beta, TB) and 2 hybrid (Hyb) domains. The other protein domains in FBN1 include the N- and C-terminal domains.

Although some very conserved amino acids are present in these regions, their functional relevance is less well known. Some examples are the fibrillin unique N-terminus domain (FUN domain), the 4 cysteine-cysteine repeats of the Hyb domains (Hyb 1 has one extra, very conserved pair), the RGD (arginine, glycine, asparagine)-sequence and the 4 cysteine-cysteine repeats at the TB domains and the Furin/PACE cleavage site at N- and C-terminus.

2.1. Scheme with important domains within the protein



Source: https://www.proteomicsdb.org/proteomicsdb/#protein/proteinDetails/55081/summary

Table: Overview of FBN1 protein with Amino Acid (AA) boundaries

Domain	From AA	To AA
Signal Peptide	1	27
NH2 unique region	28	52
4-Cys motif LTBP-like	53	80

EGF-like #01	81	112
EGF-like #02	115	146
EGF-like #03	147	178
Hybrid module #01	179	245
cb EGF-like #01	246	287
cbEGF-like #02	288	329
TGFBP #01	330	401
Proline-rich	402	446
EGF-like #04	449	489
cb EGF-like #03	490	529
cb EGF-like #04	530	571
cb EGF-like #05	572	612
cb EGF-like #06	613	653
TGFBP #02	654	721
cb EGF-like #07	723	764
cb EGF-like #08	765	806
cb EGF-like #09	807	846
Hybrid motif #02	847	909
cb EGF-like #10	910	951
TGFBP #03	952	1018

cb EGF-like #11	1028	1069
cb EGF-like #12	1070	1112
cb EGF-like #13	1113	1154
cb EGF-like #14	1155	1196
cb EGF-like #15	1197	1237
cb EGF-like #16	1238	1279
cb EGF-like #17	1280	1321
cb EGF-like #18	1322	1362
cb EGF-like #19	1363	1403
cb EGF-like #20	1404	1445
cb EGF-like #21	1446	1486
cb EGF-like #22	1487	1527
TGFBP #04	1528	1599
cb EGF-like #23	1606	1647
cb EGF-like #24	1648	1688
TGFBP #05	1689	1758
cb EGF-like #25	1766	1807
cb EGF-like #26	1808	1848
cb EGF-like #27	1849	1890
cb EGF-like #28	1891	1929

cb EGF-like #29	1930	1972
cbEGF-like #30	1973	2012
cbEGF-like #31	2013	2054
TGFBP #06	2055	2121
cb EGF-like #32	2127	2165
cb EGF-like #33	2166	2205
cb EGF-like #34	2206	2246
cb EGF-like #35	2247	2290
cb EGF-like #36	2291	2332
TGFBP #07	2333	2400
cb EGF-like #37	2402	2443
cb EGF-like #38	2444	2484
cb EGF-like #39	2485	2523
cb EGF-like #40	2524	2566
cb EGF-like #41	2567	2606
cb EGF-like #42	2607	2647
cb EGF-like #43	2648	2687
COOH unique region	2688	2710
FibuCTDIII-like motif	2711	2871

Source: http://www.umd.be/FBN1

2.2. List of exon boundaries (at cDNA level) (from Alamut)

MANE NM_000138[a]	MANE NM_000138[b]	Nucleotide	Amino acid
Exon 0 / 5'UTR	Exon 1 / 5'UTR	c.- 395 to c.-182	/
Exon 1	Exon 2	c.-181 to c.164	p.1 to p.55
Exon 2	Exon 3	c. 165 to c.247	p.55 to p.83
Exon 3	Exon 4	c. 248 to c.346	p.83 to p.116
Exon 4	Exon 5	c.347 to c.442	p.116 to p.148
Exon 5	Exon 6	c.443 to c.538	p.148 to p.180
Exon 6	Exon 7	c.539 to c.736	p.180 to p.246
Exon 7	Exon 8	c.737 to c.862	p.246 to p.288
Exon 8	Exon 9	c.863 to c.988	p.288 to p.330
Exon 9	Exon 10	c.989 to c.1147	p.330 to p.383
Exon 10	Exon 11	c.1148 to c.1327	p.383 to p.443
Exon 11	Exon 12	c.1328 to c.1468	p.443 to p.490
Exon 12	Exon 13	c.1469 to c.1588	p.490 to p.530
Exon 13	Exon 14	c.1589 to c.1714	p.530 to p.572
Exon 14	Exon 15	c.1715 to c.1837	p.572 to p.613
Exon 15	Exon 16	c.1838 to c.1960	p.613 to p.654
Exon 16	Exon 17	c.1961 to c.2113	p.654 to p.705
Exon 17	Exon 18	c.2114 to c.2167	p.705 to p.723

Exon 18	Exon 19	c.2168 to c.2293	p.723 to p.765
Exon 19	Exon 20	c.2294 to c.2419	p.765 to p.807
Exon 20	Exon 21	c.2420 to c.2539	p.807 to p.847
Exon 21	Exon 22	c.2540 to c.2677	p.847 to p.893
Exon 22	Exon 23	c.2678 to c.2728	p.893 to p.910
Exon 23	Exon 24	c.2729 to c.2854	p.910 to p.952
Exon 24	Exon 25	c.2855 to c.3082	p.952 to p.1028
Exon 25	Exon 26	c.3083 to c.3208	p.1028 to p.1070
Exon 26	Exon 27	c.3209 to c.3337	p.1070 to p.1113
Exon 27	Exon 28	c.3338 to c.3463	p.1113 to p.1155
Exon 28	Exon 29	c.3464 to c.3589	p.1155 to p.1197
Exon 29	Exon 30	c.3590 to c.3712	p.1197 to p.1238
Exon 30	Exon 31	c.3713 to c.3838	p.1238 to p.1280
Exon 31	Exon 32	c.3839 to c.3964	p.1280 to p.1322
Exon 32	Exon 33	c.3965 to c.4087	p.1322 to p.1363
Exon 33	Exon 34	c.4088 to c.4210	p.1363 to p.1404
Exon 34	Exon 35	c.4211 to c.4336	p.1404 to p.1446
Exon 35	Exon 36	c.4337 to c.4459	p.1446 to p.1487
Exon 36	Exon 37	c.4460 to c.4582	p.1487 to p.1528
Exon 37	Exon 38	c.4583 to c.4747	p.1528 to p.1583

Exon 38	Exon 39	c.4748 to c.4816	p.1583 to p.1606
Exon 39	Exon 40	c.4817 to c.4942	p.1606 to p.1648
Exon 40	Exon 41	c.4943 to c.5065	p.1648 to p.1689
Exon 41	Exon 42	c.5066 to c.5224	p.1689 to p.1742
Exon 42	Exon 43	c.5225 to c.5296	p.1742 to p.1766
Exon 43	Exon 44	c.5297 to c.5422	p.1766 to p.1808
Exon 44	Exon 45	c.5423 to c.5545	p.1808 to p.1849
Exon 45	Exon 46	c.5546 to c.5671	p.1849 to p.1891
Exon 46	Exon 47	c.5672 to c.5788	p.1891 to p.1930
Exon 47	Exon 48	c.5789 to c.5917	p.1930 to p.1973
Exon 48	Exon 49	c.5918 to c.6037	p.1973 to p.2013
Exon 49	Exon 50	c.6038 to c.6163	p.2013 to p.2055
Exon 50	Exon 51	c.6164 to c.6313	p.2055 to p.2105
Exon 51	Exon 52	c.6314 to c.6379	p.2105 to p.2127
Exon 52	Exon 53	c.6380 to c.6496	p.2127 to p.2166
Exon 53	Exon 54	c.6497 to c.6616	p.2166 to p.2206
Exon 54	Exon 55	c.6617 to c.6739	p.2206 to p.2247
Exon 55	Exon 56	c.6740 to c.6871	p.2247 to p.2291
Exon 56	Exon 57	c.6872 to c.6997	p.2291 to p.2333
Exon 57	Exon 58	c.6998 to c.7204	p.2333 to p.2402

Exon 58	Exon 59	c.7205 to c.7330	p.2402 to p.2444
Exon 59	Exon 60	c.7331 to c.7453	p.2444 to p.2485
Exon 60	Exon 61	c.7454 to c.7570	p.2485 to p.2524
Exon 61	Exon 62	c.7571 to c.7699	p.2524 to p.2567
Exon 62	Exon 63	c.7700 to c.7819	p.2567 to p.2607
Exon 63	Exon 64	c.7820 to c.8051	p.2607 to p.2684
Exon 64	Exon 65	c.8052 to c.8226	p.2684 to p.2742
Exon 65	Exon 66	c.8227 to c.8616	p.2743 to p.2871
Exon 65-3'UTR	Exon 66-3'UTR	c.*1 to c.*2684	/

[a]Historical exon numbering, only recognized by experts in the field
[b]Current exon numbering, based on the recommendations of the HGVS Nomenclature

2.3. Mutational hotspot or recurrent/founder variants

cDNA annotation	**Protein annotation**	**Number of submissions in ClinVar**
c.364C>T	p.(Arg122Cys)	11
c.718C>T	p.(Arg240Cys)	11
c.1090C>T	p.(Arg364*)	13
c.1585C>T	p.(Arg529*)	10
c.1879C>T	p.(Arg627Cys)	10
c.2581C>T	p.(Arg861*)	10
c.2645C>T	p.(Ala882Val)	14

c.2920C>T	p.(Arg974Cys)	11
c.4588C>T	p.Arg1530Cys)	13
c.4786C>T	p.(Arg1596*)	13
c.5788+5G>A		12
c.6388G>A	p.(Glu2130Lys)	10
c.6806T>C	p.(Ile 2269Thr)	12
c.6884G>A	p.(Cys2295Tyr)	12
c.7039_7040del AT	p.(Met2347Valfs*19)	16
c.7180C>T	p.(Arg2394*)	10
c.7754T>C	p.(Ile2585Thr)	22
c.8326C>T	p.(Arg2776*)	11

2.4. Major domain(s) that involves more pathogenic variants

Pathogenic variants responsible for Marfan syndrome and isolated TAAD have been described throughout the gene.

> Clinvar database: ClinVar - FBN1
> GnomAD database: gnomAD FBN1
> Mutscore: MutScore FBN1

For additional guidance on interpretation of pathogenicity for FBN1 variants, please refer to A. Drackley et al, 2024.

Substitutions more suspicious for pathogenicity:

1. Cysteine residues are frequently classified as (likely) pathogenic: Cys residues (substitution or creation) in cbEGF domains (Schrijver et al., 1999; Vollbrandt et al. 2004; Zeyer et al., 2015) and (noncb-)EGF-like domain, TB domain, hybrid domain.
2. Change of other amino acids from the cbEGF domain consensus sequence (D/N)-X-(D/N)-(E/Q)-Xm-(D/N)-Xn-(Y/F) or hydroxylation residue in cbEGF-like domain.
3. Glycine substitution between Cys2-Cys3 in cbEGF-like domain and glycine between Cys3-Cys4 if there is an upstream cbEGF domain (Handford et al., 1991; Piha-Gossack et al., 2012; Reinhardt et al., 2000).

Caveat: Asn (=N) to Ser substitution in the second Asn of de consensus sequence and Gly to Ala might be tolerated, PM1 should not be used in these cases.

3. Mode of Inheritance

Autosomal dominant with almost complete penetrance but with variable expression.

- Aneurysm-penetrance: 80% at age 60 yrs (Kühne et al., 2013).
- Ocular phenotype: 50% (more frequently in patients carrying variants affecting Cys residues) (Ashworth et al., 2000).

Rare examples of MFS families with an apparently autosomal recessive mode of inheritance have been reported (Fried & Krakowsky, 1977; Hilhorst-Hofstee et al. 2010; Khan, Bolz, & Bergmann, 2014; Vries, Pals, Odink, & Hamel, 2007).

4. Constraint Matrices and Mutational Subtypes

pLI score	pLI=1; o/e=0.08 (0.06-0.1)	gnomad v.4.1
Missense constraint*	Z=8.2; o/e=0.63 (0.61-0.66)	gnomad v.4.1
Haplo-insufficiency (nonsense or out of frame splice)	yes	(Judge et al., 2004; Meester et al. 2022; Milewicz et al., 2021)
Full gene deletion	yes	Milewicz et al., 2021
Multi-exon deletion	yes	Milewicz et al., 2021
Full gene duplication	no	
Multi-exon duplication	yes	ClinVar variation ID: 144202, 527238, 584002

5. Mode of Action of the Pathogenic Variants

Gain-of-function	No	—
Haploinsufficiency	Yes	Ashworth et al., 2000; Kühne et al., 2013
Dominant negative	Yes	Schrijver et al., 1999; Vollbrandt et al., 2004; Zeyer et al., 2015.
Loss-of-function	Yes	Vollbrandt et al., 2004; Whiteman et al., 2007

6. Additional Supportive Evidence for Pathogenicity

6.1. Clinical evidence

95% of patients with clinical diagnosis of Marfan syndrome (MFS) carry a (likely) pathogenic variant in the FBN1 gene. The clinical diagnosis of MFS is based on the revised Ghent nosology (Loeys et al., 2010).

Aortic root dilatation and ectopia lentis are the cardinal clinical features of MFS. In the absence of any family history, the combination of aortic root dilatation and ectopia lentis is sufficient for a definite diagnosis of MFS.

In the absence of either of these two, the presence of a pathogenic FBN1 variant or a combination of different systemic manifestations, is required. A scoring system has been designed for the latter.

Systemic features	**Score**
Positive wrist and thumb sign	3
Positive wrist or thumb sign	1
Pectus carinatum	2
Pectus excavatum or chest asymmetry	1
Hindfoot deformity	2
Pes planus	1
Pneumothorax	2
Dural ectasia	2
Protrusio acetabuli	2
Reduced US/LS AND increased arm/height AND no severe scoliosis	1
Scoliosis or thoracolumbar kyphosis	1
Reduced elbow extension	1
Facial features (3/5) (dolichocephaly, enophthalmos, downslanting palpebral fissures, malar hypoplasia, retrognathia)	1
Skin striae	1
Myopia > 3 diopters	1
Mitral valve prolapse (all types)	1
Diagnostic criteria In the absence of family history • Aortic sinus diameter ≥2 z-score and ectopia lentis • Aortic sinus diameter ≥2 z-score and a systemic score ≥7 • Aortic sinus diameter ≥2 z-score and a pathogenic variant in FBN1 • Ectopia lentis and a pathogenic variant in FBN1 known to cause aortic disease In the presence of family history • Aortic sinus diameter ≥2 z-score if above 20yr or ≥3 z-score if below 20yr • Systemic score ≥7 • Ectopia lentis	

6.2. Functional evidence

Are there any functional tests helpful in the interpretation that can be done easily?
Functional studies deemed appropriate (Hollister et al., 1990; Jensen et al., 2012; Jensen et al., 2015; Reinhardt et al., 2000; Zeyer et al., 2015):

- cDNA analyses showing altered FBN1 sequence.*
- Functional studies showing altered FBN1 protein or RNA expression*, proteolysis, folding, assembly, trafficking, secretion, Ca2+ binding, matrix deposition (cfr Dave Hollister assay), microfibril fragmentation/catabolism in an in vitro engineered system.

*Studies should be performed in the presence of NMD inhibitor.

Functional studies NOT deemed appropriate: non-specific altered TGF-beta signaling or histological hallmarks of medial degeneration, which are associated with many other types of variants in genes that are associated with MFS or HTAAD in general.

7. Mutation Database or Expert

7.1. Gene-specific mutation database

www.UMD.be/FBN1
https://www.ncbi.nlm.nih.gov/clinvar/?gr=0&term=FBN1%5Bgene%5D
https://databases.lovd.nl/shared/genes/FBN1
https://www.deciphergenomics.org/gene/FBN1/overview/clinical-info

7.2 Uniprot 3D protein structure

The UniProt database provides access to the 3D structure and functional annotation of FBN1:
https://www.uniprot.org/uniprotkb/P35555/entry#structure

7.3 Lab "expert" for this gene that can be contacted for advice on specific cases

University Hospital Ghent:

- Laura.muinomosquera@uzgent.be
- Sofie.symoens@uzgent.be

Bichat-Claude Bernard Hospital

- Nadine.hanna@aphp.fr
- Pauline.arnaud@aphp.fr

University Hospital Antwerp:

- Bart.loeys@uza.be
- Lut.vanlaer@uantwerpen.be

8. Phenotype Characteristics

8.1. Estimated prevalence of the disease

The estimated prevalence of disease is: 1:5000- 1:10000. The highest possible allelic frequency based on the prevalence is: 0,005%.

8.2. Youngest age of onset of aortic aneurysm

The earliest age at aortic aneurysm is the neonatal period in children with early onset MFS (eoMFS). This condition is a severe form of MFS presenting at a very young age with aortic root dilatation and severe valvular pathology frequently leading to heart failure. Most of the children affected by eoMFS carry a pathogenic variant between exons 24-32 (Faivre et al., 2007).

8.3. Youngest age of onset of aortic dissection

Several reports describe rare cases of aortic dissection related to Marfan syndrome in adolescents and young adults (Fikar et al., 2000; Shamszad et al., 2013; Zalzstein et al., 2003). Two individuals of the Marfan Pediatric Heart Network trial experienced aortic dissection during the study period. Although the age at dissection is not mentioned, all individuals included were ≤25yrs (Lacro et al., 2014).

8.4. genotype-phenotype correlation validated for this gene

A few genotype-phenotype correlations have been found for FBN1:

- More severe phenotype for variants located in the middle region of the gene (exons 24-32) (Faivre et al., 2007).
- Missense variants creating Cys residues: higher prevalence of EL and retinal detachment (Becerra-Muñoz et al., 2018; Rommel et al., 2005).

Some other genotype-phenotype correlations have been found but are disputed:

- Missense variant creating a Cys lead to less severe vascular phenotype (compared to missense variant deleting a Cys).
- Truncating variants have more striking skeletal features (Becerra-Muñoz et al., 2018; Franken et al., 2015).
- Truncating or splicing: higher percentage of aortic events occurring at younger ages (Baudhuin et al., 2014; Becerra-Muñoz et al., 2018; Franken et al., 2017; Meester et al., 2022).

8.5. Is there any consensus on management of the disease?

- A beta-blocker (BB) or an angiotensine receptor antagonist (ARB) can be used to decrease the aortic growth rate (American College of Cardiology Foundation and the American Heart Association, 2022; Fikar et al., 2000; European Society of Cardiology, 2024 (Mazzolai et al, 2024); Lacro et al., 2014; Mullen et al., 2019; Pitcher et al., 2022; Shamszad et al., 2013; Zalzstein et al., 2003).
- Surgical threshold for aortic root replacement is 50mm (American College of Cardiology Foundation and the American Heart Association, 2022; European Society of Cardiology, 2024).
- In certain cases (e.g. rapid aortic growth, family history of dissection, pre-conceptional or resistant hypertension) surgical replacement from 45mm on should be considered.
- Also consult general TAAD guidelines (Isselbacher et al 2022, Mazzolai et al, 2024, Morris et al, 2024)

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