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Marfan Database (second edition): software and database for the analysis of mutations in the human FBN1 gene

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ABSTRACT

Fibrillin is the major component of extracellular microfibrils. Mutations in the fibrillin gene on chromosome 15 (FBN1) were described at first in the heritable connective tissue disorder, Marfan syndrome (MFS). More recently, FBN1 has also been shown to harbor mutations related to a spectrum of conditions phenotypically related to MFS. These mutations are private, essentially missense, generally non-recurrent and widely distributed throughout the gene. To date no clear genotype/phenotype relationship has been observed excepted for the localization of neonatal mutations in a cluster between exons 24 and 32. The second version of the computerized Marfan database contains 89 entries. The software has been modified to accomodate new functions and routines.

Fibrillin, Marfan syndrome and type 1 fibrillinopathies

Fibrillin-1 is a large glycoprotein (320 kDa) ubiquitously distributed in connective tissues (1). It is the major component of 10–12 nm microfibrils of the extracellular matrix (1). The fibrillin-1 gene (FBN1) lies on the long arm of chromosome 15 (15q15–q21.1) (2) and its entire coding sequence of 2871 amino acids is known (3–5). It contains 65 exons encoding a multidomain and highly repetitive protein: four 'EGF-like' modules [domains with homology to a module found in human epidermal growth factor (EGF) precursor], 43 'cb EGF-like' modules (EGF-like domain presenting a calcium-binding consensus sequence), seven '8-cysteine' modules (that are homologous with transforming-growth factor-β1 binding-protein), two 'hybrid' modules that combine features of the two former, a 'NH2 Unique region' (unique N-terminal stretch of basic residues), a 'proline rich domain' and the 'COOH unique region' (4,5). Mutations in the FBN1 gene are associated with a spectrum of overlapping diseases named type 1 fibrillinopathies: complete and incomplete Marfan syndrome (6–9,11–17,23–26,29,36,39,41), severe neonatal Marfan syndrome (15,20,22,26,31–32,38,41), dominantly inherited ectopia lentis (15,18,36), isolated skeletal features of MFS (18,21,28) and the Shprintzen–Goldberg syndrome (34).

The Marfan database

The database below lists known point mutations, deletions or insertions, and splice mutations in the gene FBN1. Its purpose is to update that of last year (43) by collecting in a standardized, accessible and summary form the molecular and the clinical data on the causative mutations of Marfan syndrome and type 1 fibrillinopathies. The present version of the database contains 89 entries corresponding to mutations either published or only reported in meeting proceedings or contributed by the co-authors of this paper (Table 1). It is not intented to replace primary publications, although it does contain unpublished data. As in the previous edition, mutation names are given according to Beaudet *et al.* (44) and numbered with respect to the FBN1 gene cDNA

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Table 1.

A	B	C	D	E	F	G	H	I	J	K	L	M	N	O	P	Q	R
10	2	165	55	GGA	del83c	Stop at 100	248 +1 G->A	Gly	Frameshift	NH2 unique region	+	+	+	?	?	?	9
37	4	364	122	CGC	TGC	C->T	R122C (1)	Arg	Cys	EGF-like #2	+	+	-	?	+	?	18
85	4	364	122	CGC	TGC	C->T	R122C (2)	Arg	Cys	EGF-like #2	+	+	+	-	+	-	NP1
40	4	386	129	TGC	TAC	G->A	C129Y	Cys	Tyr	EGF-like #2	+	+	+	+	+	?	26
41	5	497	166	TGT	TTT	G->T	C166F	Cys	Phe	EGF-like #3	+	+	+	?	?	?	26
63	5	497	166	TGT	TCT	G->C	C166S	Cys	Ser	EGF-like #3	?	?	?	?	?	?	30
20	6	649	217	TGG	GGG	T->G	W217G	Trp	Gly	Hybrid motif #1	+	+	+	?	?	?	15
26	11	1426	476	TGC	GGC	T->G	C476G	Cys	Gly	EGF-like #4	+	+	+	?	?	?	16
51	13	1604	535	TTA	del1b	Stop at 578	1604delT	Leu	Frameshift	cb EGF-like #04	?	?	?	?	?	?	26
6	13	1643	548	AAC	ATC	A->T	N548I	Asn	Ile	cb EGF-like #04	+	+	+	?	+	?	9
74	13	1693	565	CGA	TGA	C->T	R565X	Arg	Stop	cb EGF-like #04	?	?	?	?	?	?	35
76	14	1760	587	TGT	TAT	G->A	C587Y	Cys	Tyr	cb EGF-like #05	+	+	-	?	?	?	36
12	15	1879	627	CGT	TGT	C->T	R627C (1)	Arg	Cys	cb EGF-like #06	+	+	+	-	-	-	12
75	15	1879	627	CGT	TGT	C->T	R627C (2)	Arg	Cys	cb EGF-like #06	?	?	?	?	?	?	35
56	16	1981	661	TGC	CGC	T->C	C661R	Cys	Arg	8-Cys #2	?	?	?	?	?	?	27
87	17	2113	705	GCG	ACG	G->A	A705T	Ala	Thr	8-Cys #2	+	+	+	?	+	?	41
86	17	2132	711	TGC	TAC	G->A	C711Y	Cys	Tyr	8-Cys #2	+	+	+	?	+	?	41
8	18	2168	723	GAT	GCT	A->C	D723A	Asp	Ala	cb EGF-like #07	+	+	+	?	?	?	9
42	18	2237	746	TAT	TGT	A->G	Y746C	Tyr	Cys	cb EGF-like #07	?	?	?	?	?	?	26
13	18	2248	750	TGC	GGC	T->G	C750G	Cys	Gly	cb EGF-like #07	+	+	+	-	-	-	12
27	21	2584	862	TGT	CGT	T->C	C862R	Cys	Arg	Hybrid motif #2	+	+	+	?	?	?	17
43	23	2776	926	TGT	CGT	T->C	C926R	Cys	Arg	cb EGF-like #10	?	?	?	?	?	?	26
77	24	2950	984	GTC	ATC	G->A	V984I	Val	Ile	8-Cys #3	?	?	?	?	?	?	37
84	24	2986	996	TGT	CGT	T->C	C996R	Cys	Arg	8-Cys #3	+	+	+	-	+	-	NP1,47
44	24	3037	1013	GGA	AGA	G->A	G1013R (1)	Gly	Arg	8-Cys #3	+	+	+	?	?	?	26
70	24	3037	1013	GGA	AGA	G->A	G1013R (2)	Gly	Arg	8-Cys #3	?	?	?	?	?	?	32
18	24	3069	1023	AAG	AAC	G->C	K1023N	Lys	Asn	8-Cys #3	+	+	+	?	+	?	15
19	25	3083	1028	GAT	del126b	del	3208 +5 G->T	Asp	Frameshift	cb EGF-like #11	+	+	+	?	?	?	15
81	25	3128	1043	AAG	AGG	A->G	K1043R	Lys	Arg	cb EGF-like #11	+	-	+	+	+	?	40
67	25	3142	1048	ATT	del3a	del	1048delATT	Ile	Frameshift	cb EGF-like #11	+	+	+	?	+	?	31
78	25	3143	1048	ATT	ACT	T->C	I1048T	Ile	Thr	cb EGF-like #11	+	-	+	?	+	?	38
66	25	3157	1053	TGC	CGC	T->C	C1053R	Cys	Arg	cb EGF-like #11	+	+	+	?	?	?	31
89	25	3163	1055	TGT	GGT	T->G	C1055G	Cys	Gly	cb EGF-like #11	+	+	+	?	+	?	41
33	25	3174	1058	GGC	ins3c	ins	3174ins TGC	Gly	Frameshift	cb EGF-like #11	+	+	+	+	+	?	20
82	25	3192	1064	GAA	del1b	Stop at 1087	3192delA	Glu	Frameshift	cb EGF-like #11	+	-	+	?	?	?	40
64	26	3215	1072	GAC	GGC	A->G	D1072G	Asp	Gly	cb EGF-like #12	+	+	+	?	?	?	31
45	26	3217	1073	GAA	AAA	G->A	E1073K (1)	Glu	Lys	cb EGF-like #12	+	+	+	?	?	?	26
68	26	3217	1073	GAA	AAA	G->A	E1073K (2)	Glu	Lys	cb EGF-like #12	+	+	+	?	?	?	31
69	26	3217	1073	GAA	AAA	G->A	E1073K (3)	Glu	Lys	cb EGF-like #12	+	-	+	?	?	?	31
17	26	3220	1074	TGC	CGC	T->C	C1074R	Cys	Arg	cb EGF-like #12	+	+	+	?	+	?	15
71	26	3258	1086	TGT	TGG	T->G	C1086W	Cys	Trp	cb EGF-like #12	?	?	?	?	?	?	32
28	27	3350	1117	TGT	TAT	G->A	C1117Y	Cys	Tyr	cb EGF-like #13	+	+	+	?	?	?	17
65	27	3349	1117	TGT	CGT	T->C	C1117G	Cys	Arg	cb EGF-like #13	+	+	+	?	?	?	31
83	27	3391	1131	AAC	TAC	A->T	N1131Y	Asn	Tyr	cb EGF-like #13	?	?	?	?	?	?	41, P
1	27	3410	1137	CGC	CCC	G->C	R1137P (1)	Arg	Pro	cb EGF-like #13	+	+	+	?	?	?	6
2	27	3410	1137	CGC	CCC	G->C	R1137P (2)	Arg	Pro	cb EGF-like #13	+	+	+	?	?	?	6
88	27	3458	1153	TGT	TAT	G->A	C1153Y	Cys	Tyr	cb EGF-like #13	+	+	+	?	+	+	41
29	28	3464	1155	GAC	del17b	Stop at 1186	3464del17	Asp	Frameshift	cb EGF-like #14	+	-	+	?	?	?	17
79	28	3463	1155	GAC	AAC	G->A	D1155N	Asp	Asn	cb EGF-like #14	+	-	+	-	+	-	39, P
58	28	3509	1170	CGT	CAT	G->A	R1170H	Arg	His	cb EGF-like #14	+	-	-	-	-	-	28
39	29	3668	1223	TGT	TAT	G->A	C1223Y (1)	Cys	Tyr	cb EGF-like #15	+	+	+	?	?	?	25
73	29	3668	1223	TGT	TAT	G->A	C1223Y (2)	Cys	Tyr	cb EGF-like #15	+	+	+	?	?	+	34
21	30	3725	1242	TGT	TAT	G->A	C1242Y	Cys	Tyr	cb EGF-like #16	+	+	+	?	?	?	15
3	30	3746	1249	TGT	TCT	G->C	C1249S	Cys	Ser	cb EGF-like #16	+	+	+	?	?	?	7
72	31	3839	1280	GAT	del126b	del	3839 -1 G->A	Asp	Frameshift	cb EGF-like #17	?	?	?	?	?	?	33
35	32	3965	1322	GAC	del123b	del	3965 -2 A->T	Asp	Frameshift	cb EGF-like #18	+	-	+	?	?	?	22
36	32	3965	1322	GAC	del123b	del	4087 +1 G->A	Asp	Frameshift	cb EGF-like #18	+	+	+	?	?	?	22
52	32	4020	1340	ACC	del1c	Stop at 1412	4020delC	Thr	Frameshift	cb EGF-like #18	?	?	?	?	?	?	26
46	33	4145	1382	AAT	AGT	A->G	N1382S	Asn	Ser	cb EGF-like #19	?	?	?	?	?	?	26
22	36	4537	1513	TGC	CGC	T->C	C1513R	Cys	Arg	cb EGF-like #22	+	+	+	?	?	?	15
30	38	4766	1589	TGT	TTT	G->T	C1589F	Cys	Phe	8-Cys #4	+	+	+	?	?	?	17
49	39	4857	1619	GGA	del1c	Stop at 1639	4857delA	Gly	Frameshift	cb EGF-like #23	+	+	+	?	+	?	26
4	40	4987	1663	TGT	CGT	T->C	C1663R	Cys	Arg	cb EGF-like #24	+	+	+	?	?	?	7
9	41	5137	1713	AAC	ins4a	ins	5137ins4	Asn	Frameshift	8-Cys #5	+	+	+	?	+	?	9
80	44	5509	1837	CCC	TCC	C->T	P1837S	Pro	Ser	cb EGF-like #26	+	-	+	-	+	-	39, P
47	46	5782	1928	TGT	CGT	T->C	C1928R	Cys	Arg	cb EGF-like #28	?	?	?	?	?	?	26
53	47	5789	1930	GAT	del129b	del	5788 +5 G->A (1)	Asp	Frameshift	cb EGF-like #29	?	?	?	?	?	?	26
54	47	5789	1930	GAT	del129b	del	5788 +5 G->A (2)	Asp	Frameshift	cb EGF-like #29	?	?	?	?	?	?	26
55	47	5789	1930	GAT	del129b	del	5788 +5 G->A (3)	Asp	Frameshift	cb EGF-like #29	?	?	?	?	?	?	26
57	51	6339	2113	TAT	TAA	T->A	Y2113X	Tyr	Stop	8-Cys #6	?	?	?	?	?	?	27
23	52	6381	2127	GAT	GAA	T->A	D2127E	Asp	Glu	cb EGF-like #32	+	-	+	?	?	?	15
14	52	6431	2144	AAT	AGT	A->G	N2144S	Asn	Ser	cb EGF-like #32	+	-	+	?	?	?	13

A	B	C	D	E	F	G	H	I	J	K	L	M	N	O	P	Q	R
24	52	6453	2151	TGC	TGG	C->G	C2151W	Cys	Trp	cb EGF-like #32	+	+	+	?	?	?	15
11	54	6617	2206	GAT	del123b	del	6739 +1 G->C	Asp	Frameshift	cb EGF-like #34	+	+	+	+	?	?	11
7	54	6662	2221	TGT	TCT	G->C	C2221S	Cys	Ser	cb EGF-like #34	+	+	+	?	?	?	7
48	55	6784	2262	CAA	TAA	C->T	Q2262X	Gln	Stop	cb EGF-like #35	?	?	?	?	?	?	26
5	56	6920	2307	TGC	TCC	G->C	C2307S	Cys	Ser	cb EGF-like #36	+	+	+	?	?	?	8
31	59	7339	2447	GAG	AAG	G->A	E2447K	Glu	Lys	cb EGF-like #38	+	+	-	?	+	?	18
15	60	7456	2486	CTT	del366a	del	7456del366	Leu	Frameshift	cb EGF-like #39	+	+	+	?	?	?	14
25	60	7531	2511	TGT	CGT	T->C	C2511R	Cys	Arg	cb EGF-like #39	+	+	+	?	?	?	15
62	63	7868	2623	CAC	CCC	A->C	H2623P	His	Pro	cb EGF-like #42	+	+	+	-	+	-	NP2
32	63	7879	2627	GGG	AGG	G->A	G2627R	Gly	Arg	cb EGF-like #42	+	+	+	?	?	?	19
59	63	8038	2680	CGC	TGC	C->T	R2680C	Arg	Cys	cb EGF-like #43	+	+	-	+	-	-	29
60	63	8052	2684	CGC	del175c	Stop at 2710	8052 -2 A->G	Arg	Frameshift	cb EGF-like #43	+	+	+	-	-	-	29
61	64	8052	2684	GGG	del175c	Stop at 2710	8051 +5 G->A	Gly	Frameshift	cb EGF-like #43	+	+	+	-	-	-	29
34	64	8176	2726	CGG	TGG	C->T	R2726W	Arg	Trp	COOH unique reg.	+	-	-	?	?	?	21
50	65	8236	2746	GAG	del2a	Stop at 2758	8236delGA	Glu	Frameshift	COOH unique reg.	+	+	+	?	+	?	26
16	65	8268	2756	TGG	TGA	G->A	W2756X	Trp	Stop	COOH unique reg.	+	+	+	?	?	?	14
38	65	8326	2776	CGA	TGA	C->T	R2776X	Arg	Stop	COOH unique reg.	+	+	+	-	-	-	24

Each line represents a single FBN1 mutation. The columns contain the following information and abbreviations:
Column A: File number.
Column B: Exon number at which the mutation is located.
Column C: Nucleotide position at which the mutation is located.
Column D: Codon number at which the mutation is located.
Column E: Normal base sequence of the codon in which the mutation occurred.
Column F: Mutated base sequence of the codon in which the mutation occurred.
Column G: Concerns base substitutions. It gives the base change, by convention, read from the coding strand. If the mutation predicts a premature protein-termination, the novel stop codon position is given, e.g. 'Stop at 2115'.
Column H: Mutation name according to Beaudet *et al*. (44).
Column I: Wild type amino acid.
Column J: Mutant amino acid. Deletion and insertion mutations which result in a frameshift are designated by 'Frameshift'. Nonsense mutations are designated by 'Stop'.
Column K: Protein domain in which the mutation occurs. Each motif group is numbered separately and according to their position with respect to the N-terminal end of the protein, e.g. 'cb EGF-like' (for calcium-binding EGF-like motifs) #1–43, 'EGF-like' (for non calcium-binding EGF-like motifs) #1–4, '8-cys' (for '8-cysteine' motifs) #1–7, 'Hybrid motifs' #1 and 2 (3–5).
Column L–Q: Diagnostic manifestations in the systems listed by Beighton *et al*. (45) and De Paepe *et al*. (46). In all these columns, '?' indicates either lack of or unspecified data until more precise information is available.
Column L: Presence (+) or absence (–) of skeletal manifestations.
Column M: Presence (+) or absence (–) of ocular manifestations.
Column N: Presence (+) or absence (–) of cardiovascular manifestations.
Column O: Presence (+) or absence (–) of pulmonary manifestations.
Column P: Presence (+) or absence (–) of manifestations in skin and integument.
Column Q: Presence (+) or absence (–) of manifestations in central nervous system.
Column R: Reference number indicating the publication in which the mutation is described. NP indicates unpublished mutations contributed by NP1 (M. Boxer and C. Black) and NP2 (D. Milewicz). P indicates references that are in press.

sequence obtained from the GenBank database (GenBank database accession number L13923; complete coding sequence of HUM-FIBRILLIN Homo sapiens fibrillin mRNA). For each mutation, information is provided at several levels: at the gene level (exon and codon number, wild type and mutant codon, mutational event, mutation name), at the protein level (wild type and mutant amino acid, affected domain) and at the clinical level (absence or presence of skeletal, ocular, cardiovascular, central nervous system and other various manifestations). The clinical data are entered with respect to the nosology proposals of Beighton *et al*. (45) recently revised by De Paepe *et al*. (46). We have included repeat observations of the same mutation. Seven recurrent mutations have been reported either twice (R122C, R627C, G1013R, R1137P and C1223Y) or thrice (E1073K and 5788 +5 G→A). Since the present version of the software cannot accomodate two mutational events in a given individual three mutations are not included in the current version of the database: the double mutant Splice exon 51 and X2113X reported by Dietz *et al*. (10), the compound deletion del3901-4; 3908-9 reported by Nijbroek *et al*. (26), and the double mutant I1071S and E1073D reported by Wang *et al*. (42). A fourth mutation is not included in the Marfan database: the 1588 +21 G→A (37) until more precise information is available on mRNA splicing or stability.

Newly developed software routines

The sofware package contains routines for the analysis of the FBN1 database that were developped with the 4th dimension® (4D) package from ACI. The purpose of the software is to facilitate the mutational analysis of the FBN1 gene at the molecular level and to provide the tools to search for genotype/phenotype correlations. Initially, six specific routines were developed (43). Three new routines have been added to the software: (i) 'Restriction enzyme' appears on the first page of the mutation file. If the mutation modifies a restriction site, the program shows a restriction map displaying the new or abolished site and the enzymes of interest. (ii) 'Amino acid type search' studies the mutations with respect to phylogenetic conservation.

In effect, the fibrillin gene has been identified and sequenced in two mammalian species [complete coding sequence of mouse fibrillin (Fbn-1) mRNA and complete coding sequence of bovine fibrillin (BovFib] mRNA, GenBank database accession numbers L29454 and L28748 respectively). The identity at the amino level between the human and bovine sequences is 97.8% and between the human and the mouse sequences of 96.2%. Therefore, the routine lists the mutations affecting non-conserved amino acids in the bovine, in the mouse, or in both sequences. (iii) 'Binary comparison' compares two mutation groups, each group being defined by distinct research criteria chosen from the database (molecular, clinical, age of onset, sex . . .). The result can be displayed as either of several graphic representations (by amino acids, by exon, or by protein domain) of the distribution of the sorted mutations. Furthermore the sorted mutations can appear in a cumulated or detailed format (insertion, deletion, missense, nonsense).

Finally, an overall modification of the software has been made to enable the simultaneous study of several routines or multi-criteria researches.

Database update and software availability

The current database and subsequent updated versions are available on request to G.C. or C.Boil. on floppy disc using Apple format and Microsoft Excel®, or by e-mail (collod@ceylan.necker.fr). Notification of omissions and errors in the current version as well as specific phenotypic data would be gratefully received by the corresponding author.

The software package is available on a collaborative basis. It will soon be available on the Internet. The software will be expanded as the database grows and according to the requirements of its users. New functions could be implemented.

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