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Software and database for the analysis of mutations in the human FBN1 gene

Gwenaëlle Collod^{1,*}, Christophe Bérout¹, Thierry Soussi², Claudine Junien^{1,3} and Catherine Boileau^{1,3}

¹INSERM U383, Hôpital Necker-Enfants Malades, Université René Descartes, Paris V, 149–161 rue de Sèvres, 75743 Paris Cedex 15, France, ²Institut de Génétique Moléculaire, INSERM U301, 27 rue Juliette Dodu, 75010 Paris, France and ³Laboratoire Central de Biochimie et de Génétique Moléculaire, CHU Ambroise Paré, 9 avenue Charles de Gaulle, 92104 Boulogne Cedex, France

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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 and many mutations will have to be accumulated before genotype/phenotype relationships emerge. To facilitate mutational analysis of the FBN1 gene, a software package along with a computerized database (currently listing 63 entries) have been created.

INTRODUCTION

Fibrillin is a large glycoprotein (320 kDa) ubiquitously distributed in connective tissues (1). Together with amorphous elastin, fibrillin-containing microfibrils form the elastic fibers. Fibrillin is also found in microfibrils that are apparently unendowed with amorphous elastin, such as those forming the ciliary zonule (1). FBN1 gene mutations are associated not only with the Marfan syndrome (MFS) (2,3–26) but also with a spectrum of conditions phenotypically related to MFS, including dominantly inherited ectopia lentis (12,15), severe neonatal Marfan syndrome (12,17,19,23), and isolated typical features of MFS (12,14,18,20,22,25,26). Marfan syndrome, the founding member of heritable disorders of connective tissue, is a dominantly inherited condition characterized by tall stature and skeletal deformities, dislocation of the ocular lens and propensity to aortic dissection (2). The syndrome is characterized by considerable variation in the clinical phenotype between families and also within the same family. Ectopia lentis (EL) is a dominantly inherited connective tissue disorder that somewhat overlaps MFS. In the literature, there are reports both of isolated EL

(27,28) and of families in which EL is associated with mild skeletal symptoms (29). The fundamental difference with MFS is the absence of cardiovascular involvement, an absolute criterion for MFS. Severe neonatal MFS has features of the Marfan syndrome and of congenital contractural arachnodactyly (CCA) present at birth, along with unique features such as loose, redundant skin, cardiac malformations and pulmonary emphysema (30,31).

The gene for FBN1 is located at chromosome 15q15–q21.1 (32). It is relatively large (~110 kb) and its coding sequence is highly fragmented (65 exons) (33–35). The deduced primary structure shows that the fibrillin gene encodes a 2871 amino acid protein that is multidomain and highly repetitive. The protein contains 47 tandem domains with homology to a motif found in human epidermal growth factor (EGF) precursor (33,34). This motif is characterized by a conserved arrangement of 6 cysteine-residues that form 3 predictably spaced intramolecular disulfide linkages resulting in an antiparallel β -sheet conformation (36,37). In 43 of the 47 EGF-like motifs, a calcium-binding consensus sequence was identified. The study of this motif in other proteins suggests a role in protein–protein, protein–ligand and cell–cell interactions. Interspersed among the EGF like motifs are 7 ‘8-cysteine’ motifs (that are homologous with transforming-growth factor- β 1 binding-protein) and two ‘hybrid’ motifs that combine features of the two former. Finally the last 3 domains found in the protein include a unique N-terminal stretch of basic residues, a proline rich domain and the C-terminal region (34).

Sixty three mutations in the FBN1 gene have been reported. These mutations are private, essentially missense, non recurrent and widely distributed throughout the gene. To date, no clear genotype/phenotype relationship has been observed. This is not surprising when considering past experience with other disease genes such as the type I procollagen genes for which many mutations were accumulated before genotype/phenotype relationships emerged (38–40). In this perspective, and to facilitate

* To whom correspondence should be addressed

Table 1. FBN1 gene mutations database. First version (September 1995)

A	B	C	D	E	F	G	H	I	J	K	L	M	N	O	P	Q	R
9	2	165	55	GGA	del83c	Stop at 99	248+1G->A	Gly	Frameshift	NH2 unique region	?	?	?	?	?	?	6
40	4	364	122	CGC	TGC	C->T	R122C	Arg	Cys	EGF-like #2	+	+	-	?	+	?	20
42	4	386	129	TGC	TAC	G->A	C129Y	Cys	Tyr	EGF-like #2	+	+	+	+	+	?	23
43	5	497	166	TGT	TTT	G->T	C166F	Cys	Phe	EGF-like #3	?	?	+	?	?	?	23
67	5	496	166	TGT	AGT	T->A	C166S	Cys	Ser	EGF-like #3	?	?	?	?	?	?	27
22	6	649	217	TGG	GGG	T->G	W217G	Trp	Gly	Hybrid motif #1	+	+	+	?	?	?	12
28	11	1426	476	TGC	GGC	T->G	C476G	Cys	Gly	EGF-like #4	+	+	+	?	?	?	13
53	13	1604	535	TTA	del1b	Stop at 577	1604delT	Leu	Frameshift	cb EGF-like #04	?	?	?	?	?	?	23
6	13	1643	548	AAC	ATC	A->T	N548I	Asn	Ile	cb EGF-like #04	+	+	+	?	?	?	6
14	15	1879	627	CGT	TGT	C->T	R627C	Arg	Cys	cb EGF-like #06	+	+	+	?	?	?	9
55	16	1981	661	TGC	CGC	T->C	C661R	Cys	Arg	8-Cys #2	?	?	?	?	?	?	24
7	18	2168	723	GAT	GCT	A->C	D723A	Asp	Ala	cb EGF-like #07	+	+	+	?	?	?	6
44	18	2237	746	TAT	TGT	A->G	Y746C	Tyr	Cys	cb EGF-like #07	?	?	?	?	?	?	23
15	18	2248	750	TGC	GGC	T->G	C750G	Cys	Gly	cb EGF-like #07	?	+	+	?	?	?	9
29	21	2584	862	TGT	CGT	T->C	C862R	Cys	Arg	Hybrid motif #2	+	+	+	?	?	?	14
45	23	2778	926	TGT	CGT	T->C	C926R	Cys	Arg	cb EGF-like #10	?	?	?	?	?	?	23
46	24	3037	1013	GGA	AGA	G->A	G1013R	Gly	Arg	8-Cys #3	+	+	+	?	?	?	23
19	24	3069	1023	AAG	AAC	G->C	K1029N	Lys	Asn	8-Cys #3	+	+	+	?	?	?	12
59	25	3083	1028	GAT	del126b	del	3209+5G->T	Asp	Frameshift	cb EGF-like #11	+	+	+	?	?	?	12
36	25	3175	1059	TTT	ins3a	Stop at 1061	3174insTGC	Phe	Frameshift	cb EGF-like #11	+	+	+	?	?	?	17
47	26	3217	1073	GAA	AAA	G->A	E1073K	Glu	Lys	cb EGF-like #12	+	?	+	?	?	?	23
18	26	3220	1074	TGC	CGC	T->C	C1074R	Cys	Arg	cb EGF-like #12	+	-	+	?	?	?	12
30	27	3350	1117	TGT	TAT	G->A	C1117Y	Cys	Tyr	cb EGF-like #13	+	+	+	?	?	?	14
11	27	3410	1137	CGC	CCC	G->C	R1137P(1)	Arg	Pro	cb EGF-like #13	+	+	+	?	?	?	3
12	27	3410	1137	CGC	CCC	G->C	R1137P(2)	Arg	Pro	cb EGF-like #13	+	+	+	?	?	?	3
31	28	3484	1155	GAC	del17b	Stop at 1185	3484del17	Asp	Frameshift	cb EGF-like #14	+	-	-	?	?	?	14
58	28	3509	1170	CGT	CAT	G->A	R1170H	Arg	His	cb EGF-like #14	+	-	-	?	?	?	25
41	29	3668	1223	TGT	TAT	G->A	C1223Y	Cys	Tyr	cb EGF-like #15	+	+	+	?	?	?	22
23	30	3725	1242	TGT	TAT	G->A	C1242Y	Cys	Tyr	cb EGF-like #16	?	+	+	?	?	?	12
2	30	3746	1249	TGT	TCT	G->C	C1249S	Cys	Ser	cb EGF-like #16	+	+	+	?	?	?	4
39	32	3965	1322	GAC	del123b	del	4088+1G->A	Asp	Frameshift	cb EGF-like #18	+	+	?	?	?	?	19

A	B	C	D	E	F	G	H	I	J	K	L	M	N	O	P	Q	R
38	32	3965	1322	GAC	del123b	del	3965-2A->T	Asp	Frameshift	cb EGF-like #18	?	-	?	?	?	?	19
54	32	4019	1340	ACC	del1b	Stop at 1411	4020delC	Thr	Frameshift	cb EGF-like #18	?	?	?	?	?	?	23
48	33	4145	1382	AAT	AGT	A->G	N1382S	Asn	Ser	cb EGF-like #19	?	?	?	?	?	?	23
24	36	4537	1513	TGC	CGC	T->C	C1513R	Cys	Arg	cb EGF-like #22	+	+	+	?	?	?	12
32	38	4766	1589	TGT	TTT	G->T	C1589F	Cys	Phe	8-Cys #4	+	+	+	?	?	?	14
51	39	4857	1619	GGA	del1c	Stop at 1638	4857delA	Gly	Frameshift	cb EGF-like #23	+	+	+	?	?	?	23
3	40	4987	1663	TGT	CGT	T->C	C1663R	Cys	Arg	cb EGF-like #24	+	+	+	?	?	?	4
8	41	5138	1713	AAC	ins4a	Stop at 1733	5137ins4	Asn	Frameshift	8-Cys #5	+	+	+	?	?	?	6
49	46	5782	1928	TGT	CGT	T->C	C1928R	Cys	Arg	cb EGF-like #28	?	?	?	?	?	?	23
61	47	5789	1930	GAT	del129b	del	5789+5G->A	Asp	Frameshift	cb EGF-like #29	?	?	?	?	?	?	23
62	47	5789	1930	GAT	del129b	del	5789+5G->A	Asp	Frameshift	cb EGF-like #29	?	?	?	?	?	?	23
63	47	5789	1930	GAT	del129b	del	5789+5G->A	Asp	Frameshift	cb EGF-like #29	?	?	?	?	?	?	23
13	51	6314	2105	GAG	del66b	del	Y1215X	Glu	Frameshift	8-Cys #6	?	?	?	?	?	?	7
56	51	6339	2113	TAT	TAA	T->A	Y2113X	Tyr	Stop	8-Cys #6	?	?	?	?	?	?	24
25	52	6381	2127	GAT	GAA	T->A	D2127E	Asp	Glu	cb EGF-like #32	+	-	+	?	?	?	12
21	52	6431	2144	AAT	AGT	A->G	N2144S	Asn	Ser	cb EGF-like #32	+	-	+	?	?	?	10
26	52	6453	2151	TGC	TGG	C->G	C2151W	Cys	Trp	cb EGF-like #32	+	+	+	?	?	?	12
20	54	6617	2206	GAT	del123b	del	6740+1G->C	Asp	Frameshift	cb EGF-like #34	+	+	+	?	?	?	8
4	54	6662	2221	TGT	TCT	G->C	C2221S	Cys	Ser	cb EGF-like #34	+	+	+	?	?	?	4
50	55	6784	2262	CAA	TAA	C->T	Q2262X	Gln	Stop	cb EGF-like #35	?	?	?	?	?	?	23
5	56	6920	2307	TGC	TCC	G->C	C2307S	Cys	Ser	cb EGF-like #36	+	+	+	?	?	?	5
33	59	7339	2447	GAG	AAG	G->A	E2447K	Glu	Lys	cb EGF-like #38	+	+	-	?	?	?	15
16	60	7456	2486	CTT	del366a	del	7456del366	Leu	Frameshift	cb EGF-like #39	?	+	+	?	?	?	11
27	60	7531	2511	TGT	CGT	T->C	C2511R	Cys	Arg	cb EGF-like #39	+	+	+	?	?	?	12
35	63	7879	2627	GGG	AGG	G->A	G2627R	Gly	Arg	cb EGF-like #42	?	+	+	?	?	?	16
64	63	8038	2680	CGC	TGC	C->T	R2680C	Arg	Cys	cb EGF-like #43	+	-	-	?	?	?	26
65	64	8053	2685	CAC	del175a	Stop at 2692	8053del175(1)	His	Frameshift	cb EGF-like #43	?	+	+	?	?	?	26
66	64	8053	2685	CAC	del175a	Stop at 2692	8053del175(2)	His	Frameshift	cb EGF-like #43	?	+	+	?	?	?	26
37	64	8178	2726	CGG	TGG	C->T	R2726W	Arg	Trp	COOH unique reg.	+	-	-	?	?	?	19
52	65	8236	2746	GAG	del2a	Stop at 2757	8237delGA	Glu	Frameshift	COOH unique reg.	+	+	+	?	?	?	23
17	65	8268	2756	TGG	TGA	G->A	W2756X	Trp	Stop	COOH unique reg.	+	+	+	?	?	?	11
60	65	8326	2776	CGA	TGA	C->T	R2776X	Arg	Stop	COOH unique reg.	+	+	+	?	?	?	21

the mutational analysis of FBN1, we have compiled a database (Table 1) and created a software package for its analysis.

DATABASE AND SOFTWARE

In an effort to standardize the information regarding FBN1 mutations, we have created a computerized database that currently contains information about the published mutations of the fibrillin gene FBN1 and some only reported in meetings proceedings. The current version of the database contains 63 entries. 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 software package contains routines for the analysis of the FBN1 database that were developed with the 4th dimension[®] (4D) package from ACI. The use of the 4D SGDB gives access to optimized multicriteria research and sorting tools to select records from any field. Moreover, six routines were specifically developed: (i) 'Position' studies the distribution of mutations at the nucleotide

level to identify preferential mutation sites, (ii) 'Statistical evaluation of mutational events' is comparable to (i) but also indicates the type of mutational event. The result can either be displayed as a table or in a graphic representation, (iii) 'Frequency of mutations' allows one to study the relative distribution of mutations at all sites and to sort them according to their frequency. A graphic representation is also available and displays a cumulative chart of mutation distributions, (iv) 'Stat exons' studies the distribution of mutations in the different exons. It enables detection of a statistically significant difference between observed and expected mutations (v) 'Protein' studies the distribution of mutational events in various protein domains ('NH₂ unique region', 'EGF-like motifs', 'cb EGF-like motifs', '8-cysteine motifs', 'Hybrid motifs', 'Proline' rich region and 'COOH unique region'), and aligns the amino acids of the consensus sequence for each motif type. (vi) 'Insertions and deletions analysis' searches for repeated sequences surrounding the mutation and possibly involved in the mutational mechanism.

Subsequently, the software will be expanded as the database grows and according to the requirements of its users. New functions could be implemented (see accompanying paper).

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. Exons are numbered with respect to the translational initiation site given by Pereira *et al.* (35).

Column **C**. Nucleotide position at which the mutation is located, numbered as above.

Column **D**. Codon number at which the mutation is located, numbered as above. If the mutation spans more than one codon, e.g. there is a deletion of several bases, only the first (5') codon is entered.

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. If the mutation is a base pair deletion or insertion this is indicated by 'del' or 'ins' followed by the number of bases deleted or inserted and the position of this deletion or insertion in the codon (a, b or c). The nucleotide position is the first that is deleted or the one preceding the insertion. For example, 'del66b' is a deletion of 66 bases including the second base of the codon; 'ins4b' is an insertion of 4 bases occurring between the second and the third base of the codon.

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.* (41). To designate missense mutations, the number of the amino acid position is flanked by the single letter code corresponding to the normal amino acid prior to the number, and the mutant amino acid following the number (e.g. Gly to Ala at codon 85 is designated 'G85A'). Nonsense mutations are designated similarly to missense mutations except that X is used to indicate any termination codon (e.g. Tyr to stop at codon 76 is designated 'Y76X'). Frameshift, insertion and deletion mutations are designated by the nucleotide number followed by 'ins' for insertion or 'del' for deletion. The nucleotide position is the first that is deleted or the one preceding it in the case of insertions. Exact nucleotides are indicated for two or less bases (e.g. 441delA). For three or more bases, the insertion or deletion is specified by the size of the change (e.g. 852del22 indicates a 22 bp deletion starting from nucleotide 852). Splicing mutations are designated by a plus (+) or minus (-) nucleotide relative to the first or last base at the nearest exon (711+1G→T is a G to T substitution in the first base of the intron following the exon that ends at nucleotide 711).

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 amino terminal end of the protein, e.g. 'cb EGF-like' (for calcium-binding EGF-like motifs) #1 to 43, 'EGF-like' (for non calcium-binding EGF-like motifs) #1 to 4, '8-cys' (for '8-cysteine' motifs) # 1 to 7, 'Hybrid motifs' # 1 to 2 (35).

Columns **L-Q**. Diagnostic manifestations in the systems listed by Beighton *et al.* (42). 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. Full citations (authors, year, title, volume, pages) are provided with the database. If the same mutation has been reported for the same patient in different papers only one entry is made. If the same mutation has been reported for unrelated patients, a separate entry is made for each patient.

Note: The present version of the database cannot accommodate two mutational events in a given allele therefore the compound deletion reported by Nijbroek *et al.* (23), i.e. del3901-4; 3908-9^d is not included.

AVAILABILITY

The current database and subsequent updated versions are (will be) available on request to G.C. or C.Be. on floppy disc using Apple format and Microsoft Excel®. Notification of omissions and errors in the current version as well as specific phenotypic data would be gratefully received by the corresponding authors. The software package is available on a collaborative basis.

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