Supplementary Material

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Supplementary Table 1 Primer pairs used to amplify the FBLN5 gene coding region.

Name		Primer	
FBLN5-1F	5´	CCTCTGGAATAAAACACCCG	3´
FBLN5-1rv	5´	AGGAATGAAGCGCTGAGAAT	3´
FBLN5-2F	5´	GTCTGGAACCACCATGACCT	3´
FBLN5-2R	5´	ACTGTAAAGCCACTCCCACC	3´
FBLN5-3fw	5´	AAACCCTGAAACCTGTCTGC	3´
FBLN5-3rv	5´	CCCCTCTCAGTGCTTAGCTC	3´
FBLN5-4fw	5´	CCCACCACTCAATATTGCAA	3´
FBLN5-4rv	5´	GGTGCATTGAATGGCAACTA	3´
FBLN5-5F	5´	TAGGATGGCAGAAGGATTCC	3´
FBLN5-5R	5´	CTTACTACCCTCAGGCAGCC	3´
FBLN5-6F	5´	GCCTTGTATTCGAGACAGCA	3´
FBLN5-6R	5´	CACAAACATAAGCTGCCAGG	3´
FBLN5-7F	5´	AGATCATGCTCCCAAAGGTC	3´
FBLN5-7R	5´	TCCCAAACTGGACATGTGTC	3´
FBLN5-8F	5´	TCCATTGCTAGAAGTGCTGG	3´
FBLN5-8R	5´	GAGCTGCCACTATGAGAGCC	3´
FBLN5-9F	5´	CTGTTGCTGCCATATTGGAT	3´
FBLN5-9R	5´	CATGACGTAGGTAGTAGGCCAG	3´
FBLN5-10F	5´	GCCAGGAGCAGAGACATTCT	3´
FBLN5-10R	5´	GGCTCAGGAGGAGAAGCAT	3´
FBLN5-11F	5´	GAAAGAGCATGGCACAGTTG	3´
FBLN5-11R	5´	AATGCCTAACGTCTGTGTCG	3´

Supplementary Table 2 Normal values of nerve conductions (range in brackets), amplitudes of motor nerves are peak-peak.

NCVs: nerve conduction studies; NCV: nerve conduction velocity in meter per second (m/sec);

NE: not examined; NR: no response

Motor median nerve: DL: 3.4-4.3 msec; AM: 4.8-10.0 mV; NCV: 48.0-60.0 m/sec

Sensory median nerve: AM: 10.0-30.0µV; NCV: 45.0-56.0 m/sec

Motor peroneal nerve: DL: 4.5-5.8 msec; AM: 4.5-9.0 mV; NCV: 44.0-50.0 m/sec

Sural nerve: AM: 8.0-20.0µV; NCV: 44.0-52.0 m/sec

FAMILY AND MEMBER	FBLN5 SEQUENCE VARIATION	NCVS PERONEAL MOTOR/ SURAL NERVE NCV-DL-AM//NCV	NCVS MEDIAN MOTOR/ SENSORY NERVE NCV-DL-AM//NCV
Family A			
A11	p.R373C	NR // NR	NR // NR
A14	p.R373C	NE // NE	22.0-8.4-1.1 // NR
A16	p.R373C	20.7-9.0-0.2 // NR	NE//NE
A17	p.R373C	21.0-6.4-5.0 // NR	28.0-7.0-11.0 // NR
A22	p.R373C	NE // NE	37.5-8.1-11.5 // NE
A23	p.R373C	24.0-6.5-2.4 // NE	35.0-7.2-5.1 // 29.0
Family B			
B5	p.R373C	NE // NE	NE // NE
B9	p.R373C	NR // NR	23.8-7.4-8.4 // 27.9
Family C			
C1	p.G90S	35.5-8.2-0.1 // 51.6	52.6-3.8-1.6 // 65.1
C2	p.G90S	NR // NE	NE-3.9-4.1 // 50.0
C3	p.G90S	48.0-3.0-5.7 // NE	54.0-3.5-22.0 // 39.0
C4	p.G90S	40.6-6.8-2.6 // NE	56.3-4.2-9.3 // NE
C5	p.G90S	47.4-4.4-3.1 // NE	55.9-3.3-7.8 // 44.4
Family D			
D1	p.V126M	51.0-5.4-5.2 // 44.0	59.0-4.0-4.2 // 53.0
D2	p.V126M	40.4-5.6-1.5 // NE	53.6-5.1-13.7 // NE
AMD-Pat			
E	p.V126M	NE // NE	NE // NE
F	p.V126M	43.8-4.8-4.1 // NE	NE // NE
G	p.G90S	34.2-5.0-0.8 // NE	46.2-4.0-3.6 // NE
H	p.T48I	44.0-4.5-5.3 // NE	58.0-4.8-4.6 // NE
K	p.G267S	NE	NE
L	p.G267S	40.3-5.6-0.9 // NR	56.7-4.5-9.0 // 50.7
Controls			
I	p.V126M	NR // NE	52.4-5.4-3.7 // NE
J	p.V126M	41.4-4.9-1.4 // NE	50.0-3.8-4.4 // NE

Supplementary Table 3 Sequencing statistics and list of the observed High Confidence Differences.

Variations are sorted based on their variation types; ns (non-synonymous) and s (synonymous).

Supplementary Table 3A

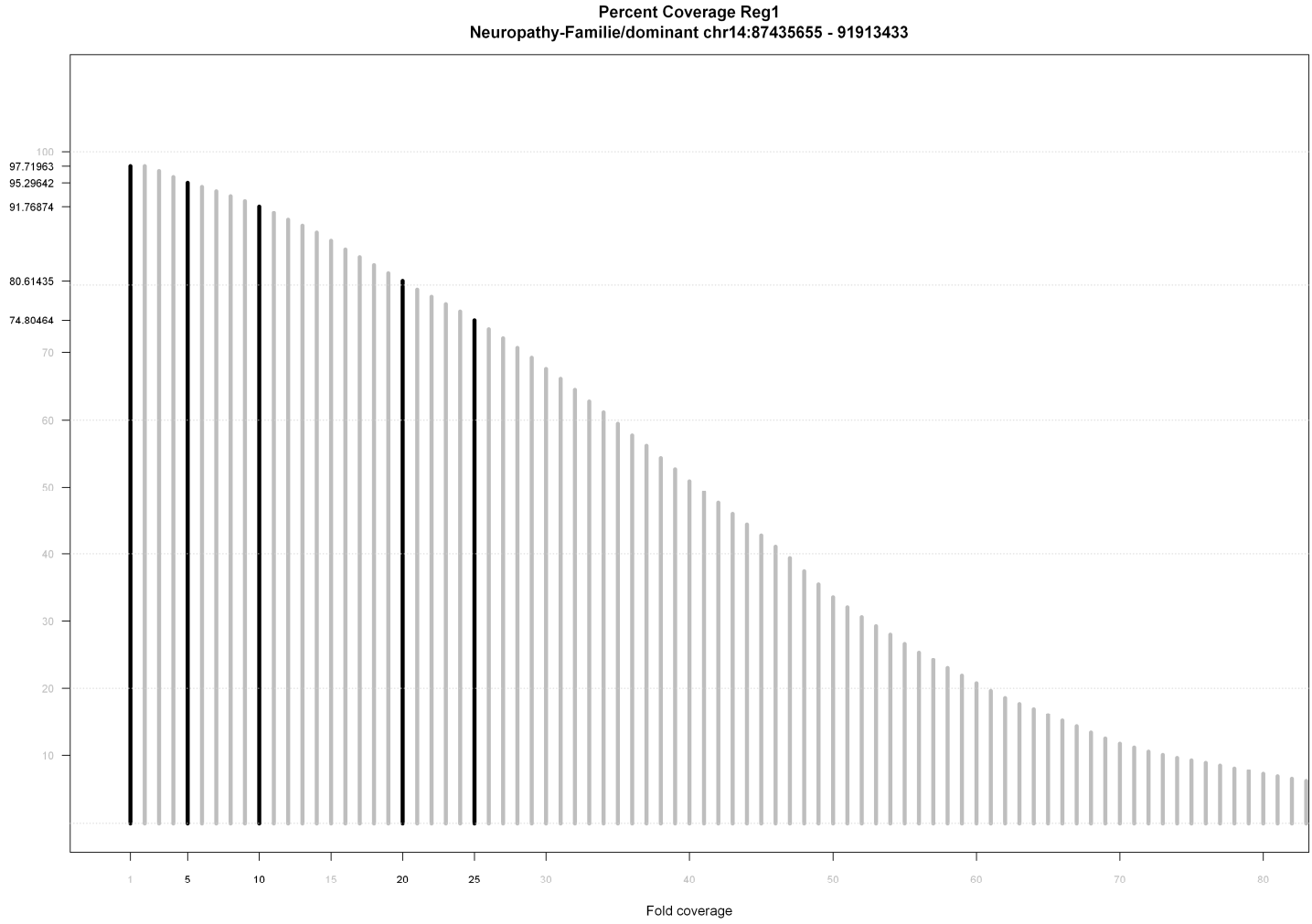
Total sequence information	72.263Mb
Capture Array Target Region	695.5kb
Disease linked exome size	120.4kb
Target bp with a coverage >10-fold	>91%
Total nr. of variants	82
Variants in coding sequence	30
synonymous	18
novel synonymous	1
non- synonymous	12
novel non- synonymous	1

Supplementary Table 3B

Reference Accno	Start Pos	End Pos	Ref Nuc	Var Nuc	Total Depth	Var Freq	Ref AA	Var AA	Region Name	Known SNP's	Variation Type
chr14	87470966	87470966	T	C	55	100%	T	A	GALC	rs421262	ns
chr14	87477641	87477641	A	G	30	37%	I	T	GALC	rs398607	ns
chr14	87932282	87932282	G	A	35	60%	V	M	SPATA7	rs3179969	ns
chr14	88008405	88008405	A	G	60	58%	V	A	PTPN21	rs2274736	ns
chr14	88016375	88016375	G	A	14	50%	L	F	PTPN21	rs2401751	ns
chr14	88275018	88275018	T	C	51	57%	I	V	EML5	rs17188228	ns
chr14	90712148	90712148	G	A	26	58%	S	N	C14orf159	rs34302825	ns
chr14	90808834	90808834	A	G	12	50%	L	P	CCDC88C	rs941920	ns
chr14	91338368	91338368	T	G	37	100%	K	T	TC2N	rs2402073	ns
chr14	91413652	91413652	G	A	25	48%	R	C	FBLN5	**novel**	ns
chr14	91510819	91510819	C	T	30	43%	G	S	TRIP11	rs1051340	ns
chr14	91575668	91575668	T	A	35	40%	M	L	TRIP11	rs17127898	ns
chr14	87477628	87477628	T	A	31	97%	V	V	GALC	rs421466	s
chr14	87481700	87481700	T	C	48	100%	T	T	GALC	rs367327	s
chr14	87501651	87501651	C	T	38	37%	Q	Q	GALC	rs12888666	s
chr14	87547166	87547166	C	T	74	100%	T	T	GPR65	rs6574978	s
chr14	87722142	87722142	C	T	23	65%	A	A	KCNK10	rs3742692	s
chr14	87763478	87763478	G	C	65	58%	V	V	KCNK10	rs2277524	s
chr14	88005678	88005678	A	G	57	58%	T	T	PTPN21	rs2297129	s
chr14	88015344	88015344	A	G	13	38%	P	P	PTPN21	rs879932	s
chr14	89799824	89799824	C	T	59	100%	I	I	PSMC1	rs11554757,rs4811	s
chr14	90193328	90193328	T	C	18	100%	P	P	TTC7B	rs3742660	s
chr14	90231615	90231615	C	T	27	63%	T	T	TTC7B	rs10146731	s
chr14	91017796	91017796	T	C	81	64%	T	T	SMEK1	rs17127374	s
chr14	91153757	91153757	C	G	42	55%	V	V	CATSPERB	rs1620238	s
chr14	91157769	91157769	G	A	36	47%	I	I	CATSPERB	rs1296082	s
chr14	91321340	91321340	A	G	44	48%	L	L	TC2N	**novel**	s
chr14	91417433	91417433	A	G	20	45%	I	I	FBLN5	rs2430347	s
chr14	91862008	91862008	G	A	45	100%	T	T	SLC24A4	rs941646	s
chr14	91978826	91978826	T	C	4	100%	H	H	SLC24A4	rs941650	s

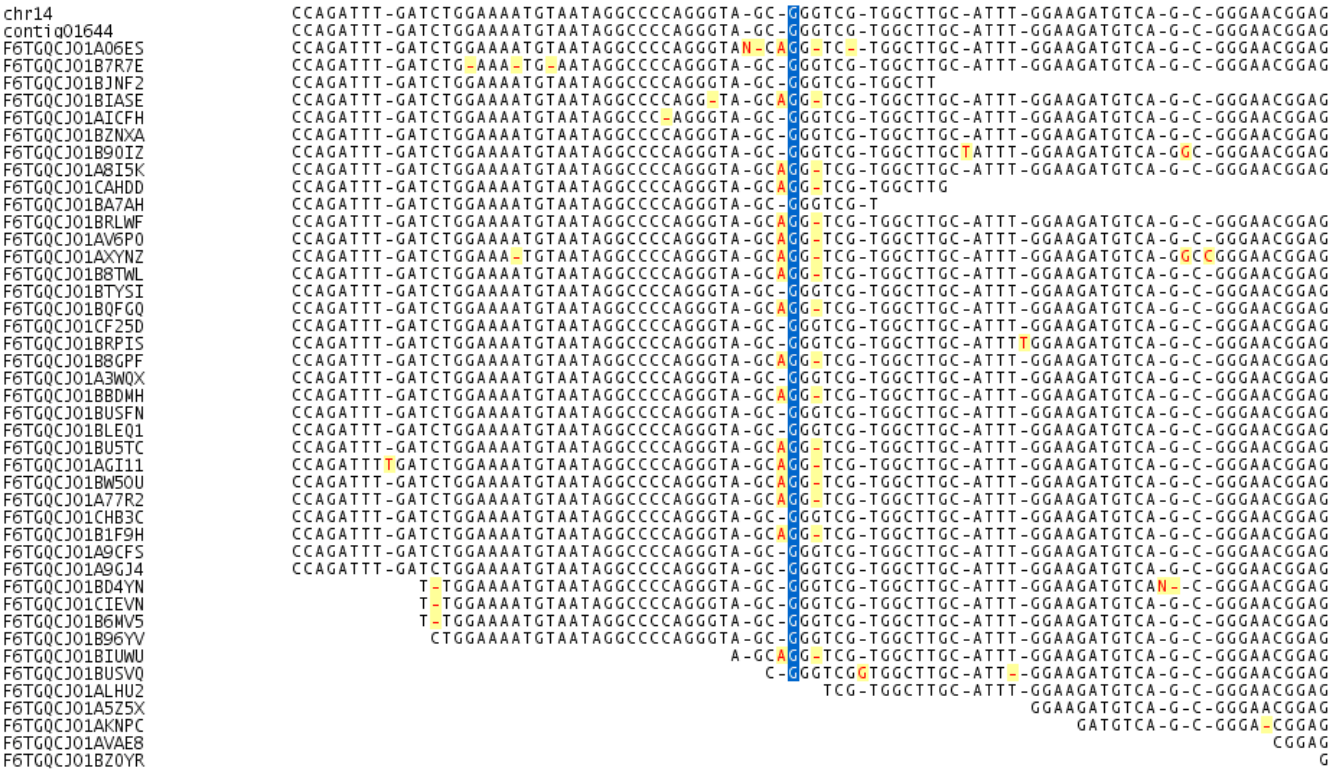
Supplementary Figure 1 Sequence coverage of the disease linked interval (chr.14: bp 87,435,655 – 91,913,433).

The x-axis indicates the calculated coverage per target nucleotide and the y-axis represents the percentage of sequenced target nucleotides. Bars in bold highlight the observed sequencing depth of 25-, 20-, 10-, 5- and 1-fold. >91% of the target nucleotides were sequenced to a minimum depth of 10-fold.



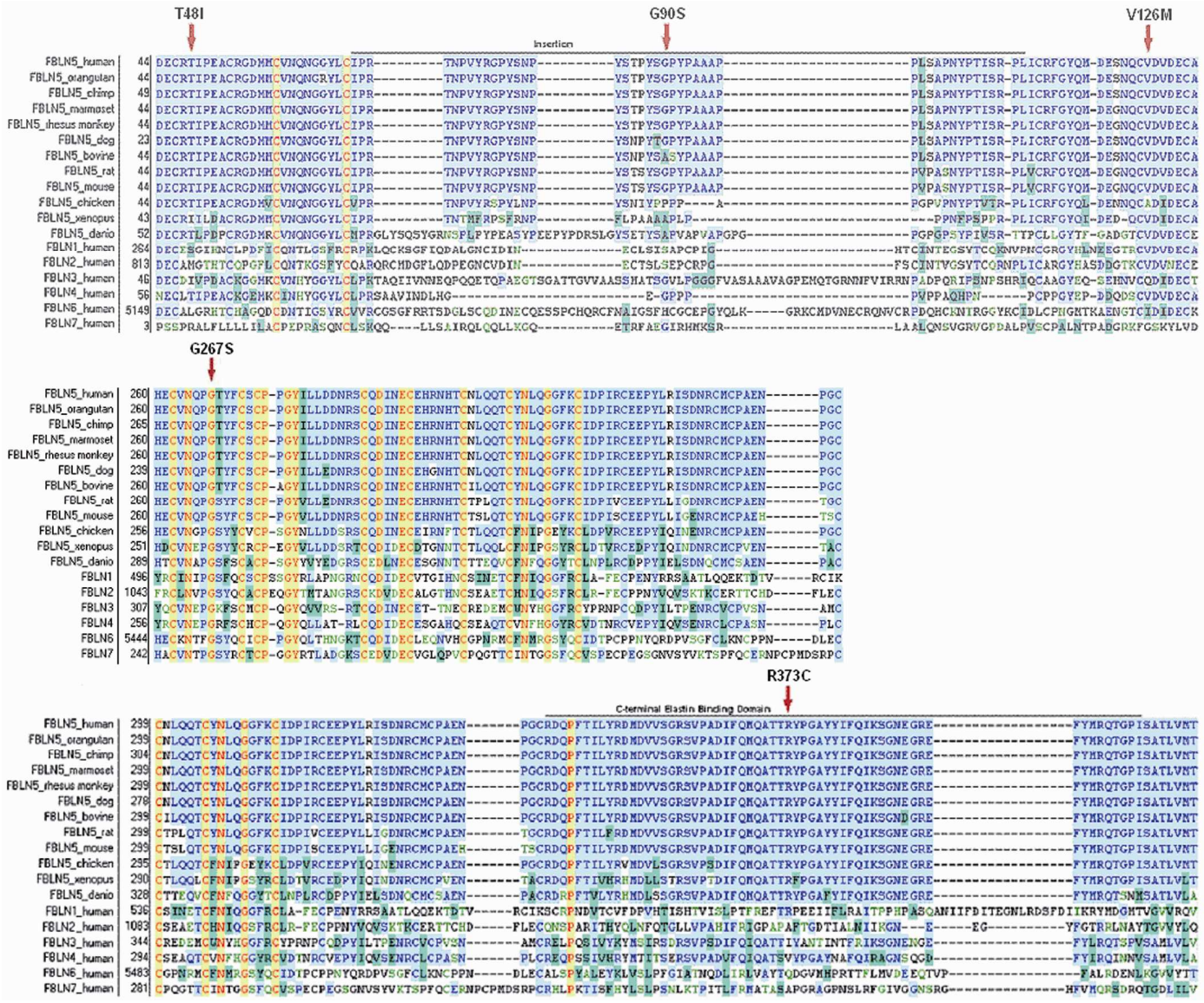
Supplementary Figure 2 Sequence traces from the 37 unique reads covering the *FBLN5* c.1117 C>T (p.R373C) mutation (obtained from patient A16).

The mutated nucleotide at position 91413652 was covered by 37 unique sequence reads, in 22 of the reads the reference allele (G on the anti-sense strand) and in the other 17 reads the mutant allele (A on the antisense strand) was detected indicating that the mutation is present in a heterozygous state. The *FBLN5* gene is transcribed from the minus-strand of chromosome 14; therefore the substitution of a cytosine by a thymidine is represented by a guanine (reference allele) and an adenine (mutant allele) nucleotide in mapping diagram.



Supplementary Figure 3 Evolutionary conservation of the FBLN5 protein.

The *FBLN5* sequence was compared to its orthologues and paralogues with VectorNTI software. Human (NP_006320.2), Orangutan (NP_001125375.1), Chimpanzee (XP_001145383.1), White-tufted-ear marmoset (XP_002754249.1), Rhesus monkey (XP_001092011.1), Dog (XP_537350.2), Bovine (NP_001014946.1), Rat (NP_062026.2), Mouse (NP_035942.1), Chicken (XP_421323.1), Xenopus (NP_001025619.1), Danio (NP_001005979.1), *FBLN1* (NP_006477.2), *FBLN2* (NP_001004019.1), *FBLN3* (NP_001034438.1), *FBLN4* (NP_058634.3), *FBLN6* (NP_114141.2), *FBLN7* (NP_694946.2). The arrows indicate mutation sites found in exons 4, 8 and 10.



Supplementary Figure 4 Simplified and schematic model of elastic fiber assembly.

A. Pericellular assembly of tropoelastin into globules and stabilizing through cross-linking by LOX. FBLN4 and LOX form together with tropoelastin a ternary complex. The binding of FBLN4 with LOX facilitates the cross-linking of tropoelastin. *B.* FBLN5 associates with elastin globules. *C.* FBLN5 facilitates direct high affinity binding of elastin on microfibrils. This is mutually inhibitory to the interaction of FBLN5 and tropoelastin due to the same or overlapping binding site. Fibrillin also disrupts FBLN4 binding to LOX and tropoelastin. FBLN4 and FBLN5 thus do not have compensatory roles in this process. Active LOX cross-links by coalescing elastin globules on microfibrils. *D.* LOX, FBLN4 and FBLN5 may remain associated with microfibrils or dissociate to begin a new cycle of assembly.