Supplementary Table 1 I Study cohort consisting of families including one to four affected individuals.

# of individual exomed per family	Family ID	# of Affecteds
2 individuals	1 and 13	3
	17 and 19	3
	3 and 21	2
	4/22 and 23	2
	26 and 27	2
	7 and 35	4
	8/37 and 39	3
	40 and 41	3
	43 and 44	4
	47 and 48	4
	10 and 54	2
One individual	25	2
	28	2
	32	2
	52	2
	56	2
	59	1
	60	1
	61	1
	62	1

Supplementary Table 2 I WES Quality Metrics of 31 probands from 20 unrelated families.

METRIC	VALUE (AVERAGE)
TOTAL_READS	68,176,055
MEAN_TARGET_COVERAGE	65.17
PF_MISMATCH_RATE	0.19%
PF_HQ_ERROR_RATE	0.17%
PCT_USABLE_BASES_ON_TARGET	46.55%
ZERO_CVG_TARGETS_PCT	0.75%
PCT_TARGET_BASES_10X	93.14%
PCT_TARGET_BASES_20X	84.89%
PCT_TARGET_BASES_30X	74.74%

Supplementary Table 3 I Candidate list of variants of unknow significance were identified in the study population by whole exome sequencing in FBN3

Gene Symbol	Chr.	Pos.	Ref_Allele	Alt_Allele	Zygosity	# of Family(ies) / Affecteds / Tested Individuals	Trancript_ID	HGVS coding	HGVS Protein	Location	Mutation Type	dbSNP	GME Variome AF
FBN3	19	8168562	T	C	HET	1 / 2 / 1	ENST00000600128.1	c.4823A>G	E1608G (p.Glu1608Gly)	exon 39 of 64	Missense	NA	None
	19	8174231	C	T	HET	1 / 2 / 2	ENST00000600128.1	c.4498G>A	G1500R (p.Gly1500Arg)	exon 36 of 64	Missense	rs745616791	0.00050352467270 8962
FN1	2	216283982	G	A	HET	1 / 2 / 1	ENST00000354785.4	c.1802C>T	P601L (p.Pro601Leu)	exon 12 of 46	Missense	NA	None

3 and FN1 genes

GNOMAD (Total AF)	Revel	VEST3
None	Damaging (score:0.8939)	Damaging (score:0.711)
0.00002386	Damaging (score:0.7319)	Damaging (score:0.824)
None	Damaging (score:0.431)	Damaging (score.0,91)

Supplementary Table 4 I First and second neighbours of FBN3 according to STRING database

	First neighbours	**Second neighbours**
FBN3	MFAP5	FN1
	MFAP2	TGFB1
	FBN2	ITGA4
	ITGA5	FLNA
	ITGAV	SHC1
	FURIN	ITGA2B
	FBN1	ITGB8
	ITGB3	ITGA6
	ITGB6	ITGA8
	ITGB1	ITGA3

Supplementary Table 5 I Bioinformatic results for *FBN3* and *FN1* amino acid substitutions.

Prediction	FBN3:c.4823A>G:p.E1608G	FBN3:c.4498G>A:p.G1500R	FN1:c.1802C>T:p.P601L
PROVEAN	Damaging (-6.09)	Damaging (-5.68)	Damaging (-3.88)
SIFT	Damaging (0)	Damaging (0.003)	Damaging (0.001)
Polyphen2_HDIV	Probably_damaging (0.988)	Probably_damaging (1)	Probably_damaging (1)
Polyphen2_HVAR	Possibly_damaging (0.815)	Probably_damaging (0.998)	Probably_damaging (1)
CADD	Damaging (24.6)	Damaging (29)	Damaging (34)
LRT	Unknown	Unknown	Deleterious
MetaSVM	Damaging (1.084)	Damaging (0.881)	Tolerable (-1.051)
MetaLR	Damaging (0.971)	Damaging (0.879)	Tolerable (0.152)
MutationAssessor	Medium (2.52)	Medium (3.255)	Low (1.935)
VEST3	Damaging (0.711)	Damaging (0.824)	Damaging (0.91)
MutationTaster	Disease_causing (1)	Disease_causing (1)	Disease_causing (1)
REVEL	Damaging (0.894)	Damaging (0.732)	Damaging (0.431)
GERP score	Conserved (3.61)	Conserved (4.12)	Conserved (6.06)
PhastCons	Conserved (1)	Conserved (1)	Conserved (1)
PhyloP	Conserved (7.398)	Conserved (7.357)	Conserved (10.003)
FATHMM	Damaging (-5.18)	Damaging (-3.16)	Tolerable (1.92)
FATHMM_MKL	Damaging (0.966)	Damaging (0.991)	Damaging (0.981)
DANN	Damaging (0.999)	Damaging (0.999)	Damaging (0.999)
Eigen	Damaging (0.234)	Damaging (0.476)	Damaging (0.883)

PROVEAN prediction (score)1)
SIFT prediction (score)2)
PolyPhen-2 prediction (score)3)
CADD prediction (phred-like score)4)
LRT prediction (LRTnew score)5)
MetaSVM and MetaLR prediction (score)6)
MutationAssessor prediction (score)7)
VEST3 score8)

MutationTaster2 prediction (score)9)
REVEL prediction (score)10
GERP++ score11)
PhastCons100way score12)
PhyloP100way score12)
FATHMM and FATHMM_MKL score 13)
DANN score14)
Eigen score15)

1)PROVEAN (Choi et al., 2012) scores equal or below -2.50 are considered “deleterious”.
2)SIFT (Kumar et al., 2009) scores ≤0.05 are assigned the prediction “damaging”.
3)PolyPhen-2 (Adzhubei et al., 2010) scores near 1 are most strongly predicting a “damaging” effect of an amino substitution.
4)CADD (Kircher et al., 2014) phred-like rank scores above 15 (for a more conservative estimate: above 20) are considered “damaging”.
5)Values for the LRTnew (Chun & Fay, 2009) score range from 0 to 1 with higher values indicating a variant is more likely to be “deleterious”.
6)MetaSVM and MetaLR (Dong et al., 2015) scores range from 0 to 1 with higher values indicating a variant is more likely to be “deleterious”.
7)MutationAssessor (Reva et al., 2011) scores range from -5.14 to 6.49 with higher scores indicating increasing likelihood of functional impact of a variant. Score c
8)VEST3 (Carter et al., 2013) score ranges from 0 to 1. The larger the score the more likely the variant may cause functional change.
9)The probability value given by MutationTaster2 (Schwarz et al., 2010) is the probability of the prediction, i.e. a value close to 1 indicates a high “security” of the
10)REVEL(Shihab et al., 2014) classifier outputs a prediction score between 0 and 1; mutations scoring from 0 to 0.5 are classified as “likely benign”, and those scc
11)GERP++ (Davydov et al., 2010) estimates evolutionary constraint of specific positions in 36 mammalian species. Scores range from -12.36 to 6.18 with higher sc
12)PhastCons and PhyloP (Pollard et al., 2010) conservation scores are based on multiple alignments of 100 vertebrate genomes. Scores range from 0 to 1 for Pha
13)FATHMM and FATHMM_MKL score (Shihab et al. 2013) scores range from 0 to 1 with higher values indicating a variant is more likely to be “deleterious”.
14)DANN score (Quang et al. 2015) score range from 0 to 1 with higher values indicating a variant is more likely to be “deleterious”.
15)Eigen score (Ionita-Laza et al. 2016)

stCons and from -20 to 9.87 for PhyloP with higher scores suggesting stronger conservation of the site.

Supplementary Table 6 I Clinical and laboratory features of patients with variants of unknow significance in *FBN3* and *FN1* genes.

Family_Number	**Family_3**		**Family_10**	**Family_16**
Patient ID	22	23	28	56
Reported Consanguinity	daughter of 23	mother of 22	daughter of 30, sister of 29	sister of 55
# of Affecteds	2 (1 mother 1 daughter)		2 (1 mother 1 daughter)	2 sisters
Oligomenorrhea / Amenorrhea	NO	NO	NO	NO
Polycystic ovary	YES	history of PCOS	YES	YES
Hyperandrohgenemia	YES	YES	YES	YES
Infertility	YES	NO	NO	NO
Age (years)	23	51	26	25
Body mass index (kg/m2)	29,8	34,1	23,4	20
Waist circumference (cm)	95	101	86	63
Hip circumference (cm)	114	119	98	86
Ferriman-Gallwey scale	18	8	8	9
Anti mullerian hormone (ng/mL; 0,07-7,35)	2,4	0,2	4,1	1,5
Dehydroepiandrosterone sulfate (µg/dL; 23-266)	273,2	186,4	190,8	182,4
Total Testesterone (ng/L; 0.15-0.7)	0,55	0,28	0,38	0,5
Androstenedione (ng/dL; 0,3-3,3)	5,91	4,45	5,7	6,17
Sex hormone-binding globulin (nmol/L; 18-144)	34,02	33,36	21,45	153,05
Triglyceride (mg/dL; <150)	122	162	70	62
Cholesterol (mg/dL; <200)	200	221	182	159
High-density lipoprotein cholesterol (mg/dL; >50)	50	43	64	55
Low-density lipoprotein cholesterol (mg/dL; <130)	126	145	104	91
Fasting blood insulin level (mIU/L)	5,45	5,02	4,87	3,83
Fasting glucose(mmol/L)	92	78	76	86
Gene	*FBN3 (NM_032447.5)*		*FBN3* (NM_032447.5)	*FN1* (NM_212482.4)
Variant	c.4498G>A, p.Gly1500Arg		c.4823A>G, p.Glu1608Gly	c.1802C>T; p.Pro601Leu

Supplementary Table 7 I Fibronectin related 3 known interactions (drugs) according to QuartataWeb Server and DrugBank Database.

No.	Group	Type	Drug ID	Drug Name
1	Approved; Investigational	SmallMoleculeDrug	DB01593	Zinc
2	Investigational	BiotechDrug	DB06245	Lanoteplase
3	Approved	BiotechDrug	DB08888	Ocriplasmin

The DrugBank database identifies 3 drugs for this target protein:

Generic name:	DB11348 calcium phosphate
Generic name:	DB11093 calcium citrate
Generic name:	DB14481 calcium phosphate dihydrate

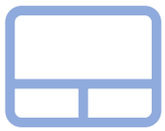
Supplementary Table 8 I Enrichment analysis of 1827 variant-carrying genes that were identified in multiple families

source	term_name	term ID	adjusted p-value
GO:CC	supramolecular polymer	GO:0099081	1.67E-14
GO:MF	extracellular matrix structural constituent	GO:0005201	5.78E-14
GO:CC	supramolecular fiber	GO:0099512	8.82E-14
GO:CC	supramolecular complex	GO:0099080	1.88E-12
GO:BP	biological adhesion	GO:0022610	2.17E-11
GO:BP	cell adhesion	GO:0007155	2.53E-11
GO:CC	basement membrane	GO:0005604	2.57E-11
GO:MF	dynein light intermediate chain binding	GO:0051959	1.47E-09
GO:CC	cell periphery	GO:0071944	1.65E-09
GO:CC	plasma membrane	GO:0005886	2.25E-09
GO:MF	structural molecule activity	GO:0005198	2.33E-09
REAC	Collagen chain trimerization	REAC:R-HSA-8	6.92E-09
GO:MF	extracellular matrix structural constituent conferring tensile strength	GO:0030020	1.13E-08
GO:CC	polymeric cytoskeletal fiber	GO:0099513	1.18E-08
GO:CC	cytoskeleton	GO:0005856	1.43E-08
GO:MF	motor activity	GO:0003774	1.58E-08
GO:CC	extracellular matrix	GO:0031012	1.60E-08
REAC	ECM proteoglycans	REAC:R-HSA-3	2.82E-08
KEGG	ECM-receptor interaction	KEGG:04512	3.19E-08
GO:CC	collagen-containing extracellular matrix	GO:0062023	7.97E-08
REAC	Extracellular matrix organization	REAC:R-HSA-1	8.36E-08
GO:MF	ATP-dependent microtubule motor activity, minus-end-directed	GO:0008569	1.28E-07
REAC	Assembly of collagen fibrils and other multimeric structures	REAC:R-HSA-2	1.77E-07
GO:MF	calcium ion binding	GO:0005509	1.81E-07
REAC	Degradation of the extracellular matrix	REAC:R-HSA-1	2.54E-07
KEGG	Protein digestion and absorption	KEGG:04974	3.83E-07
GO:MF	microtubule motor activity	GO:0003777	3.86E-07
GO:MF	ATP-dependent microtubule motor activity	GO:1990939	4.07E-07
REAC	Non-integrin membrane-ECM interactions	REAC:R-HSA-3	5.46E-07
GO:CC	intermediate filament	GO:0005882	2.04223E-06
GO:BP	multicellular organismal process	GO:0032501	4.41621E-06
GO:CC	keratin filament	GO:0045095	7.17465E-06
REAC	Collagen formation	REAC:R-HSA-1	1.04754E-05
REAC	Collagen biosynthesis and modifying enzymes	REAC:R-HSA-1	1.23034E-05
GO:CC	intermediate filament cytoskeleton	GO:0045111	1.40041E-05
GO:MF	dynein intermediate chain binding	GO:0045505	2.54831E-05
GO:MF	ATP binding	GO:0005524	4.48364E-05
GO:MF	adenyl ribonucleotide binding	GO:0032559	7.12763E-05
GO:BP	homophilic cell adhesion via plasma membrane adhesion molecules	GO:0007156	7.75815E-05
GO:CC	collagen trimer	GO:0005581	7.86649E-05
GO:CC	Z disc	GO:0030018	9.88667E-05
REAC	NCAM1 interactions	REAC:R-HSA-4	9.91098E-05
GO:MF	ATPase activity	GO:0016887	0.000101732
GO:MF	adenyl nucleotide binding	GO:0030554	0.000112851
GO:CC	dynein complex	GO:0030286	0.000114771

GO:BP	multicellular organism development	GO:0007275	0.000125118
REAC	Collagen degradation	REAC:R-HSA-1	0.000134526
GO:CC	plasma membrane region	GO:0098590	0.0001653
GO:BP	skin development	GO:0043588	0.000166819
GO:BP	system development	GO:0048731	0.000213147
GO:BP	developmental process	GO:0032502	0.000234359
GO:CC	I band	GO:0031674	0.000236068
REAC	MET activates PTK2 signaling	REAC:R-HSA-8	0.000242775
REAC	Laminin interactions	REAC:R-HSA-3	0.000242775
REAC	Keratinization	REAC:R-HSA-6	0.000243058
REAC	Integrin cell surface interactions	REAC:R-HSA-2	0.000250707
GO:BP	anatomical structure development	GO:0048856	0.0002636
GO:BP	cytoskeleton organization	GO:0007010	0.000306618
GO:BP	keratinization	GO:0031424	0.000448565
REAC	NCAM signaling for neurite out-growth	REAC:R-HSA-3	0.000793503
GO:BP	cell-cell adhesion via plasma-membrane adhesion molecules	GO:0098742	0.000831677
GO:CC	complex of collagen trimers	GO:0098644	0.000989418
GO:CC	membrane	GO:0016020	0.001091294
GO:CC	myofibril	GO:0030016	0.001451939
GO:BP	cell-cell adhesion	GO:0098609	0.00146937
GO:CC	cell projection	GO:0042995	0.001598052
GO:CC	contractile fiber	GO:0043292	0.001804352
GO:BP	extracellular matrix organization	GO:0030198	0.001895027
REAC	MET promotes cell motility	REAC:R-HSA-8	0.001904787
GO:BP	extracellular structure organization	GO:0043062	0.002072227
GO:MF	cytoskeletal protein binding	GO:0008092	0.002520355
GO:CC	apical plasma membrane	GO:0016324	0.003301769
GO:CC	cornified envelope	GO:0001533	0.003392847
GO:CC	microtubule cytoskeleton	GO:0015630	0.004075773
GO:MF	ion binding	GO:0043167	0.004180248
GO:MF	protein-containing complex binding	GO:0044877	0.004224419
GO:CC	sarcomere	GO:0030017	0.0044201
GO:BP	epidermis development	GO:0008544	0.004675443
GO:CC	non-membrane-bounded organelle	GO:0043228	0.005087849
GO:MF	structural constituent of nuclear pore	GO:0017056	0.005762247
GO:CC	laminin complex	GO:0043256	0.006041182
GO:BP	animal organ development	GO:0048513	0.006315637
GO:CC	microtubule associated complex	GO:0005875	0.006419787
GO:BP	microtubule-based process	GO:0007017	0.006782062
GO:BP	movement of cell or subcellular component	GO:0006928	0.007710079
GO:CC	axonemal dynein complex	GO:0005858	0.00912463
GO:CC	endoplasmic reticulum lumen	GO:0005788	0.009191476
GO:BP	keratinocyte differentiation	GO:0030216	0.009282275
GO:MF	actin binding	GO:0003779	0.00943882
GO:CC	intracellular non-membrane-bounded organelle	GO:0043232	0.00960729
CORUM	Fanconi anemia FAAP100 complex	CORUM:6884	0.012080286
GO:BP	microtubule-based movement	GO:0007018	0.01210945
GO:CC	cell surface	GO:0009986	0.012490275
GO:BP	epidermal cell differentiation	GO:0009913	0.01264555
GO:CC	apical part of cell	GO:0045177	0.015539784
TF	Factor: SREBP-1; motif: CACSCCA	TF:M00749	0.016090643

GO:BP	cellular component organization	GO:0016043	0.018508118
GO:CC	inner dynein arm	GO:0036156	0.01851598
TF	Factor: ZNF692; motif: SYNGGSCCCASCCNC; match class: 1	TF:M09734_1	0.020175167
GO:MF	actinin binding	GO:0042805	0.021935067
GO:CC	microtubule	GO:0005874	0.025113843
GO:BP	cellular component organization or biogenesis	GO:0071840	0.027179913
KEGG	Amoebiasis	KEGG:05146	0.028318445
KEGG	Focal adhesion	KEGG:04510	0.033604016
GO:MF	carbohydrate derivative binding	GO:0097367	0.03850305
GO:MF	alpha-actinin binding	GO:0051393	0.038617668
CORUM	FA complex (Fanconi anemia complex)	CORUM:1152	0.041061481

DNA reads



Next Generation Sequencing

Illumina HiSeq 2000

Illumina Casava 1.8

ATCAGC CGTCCGC GCAACG
AAAAGT GCGAATTAA AGGC

FASTQ file

Reference Human Genome

BWA Aligner

ATCCGCAACGTCCGCGAAATTAAAATTC

ATCAGC CGTCCGC AAAAGG
GCAACG GCGAATTAA AGGC

Alignment

GATK Genome Analysis Tookit

ATCCGCAACGTCCGCGAAATTAAAATTC

ATCAGC CGTCCGC AAAAGG
GCAACG GCGAATTAA AGGC

SNVs / InDel calling

Ensembl-VEP - Variant Effect Predictor

Variant Annotation and Prioritization

Disease associated novel variants