

Table S1. Clinical findings of the 59 patients with cEDS (Supplementary Data).

Patient number	Gene	Variant	Protein	rs	Varsome	Major criteria			Minor criteria	Other features
						Skin hiper-extensibility	Atrophic scarring	Generalized joint hypermobility		
1	COL5A1	c.1989+1G>T	splice variant	not reported	Pathogenic	(+)	(+)	(+)	soft, velvety skin, easy bruising, dislocations of joints	poor wound healing, feet valgity, gastroesophageal reflux, astigmatism
2	COL5A1	c.1273_1276dupAGTC	p.Ser426Ter	not reported	Likely Pathogenic	(+)	(-)	(+)	soft skin, hernias, epicanthal fold, joint pain	delayed motor development, high palate
3 (mother of patients 4 and 5)	COL5A1	c.5021delC	p.T1674Kfs*55	not reported	Pathogenic	(+)	(+)	(+)	soft, velvety skin, easy bruising, dislocations of joints, joint pain, family history of cEDS	poor wound healing, chronic fatigue, preterm delivery (patient 4 and 5), coronary arterial disease and chronic duodenal ulcer disease
4 (daughter of 3)	COL5A1	c.5021delC	p.T1674Kfs*55	not reported	Pathogenic	(+)	(+)	(+)	soft, velvety skin, easy bruising, dislocations of joints, joint pain, family history of cEDS	poor wound healing, arrhythmia, chronic fatigue

5 (daughter of 3)	COL5A1	c.5021delC	p.T1674Kfs*55	not reported	Pathogenic	(+)	(+)	(+)	soft, velvety skin, easy bruising, dislocations of joints, joint pain, family history of cEDS	poor wound healing, arrhythmia, mitral valve prolapse
6 (mother of 7)	COL5A1	c.4050dupC	p.Gly1351Argfs*814	not reported	Likely Pathogenic	(+)	(-)	(+)	velvety skin, easy bruising, dislocations of joints, joint pain	flatfoot, preterm delivery of a daughter (patient 7) in 36 hbd and a son born in 27 hbd (not tested for cEDS)
7 (daughter of 6)	COL5A1	c.4050dupC	p.Gly1351Argfs*814	not reported	Likely Pathogenic	(+)	(-)	(+)	soft, doughy skin, easy bruising, family history of cEDS	congenital hip dysplasia, scoliosis, mitral valve prolapse
8	COL5A1	c.1726C>T	p.Pro576Ser	rs763246328	Likely Benign	(+)	(+)	(+)	dislocations of joints, whole body pain	-
	COL6A3	c.6930+5G>A	splice variant	rs749037028	VUS					
9 (described in [7])	COL5A1	c.944C>T	p.Thr315Met	rs145093766	Likely Benign	(+)	(-)	(+)	pain, family history of cEDS	flatfoot, scoliosis, chronic osteoporosis, short stature, muscle hypotonia, diarrhea, chronic fatigue syndrome
10 (mother of patients 11-13)	COL5A1	c.3023C>T	p.Thr1008Met	rs199735010	Likely Benign	(+)	(-)	(+)	soft, velvety skin, dislocations of joints, family	varicose veins

									history of cEDS	
11 (daughter of 10)	COL5A1	c.3023C>T	p.Thr1008Met	rs199735010	Likely Benign	(+)	(+)	(+)	soft, velvety skin, dislocations of joints, epicanthal fold, positive family history	scoliosis
12 (daughter of 10)	COL5A1	c.3023C>T	p.Thr1008Met	rs199735010	Likely Benign	(+)	(+)	(+)	soft, velvety skin, dislocations of joints, joint pain, family history of cEDS	scoliosis, Raynaud's syndrome
13 (daughter of 10)	COL5A1	c.3023C>T	p.Thr1008Met	rs199735010	Likely Benign	(+)	(+)	(+)	soft, velvety skin, dislocations of joints, whole body pain, family history of cEDS	
14	COL5A1	c.3398G>A	p.Arg1133Gln	rs759580799	Likely Benign	(+)	(+)	(+)	soft skin, dislocations of joints, joint pain	scoliosis, mitral valve prolapse
15 (described in [7])	COL5A1	c.1089C>G	p.Asn363Lys	rs773870913	Likely Benign	(+)	(-)	(+)	easy bruising, dislocations of joints, flat feet,	-
16 (described in [7])	COL5A1	c.193C>T	p.Arg65Trp	rs139468527	Benign	(+)	(-)	(+)	dislocations of joints, whole body pain	feet valgity, osteoporosis, high palate
	COL5A1	c.514G>T	p.Val172Phe	rs150147262	Likely Benign					
17 (described in [7])	COL5A1	c.367C>G	p.Gln123Glu	rs142114921	Likely Benign	(+)	(-)	(+)	easy bruising, slow wound healing, joints dislocations	feet and knees valgity, high palate, chronic fatigue syndrome

18 (described in [7])	COL5A1	c.4483G>A	p.Gly1495Ser	not reported	VUS	(+)	(-)	(+)	velvety skin, easy bruising, navel hernia, family history of cEDS	knees and heels valgity, scoliosis, muscle hypotonia, delayed motor development, high palate, reflux gastrointestinal, blue sclera
19 (described in [7])	COL5A1	c.2588A>T	p.Glu863Val	rs139788610	Benign	(+)	(-)	(+)	velvety skin, easy bruising, dislocations of joints, family history of cEDS	congenital hip dysplasia, flatfoot and valgus foot, scoliosis, delayed motor development, osteoporosis, arrhythmia, mitral insufficiency, gastrointestinal disorders
	COL5A1	c.3418G>A	p.Val1140Met	rs149616140	Benign					
20 (described in [7])	COL5A1	c.3418G>A	p.Val1140Met	rs149616140	Benign	(+)	(-)	(+)	velvety skin, dislocations of joints, family history of cEDS	-
21	COL5A2	c.2555G>A	p.Gly852Asp	not reported	Likely Pathogenic	(+)	(-)	(+)	soft, velvety skin, hernias, epicanthal fold	stretch marks, irritable bowel syndrome, bradycardia
22	COL1A1	c.2451T>C	p.Pro817=	rs374465457	Likely Pathogenic	(+)	(+)	(+)	soft, velvety skin, easy bruising, dislocations of joints, whole body pain,	-

									family history of cEDS	
23	COL1A1	c.517G>A	p.Gly173Arg	rs193922157	VUS	(+)	(+)	(+)	easy bruising, dislocations of joints, family history of cEDS	irritable bowel syndrome, mitral insufficiency, migraines, myopia, marfanoid habitus, ADHD (in childhood), suspicion of bleeding disorders
24	COL1A1	c.1984-5C>A	splice variant	rs66592376	Benign	(+)	(+)	(+)	soft, velvety skin, easy bruising with delayed wound healing dislocations of joints, joint pain	delayed motor development, high palate, pigeon chest (pectus carinatum), ADHD, a tendency to self-injury, hypersensitivity to sounds, MCAS (Mast Cell Activation Syndrome), mitral valve prolapse
25	COL1A2	c.601C>A	p.Pro201Thr	not reported	VUS	(+)	(+)	(+)	easy bruising, velvety skin, dislocations of joints, joint pain, and whole body pain	delayed wound healing, stretch marks, gastroesophageal reflux, irritable bowel disease, scoliosis, osteoporosis, osteomalacia,
	COL1A2	c.661G>A	p.Gly221Ser	not reported	VUS					

										chondromalacia, gluten intolerance
26	COL1A2	c.3706A>G	p.Ser1236Gly	rs781184808	VUS	(+)	(-)	(+)	soft, velvety, doughy skin,	collarbone fracture (1x), pigeon chest (pectus carinatum), blue sclera flatfoot, valgus knees
27	COL1A2	c.2776C>T	p.Arg926Cys	rs745363291	VUS	(+)	(+)	(+)	soft, velvety skin, easy bruising, dislocations of joints, joint pain	delayed wound healing, hand fracture in childhood (1x), hyperalgesia, pigeon chest (pectus carinatum), gothic palate, irritable bowel disease, POTS (Postural Tachycardia Syndrome), depressed mood
28	COL1A2	c.118C>A	p.Pro40Thr	rs1363689462	VUS	(+)	(+)	(+)	soft, velvety, doughy skin, easy bruising, delayed wound healing, dislocations of joints, joints and whole body pain	gastroesophageal reflux, irritable bowel syndrome
29	COL1A2	c.2642A>C	p.Glu881Ala	rs751201659	VUS	(+)	(-)	(+)	soft, velvety skin, easy bruising,	gastroesophageal reflux, hernia,

									delayed wound healing, hernias, dislocations of joints, joint pain	blue sclera, depressed mood
30	COL1A2	c.3313G>A	p.Gly1105Ser	rs139851311	VUS	(+) (-)	(+) (-)	(+) (-)	soft, velvety skin, easy bruising	gothic palate
	COL6A3	c.4184G>A	p.Arg1395Gln	rs80272723	Benign					
	NOTCH1	c.3142C>T	p.Pro1048Ser	rs770521856	VUS					
31	no mutation	-	-	-	-	(+)	(+)	(+)	easy bruising, dislocations of joints	delayed wound healing, POTS (Postural Tachycardia Syndrome)
32	no mutation	-	-	-	-	(+)	(-)	(+)	soft, velvety skin, hernias, stretch mark, joint pain	irritable bowel syndrome
33	no mutation	-	-	-	-	(+)	(+)	(+)	soft, and velvety skin, dislocations of joints, joint pain	flatfoot, blue sclera
34	no mutation	-	-	-	-	(+)	(+)	(+)	soft, doughy skin, easy bruising, hernias, dislocations of joints, joints and whole body pain	delayed wound healing
35	no mutation	-	-	-	-	(+)	(+)	(+)	soft, velvety skin, dislocations of joints, joint pain	Raynaud's syndrome

36	no mutation	-	-	-	-	(+)	(-)	(+)	soft, velvety skin, dislocations of joints, joint pain	varicose veins, Raynaud's syndrome
37	no mutation	-	-	-	-	(+)	(+)	(+)	soft, velvety, easy bruising skin, dislocations of joints, joint pain	poor wound healing, mitral valve prolapse
38	no mutation	-	-	-	-	(+)	(+)	(+)	soft skin, hernias, dislocations of joints, joint pain	flatfoot, scoliosis
39	no mutation	-	-	-	-	(+)	(-)	(+)	soft, velvety skin, easy bruising with hernias, dislocations of joints, joint pain	delayed wound healing, flatfoot, gastroesophageal reflux, blue sclera
40	no mutation	-	-	-	-	(+)	(-)	(+)	soft skin, hernias, epicanthal fold, joint pain	delayed motor development, high palate, blue sclera
41	no mutation	-	-	-	-	(+)	(+)	(+)	dislocations of joints, whole body pain	POTS
42	no mutation	-	-	-	-	(+)	(+)	(+)	soft, velvety, doughy skin, dislocations of joints, pain of joints and whole body	delayed wound healing, gastroesophageal reflux, irritable bowel syndrome
43	no mutation	-	-	-	-	(+)	(-)	(+)	soft, and velvety skin,	stretch marks, irritable bowel

									hernias, joint pain	syndrome, blue sclera
44	no mutation	-	-	-	-	(+)	(+)	(+)	soft, doughy skin easy bruising, hernias, epicanthal fold, dislocations of joints, the pain of joints and whole body	gastroesophageal reflux, blue sclera
45	no mutation	-	-	-	-	(+)	(+)	(+)	dislocations of joints, joints and whole body pain, hernias	-
46	no mutation	-	-	-	-	(+)	(-)	(+)	soft, velvety skin, easy bruising with, hernias, dislocations of joints, joint pain	delayed wound healing, varicose veins, blue sclera
47	no mutation	-	-	-	-	(+)	(+)	(+)	soft, velvety skin, dislocations of joints, joint pain	delayed wound healing, gastroesophageal reflux
48	no mutation	-	-	-	-	(+)	(-)	(+)	soft, and velvety skin, hernias, epicanthal fold	stretch marks, irritable bowel syndrome, arrhythmia
49	no mutation	-	-	-	-	(+)	(-)	(+)	soft, velvety skin, hernias, joint pain	stretch marks, flatfoot, arrhythmia, irritable bowel

										syndrome, blue sclera
50	no mutation	-	-	-	-	(+)	(+)	(+)	soft, doughy skin, easy bruising, hernias, dislocations of joints, joint pain	gastroesophageal reflux
51	no mutation	-	-	-	-	(+)	(+)	(+)	soft, doughy skin, easy bruising, hernias, dislocations of joints	food intolerance
52	no mutation	-	-	-	-	(+)	(-)	(+)	soft, velvety skin, dislocations of joints, joint pain,	varicose veins, Raynaud's syndrome, blue sclera
53	no mutation	-	-	-	-	(+)	(+)	(+)	soft, velvety skin, easy bruising, dislocations of joints, whole body pain, family history of cEDS	-
54	no mutation	-	-	-	-	(+)	(-)	(+)	soft skin, hernias, epicanthal fold, joint pain	delayed motor development, high palate, blue sclera
55	no mutation	-	-	-	-	(+)	(+)	(+)	soft, velvety skin, dislocations of joints	delayed wound healing, gastroesophageal reflux

56	no mutation	-	-	-	-	(+)	(-)	(+)	soft, velvety skin, hernias, joint pain	delayed wound healing, stretch marks, irritable bowel syndrome, gastroesophageal reflux, blue sclera
57	no mutation	-	-	-	-	(+)	(-)	(+)	soft, velvety skin, easy bruising with delayed hernias, dislocations of joints, joint pain	wound healing, gastroesophageal reflux, blue sclera
58	no mutation	-	-	-	-	(+)	(-)	(+)	soft skin, hernias, epicanthal fold, joint pain	delayed motor development, high palate
59	no mutation	-	-	-	-	(+)	(+)	(+)	soft, velvety skin, easy bruising, dislocations of joints, whole body pain, family history of cEDS	-

Legend: (+) clinical feature detected, (-) clinical feature not detected, - do not concern