Supplementary Table 18. Rare variants (CADD > 20) identified in EDS patients of differing clinical EDS subtypes, in genes not currently associated with human disease or variants in genes not currently associated with an EDS phenotype. These variants have high in silico pathogenicity scores and some published evidence of biological plausibility.

Patient ID	Variant ID	Age	Sex	Clinical Diagnosis	Beighton score	Villefranche Major/ Minor	Aortic & Other Vascular involvent	Auto. Dom. Family History	Skin Biopsy	Gene NM	Current Gene annotation	Protein Domain	Rs ID ClinVar	gnomAD allele frequency	CADD DANN	ACMG classification (See footnote) criteria
34	50	30-39	F	HDCT	3	A, C, E, H, I d,i	Carotid artery dissection	–	normal	PTGER4 NM_000958.3 c.644G>T	a)	p.Arg215Leu helical transmembrane (3AA)	– –	0	29.2 0.998	
404	51	40-49	M	hEDS	9	A, C, H, I a, d, f, i, u	–	+	Occasional irregular collagen fibril	MMP25 NM_022468.5 c.580C>T	a)	p.His194Tyr	rs1004972120 –	0	28.9 –	
446	52	40-49	M	HDCT	4	A, C, E, I d, i, f, u	Carotid artery dissection	+	irregular collagen fibril size	ADAMTS5 NM_007038.5 c.2314A>G	a)	p.Thr772Ala spacer domain	– –	0	22.6 0.998	
446	53	40-49	M	HDCT	4	A, C, E, I d, i, f, u	Carotid artery dissection	+	irregular collagen fibril size	ADAMTS16 NM_139056.4 c.2459G>A	a)	p.Arg820Gln spacer domain	rs748937514 –	0.0000281	32 0.999	
446	54	40-49	M	HDCT	4	A, C, E, I d, i, f, u	Carotid artery dissection	+	irregular collagen fibril size	NFAT5 NM_138713.4 c.3446T>A	a)	p.Val1149Asp	– –	0	25.8 0.981	
505	55	10-19	F	HDCT	–	H g, l, u	–	+	–	ROBO2 NM_002942.5 c.2018G>A	c)	p.Arg673His Fibronectin III2	rs376737394 346696 (LB)	0.000121	34 0.999	VUS PM2, PP3 (Supp) BP6 (S)
566	56	60-69	M	hEDS	5	A, C, E, H, I , J x, y, aa	–	biparental	Collagen fibril size variability	SYAP1 NM_032796.4 c.37C>T	a)	p.Gln13Ter	– –	0	36 0.998	
703	57	10-19	F	hEDS	–	C, H t, u	–	–	–	LZTS1 NM_021020.5 c.1483G>A	a)	p.Glu495Lys	rs150225368 –	0.0005212	22.8 0.997	
761	58	20-29	M	hEDS	6	B, C, H, I, J d, f, t, u, v		+	–	C9 NM_001737.5 c.1052C>G	c)	p.Ser351Cys Transmembrane	rs1999424520 –	0.0000318	25.5 0.991	VUS PM2
1396	59	0-9	M	kEDS	7	C, H, J e, f, u, w	–	+	–	INO80D NM_017759.5 c.1822–1823delAC	a)	p.Thr608Ter	– –	0	35 –	
1450	60	30-39	F	hEDS	–	B, C, H, I a, t, u premature rupture of membranes	–	+	Collagen fibril size variability	MMP8 NM_002424.3 c.679C>T	a)	p.His227Tyr	rs769627751 –	0.00000518	23.6 0.995	
1491	61	20-29	F	hEDS	6	C, H d, f, t, y	–	–	–	FBN3 NM_032447.5 c.6988C>T	a)	p.Arg2330Trp TB 9 domain	rs372443838 –	0.0000678	34 0.999	
1620	62	20-29	M	hEDS	6	C, H, I d, f, t, u	–	+	–	ITGA2 NM_002203.4 c.1027A>G	c)	p.Asn343Asp	– –	0	28.4 0.998	VUS PM2
1625	63	60-69	F	HDCT	–	– g, r, t megacolon	AoR	–	–	TGFB1/1, NM001042454.3 c.199C>T	a)	p.Arg67Trp Nr Phosphoserine	– –	0	35 0.999	
1695	64	20-29	F	hEDS	8	C, H, I f, u	–	+	–	NOTCH4 NM_004557.4 c.3203C>A	a)	p.Pro1068His	rs765636311 –	0	22.4 0.994	
1717	65	40-49	F	hEDS	7	C, H d, t	–	–	–	C3 NM_000064.3 c.910C>T	c)	p.Arg304Trp Neighbours phosphoserine	rs1189452748 –	0.00000399	24.4 0.999	VUS PM2

ACMG criteria as per Richards *et al.* (9): P = pathogenic, LP = likely pathogenic, VUS/LP = variant of uncertain significance close to criteria for LP classification, VUS = variant of uncertain significance, LB = likely benign, B = benign. Individual criteria ((9), Table 3)

VUS* are defined here as including VUS that according to ACGS criteria are "hot", "warm" or "tepid" Variants of Uncertain Significance (Figure 6 of https://www.acgs.uk.com/media/11631/uk-practice-guidelines-for-variant-classification-v4-01-2020.pdf). Segregation analysis, re-evaluation for specific phenotypic features and/or further functional analysis may enable variant reclassification, using ACMG criteria.
EDS Diagnostic Criteria as per list in Supplementary Table 1.