Supplementary Table 7. Variants of uncertain significance (CADD> 15) in EDS/LDS/HTAD and syndromic genes in this cohort which are close to Likely Pathogenic classification (VUS*).

Patient ID	Variant ID	Age	Sex	Clinical Diagnosis	Beighton score	Villefranche Criteria Major Minor	Aortic & Other Vascular involvement	Auto. Dom. Family History	Skin Biopsy	Gene. NM	Protein	Rs ID ClinVar ID	gnomAD allele frequency	CADD DANN	ACMG classification (See footnote) ACMG criteria
45	20	50-59	F	HDCT	5	C, E, H u	Carotid dissection	+	abnormal packing	VCAN ENST00000265077.3 c.10063+2dup	?	– –	0	25.2 –	VUS* PM2 PVS1 (M)
72	21	50-59	M	HDCT	–	A, C, E j, r finger aplasia	Femoral artery aneurysm, FHx HTAD	+	–	WNT10A NM_025216.3 c.443C>T	p.Ala148Val	rs373695499 899013 (VUS)	0.0000199	29.9 0.999	VUS* PM2 PP3 (M)
107	22	40-49	M	hEDS	4	E, H, I r, u	FHx Aneurysm	+	normal	KCNH1 NM_172362.3 c.1036A>G	p.Ile346Val (exomiser)	– –	0	– 0.998	VUS* PM2, PP2 PP3 (Supp)
107	23	40-49	M	hEDS	4	E, H, I r, u	FHx aneurysm	+	normal	ULK4 NM_017886.4 c.2979-1G>T	?	– –	0	26.7 0.994	VUS* PM2
474	24	60-69	F	HDCT	0	D, E n	Epidural haemorrhage	–	abnormal	NEDD4L NM_001144967.3 c.2425G>A	p.Asp809Asn HECT domain	rs868820698 956262 (VUS)		26.3 0.998	VUS* PM2 PP3 (Supp) PP2
475	25	30-39	F	hEDS	7	H, I a, d, g, i, u,	–	+	normal	PIEZO2 NM_022068.3 c.713T>G	p.Leu238Trp	rs927091191 427172 (VUS)	0.000142	27.4 0.834	VUS* PM2 PP2
479	26	20-29	F	HDCT	6	A, C, H, I, J, K e, f, g, t, w	–	+	normal	PIEZO1 ENST00000301015.9 c.2492C>T	p.Ser831Leu Transmembrane domain (helical)	rs1471934686 829803 (VUS/LP)	0.000013	32 0.999	VUS* PM2 PP5 (S)
482	27	20-29	F	vEDS	6	C, D, H, I d, g, h, i, t, u	–	Biparental	normal	SCN9A NM_002977.3 c.3930C>G	p.Ile1310Met	rs200947663 –	0	26.2 0.998	VUS* PM2 PP3 (M)
583	29	10-19	F	cEDS	8	A, B, C, H, I, J d, f, g, i, s, t, u	–	+	Small number Cauliflower fibrils	COL5A1 NM_001278074.1c.5130dupG	p.Ser1711ValfsTer67 (exomiser)	rs779189580 –	0.0000166	– 0.957	VUS* PVS1 (Exon 64) PM2
595	31	30-39	M	cEDS	6	A, C, H, I a, d, g, k, q	MVR	+	–	TGFB3 NM_003239.4 c.128T>C	p.Ile43Thr	rs765490133 –	0.00000398	25 0.998	VUS* PM2 PP3 (Supp)
806	35	10-19	M	cEDS	–	B, C, H, J e, I, u	–	+	normal	COL5A1 NM_000093.5 c.5136+151_5136+164del	?	rs762698019 –	0	– 0.957	VUS* (Intron 64) PM2
967	36	10-19	F	hEDS	8	C, H, I a, d, f, i, s, u	–	+	–	FLCN NM_144997.7 c.716G>A	p.Arg239His	rs753948488 253233 (VUS)	0.0000278	34 0.999	VUS* PM2, PM5 PP3 (M)
1002	37	50-59	F	cEDS	7	A, C, H, I d, i, s, u	–	+	Irregular collagen fibrils	MAP3K7 NM_145331.3 c.820C>T	p.Arg274Cys	– –	0	35 0.999	VUS* PM2 PP3 (Supp) PP5
1421	39	10-19	M	hEDS	7	C, H, I a, u	–	+	–	PIEZO2 NM_022068.3 c.6053A>G	p.Tyr2018Cys	rs772793550 –	0.000284	23.1 0.927	VUS* PM2 PP2 PP3 (Supp)
1451	40	10-19	F	cEDS	9	A, C, H, I d, g, i, t	fhx aneurysm	+	–	COL9A3 NM_001853.4 c.130G>A	p.Gly44Ser	rs770649938 –	0.0000495	23.5 0.976	VUS* PM2 (m) PP3 (M)
1495	42	20-29	F	hEDS	7	C, H, I d, t, u	–	+	–	PCNT NM_006031.6 c.8182C>T	p.Arg2728Cys	rs762890408 –	0.0000399	35 0.999	VUS* PM2 PP5
1498	43	40-49	M	hEDS	–	A, C, H, I, J i, u, y, bb	–	+	–	COL6A3 NM_004369.3 c.2042T>G	p.Val681Gly	rs753741086 938432 (VUS)	0.00000398	22.9 0.998	VUS* PM2 PP3 (Supp)

1530	45	10-19	F	hEDS	6	H, I g, u	–	Biparental	–	UPF3B NM_080632.3 c.263+2delT	?	rs118945278 –	0.0000593	25.2 –	VUS* PVS1 (VS)
1607	47	40-49	F	hEDS	6	C, H, I d, f, t, u GI dysfunction	–	+	–	SPTLC1 NM_006415.4 c.287del	p.Asn96MetfsTer6	– –	0	32 –	VUS* PM2
1620	48	20-29	M	hEDS	6	C, H, I d, f, t, u	–	+	–	PIEZO2 NM_022068.3 c.716C>T	p.Pro239Leu	rs776926434 1050407 (VUS)	0.0000071	34 0.973	VUS* PM2 PP2 PP3 (M)
1714	49	40-49	F	hEDS	5	C, H t,	–	–	–	MAT2A NM_005911.6 c.553A>G	p.Thr185Ala	– –	0	25 0.998	VUS* PM2 PP3 (M) PP2

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 and Abbreviations as per lists in Supplementary Table 1.