

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	Aortic & Other Vascular involvement	Auto. Dom. Family History	Skin Biopsy	Gene. NM	Protein	Rs ID	gnomAD allele frequency	CADD DANN	ACMG classification (See footnote)
45	20	50-59	F	HDCT	5	C, E, H u	Carotid dissection	+	abnormal packing	VCAN ENS00000265077.3 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)	0.000199	29.9	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	-	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	VUS* PM2
474	24	50-59	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	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	VUS* PM2 PP2
479	26	20-29	F	HDCT	6	A, C, H, I, J, K e, f, g, t, w	-	+	normal	PIEZO1 ENS00000301015.9 c.2492C>T	p.Ser831Leu Transmembrane domain (helical)	rs1471934686 829803 (VUS/LP)	0.000013	32	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	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	-	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	0.0000398	25	VUS* PM2 PP3 (Supp) VUS*
806	35	10-19	M	cEDS	-	B, C, H, J e, l, u	-	+	normal	COL5A1 NM_000093.5 c.5136+151_5136+164del	?	rs762698019	0	0.957	(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	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	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	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.Gly445Ser	rs770649938	0.0000495	23.5	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	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	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*
1607	47	40-49	F	HEDS	6	C, H, I d, f, t, u GI dysfunction	-	+	-	SPTLC1 NM_006415.4 c.287del	p.Asn96Metfs Ter6	-	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	0.0000071	34	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	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.