Supplementary Table 11. Rare variants, (CADD> 15), in genes associated with syndromes with EDS associated features and Mendelian disorders with EDS symptomatology.

Patient ID	Clinical Diagnosis	Gene NM	Protein	CADD	gnomAD allele frequency	Exon or intron number / total number of exons	ClinVar ID classification	Rs ID	DANN	Vascular Involvement	ACMG classification (See footnote)
75	cEDS	PIEZO2 NM_022068.3 c.3236A>G	p.Tyr1079Cys	26.2	0.00027	22/52	430213 (VUS)	rs192225494	0.980	–	VUS PM2, PP2
79	HDCT	EMILIN NM_007046.3 c.82G>A	p.Gly28Ser	25.6	0	1/8	–	rs1174686741	0.998	aneurysm	VUS PM2
107	hEDS	IFIH1 NM_022168.4 c.2242G>A	p.Gly748Arg	–	0.0000119	11/16	1428095 (VUS)	rs764553894	0.999	fhx aneurysm	VUS PM2
385	hEDS	LAMA5 NM_005560.6 c.2623C>A	p.Arg875Ser Domain 4b	28.9	0.00000416	22/80	–	rs371962250	0.997		VUS PM2 BP4 (Supp)
396	cEDS	SCN9A NM_002977.3 c.2102C>G	p.Pro701Arg	23.5	0.00000485	14/27	376819 (VUS)	rs867106113	0.995	subclavian artery	VUS PM2 PP3 (Supp)
396	cEDS	ATP7A NM_000052.7 c.3790A>G	p.Ile1264Val	19.5	0	19/23	573762 (VUS)	rs782323741	0.996	subclavian artery	VUS PM2
397	hEDS	KCNH1 NM_172362.3 c.2762C>A	p.Thr921Lys	16.5	0	11/11	–	–	0.97	–	VUS PM2, PP2
422	HDCT	MED12 NM_005120.3 c.6201_6227del	p.Gln2068–Gln 2076del In frame Deletion	19.11	0	42/45	–	–	–	–	VUS PM2, BP3
475	hEDS	SYNE1 NM_182961.4 c.18193C>T	p.Arg6065Trp	35	0.0000398	96/146	284767 VUS	rs200209279	0.999	–	VUS PM2, BP6
505	HDCT	EMILIN NM_007046.4 c.1877T>A	p.Leu626Gln	26.2	0	4/8	–	–	0.996	–	VUS PM2
526	HDCT	IFIH1 NM_022168.4 c.2962G>A	p.Val988Ile	31	0	16/16	574103 (VUS)	rs74162090	0.998	fhx MVP, aortic valve dis.	VUS PM2
620	HDCT	SDSL NM_138342.4 c.626C>T Homozygous	p.Ala209Val	23	0.001 (0 homozy)	7/9	–	rs144688002	0.998	–	VUS PM2
635	HDCT	SYNE1 NM_182961.4 c.19730G>A	p.Arg6577Gln	32	0.000346	107/146	288606 (LB/VUS)	rs150387338	0.999	–	VUS/ LB BS2, BP6
718	cEDS	EMILIN NM_007046.4 c.2116C>T	p.Arg706Cys	26.2	0.0000119	4/8	–	rs747249536	0.999	–	VUS PM2
768	HDCT	IFIH1 NM_022168.4 c.1783C>T	p.Arg595Cys	26.6	0.0000165	10/16	–	rs191839015	0.997	infrarenal aortic dissection	VUS PM2
777	HDCT	MYH2 NM_001100112.1 c.1115G>A	p.Arg372His	35	0.0000119	12/40	–	rs750569547	0.999	FHx ICA	VUS PM2, PP3 (M)
806	cEDS	ACAN NM_013227.3 c.7204C>T	p.Arg2402Cys	34	0.0000161	17/19	1493820 (VUS)	rs751606366	0.999	–	VUS PM2
1464, 1620	hEDS	LAMA5 NM_005560.6 c.3964G>A	p.Gly1322Ser Domain 4b	32	0.000324	31/80	–	rs150741810	0.999	–	VUS PM2

1526	hEDS	WNK1 NM_213655.4 c.3188C>T	p.Ser1063Leu	16.8	0	9/28	–	–	0.996	–	VUS PM2 (m) BP4 (Supp)
1528	cEDS	WNK1 NM_001184985.1 c.3815G>T	p.Gly1272Val	23.5	0.00000795	12/28	–	rs750516612	0.697	–	VUS PM2, BP6
1530	hEDS	KIT NM_000222.3 c.867G>A	p.Met289Ile	22.1	0	5/21	–	–	0.993	–	VUS PM2 BP4 (Supp)
1596	hEDS	SYNE1 NM_182961.4 c.18679C>T	p.Arg6227Trp	34	0.0000517	99/146	284132 (VUS)	rs201873107	0.999	–	VUS PM2, BP6
1605	hEDS	LAMA5 NM_005560.6 c.2248G>A	p.Val750Met laminin EGF like 9 & disulfide	27.6	0.000112	18/80	2077900 (VUS)	rs201119098	0.999	–	VUS PM2

ACMG criteria as per Richards et al. ref 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.

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.