Supplementary Table 10. Rare variants of uncertain significance (CADD> 15) in genes associated with HTAD as per gene list in Supplementary Methods.

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	ACMG classification (See footnote)	Vascular Involvement
65	hEDS	ROBO4 NM_019055.6 c.1475G>A	p.Arg492Gln	29.8	0.0000243	9/18	–	rs777639467	0.999	VUS PM2	femoral artery aneurysm
72	HDCT	ROBO4 NM_019055.6 c.713T>C	p.Leu238Pro	18.22	0.00000398	5/18	–	rs1446614640	0.966	VUS PM2	FHx HTAD
372	vEDS	SMAD3 NM_005902.4 c.207-3C>A	Splice	17.52	0.0000119	Int 1/8	580639 (VUS)	rs757772685	0.967	VUS PM2 PP3 (Supp)	N
428	hEDS	FBN2 NM_001999.4 c.3686C>A	p.Pro1229His	–	0.00000796	26/65	–	rs151192448	0.993	VUS PM2	N
453	HDCT	PRKG1 NM_006258.4 c.1427_1428insTACTAACACTTTGTATCAACGTTTAAGTTAGACAATACTTGTGCAAACTCT	p.Arg477ThrfsTer31	35	0	13/18	–	–	–	VUS	carotid artery dissection
475	hEDS	TGFBR1 NM_004612.4 c.214A>T	p.Ile72Leu	12.24	0.000199	2/9	178136 (VUS/LB)	rs111513627	0.976	VUS PM2, PP2 BP6	N
534	cEDS	FBN2 NM_001999.4 c.2536G>A	p.Glu846Lys	28.8	0.000135	25/71	213392 (LB/VUS)	rs375666281	–	VUS PM2, BP6	N
538	hEDS	FLNA NM_001110556.2 c.7813del	p.Leu2605TrpfsTer2	35	0	48/48	– –	–	–	P, reported PMID: **23032111**	AoR
560, 538	HDCT (538), hEDS (560)	PRKG1 NM_006258.4 c.980C>A	p.Thr327Asn	22.8	0.0000279	8/18	520129 (VUS)	rs138485549	0.989	VUS PM2	N
611	cEDS	FBN2 NM_001999.4 c.4328A>T	p.Asp1443Val	34	0.0000875	39/71	411817 (VUS/LB)	rs751400994	0.999	VUS PM2, PP3 (M) BP6	N
638	hEDS	NOTCH1 NM_017617.5 c.2935C>T	p.His979Tyr	24.1	0.00000402	18/37	–	rs1380298048	0.997	VUS PM2, PP2 BP6	N
651	HDCT	MYLK NM_053025.3 c.571C>G	p.Gln191Glu	19.02	0	7/34	198605 (VUS)	rs794727880	0.59	VUS PM2 BP4 (Supp)	fhx AoR
681	hEDS	TGFBR2 NM_003242.6 c.95-7T>C	?	–	0.0000083	Int 1/6	–	rs1386890539	0.873	VUS PM2 BP4 (Supp)	fhx aneurysm
755	hEDS	NOTCH1 NM_017617.5 c.1843G>A	p.Gly615Arg	28.4	0.00000818	11/34	576931 (VUS/LB)	rs764942073	0.999	VUS PM2, PP3 (M) PP2, BP6	N
798	vEDS	MYLK NM_053025.3 c.5477C>T	p.Ala1826Val	26.9	0.000291	33/34	252775 (LB/VUS)	rs147187907	0.999	VUS PM2, BP6	cavernoma
1393	hEDS	BGN NM_001711.6 c.1000G>A	p.Gly334Ser	33	0	8/8	–	rs1209725855	0.999	VUS PM2	AoR

1399 &1397	hEDS	ELN NM_000501.4 c.1543G>A	p.Val515Met	16.95	0.0000437	11/33	1008316 (VUS)	rs376258672	0.946	VUS PM2 BP4 (Supp)	N
1403	hEDS	TGFB2 NM_001135599.3 c.727G>T	p.Asp243Tyr	29.3	0	4/8	–	–	0.996	VUS PM2 PP3 (Supp)	AoR ICA
1421	hEDS	MFAP5 NM_002403.4 c.383G>A	p.Arg128His	32	0.00000796	8/9	–	rs373562256	0.999	VUS PM2 (M)	N
1443	hEDS	SMAD6 NM_005585.5 c.872T>C	p.Leu291Pro splice –3.	24.9	0.00000398	2/4	–	rs768096418	0.999	VUS PM2	fhx aneurysm
1600	hEDS	MYH11 NM_001040114.1 c.3895G>A	p.Val1299Ile	25.4	0.0000358	30/42	547546 (VUS/LB)	rs151058774	0.996	VUS PM2, BP6	N
1607	hEDS	FBN1 NM_000138.4 c.6819G>A	p.Met2273Ile	21.8	0.0000279	56/66	450683 (LB/VUS)	rs778027769	0.975	VUS PM2, PP2 BP6	N
1629	hEDS	SMAD6 NM_005585.5 c.475C>A	p.Arg159Ser MH1 domain	14.29	–	1/4	–	–	0.995	VUS PM2	N

Key: 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. 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.