Supplementary Table 9. Rare variants of uncertain significance, (CADD> 15), in genes associated with EDS (1), 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 (Classification)	Rs ID	DANN	ACMG Classification (See footnote)
60	HDCT	COL6A1 NM_001848.2 c.2821C>T	p.Leu941Phe	23.5	0.000133	35/35	196948 (VUS/ LB)	rs147882179	0.994	VUS PM2, BP6
73	HDCT	COL6A1 NM_001848.2 c.1315C>T	p.Arg439Trp	29.8	0.0000309	19/35	662422 (VUS)	rs368239109	0.991	VUS PM2, BP6
372	vEDS	COL6A1 NM_001848.2 c.2873C>A	p.Ala958Asp	24.4	0.0000931	35/35	284877 (LB/ VUS)	rs763228065	0.997	VUS PM2, BP6
385	hEDS	C1R NM_001733.7 c.1286G>A	p.Cys377Tyr	–	0	8/9	–	–	0.999	VUS PM2
428	hEDS	COL6A3 NM_004369.3 c.3878A>G	p.Asp1293Gly	22.6	0	9/44	–	rs1222267030	0.998	VUS PM2
482	vEDS	COL6A3 NM_004369.3 c.3923G>A	p.Arg1308Gln	15.42	0.995	9/44	199093 (VUS)	rs774461787	0.995	VUS PM2, BP6
495	hEDS	COL5A1 NM_000093.5 c.3852+5G>T	Splice	–	0	48 / 65	–	rs763999542	0.733	VUS PM2 PP3 (Supp)
536	hEDS	COL12A1 NM_004370.6 c.1906A>G	p.Lys636Glu	14.72	0.0000163	11/66	–	rs754916465	0.991	VUS PM2 BP4 (Supp)
566	hEDS	COL6A2 NM_001849.3 c.2558G>T	p.Arg853Leu	22.1	0	28/28	–	–	0.961	VUS PM2
620	HDCT	COL12A1 NM_004370.6 c.6724+5G>A	Splice	20.1	0.00000405	41/65	–	rs746208956	0.966	VUS PM2 PP3 (Supp)
635	HDCT	COL6A1 NM_001848.2 c.3053A>G	p.His1018Arg	17.8	0.00000402	35/35	–	rs1310931207	0.967	VUS PM2
651	HDCT	COL6A3 NM_004369.3 c.8377G>A	p.Val2793Ile	19.41	0.0000159	38/44	500364 (VUS)	rs569907876	0.937	VUS PM2, BP6
768	HDCT	COL6A3 NM_004369.3 c.8377G>A	p.Val2793Ile	19.41	0.0000159	38/44	500364 (VUS)	rs569907876	0.937	VUS PM2, BP6
803	cEDS	COL6A2 NM_001849.3 c.1829G>A	p.Arg610His	23	0.0000519	25/28	896443 (LB/ VUS)	rs758550765	0.996	VUS PM2, BP6
806	cEDS	COL6A3 NM_004369.3 c.3754C>T	p.Arg1252Cys	24.6	0.000124	9/44	285636 (VUS)	rs563530370	0.999	VUS PM2, BP6 PP3 (M)
821	kEDS	COL6A3 NM_004369.3 c.4510C>T	p.Arg1504Trp	24.2	0.000434	9/43	166943 (VUS)	rs144223596	0.997	VUS PM2, BP6

1397	hEDS	COL1A1 NM_000088.4 c.3754C>T	p.Arg1252Cys	26.3	0.000012	48/51	1037654 (VUS)	rs781614679	0.998	VUS PM2 PP2 PP3 (Supp) BP6
1421	hEDS	C1R NM_001733.7 c.419C>T	p.Ala140Val	29.5	0.000135	3/11	–	rs200539827	0.999	VUS PM2 PP3 (Supp)
1451	cEDS	COL5A1 NM_000093.5 c.3013A>G	p.Thr1005Ala	18.24	0	39/66	212954 (VUS)	–	0.943	VUS PM2
1451	cEDS	COL5A1 NM_000093.5 c.3874G>A	p.Glu1292Lys	21.7	0	49/66	955996 (VUS)	–	0.993	VUS PM2
1502	hEDS	C1R NM_001733.7 c.158G>T	p.Gly52Val	32	0.00000408	2/11	–	rs1181587267	0.998	VUS PM2
1528	cEDS	COL1A1 NM_000088.4 c.1200+5G>A	Splice	21	0.00004501	18/50	566740 (VUS)	rs374322003	0.98	VUS PM2 PP3 (Supp)
1581	hEDS	COL5A2 NM_000393.5 c.4085A>G	p.Tyr1362Cys	24	0.0000279	52/54	573793 (VUS)	rs141206016	0.989	VUS PM2 PP3 (Supp)
1600	hEDS	COL6A3 NM_004369.3 c.7133C>G	p.Ala2378Gly	15.19	0	34/44	–	–	0.843	VUS PM2
1604	hEDS	COL6A2 NM_001849.4 c.1336G>A	p.Asp446Asn	24.8	0.000418	16/28	194621 (B/LB/VUS)	rs535007570	0.993	VUS BP6
1642	hEDS	COL6A3 NM_004369.3 c.7670T>A	p.Ile2557Asn	22.1	0.0000239	41/44	577635 (VUS)	–	0.932	VUS PM2

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.