

Supplementary Table 13. Rare germline variants (CADD>15) in genes previously published in a linkage study (29) and genome wide association studies associated with, ($p < 5 \times 10^{-8}$), pelvic organ prolapse (PMID: 32184442), knee pain and rotator cuff injury (<https://www.ebi.ac.uk/gwas/>)

Patient ID	Clinical Diagnosis	Current Gene annotation	Gene	HGVSc	HGVSp	CADD	Rs ID	Exon or Intron / Total no. exons	gnomAD allele frequency	ACMG Classification (See footnote)
79	HDCT	c)	LAMC2	ENST00000264144.4 c.1669T>C	ENSP00000264144.4 p.Tyr557His	24	–	11/23	0	VUS PM2 PP3 (Supp)
100	hEDS	a)	HAS1	ENST00000222115.1 c.874G>A	ENSP00000222115.1 p.Glu292Lys	33	–	3/5	0	
136	cEDS	c)	TBX5	ENST00000310346.4 c.1203G>T	ENSP00000309913.4 p.Trp401Cys	33	rs377649723	9/9	0.00001221	VUS PM2
383	cEDS	a)	HAS1	ENST00000222115.1 c.1679G>A	ENSP00000222115.1 p.Trp560Ter	40	rs200444967	5/5	0.0001912	
428	hEDS	c)	FAT4	ENST00000394329.3 c.11147G>A	ENSP00000377862.3 p.Arg3716His	21.9	rs139635339	9/17	0.00013	VUS PM2
474	HDCT	c)	LAMC2	ENST00000264144.4 c.1105C>T	ENSP00000264144.4 p.Arg369Cys	34	rs552102778	9/23	0.000008122	VUS PM2
495, 505	hEDS (495), HDCT (505)	c)	ROBO2	ENST00000487694.3 c.2066G>A	ENSP00000417335.2 p.Arg689His	34	rs376737394	15/27	0.0001099	VUS PM2 PP3 (Supp)
560	hEDS	c)	LAMC3	ENST00000361069.4 c.236C>T	ENSP00000354360.4 p.Ala79Val	27.2	rs186188737;rs772194826	1/28	0.00009384	VUS PM2
566	hEDS	c)	TBX5	ENST00000310346.4 c.330C>G	ENSP00000309913.4 p.Asp110Glu	24.5	–	4/9	0	VUS PM2 PP3 (Supp)
630	hEDS	c)	LAMC3	ENST00000361069.4 c.449G>A	ENSP00000354360.4 p.Arg150His	31	rs774775769	2/28	0.00001224	VUS PM2 PP3 (M)
967	hEDS	c)	FAT4	ENST00000394329.3 c.10063A>G	ENSP00000377862.3 p.Ile3355Val	22.5	–	9/17	0	VUS PM2
1263	hEDS	c)	SALL1	ENST00000251020.4 c.2920T>C	ENSP00000251020.4 p.Ser974Pro	20.6	rs144429956	2/3	0.00002034	VUS PM2 PP3 (Supp)
1393	hEDS	c)	LAMC3	ENST00000361069.4 c.1682C>T	ENSP00000354360.4 p.Thr561Ile	22.1	rs199701268	10/28	0	VUS PM2 BP4 (Supp)
1403	hEDS	c)	LAMC2	ENST00000264144.4 c.1079T>C	ENSP00000264144.4 p.Ile360Thr	25.7	–	9/23	0	VUS PM2
1421	hEDS	a)	HOOK3	ENST00000307602.4 c.1945A>T	ENSP00000305699.3 p.Lys649Ter	48	–	21/22	0	
1450	hEDS	a)	HAS1	ENST00000222115.1 c.1679G>A	ENSP00000222115.1 p.Trp560Ter	40	rs200444967	5/5	0.0001912	

1495	hEDS	c)	TBX5	ENST00000310346.4 c.113C>G	ENSP00000309913.4 p.Ser38Cys	25.6	–	2/9	0	VUS PM2
1626	hEDS	c)	SALL1	ENST00000251020.4 c.1673C>T	ENSP00000251020.4 p.Pro558Leu	20.2	–	2/3	0	VUS PM2 BP4 (Supp)
1642	hEDS	a)	LAMC1	ENST00000258341.4 c.4729C>T	ENSP00000258341.3 p.Arg1577Ter	37	rs1031794706	28/28	0	
1642	hEDS	a)	ADAM33	ENST00000356518.2 c.706C>T	ENSP00000348912.2 p.Arg236Cys	34	rs750423431	8/22	0.000004061	

Current gene annotation:

- a) Germline variants in this gene not currently associated with Mendelian disorder
- b) Germline variants in this gene associated with disorder of bone metabolism or skeletal dysplasia
- c) Germline variants in this gene associated with non-EDS / HTAD phenotype

ACMG classification as per Richards et al. (9): P = pathogenic, LP = likely pathogenic, = 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.