

Supplementary Table 17. Rare germline variants (CADD>15) in genes previously published in genome wide association studies, associated with, ($p < 5 \times 10^{-8}$), self-assessed Beighton Score > 5 (6), list of genes in supplementary methods.

Patient ID (Beighton Score)	Clinical Diagnosis	Rs ID	CADD DANN	Current Gene annotation	Gene	Exon or Intron / Total no. exons	HGVSc	HGVSp Domain	gnomAD allele frequency	ACMG classification (See footnote)
44 (5)	vEDS	–	28.6 0.999	c)	PIEZO1	25/51	ENST00000301015.9 c.3575C>T	ENSP00000301015.9 p.Ala1192Val Transmembran	0	VUS PM2
44 (5)	vEDS	–	23.7 0.972	b)	COL27A1	34/61	ENST00000356083.3 c.3481C>G	ENSP000003481.3 p.Pro1161Ala Collagen like 9	0	VUS PM2
45 (5)	HDCT	rs200031013	23 0.975	c)	PIEZO1	39/51	ENST00000301015.9 c.5647C>T	ENSP00000301015.9 p.Arg1883Trp none	0.0002472	VUS PM2
60 (0)	HDCT	rs752193524	29.2 0.998	b)	COL27A1	26/61	ENST00000356083.3 c.3040C>T	ENSP000003481.3 p.Arg1014Cys Collagen like 7	0.000004063	VUS* PM2 PP3 (M)
61 (n/a)	hEDS	–	26 0.994	c)	PIEZO1	42/51	ENST00000301015.9 c.5978C>T	ENSP00000301015.9 p.Ser1993Phe Helical transme	0	VUS PM2
61 (n/a)	hEDS	rs758079877	23.5 0.996	b)	COL27A1	60/61	ENST00000356083.3 c.5413G>A	ENSP000003481.3 p.Glu1805Lys Cterminal prop	0.00001221	VUS PM2
99 (0)	HDCT	rs924560632 rs755738951	18.1 0.945	c)	PIEZO1	39/51	ENST00000301015.9 c.5602C>T	ENSP00000301015.9 p.Arg1868Cys none	0.00006886	VUS PM2
385 (n/a)	hEDS	rs753059506	26.6 0.998	b)	COL27A1	50/61	ENST00000356083.3 c.4597G>A	ENSP000003481.3 p.Glu1533Lys Triple helical	0.00001218	VUS PM2
395, 397 (n/a, n/a)	hEDS	rs766146854	24 0.991	a)	NEDD4L	15/31	ENST00000400345.3 c.1370C>T	ENSP000003833.3 p.Pro457Leu Neighbouring p	0.000008.195	VUS PM2, PP2 BP6 (S)
422 (6)	HDCT	rs756716936	21.5 –	a)	STON1	1/3	NM_006873.4 c.773dup	ENSP0000031015.9 p.Asn258Lysfs* LoF z = 1.08	0.0001535	
428 (n/a)	hEDS	rs750927939	27.5 0.994	c)	PIEZO1	51/51	ENST00000301015.9 c.7415C>T	ENSP00000301015.9 p.Pro2472Leu None	0.00001323	VUS PM2

453 (4)	HDCT	rs756716936	24.5 –	a)	STON1	1/3	NM_006873.4 c.773dup	ENSP00000310 p.Asn258Lysfs* LoF z = 1.08	0.0001535	
475 (7)	hEDS	–	24.5 0.995	c)	PIEZO1	47/51	ENST0000030 1015.9 c.6795C>G	ENSP00000301 p.Ile2265Met None	0	VUS PM2
479 (6)	HDCT	rs781648726	19.6 0.936	a)	NEDD4	1/22	ENST0000033 8963.2 c.1006G>A	ENSP00000345 p.Gly336Arg None	0.00002443	
526 (7)	HDCT	rs763621682	17.2 0.631	b)	COL27A1	27/61	ENST0000035 6083.3 c.3136C>T	ENSP00000348 Pro1046Ser Collagen like 7	0.00001633	VUS PM2
532 (2)	HDCT	rs150886795	18.24 0.990	a)	NEDD4	1/22	ENST0000033 8963.2 c.385G>A	ENSP00000345 p.Asp129Asn none	0.0003058	
635 (7)	HDCT	rs775232854	16.72 0.967	c)	VCAN	8/15	ENST0000026 5077.3 c.4380A>C	ENSP00000265 p.Glu1460Asp	0.000008149	VUS PM2 BP4 (Supp)
650 (7)	hEDS	–	34 –	a)	NOTCH4	27/30	ENST0000037 5023.3 c.4772del	ENSP00000364 p.Leu1591Argf LOEUF=0.74	0.000008257	
670 (8)	hEDS	rs532112751	24.4 0.996	c)	PIEZO1	27/51	ENST0000030 1015.9 c.3922C>G	ENSP00000301 p.Leu1308Val None	0.0001946	VUS PM2
673 (3)	hEDS	–	23.9 0.998	a)	NEDD4	15/22	ENST0000033 8963.2 c.3103A>G	ENSP00000345 p.Ile1035Val HECT	0.0000398	
769 (3)	hEDS	rs781127798	24.1 0.995	a)	MAB21L4	1/5	ENST0000038 8934.4 c.94C>T	ENSP00000373 p.Arg32Cys	0.00002893	
777 (7)	HDCT	rs778125678	22.6 0.996	a)	STON1	1/3	NM_006873.4 c.702A>C	ENSP00000310 p.Glu234Asp None	0.000005414	
778 (7)	hEDS	–	16.91 0.986	c)	PIEZO1	17/51	ENST0000030 1015.9 c.2279A>T	ENSP00000301 p.Asp760Val Neighbouring p	0	VUS PM2
814 (8)	HDCT	–	31 0.997	c)	NEDD4L	31/31	ENST0000040 0345.3 c.2893G>T	ENSP00000383 p.Val965Leu HECT	0	VUS PM2 PP2

884 (9)	hEDS	rs781001928	35 0.999	a)	ARHGAP44	19/21	ENST0000037 9672.5 c.1933C>T	ENSP00000368 p.Arg645Trp none	0.00002056	
1002 (7)	cEDS	rs568280615	24.3 0.997	c)	PIEZO1	22/51	ENST0000030 1015.9 c.3000C>A	ENSP00000301 p.Phe1000Leu Transmembran	0.0002875	VUS PM2
1396 (7)	kEDS	rs144412674	17.1 0.998	a)	STON1	1/3	NM_006873.4 c.1258G>A	ENSP00000310 p.Val420Met MHD	0.00004111	
1399 (4)	hEDS	rs144412674	17.1 0.998	a)	STON1	1/3	NM_006873.4 c.1258G>A	ENSP00000310 p.Val420Met MHD	0.00004111	
1420 (n/a)	HDCT	rs777936815	19.92 0.955	b)	COL27A1	12/61	ENST0000035 6083.3 c.2365_2367d up inframe insertion	ENSP00000348 p.Pro789dup LOUEF = 0.3	0.000008122	VUS PM2 PM4
1421 (7)	hEDS	rs754511035	16.14 0.955	b)	COL27A1	3/61	ENST0000035 6083.3 c.409G>A	ENSP00000348 p.Val137Ile N terminal prop	0.000004189	VUS PM2 BP4 (Supp)
1511 (7)	hEDS	rs767968797	23.9 0.999	a)	ABI3BP	3/35	ENST0000028 4322.5 c.311G>A	ENSP00000284 p.Arg104Gln None	0.00002849	
1527 (3)	hEDS	-	24.2 0.997	a)	XKR6	2/3	ENST0000041 6569.2 c.844T>C	ENSP00000418 p.Tyr282His	0	
1616 (8)	hEDS	rs141525894	24.3 0.996	a)	NOTCH4	30/30	ENST0000037 5023.3 c.5764G>A	ENSP00000364 p.Gly1922Arg none	0.000133	
1626 (8)	hEDS	rs773623130	16.31 -	a)	ABI3BP	intron 9/67	NM_0013755 47.2 c.910+5_910+ 6insA	? LOUEF = 0.56	0.0001247	
1666 (8)	hEDS	rs191960195	17.07 0.963	a)	ABI3BP	7/35	ENST0000028 4322.5 c.722C>T	ENSP00000284 p.Ala241Val None	0.0001058	
1695 (8)	hEDS	rs765636311	22.4 0.994	a)	NOTCH4	20/30	ENST0000037 5023.3 c.3203C>A	ENSP00000364 p.Pro1068His multiple	0	

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, V = 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.