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	ENSP00000301 p.Ala1192Val Transmembran	0	VUS PM2
44 (5)	vEDS	–	23.7 0.972	b)	COL27A1	34/61	ENST00000356083.3 c.3481C>G	ENSP00000348 p.Pro1161Ala Collagen like 9	0	VUS PM2
45 (5)	HDCT	rs200031013	23 0.975	c)	PIEZO1	39/51	ENST00000301015.9 c.5647C>T	ENSP00000301 p.Arg1883Trp none	0.0002472	VUS PM2
60 (0)	HDCT	rs752193524	29.2 0.998	b)	COL27A1	26/61	ENST00000356083.3 c.3040C>T	ENSP00000348 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	ENSP00000301 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	ENSP00000348 p.Glu1805Lys C terminal prop	0.00001221	VUS PM2
99 (0)	HDCT	rs924560632 rs755738951	18.1 0.945	c)	PIEZO1	39/51	ENST00000301015.9 c.5602C>T	ENSP00000301 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	ENSP00000348 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	ENSP00000383 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	ENSP00000310 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	ENSP00000301 p.Pro2472Leu None	0.00001323	VUS PM2

453 (4)	HDCT	rs756716936	21.5 –	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	ENST00000379672.5 c.1933C>T	ENSP00000368 p.Arg645Trp none	0.00002056	
1002 (7)	cEDS	rs568280615	24.3 0.997	c)	PIEZO1	22/51	ENST00000301015.9 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	b)	COL27A1	12/61	ENST00000356083.3 c.2365_2367dup 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	ENST00000356083.3 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	ENST00000284322.5 c.311G>A	ENSP00000284 p.Arg104Gln None	0.00002849	
1527 (3)	hEDS	–	24.2 0.997	a)	XKR6	2/3	ENST00000416569.2 c.844T>C	ENSP00000416 p.Tyr282His	0	
1616 (8)	hEDS	rs141525894	24.3 0.996	a)	NOTCH4	30/30	ENST00000375023.3 c.5764G>A	ENSP00000364 p.Gly1922Arg none	0.000133	
1626 (8)	hEDS	rs773623130	16.31 –	a)	ABI3BP	intron 9/67	NM_001375547.2 c.910+5_910+6insA	? LOEUF = 0.56	0.0001247	
1666 (8)	hEDS	rs191960195	17.07 0.963	a)	ABI3BP	7/35	ENST00000284322.5 c.722C>T	ENSP00000284 p.Ala241Val None	0.0001058	
1695 (8)	hEDS	rs765636311	22.4 0.994	a)	NOTCH4	20/30	ENST00000375023.3 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, = 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.