Supplementary Table 14. Rare germline variants (CADD> 15) in genes previously published as abnormally expressed in skin fibroblasts from hEDS patients (15), list of genes in supplementary methods.

Patient ID	Clinical Diagnosis	Rs ID	CADD/ DANN	Current Gene annotation	Gene	Exon or intron / total number of exons	HGVSc	HGVSp Domain	gnomAD allele frequency	ACMG classification (See footnote)
34	HDCT	rs752525603	10.24 0.868	c)	ITGB3	1/15	ENST00000559488.1 c.16C>T	ENSP00000452786.1 p.Arg6Trp Signal Peptide	0.0002439	VUS PM2 PP2 BP4 (Supp)
45	HDCT	rs781077349	22.5 0.995	a)	ILKAP	7/12	ENST00000254654.3 c.571C>A	ENSP00000254654.3 p.Leu191Ile Metal ion binding, pLi=0.98	0.00002437	
61	hEDS	rs370293437	27 0.999	a)	C1QTNF9B	1/3	ENST00000382137.3 c.139G>A	ENSP00000371572.3 p.Gly47Arg Collagen like	0.00001629	
75	cEDS	rs140610274	29.5 0.998	c)	TNFAIP3	8/9	ENST00000237289.4 c.2036T>C	ENSP00000237289.4 p.Ile679Thr NFKB regulator	0.00009745	VUS PM2
385	hEDS	rs150777320	23.1 0.989	b)	TNFRSF11B	2/5	ENST00000297350.4 c.104C>A	ENSP00000297350.4 p.Thr35Asn Repeat region	0.0001422	VUS PM2 BS2
395	hEDS	rs747279227	21.3 0.991	a)	TNFRSF10A	4/10	ENST00000221132.3 c.614G>T	ENSP00000221132.3 p.Arg205Leu Repeat region	0.00002031	
395	hEDS	rs747279227	21.3 0.991	a)	TNFRSF10A	4/10	ENST00000221132.3 c.614G>T	ENSP00000221132.3 p.Arg205Leu, Repeat region	0.00002031	
397	hEDS	rs747279227	21.3 0.991	a)	TNFRSF10A	4/10	ENST00000221132.3 c.614G>T	ENSP00000221132.3 p.Arg205Leu Repeat region	0.00002031	
428	hEDS	rs773639782	24.6 0.999	a)	TNFAIP8L3	3/3	ENST00000327536.5 c.347C>T	ENSP00000328016. 5p.Ala116Val phosphoinositide binding	0.00004613	
431	cEDS	–	14.65 0.986	a)	TNFSF10	1/5	ENST00000241261.2 c.89G>A	ENSP00000241261.2 p.Cys30Tyr helical	0	
534	cEDS	–	27.7 0.998	c)	NFKB1	16/24	ENST00000226574.4 c.1678G>A	ENSP00000226574.4 p.Val560Met ANK1 CFLAR	0	VUS PM2 PP2 (Supp)
564	HDCT	rs202134968	25.2 0.998	a)	GSK3B	2/12	ENST00000316626.5 c.233C>T	ENSP00000324806.5 p.Ser78Leu Kinase	0.00001659	
768	HDCT	–	25.5 0.998	a)	SNAI3	3/3	ENST00000332281.5 c.764A>G	ENSP00000327968.5 p.His255Arg Zinc Finger	0	
769	hEDS	rs755736608	32 0.999	a)	TNFAIP8	2/2	ENST00000504771.2 c.133G>A	ENSP00000422245.1 p.Asp45Asn	0.00001308	
777	HDCT	rs766761788	14.59 0.970	a)	C1QTNF2	2/3	ENST00000393975.3 c.359G>A	ENSP00000377545.3 p.Arg120Gln collagen like	0.00004914	
798	vEDS	–	24	a)	TNFRSF25	7/10	ENST00000377782.3 c.720del	ENSP00000367013.3 p.Lys240Asnfs Ter14	0	

1002	cEDS	rs373918716	23.5 0.978	a)	TNFAIP8L3	3/3	ENST0000032 7536.5 c.613A>C	ENSP0000032 8016.5 p.Met205Leu phosphoinositi de binding	0.00003657	
1341	hEDS	–	27.1 0.996	a)	C1QTNF4	2/2	ENST0000030 2514.3 c.886G>T	ENSP0000030 2274.3 p.Ala296Ser C1Q2 domain	0.00001374	
1344	hEDS	–	27.1 0.996	a)	C1QTNF4 –	2/2	ENST0000030 2514.3 c.886G>T	ENSP0000030 2274.3 p.Ala296Ser C1Q domain	0.00001374	
1346	vEDS	rs756818049	26.5 0.993	a)	C1QTNF2	2/3	ENST0000039 3975.3 c.271G>A	ENSP0000037 7545.3 p.Gly91Ser helical	0.00001315	
1397	hEDS	–	24.9 0.996	a)	ITGBL1	2/11	ENST0000037 6180.3 c.154C>G	ENSP0000036 5351.3 p.Arg52Gly Repeat region	0	
1498	hEDS	rs766972313	24.9 0.992	c)	C1QTNF5 LORD	14/15	NM_00127843 1.2 c.6G>C	ENSP0000040 2389.2 p.Arg2Ser signal peptide	0.000007461	VUS PM2
1502	hEDS	rs139306246	22.7 0.996	a)	ILKAP	12/12	ENST0000025 4654.3 c.1166G>A	ENSP0000025 4654.3 p. Arg3 89Gln	0.00004088	
1511	hEDS	–	24.4 0.998	b)	TNFRSF11B	3/5	ENST0000029 7350.4 c.401G>C	ENSP0000029 7350.4 p.Gly134Ala, ? LOEUF = 0.5	0	VUS PM2 PP3 (Supp)
1527	hEDS	rs781311887	24.7 0.999	a)	AKTIP	6/10	ENST0000039 4657.7 c.415C>T	ENSP0000037 8152.6 p.Arg139Cys, ADA 0.992	0.00002851	
1527	hEDS	rs781311887	24.7 0.999	a)	AKTIP	6/10	ENST0000039 4657.7 c.415C>T	ENSP0000037 8152.6 p.Arg139Cys, ADA 0.992	0.00002851	
1603	hEDS	rs376335031	23.8	a)	TNFAIP8	2/2	ENST0000050 4771.2 c.107A>G	ENSP0000042 2245.1 p.Lys36Arg	0	
1603	hEDS	rs376335031	23.8 0.999	a)	TNFAIP8 –	2/2	ENST0000050 4771.2 c.107A>G	ENSP0000042 2245.1 p.Lys36Arg,	0.0001135	
1609	hEDS	–	23.1 0.998	c)	AKT3	4/14	ENST0000036 6539.1 c.259T>C	ENSP0000035 5497.1 p.Phe87Leu PH	0	VUS PM2 PP3 (Supp)
1629	hEDS	–	18.38	a)	TNFRSF10A	6/10	ENST0000022 1132.3 c.742_743del	ENSP0000022 1132.3 p.Leu248Glyfs Ter44 pLi=0, LOEUF = 1.6	0	
1669	hEDS	rs377409471	24.9 0.999	a)	PARVG	11/14	ENST0000044 4313.3 c.677G>A	ENSP0000039 1583.2 p.Arg226His CH2	0.000004061	
1682	hEDS	rs143172535	17.17 0.928	a)	TNFRSF25	7/10	ENST0000037 7782.3 c.626T>C	ENSP0000036 7013.3 p.Val209Ala Helical transmembran e domain, LOEUF = 0.6	0.00002969	

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.