

Supplementary Table 14. Rare germline variants (CADD&gt;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	ENST0000059488.1 c.16C>T	ENSP00000452786.1 p.Arg67Trp 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)	CIQTNF9B	1/3	ENST00000382137.3 c.139G>A	ENSP00000371572.3 p.Gly47Arg Collagen like	0.00001629	
75	hEDS	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	hEDS	-	14.65 0.986	a)	TNFSF10	1/5	ENST00000241261.2 c.89G>A	ENSP00000241261.2 p.Cys30Tyr helical	0	
534	hEDS	-	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	ENSP00000337968.5 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)	CIQTNF2	2/3	ENST00000393975.3 c.359G>A	ENSP00000377545.3 p.Arg120Gln collagen like	0.00004914	
798	hEDS	-	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 phosphoinositide binding	0.00003657	
1341	HEDS	-	27.1 0.996	a)	CIQTNF4	2/2	ENST0000030 2514.3 c.886G>T	ENSP0000030 2274.3 p.Ala296Ser CIQ2 domain	0.00001374	
1344	HEDS	-	27.1 0.996	a)	CIQTNF4	2/2	ENST0000030 2514.3 c.886G>T	ENSP0000030 2274.3 p.Ala296Ser CIQ domain	0.00001374	
1346	VEDS	rs756818049	26.5 0.993	a)	CIQTNF2	2/3	ENST0000039 3975.3 c.271G>A	ENSP0000037 7545.3 p.Gly915Ser 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)	CIQTNF5 LORD	14/15	NM_00127848 1.2 c.6G>C	ENSP0000040 2389.2 p.Arg25Ser 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 0.999	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 0.999	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 transmembrane 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.