

Supplementary Table 12. Rare variants, (CADD&gt;15), in genes in linked regions for hEDS (Syx et al. ref 26).

Patient ID	Clinical Diagnosis	Rs ID	CADD DANN	Current Gene annotation	Gene	Exon or intron number / total number of exons	HGVSc	HGVSp	gnomAD allele frequency	ACMG classification (See footnote)
60	HDCT	rs376054888	25.5 0.997	a)	FGL1	6/10	ENST00000398056.2c.284G>C	ENSP00000381p.Gly95Ala	0.00007318	
65	hEDS	rs150106411	21.5 0.983	a)	POLR3D	6/8	ENST00000397802.4c.671G>A	ENSP00000380904.3p.Arg224Gln	0	
65	hEDS	rs150161793	15 0.989	b)	BMP1	18/20	ENST00000306385.5c.2446C>G	ENSP00000305714.5p.Pro816Ala	0.0001382	VUS PM2
73	HDCT	–	26.6	a)	CCAR2	17/20	ENST00000308511.4c.2220+1G>A	splice variant	0	
74	hEDS	rs760116990	34	a)	NPM2	5/9	ENST00000397940.1c.302_303del	ENSP00000381032.1p.Pro101ArgfsTer21 pLi = 0	0.00006498	
107	hEDS	–	23.6 0.996	a)	PCM1	9/39	ENST00000325083.8c.1268A>G	ENSP00000327077.8p.Gln423Arg	0	
136	cEDS	rs61756237	14.37 0.975	c)	TNFRSF10B	9/9	ENST00000276431.4c.1127C>T	ENSP00000276431.4p.Ala376Val	0.0001584	VUS PM2
191	hEDS	rs35294054	34 0.999	a)	PDGFRL	4/7	ENST00000541323.1c.370C>T	ENSP00000444211.1p.Arg124Cys	0.0002507	
383	cEDS	–	29.9 0.998	a)	PCM1	31/39	ENST00000325083.8c.5012A>G	ENSP00000327077.8p.Asp1671Gly	0	
396	cEDS	–	24.6 0.998	a)	ADAM7	10/22	ENST00000175238.6c.905G>C	ENSP00000175238.5p.Gly302Ala	0	
397	hEDS	–	24.6 0.998	a)	ADAM7	10/22	ENST00000175238.6c.905G>C	ENSP00000175238.5p.Gly302Ala	0	
564	HDCT	–	29.4 0.984	a)	PCM1	27/39	ENST00000325083.8c.4523A>C	ENSP00000327077.8p.Asp1508Ala	0	
583	cEDS	–	14.82 0.818	a)	DOCK5	2/52	ENST00000276440.7c.58A>G	ENSP00000276440.7p.Asn20Asp	0	
583	cEDS	rs762023686	34 0.999	a)	SORBS3	18/21	ENST00000240123.7c.1496C>T	ENSP00000240123.7p.Thr499Met	0.00001229	
595	cEDS	rs201363003	20.7 0.998	a)	CCAR2	13/21	ENST00000308511.4c.1535G>A	ENSP00000310670.4p.Arg512His	0.00004874	
650	hEDS	rs748585448	33 0.996	a)	PDLIM2	3/10	ENST00000308354.7c.979C>T	ENSP00000312634.7p.Arg327Trp	0.00003242	
673	hEDS	rs376663203	28.2 0.998	a)	DOCK5	7/52	ENST00000276440.7c.485A>G	ENSP00000276440.7p.Asp162Gly	0.00007929	
703	hEDS	rs150225368	22.8 0.997	a)	LZTS1	4/4	ENST00000381569.1c.1483G>A	ENSP00000370981.1p.Glu495Lys	0.0005212	
707	HDCT	rs769203969	16.53 0.956	a)	PCM1	3/39	ENST00000325083.8c.32G>T	ENSP00000327077.8p.Gly11Val	0.00002043	

718	cEDS	rs143724214	14.58 0.892	b), c)	SLC39A14	3/9	ENST0000035 9741.5c.395C> T	ENSP0000035 2779.5 p.Ser132Leu	0.00013	VUS  PM2 BP4 (Supp)
769	hEDS	–	24.5 0.999	a)	ADAM28	9/23	ENST0000026 5769.4c.737A >G	ENSP0000026 5769.4 p.Asn246Ser	0	
798	vEDS	rs746383239	24.7 0.996	b)	CSGALNACT1	5/10	ENST0000045 4498.2c.845A >C	ENSP0000041 1816.2 p.Asn282Thr	0.00002437	VUS  PM2
821	kEDS	–	14.77 0.826	c)	SFTPC	4/6	ENST0000031 8561.3c.426C> A	ENSP0000031 6152.3 p.His142Gln	0	VUS  PM2
1346	vEDS	rs760460873	17.35 0.995	a)	DOCK5	8/52	ENST0000027 6440.7c.649A >G	ENSP0000027 6440.7 p.Ser217Gly	0.000008135	
1464	hEDS	rs369514263	17.1 0.987	a)	FGL1	5/10	ENST0000039 8056.2c.82C> G	ENSP0000038 1133.2 p.Gln28Glu	0.00002849	
1484	hEDS	–	26.3 0.997	a)	FGF17	3/5	ENST0000035 9441.3c.211C> T	ENSP0000035 2414.3 p.Arg71Cys	0	
1498	hEDS	rs758593640	35 0.999	a)	CCAR2	18/21	ENST0000030 8511.4c.2269C >T	ENSP0000031 0670.4 p.Arg757Trp	0.000008122	
1499	hEDS	rs758593640	35 0.999	a)	CCAR2	18/21	ENST0000030 8511.4c.2269C >T	ENSP0000031 0670.4 p.Arg757Trp	0.000008122	
1504	HDCT	rs771448146	18.04 0.968	a)	PCM1	31/39	ENST0000032 5083.8c.5132C >A	ENSP0000032 7077.8 p.Thr1711Asn	0	
1524	cEDS	rs774318933	25.5 0.998	a)	PDGFRL	7/7	ENST0000054 1323.1c.1004C >T	ENSP0000044 4211.1 p.Thr335Met	0.00001219	
1528	cEDS	rs749514722	14.15 0.915	a)	ADAM7	12/22	ENST0000017 5238.6c.1156 A>C	ENSP0000017 5238.5 p.Lys386Gln	0.000004076	
1582	hEDS	rs374187681	17.51 0.998	c)	ASAH1	10/14	ENST0000038 1733.4: c.766A>C	ENSP0000037 1152.4 p.Ile256Leu	0.00006906	VUS  PM2 PP2
1582	hEDS	rs145928227	23.5 0.994	a)	CCAR2	12/21	ENST0000030 8511.4c.1235 A>T	ENSP0000031 0670.4 p.Gln412Leu	0.00002847	
1616	hEDS	–	13.44 0.991	b)	CSGALNACT1	10/10	ENST0000045 4498.2c.1548 A>G	ENSP0000041 1816.2 p.Ile516Met	0.00001218	VUS  PM2
1630	hEDS	rs78484373	15.81 0.891	a)	FGL1	5/10	ENST0000039 8056.2c.113G >A	ENSP0000038 1133.2 p.Arg38His	0.00003658	
1665	hEDS	rs149782492	27.4 0.999	a)	SORBS3	18/21	ENST0000024 0123.7c.1549C >T	ENSP0000024 0123.7 p.Arg517Trp	0.00006939	

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.