Supplementary Table 12. Rare variants, (CADD>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	ENSP00000380904.3 p.Arg224Gln	0	
65	hEDS	rs150161793	15 0.989	b)	BMP1	18/20	ENST00000306385.5c.2446C>G	ENSP00000305714.5 p.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	ENSP00000381032.1 p.Pro101Argfs Ter21 pLi = 0	0.00006498	
107	hEDS	–	23.6 0.996	a)	PCM1	9/39	ENST00000325083.8c.1268A>G	ENSP00000327077.8 p.Gln423Arg	0	
136	cEDS	rs61756237	14.37 0.975	c)	TNFRSF10B	9/9	ENST00000276431.4c.1127C>T	ENSP00000276431.4 p.Ala376Val	0.0001584	VUS PM2
191	hEDS	rs35294054	34 0.999	a)	PDGFRL	4/7	ENST00000541323.1c.370C>T	ENSP00000444211.1 p.Arg124Cys	0.0002507	
383	cEDS	–	29.9 0.998	a)	PCM1	31/39	ENST00000325083.8c.5012A>G	ENSP00000327077.8 p.Asp1671Gly	0	
396	cEDS	–	24.6 0.998	a)	ADAM7	10/22	ENST00000175238.6c.905G>C	ENSP00000175238.5 p.Gly302Ala	0	
397	hEDS	–	24.6 0.998	a)	ADAM7	10/22	ENST00000175238.6c.905G>C	ENSP00000175238.5 p.Gly302Ala	0	
564	HDCT	–	29.4 0.984	a)	PCM1	27/39	ENST00000325083.8c.4523A>C	ENSP00000327077.8 p.Asp1508Ala	0	
583	cEDS	–	14.82 0.818	a)	DOCK5	2/52	ENST00000276440.7c.58A>G	ENSP00000276440.7 p.Asn20Asp	0	
583	cEDS	rs762023686	34 0.999	a)	SORBS3	18/21	ENST00000240123.7c.1496C>T	ENSP00000240123.7 p.Thr499Met	0.00001229	
595	cEDS	rs201363003	20.7 0.998	a)	CCAR2	13/21	ENST00000308511.4c.1535G>A	ENSP00000310670.4 p.Arg512His	0.00004874	
650	hEDS	rs748585448	33 0.996	a)	PDLIM2	3/10	ENST00000308354.7c.979C>T	ENSP00000312634.7 p.Arg327Trp	0.00003242	
673	hEDS	rs376663203	28.2 0.998	a)	DOCK5	7/52	ENST00000276440.7c.485A>G	ENSP00000276440.7 p.Asp162Gly	0.00007929	
703	hEDS	rs150225368	22.8 0.997	a)	LZTS1	4/4	ENST00000381569.1c.1483G>A	ENSP00000370981.1 p.Glu495Lys	0.0005212	
707	HDCT	rs769203969	16.53 0.956	a)	PCM1	3/39	ENST00000325083.8c.32G>T	ENSP00000327077.8 p.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 4498.2:c.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.