

**Supplementary Table 16. Rare germline variants (CADD> 15) in genes previously published as abnormally expressed in skin fibroblasts from cEDS patients (Ref 30), list of genes in supplementary methods.**

Patient ID	Clinical Diagnosis	Rs ID	CADD	Current Gene	Gene	Exon or Intron / Total no. exons	HGVS <sub>c</sub>	HGVS <sub>p</sub>	gnomAD	ACMG classification
			DANN	annotation					allele frequency	(See footnote) criteria
395	hEDS	–	22.5 0.998	a)	DTL	14/15	ENST00000366 c.1993G>A	ENSP00000355 p.Ala665Thr	0.0001178	
534	cEDS	–	29.4 0.999	a)	POSTN	9/23	ENST00000379 c.1160T>C	ENSP00000369 p.Leu387Pro	0	
967	hEDS	rs755934955	25.7 0.999	a)	EDIL3	9/11	ENST00000296 c.994G>A	ENSP00000296 p.Asp332Asn	0.00002033	
1289	hEDS	–	27.5 0.998	c)	KIF4A	8/31	ENST00000374 c.836A>G	ENSP00000363 p.Asp279Gly	0	VUS PM2 PP3 (Supp)
1421	hEDS	rs768395830	28.3 0.998	c)	CSPP1	12/29	ENST00000262 c.1576A>G	ENSP00000262 p.Asn526Asp	0.000008126	VUS PM2
1464	hEDS	rs142868256	23.5 0.985	c)	C3	37/41	ENST00000245 c.4535G>A	ENSP00000245 p.Arg1512His	0.0001178	VUS PM2 PP5 BP6
1642	hEDS	–	23.3 0.995	a)	POSTN	7/23	ENST00000379 c.766A>T	ENSP00000369 p.Thr256Ser	0	
1681	hEDS	rs142868256	23.5 0.985	c)	C3	37/41	ENST00000245 c.4535G>A	ENSP00000245 p.Arg1512His	0.0001178	VUS PM2 PM5 BP6
1717	hEDS	rs759948962	24.4 0.998	c)	C3	9/41	ENST00000245 c.910C>T	ENSP00000245 p.Arg304Trp	0.000004067	VUS PM2
1717	hEDS	rs141915646	26.7 0.998	a)	MKI67	8/15	ENST00000368 c.1513C>T	ENSP00000357 p.Arg505Cys	0.00003249	

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.