Supplementary Table 19. Variants identified in EDS patients of differing clinical EDS subtypes with a 'candidate gene' approach based on reported Marfan mouse models, EDS mechanisms, Skeletal dysplasia, Matrisome, Myopathies, Integrins, Dedicator of cytokinesis (DOCK), circadian rhythm genes, Ephrins, Tetraspanins (TSPANs) and serine proteases.

Patient ID	Clinical Diagnosis	Current Gene annotation	Gene	HGVSc	HGVSp	CADD	Rs ID	Exon	gnomAD allele frequency	ACMG Classification (See footnote) criteria
Marfan Mouse Model genes										
61	hEDS	c)	IRF7	ENST00000397566.1 c.1424T>C	ENSP00000380697.1 p.Leu475Pro	20.4	rs376761232	9/9	0.00002048	VUS PM2 PP3 (Supp)
75	cEDS	a)	TMEM176B	ENST00000447204.2 c.16G>A	ENSP00000410269.2 p.Val6Met	22.5	–	2/7	0	
404	hEDS	a)	MMP25	ENST00000336577.4 c.580C>T	ENSP00000337816.4 p.His194Tyr	28.9	–	4/10	0	
474	HDCT	c)	SCUBE3	NM_152753.4 c.2578G>A	p.Val860Ile CUB domain	24.8	rs76742237	19/22	0..0000159	VUS PM2
567	HDCT	c)	IRF7	ENST00000397566.1c.1180G>T	ENSP00000380697.1p.Gly394Cys	27.5	rs368953784	7/9	0.00001254	VUS PM2 PP3 (Supp)
653	cEDS	a)	MMP25	ENST00000336577.4 c.85_86insGCGCGTCGCCGCACCGTTAAAAATCACGTCCTGCATACTCTCGCCGCGAAGC	ENSP00000337816.4 p.Val29GlyfsTer7	28.6	–	1/10	0	
922	hEDS	a)	NFAT5	NM_138713.4 c.1165G>A	p.Gly389Ser RH domain	23.3	rs753948488	6/15	0.0000244	
1387	HDCT	a)	TMBIM1	NM_022152.6 c.847G>A	p.Glu283Lys	34	rs76243510	12/12	0.0004781	
1444	hEDS	c)	SCUBE3	NM_152753.4 c.2518C>T	p.Arg840Cys	35	rs1464548360	19/22	0.00000398	VUS PM2
1451	cEDS	a)	IGFBP2	ENST00000233809.4 c.221C>T	ENSP00000233809.4 p.Pro74Leu	23.1	–	1/4	0	
1500	hEDS	a)	TMBIM1	NM_022152.6 c.817C>G	p.Leu273Val	23.3	–	12/12	0	
1524	cEDS	a)	TMBIM1	NM_022152.6 c.412del	p.Tyr138ThrfsTer12 LOEUF = 1.11	35	rs775344685	5/12	0.0000159	
1595	hEDS	a)	NFAT5	NM_138713.4 c.2907G>C	p.Gln969His	22.8	rs759928002	13/15	0.0000398	

EDS candidate Genes										
107	hEDS	a)	COL5A3	ENST00000264828.3 c.1307G>A	ENSP00000264828.3 p.Arg436Gln	24.8	rs773225571	12/67	0.00001642	
534	cEDS	a)	FBN3	NM_032447.5 c.6661C>T	p.Arg2221Trp EGF like 36 & cysteine disulfide domains	27.3	rs202020932	54/64	0.0000123	
538, 560	HDCT (538), hEDS (560)	c)	C2	ENST00000299367.5 c.1716G>C	ENSP00000299367.5 p.Lys572Asn	23.9	rs376278843	13/18	0.0001411	VUS PM2
584	hEDS	a)	CR1L	NM_175710.2 c.382C>T	p.Arg128Ter LOEUF = 1.6 Splice + 5	36	rs199942497	04/12	0.000223	
769	hEDS	a)	ADAM28	ENST00000265769.4 c.737A>G	ENSP00000265769.4 p.Asn246Ser	24.5	–	9/23	0	
798	vEDS	a)	COL5A3	ENST00000264828.3 c.361G>A	ENSP00000264828.3 p.Ala121Thr	24.1	rs199691548	3/67	0.00006152	
810	HDCT	a)	COL5A3	ENST00000264828.3 c.2260C>T	ENSP00000264828.3 p.Pro754Ser	15.55	–	30/67	0	
1346	vEDS	a)	ADAMTS20	ENST00000389420.3 c.1957C>T	ENSP00000374071.3 p.Arg653Cys	32	rs79065113	14/39	0.00004138	
1387	HDCT	a)	ADAM23	ENST00000264377.3 c.1369G>A	ENSP00000264377.3 p.Gly457Ser	18.3	rs759614751	14/26	0.00001219	
1450	hEDS	a)	MMP8	ENST00000236826.3 c.679C>T	ENSP00000236826.3 p.His227Tyr	23.6	rs769627751	5/10	0.00005286	
1484	hEDS	c)	C8A	ENST00000361249.3 c.1528C>T	ENSP00000354458.3 p.Leu510Phe	27.9	rs200018561	10/11	0.00008122	VUS PM2
1630	hEDS	a)	FBN3	NM_032447.5 c.4886C>T	p.Thr1629Ile EGF like 25 domain	28.5	rs376299515	39/64	0.000203	
1641	hEDS	a)	ADAMTS20	ENST00000389420.3 c.4781_4782dup	ENSP00000374071.3 p.Ala1595GlnfsTer39	36	–	31/39	0	
1642	hEDS	a)	ADAM33	ENST00000356518.2 c.706C>T	ENSP00000348912.2 p.Arg236Cys	34	rs750423431	8/22	0.00000406	
1681	hEDS	a)	MMP8	ENST00000236826.3 c.782A>C	ENSP00000236826.3 p.Tyr261Ser	27.6	–	5/10	0.00001669	
1688	HDCT	a)	ADAMTS4	ENST00000367996.5 c.1700G>A	ENSP00000356975.4 p.Arg567His	33	rs139714128	6/9	0.00006548	
1688	HDCT	a)	MMP24	ENST00000246186.6 c.794C>T	ENSP00000246186.6 p.Thr265Met	33	rs770843975	4/9	0.00004088	

Skeletal Dysplasia										
1450	hEDS	b)	TRPV4	NM_021625.5 c.1634T>C	p.Ile545Thr	20.7	rs757630049	10/16	0	VUS PM2 PM1
Matrisome										
383	cEDS	a)	DSEL	ENST00000310045.7 c.2788C>T	ENSP00000310565.7 p.Arg930Ter	42	–	2/2	0	
595	cEDS	a)	ROCK1	ENST00000399799.2 c.1208G>A	ENSP00000382697.1 p.Arg403His	22.9	rs374052961	10/33	0.00008004	
635	HDCT	c)	CHSY1	ENST00000254190.3 c.278C>G	ENSP00000254190.3 p.Thr93Ser	22.7	rs142148989	1/3	0.0002626	VUS PM2
1289	hEDS	a)	CHPF	ENST00000243776.6 c.2026G>A	ENSP00000243776.6 p.Glu676Lys	34	–	4/4	0	
1443	hEDS	a)	CHPF2	ENST00000035307.2 c.1375C>T	ENSP00000035307.2 p.Arg459Trp	32	rs749772535	4/4	0.00004971	
1443	hEDS	a)	DSEL	ENST00000310045.7 c.607A>T	p.Arg203Ter	35	rs143469336	2/2	0.00000796	
1665	hEDS	a)	DSEL	N_032160.3 c.1061A>C	p.Asn354Thr	24.3	rs374976853	2/2	0.0000159	
1669	hEDS	a)	CHSY3	ENST00000305031.4 c.1013C>T	ENSP00000302629.4 p.Thr338Met	34	rs761257284	2/3	0.000004061	
Myopathy										
703	17	d)	MYH2	ENST00000245503.5 c.5540G>A	ENSP00000245503.5 p.Arg1847His	33	rs748605415	38/40	0.0001462	VUS PM2 BS2
777	HDCT	d)	MYH2	ENST00000245503.5c.1115G>A	ENSP00000245503.5p.Arg372His	35	rs750569547	12/40	0.00001218	VUS* PM2 PP3 (M)
1477	hEDS	a)	ABLIM2	ENST00000447017.2 c.1768G>A	ENSP00000393511.2 p.Val590Ile	23.9	rs200508979	20/21	0.0002302	
1620	hEDS	a)	ABLIM2	ENST00000447017.2 c.337C>T	ENSP00000393511.2 p.Arg113Trp	31	–	3/21	0	
Integrins										
44	vEDS	a)	ITGA10	ENST00000369304.3 c.1655C>T	ENSP00000358310.3 p.Ala552Val	33	–	14/30	0	
383	cEDS	a)	ITGA10	ENST00000369304.3 c.2592G>T	ENSP00000358310.3 p.Lys864Asn	24.2	–	21/30	0	
475	hEDS	a)	ITGA10	ENST00000369304.3 c.2071C>T	ENSP00000358310.3 p.Arg691Cys	28.2	rs782455269	16/30	0.00002031	
612	hEDS	a)	ITGA10	ENST00000369304.3 c.790C>T	ENSP00000358310.3 p.Arg264Ter	36	rs782338989	8/30	0.00002872	
673	hEDS	a)	ITGA2	ENST00000296585.5 c.757T>A	ENSP00000296585.5 p.Phe253Ile	33	–	7/30	0	

673	hEDS	a)	ITGA2	ENST00000296585.5 c.764C>T	ENSP00000296585.5 p.Ala255Val	34	–	7/30	0	
718	cEDS	a)	ITGA2	ENST00000296585.5 c.85G>A	ENSP00000296585.5 p.Ala29Thr	31	rs374701439	2/30	0.00005286	
1504	HDCT	a)	ITGA2	ENST00000296585.5 c.2474T>G	ENSP00000296585.5 p.Phe825Cys	27.5	rs759539816	20/30	0.00003259	
1504	HDCT	a)	ITGA2	ENST00000296585.5 c.1790G>A	ENSP00000296585.5 p.Arg597His	23.4	rs770216834	14/30	0.00004895	
1620	hEDS	a)	ITGA2	ENST00000296585.5 c.1027A>G	ENSP00000296585.5 p.Asn343Asp	28.4	–	9/30	0	
1681	hEDS	a)	ITGA10	ENST00000369304.3 c.1562G>A	ENSP00000358310.3 p.Arg521His	29	–	13/30	0	
1743	hEDS	c)	ITGA2B	ENST00000262407.5 c.2902T>C	ENSP00000262407.5 p.Tyr968His	24.3	rs5914	28/30	0	VUS PM2 PP2
DOCK										
73	HDCT	c)	DOCK6	ENST00000294618.7 c.1631A>G	ENSP00000294618.6 p.His544Arg	23	–	14/48	0	VUS PM2
74	hEDS	c)	DOCK6	ENST00000294618.7 c.4445G>A	ENSP00000294618.6 p.Ser1482Asn	23.8	–	35/48	0	VUS PM2
385	hEDS	c)	DOCK6	NM_020812.4 c.484G>A	p..Glu162Lys	20	rs766200535	5/48	0.00000971	VUS PM2 BP4 (Supp)
385	hEDS	a)	DOCK9	ENST00000376460.1 c.4223C>T	ENSP00000365643.1 p.Ser1408Phe	28.3	–	39/57	0	
1424	hEDS	c)	DOCK2	NM_004946.3 c.4090C>T	ENSP00000256935.8 p.Arg1364Cys	35	rs536724336	41/52	0.00002033	VUS PM2 PP2
1450	hEDS	c)	DOCK6	ENST00000294618.7 c.4641C>A	ENSP00000294618.6 p.Phe1547Leu	22.8	–	36/48	0	VUS PM2
1491	hEDS	c)	DOCK6	NM_020812.4 c.2629C>T	p.Arg877Cys		rs199553475	22/48	0.000181	VUS PM2
1503	HDCT	c)	DOCK6	NM_020812.4 c.3811C>T	p.Arg1271Cys	24.4	rs376724815	30/48	0.0000563	VUS PM2 BP4 (Supp)
1613	hEDS	a)	DOCK9	ENST00000376460.1 c.2438C>T	ENSP00000365643.1 p.Ser813Phe	29.9	rs778275450	22/57	0.000008204	
1630	hEDS	c)	DOCK6	NM_020812.4 c.3310C>T	p.Arg1104Trp	35	rs767376510	27/48	0.0000377	VUS PM2
1656	hEDS	c)	DOCK3	ENST00000266037.9c.1490T>C	ENSP00000266037.8 p.Ile497Thr	26.8	rs748558159	16/53	0.00002032	VUS PM2 PP2

Circadian Genes										
446	HDCT	c)	PER2	ENST00000254657.3 c.2434G>A	ENSP00000254657.3 p.Gly812Arg	22.6	rs201525818	19/23	0.0002591	VUS PM2 BP4 (Supp)
526	HDCT	a)	ZFHX3	ENST00000268489.5 c.2443G>A	ENSP00000268489.5 p.Val815Met	24	–	2/10	0	
564	HDCT	c)	PER1	ENST00000317276.4 c.3223T>C	ENSP00000314420. 4p.Ser1075Pro	26.8	–	20/23	0	VUS PM2
635	HDCT	a)	ZFHX3	ENST00000268489.5 c.9872T>C	ENSP00000268489.5 p.Leu3291Pro	19.21	–	10/10	0	
671	HDCT	a)	SEC61B	ENST00000223641.4 c.137G>A	ENSP00000223641.4 p.Arg46His	34	–	03/04	0.0000131	
821	kEDS	c)	PER1	ENST00000317276.4 c.3583C>G	ENSP00000314420.4 p.Arg1195Gly	24.1	rs200744636	22/23	0.0000004	VUS PM2
1443	hEDS	a)	ZFHX3	ENST00000268489.5 c.2213A>G	ENSP00000268489.5 p.Lys738Arg	22	rs755685914	2/10	0.000028	
1528	cEDS	a)	ZFHX3	ENST00000268489.5 c.7561G>A	ENSP00000268489.5 p.Ala2521Thr	21.4	rs140414544	9/10	0.0000077	
1717	hEDS	a)	ZFHX3	ENST00000268489.5 c.5821A>G	ENSP00000268489.5 p.Arg1941Gly	22.6	rs760103457	9/10	0.000012	
Ephrins										
372	vEDS	a)	EPHA8	NM_020526.5 c.2635C>T	p.Arg879Trp protein kinase domain	33	rs147803148	15/17	0.0000325	
409	cEDS	a)	EPHA8	NM_020526.5 c.2753G>A	p.Arg918Gln	25.5	rs141279306	16/17	0.000121	
777	HDCT	a)	EFNA1	NM_004428.3 c.556C>T	p.Arg186Cys	35	rs760306344	5/5	0.0000119	
TSPANs										
75	cEDS	c)	TSPAN12	NM_012338.4 c.184G>A	p.Val64Met	29.9	–	04/08	0	VUS PM2
99	HDCT	a)	TSPAN14	NM_030927.4 c.20C>G	p.Ser7Cys	26.1	–	02/09	0	
136	cEDS	a)	TSPAN2	NM_005725.6 c.626T>C	p.Val209Ala	24.9	rs34749181	8/8	0.000171	
396	cEDS	a)	TSPAN9	NM_00116832(c.620C>T	p.Thr207Met	33	rs141218062	07/08	0.0000723	
564	HDCT	a)	TSPAN17	NM_130465.5 c.355G>T	p.Asp119Tyr	31	rs367611196	4/9	0.0000066	
595	cEDS	a)	TSPAN3	NM_005724.6 c.380A>G	p.Asn127Ser	21.2	rs370307435	04/07	0.000013	
1387	HDCT	a)	TSPAN15	NM_012339.5 c.649C>T	p.Arg.217Trp	33	rs200107830	07/08	0.000131	
1462	hEDS	a)	TSPAN17	NM_130465.5 c.620G>C	p.Arg207Pro	33	–	06/09	0	
1681	hEDS	a)	TSPAN32	NM_139022.3 c.913A>T	p.Arg305Ter	35	–	10/10	0	

1656	hEDS	a)	TSPAN9	NM_00116832(c.661G>A	p.Ala221Thr	23.3	rs149866702	08/08	0.000046	
1665	hEDS	a)	TSPAN1	NM_005727.4 c.643G>A	p.Val215Met	24.7	rs149302587	09/09	0.000125	
Serine proteases										
60	HDCT	c)	TMPRSS5	NM_030770.4 c.702C>G	p.Ser234Arg	22	–	8/13	0	
99	HDCT	c)	TMPRSS5	NM_030770.4 c.1216G>A c.1216G>A	p.Gly406Arg	25.8	–	12/13	0.0000197	
396	cEDS	a)	PRSS36	NM_173502.5 c.2371G>T	p.Glu791Ter	39	rs201757658	15/15	0.0000591	
396	cEDS	a)	TMPRSS15	NM_002772.3 c.687T>G	p.Phe229Leu	27	rs138300762	7/25	0.00000657	
397	hEDS	a)	PRSS36	NM_173502.5 c.2371G>T	p.Glu791Ter	39	rs201757658	15/15	0.000591	
423	HDCT	a)	PRSS35	NM_153362.3 c.410G>A	p.Arg137Met	22.9	rs148479497	02/02	0.000177	
475	hEDS	a)	TMPRSS9	NM_182973.3 c.1253C>T	p.Pro418Leu	24.3	rs150970765	9/17	0.000131	
567	HDCT	a)	PRSS50	NM_013270.5 c.115G>T	p.Gly39Cys	23.1	rs151210292	7/11	0.0000197	
922	hEDS	a)	PRSS53	NM_00103950 c.91C>T	p.Arg31Cys	34	rs377044450	03/11	0.0000197	
1424	hEDS	c)	TMPRSS6	NM_00137450 c.290G>A	p.Arg97Gln	24.6	rs531422898	03/18	0.0000197	VUS PM2 BP4 (Supp)
1461	hEDS	a)	PRSS22	NM_022119.4 c.433G>A	p.Val145Met	24.4	–	04/06	0	
1462	hEDS	c)	PRSS12	NM_003619.12 c.419G>T	p.Ser140Ile	25.2	rs775377995	01/13	0.000046	VUS PM2
1462	hEDS	a)	TMPRSS9	NM_182973.3 c.682del	p.Cys228Valfs Ter71	33	–	07/18	0	
1484	hEDS	c)	PRSS12	NM_003619.4 c.1640C>A	p.Ala547Asp	33	rs201005601	09/13	0.0000855	VUS PM2
1579	hEDS	a)	TMPRSS12	NM_182559.3 c.805G>A	p.Gly269Arg	32	rs369598424	05/05	0.000105	

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

d) Germline variants in this gene associated with a myopathy 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.