**Supplementary Table 13. Rare germline variants (CADD> 15) in genes previously published in a linkage study (29) and genome wide association studies associated with, (p < 5 x 10-8), pelvic organ prolapse (PMID: 32184442), knee pain and rotator cuff injury (https://www.ebi.ac.uk/gwas/)**

| Patient ID | Clinical Diagnosis | Current Gene annotation | Gene | HGVSc | HGVSp | CADD | Rs ID | Exon or Intron / Total no. exons | gnomAD allele frequency | ACMG Classification (See footnote) |
|---|---|---|---|---|---|---|---|---|---|---|
| 79 | HDCT | c) | LAMC2 | ENST00000264144.4 c.1669T>C | ENSP00000264144.4 p.Tyr557His | 24 | – | 11/23 | 0 | VUS PM2 PP3 (Supp) |
| 100 | hEDS | a) | HAS1 | ENST00000222115.1 c.874G>A | ENSP00000222115.1 p.Glu292Lys | 33 | – | 3/5 | 0 | |
| 136 | cEDS | c) | TBX5 | ENST00000310346.4 c.1203G>T | ENSP00000309913.4 p.Trp401Cys | 33 | rs377649723 | 9/9 | 0.00001221 | VUS PM2 |
| 383 | cEDS | a) | HAS1 | ENST00000222115.1 c.1679G>A | ENSP00000222115.1 p.Trp560Ter | 40 | rs200444967 | 5/5 | 0.0001912 | |
| 428 | hEDS | c) | FAT4 | ENST00000394329.3 c.11147G>A | ENSP00000377862.3 p.Arg3716His | 21.9 | rs139635339 | 9/17 | 0.00013 | VUS PM2 |
| 474 | HDCT | c) | LAMC2 | ENST00000264144.4 c.1105C>T | ENSP00000264144.4 p.Arg369Cys | 34 | rs552102778 | 9/23 | 0.0000008122 | VUS PM2 |
| 495, 505 | hEDS (495), HDCT (505) | c) | ROBO2 | ENST00000487694.3 c.2066G>A | ENSP00000417335.2 p.Arg689His | 34 | rs376737394 | 15/27 | 0.0001099 | VUS PM2 PP3 (Supp) |
| 560 | hEDS | c) | LAMC3 | ENST00000361069.4 c.236C>T | ENSP00000354360.4 p.Ala79Val | 27.2 | rs186188737;rs772194826 | 1/28 | 0.00009384 | VUS PM2 |
| 566 | hEDS | c) | TBX5 | ENST00000310346.4 c.330C>G | ENSP00000309913.4 p.Asp110Glu | 24.5 | – | 4/9 | 0 | VUS PM2 PP3 (Supp) |
| 630 | hEDS | c) | LAMC3 | ENST00000361069.4 c.449G>A | ENSP00000354360.4 p.Arg150His | 31 | rs774775769 | 2/28 | 0.00001224 | VUS PM2 PP3 (M) |
| 967 | hEDS | c) | FAT4 | ENST00000394329.3 c.10063A>G | ENSP00000377862.3 p.Ile3355Val | 22.5 | – | 9/17 | 0 | VUS PM2 |
| 1263 | hEDS | c) | SALL1 | ENST00000251020.4 c.2920T>C | ENSP00000251020.4 p.Ser974Pro | 20.6 | rs144429956 | 2/3 | 0.00002034 | VUS PM2 PP3 (Supp) |
| 1393 | hEDS | c) | LAMC3 | ENST00000361069.4 c.1682C>T | ENSP00000354360.4 p.Thr561Ile | 22.1 | rs199701268 | 10/28 | 0 | VUS PM2 BP4 (Supp) |
| 1403 | hEDS | c) | LAMC2 | ENST00000264144.4 c.1079T>C | ENSP00000264144.4 p.Ile360Thr | 25.7 | – | 9/23 | 0 | VUS PM2 |
| 1421 | hEDS | a) | HOOK3 | ENST00000307602.4 c.1945A>T | ENSP00000305699.3 p.Lys649Ter | 48 | – | 21/22 | 0 | |
| 1450 | hEDS | a) | HAS1 | ENST00000222115.1 c.1679G>A | ENSP00000222115.1 p.Trp560Ter | 40 | rs200444967 | 5/5 | 0.0001912 | |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| 1495 | hEDS | c) | TBX5 | ENST00000310346.4 c.113C>G | ENSP00000309913.4 p.Ser38Cys | 25.6 | – | 2/9 | 0 | VUS<br><br>PM2 |
| 1626 | hEDS | c) | SALL1 | ENST00000251020.4<br><br>c.1673C>T | ENSP00000251020.4<br><br>p.Pro558Leu | 20.2 | – | 2/3 | 0 | VUS<br><br>PM2<br>BP4 (Supp) |
| 1642 | hEDS | a) | LAMC1 | ENST00000258341.4 c.4729C>T | ENSP00000258341.3 p.Arg1577Ter | 37 | rs1031794706 | 28/28 | 0 | |
| 1642 | hEDS | a) | ADAM33 | ENST00000356518.2 c.706C>T | ENSP00000348912.2 p.Arg236Cys | 34 | rs750423431 | 8/22 | 0.000004061 | |

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.