### Supplementary Table 1. In silico prediction of missense variants

| Family no. | Gene   | Nucleotide change | Protein change | PolyPhen-2\(^{\text{a)}}\) | SIFT               | PROVEAN\(^{\text{b)}}\) |
|------------|--------|-------------------|----------------|---------------------------|--------------------|------------------------|
| 21         | ENG    | c.821C>T          | p.Thr274Ile    | Probably damaging (0.999) | Predict tolerated  | Deleterious (–3.531)  |
| 6          | ACVRL1 | c.199C>T          | p.Arg67Trp     | Probably damaging (0.998) | Predict not tolerated | Deleterious (–3.694)  |
| 10         | ACVRL1 | c.925G>A          | p.Gly309Ser    | Probably damaging (0.999) | Predict not tolerated | Deleterious (–5.959)  |
| 12         | ACVRL1 | c.781G>C          | p.Ala261Pro    | Probably damaging (1.000) | Predict not tolerated | Deleterious (–4.293)  |
| 30         | ACVRL1 | c.605T>G          | p.Val202Gly    | Probably damaging (0.998) | Predict not tolerated | Deleterious (–6.296)  |
| 32         | ACVRL1 | c.1124A>G         | p.Tyr375Cys    | Probably damaging (1.000) | Predict not tolerated | Deleterious (–8.984)  |
| 38         | ACVRL1 | c.1005T>G         | p.Asr335Lys    | Probably damaging (1.000) | Predict not tolerated | Deleterious (–5.957)  |

\(^{\text{a)}}\text{Reference sequences to describe variants are NC_000009.12 (ENG genomic DNA), NM_000118.3 (ENG coding DNA), and NP_000109.1 (ENG protein), NC_000012.12 (ACVRL genomic DNA), NM_000020.3 (ACVRL coding DNA), and NP_000011.2 (ACVRL protein).}\n
\(^{\text{b)}}\text{The score is indicated in parentheses.}\n
\(^{\text{c)}}\text{The score is indicated in parentheses and the cutoff value is –2.5.}\n