

Supplementary Table 1. In silico prediction of missense variants

Family no.	Gene	Nucleotide change <sup>a)</sup>	Protein change <sup>a)</sup>	PolyPhen-2 <sup>b)</sup>	SIFT	PROVEAN <sup>c)</sup>
21	<i>ENG</i>	c.821C>T	p.Thr274Ile	Probably damaging (0.999)	Predict tolerated	Deleterious (-3.531)
6	<i>ACVRL1</i>	c.199C>T	p.Arg67Trp	Probably damaging (0.998)	Predict not tolerated	Deleterious (-3.694)
10	<i>ACVRL1</i>	c.925G>A	p.Gly309Ser	Probably damaging (0.999)	Predict not tolerated	Deleterious (-5.959)
12	<i>ACVRL1</i>	c.781G>C	p.Ala261Pro	Probably damaging (1.000)	Predict not tolerated	Deleterious (-4.293)
30	<i>ACVRL1</i>	c.605T>G	p.Val202Gly	Probably damaging (0.998)	Predict not tolerated	Deleterious (-6.296)
32	<i>ACVRL1</i>	c.1124A>G	p.Tyr375Cys	Probably damaging (1.000)	Predict not tolerated	Deleterious (-8.984)
38	<i>ACVRL1</i>	c.1005T>G	p.Asn335Lys	Probably damaging (1.000)	Predict not tolerated	Deleterious (-5.957)

<sup>a)</sup>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 (*ACVRL1* genomic DNA), NM\_000020.3 (*ACVRL1* coding DNA), and NP\_000011.2 (*ACVRL1* protein). <sup>b)</sup>The score is indicated in parentheses.

<sup>c)</sup>The score is indicated in parentheses and the cutoff value is -2.5.