Autosomal Dominant Growth Hormone Deficiency due to a Novel Mutation in the gh1 Gene.

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INTRODUCTION
Congenital idiopathic growth hormone deficiency (IGHD) occurs in 1 in 4,000 to 1 in 10,000 live births with 3-30% being familial. Familial GHD with an autosomal dominant inheritance pattern (isolated GHD type II) due to multiple different mutations in the gh1 gene have been described.

CLINICAL DESCRIPTION
GHD was first identified in the female proband at 6y1m, Height SDS -3.21 with a peak stimulated GH of 4.9 ng/mL. GHD was subsequently identified in her female sibling (6y0m, Ht SDS -1.67, peak GH 2.9 ng/mL) and female maternal half-sibling (3y1m, Ht SDS -1.68, peak GH 6.6 ng/mL). The mother had previously been diagnosed with GHD at age 7 years.

Due to the family history, sequencing of the GH1 gene was performed and identified a heterozygous change in the gh1 gene (c.178G>A) resulting change in the GH protein (p.Ala60Thr) in all four affected individuals. This genetic variant has not been recorded in the ExAc dataset representing >60,000 individuals. This amino acid is weakly conserved. The amino acid change is not predicted to cause a significant structural change in the protein.

CONCLUSION
The presence of the heterozygous gh1 gene variant (c.178G>A, p.Ala60Thr) in four individuals with GHD inherited in an autosomal dominant pattern suggests this novel mutation is likely pathogenic and causes GHD. Functional studies of the mutant GH (p.Ala60Thr) are needed to confirm the negative impact of this mutation on protein function.

REFERENCE