Autosomal Dominant Growth Hormone Deficiency due to a novel c.178G>A mutation in the gh1 gene causing instability of the mutant GH protein (p.Ala34Thr).

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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 Broad ExAC dataset representing >60,000 children without severe childhood onset disease. This amino acid is weakly conserved and buried. The amino acid change is not predicted to cause a significant structural change in the protein.

NORMAL SECRETION OF MUTANT PROTEIN

REDUCED STABILITY OF MUTANT PROTEIN

CONCLUSION
• The presence of the heterozygous gh1 gene variant (c.178G>A, p.Ala34Thr) in four individuals with GHD suggests this is a novel cause of IGHD type II.
• This mutation leads to alternate splicing resulting in increased expression of the smaller isoform of GH missing exon 3.
• RT-PCR analysis showed instability of mutant mRNA.
• Mutant protein expressed in bacteria show decreased stability based upon Guanine HCl denaturation and fast parallel proteolysis (FASTpp).
• Secretion of mutant GH protein by mammalian cells was normal.
• Binding studies of the mutant protein to the GHR are underway to determine the mechanism causing the apparent dominant negative phenotype

REFERENCE