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).

P1-141: GH and IGFs 1

Bradley S. Miller, MD, PhD*[1], Jimmy W. L. Tan, MSc[2], Shaheena Parween, PhD[2], Andreè Eblè, BMA, HF[2], Christine Ternand, MD[3], Louise Gregory, PhD[4], Mehul Dattani, DCH, FRCPCH, FRCP, MBBS, MD[4], Amit Pandey, PhD[2].

[1]Pediatric Endocrinology, University of Minnesota Masonic Children's Hospital, Minneapolis, MN, USA; [2]University Children's Hospital Bern, Bern, Switzerland; [3]Pediatric Endocrinology, Children's Hospitals of Minnesota, Minneapolis, MN, USA; [4]University College London, Institute of Child Health, London, United Kingdom.

INTRODUCTION

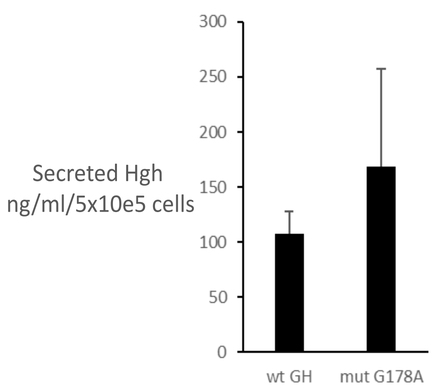
Congenital idiopathic growth hormone deficiency (IGHD) occurs in 1 in 4,000 to 1 in 10,000 live births with 3-30% being familial. Familial GHD with an autosomal dominant inheritance pattern (isolated GHD type II) due to multiple different mutations in the *gh1* gene have been described.

CLINICAL DESCRIPTION

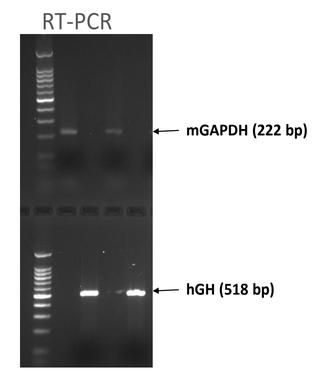
GHD was first identified in the female proband at 6y1m, Height SDS -3.21 with a peak stimulated GH of 4.9 ng/mL. GHD was subsequently identified in her female sibling (6y0m, Ht SDS -1.67, peak GH 2.9 ng/mL) and female maternal half-sibling (3y1m, Ht SDS -1.68, peak GH 6.6 ng/mL). The mother had previously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

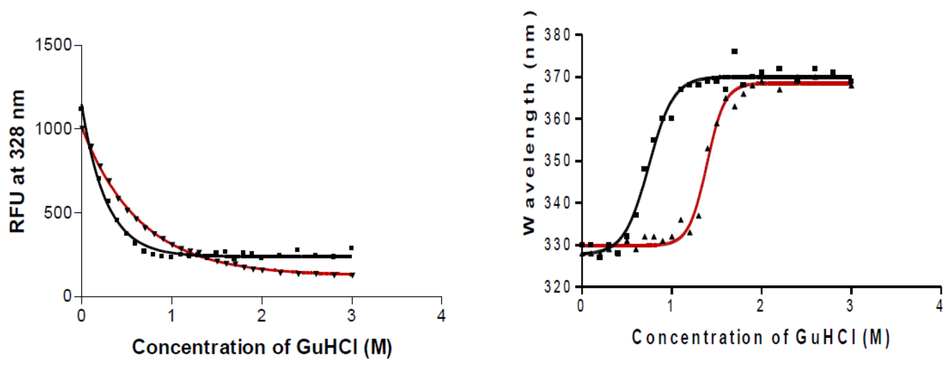
NORMAL SECRETION OF MUTANT PROTEIN

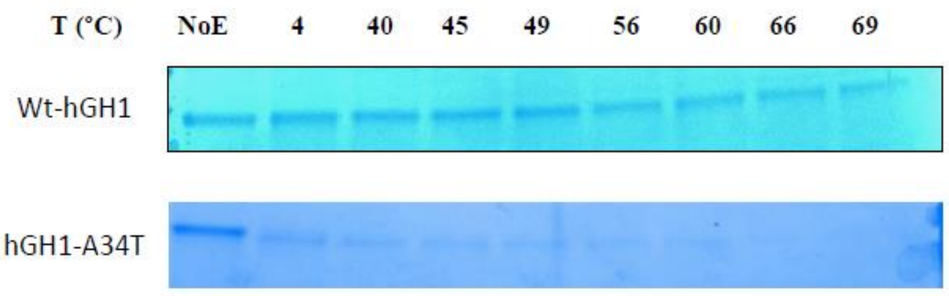


INSTABILITY OF MUTANT RNA



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

GROWTH HORMONE STIMULATION TEST

Patient	Date	Peak GH	IGF-1	IGF-1 Normal Range	IGFBP-3
AM	Feb 2011	4.9	56	82-262	2.0
GK	Jul 2013	2.9	55	39-198	1.6
MK	Mar 2015	6.6	54	26-162	1.7
BM	May 1990	<2			

BASELINE PARAMETERS AT START OF GROWTH HORMONE

Patient	Age	Wt (kg)	Ht (cm)	Ht SDS	Dose (mg/kg/wk)
AM	6yr 4mo	15.8	100.6	-3.36	0.29
GK	6yr 0mo	18.6	106.9	-1.64	0.26
MK	3yr 3mo	13.5	88.1	-1.13	0.26
BM	12yr 4mo	29.0	125.1	-3.44	0.30

GROWTH RESPONSE TO GROWTH HORMONE THERAPY

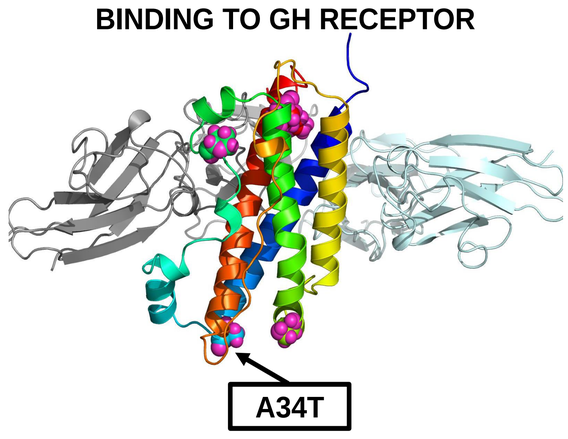
Patient AM	Yr 1	Yr 2	Yr 3	Yr 4	Yr 5
GV (cm/yr)	11.4	7.5	8.6	6.5	9.4
Ht (cm)	111.4	119	127.8	134.3	144.2
Ht SDS	-2.26	-1.75	-1.08	-0.77	-0.33
GH Dose (mg/kg/wk)	0.27	0.20	0.17	0.15	0.27
IGF-1	184-352	178-409	278-400	255-398	429-600
IGF-1 Reference	112-276	64-259	96-400	104-430	268-646

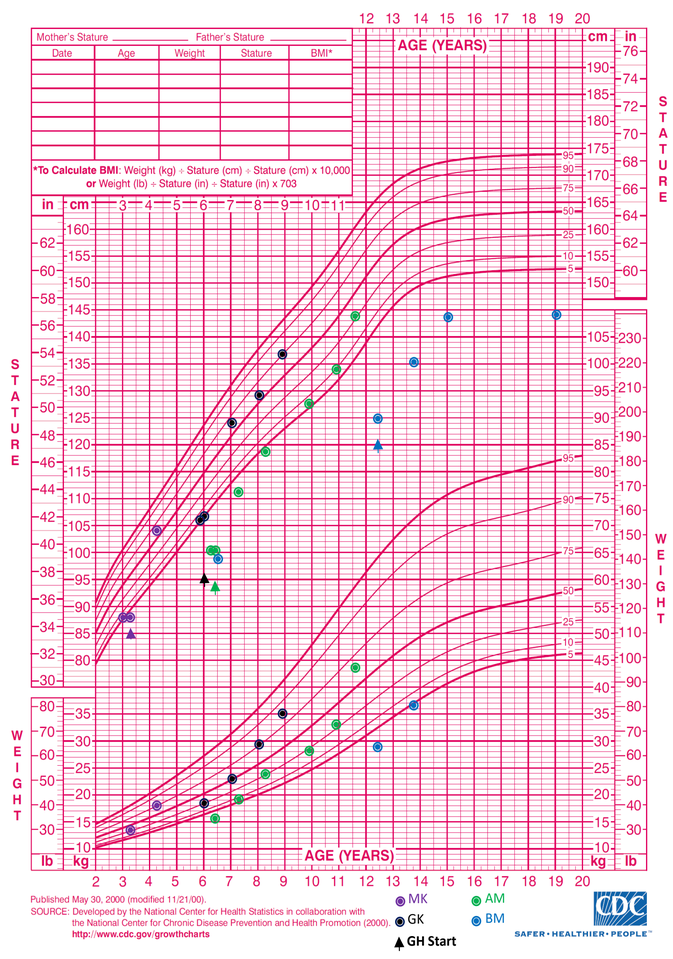
Patient GK	Yr 1	Yr 2	Yr 3
GV (cm/yr)	16.3	5.2	9.6
Ht (cm)	124.4	129.6	137.1
Ht SDS	+0.39	+0.23	+0.71
GH Dose (mg/kg/wk)	0.21	0.15	0.13
IGF-1	171-237	154-294	253-352
IGF-1 Reference	55-238	64-259	64-259

Patient MK	Yr 1
GV (cm/yr)	12.7
Ht (cm)	104.2
Ht SDS	+0.33
GH Dose (mg/kg/wk)	0.16
IGF-1	127-229
IGF-1 Reference	32-179

Patient BM	Yr 1
GV (cm/yr)	7.6
Ht (cm)	135.2
Ht SDS	-3.64
GH Dose (mg/kg/wk)	0.24

MODEL OF GROWTH HORMONE BINDING TO GH RECEPTOR





REFERENCE

Alatzoglou, K.S., et al, Endocrine Reviews 35(3):376–432, 2014.