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

P1-623: GH and IGFs

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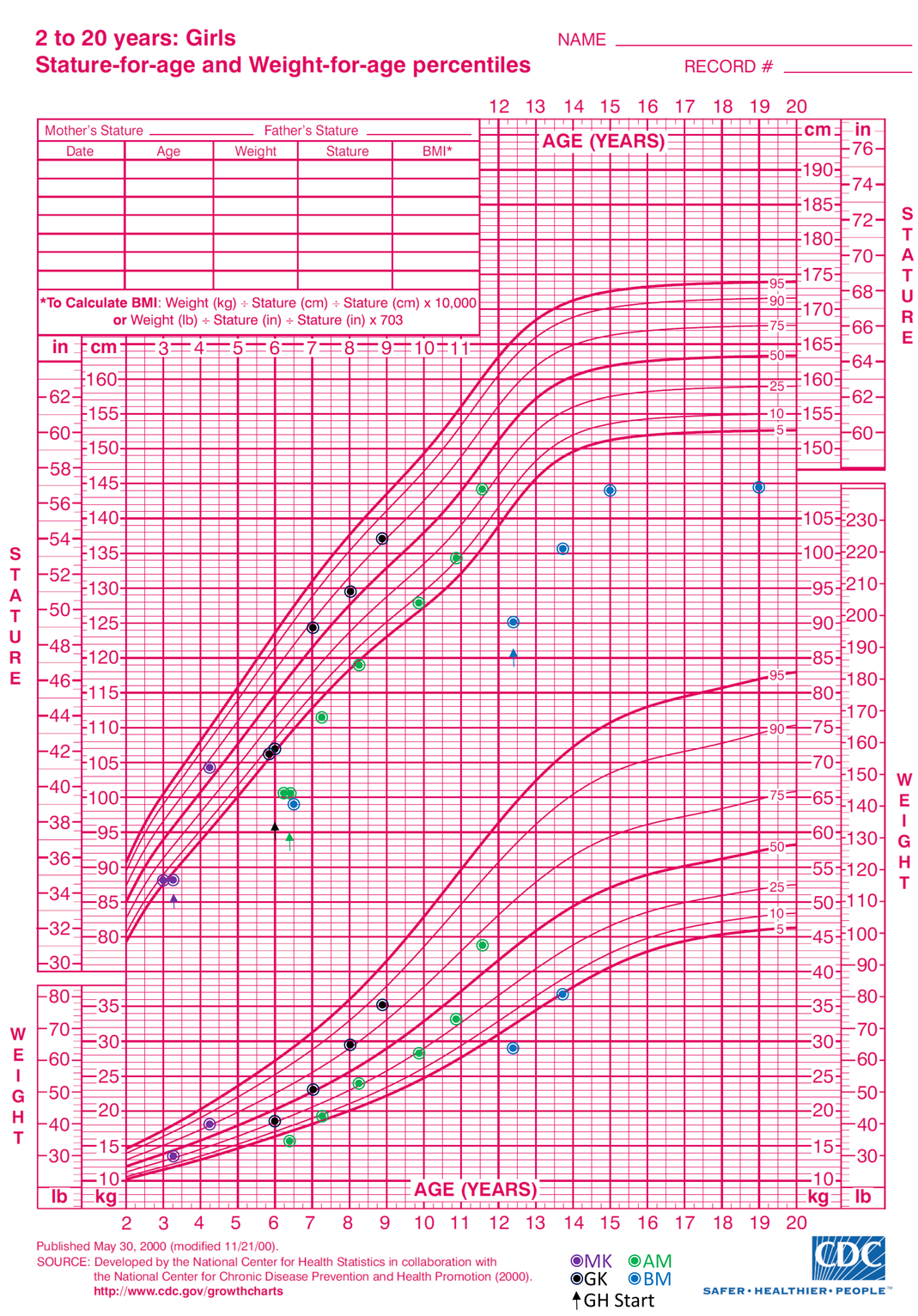
INTRODUCTION

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. The amino acid change is not predicted to cause a significant structural change in the protein.



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

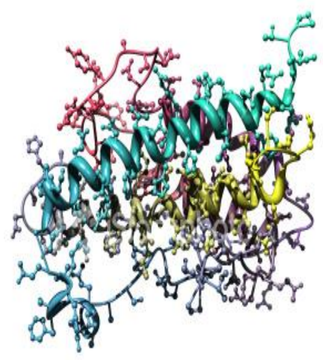
GROWTH RESPONSE TO GROWTH HORMONE THERAPY

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



GH PROTEIN SEQUENCE

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        10         20         30         40         50
MATGSRTSLL LAFGLLCLPW LQEGSAFPTI PLSRLFDNAM LRAHRLHQLA
        60         70         80         90        100
FDTYQEFEEA YIPKEQKYSF LQNPQTSLCF SESIPTPSNR EETQQKSNLE
       110        120        130        140        150
LLRISLLLIQ SWLEPVQFLR SVFANSLVYG ASDSNVYDLL KDLEEGIQTL
       160        170        180        190        200
MGRLEDGSPR TGQIFKQTYS KFDTNSHNDD ALLKNYGLLY CFRKDMDKVE
       210
                        PREVIOUSLY REPORTED MUTATION
TFLRIVQCRS VEGSCGF       SIGNAL PEPTIDE   A/T MUTATION
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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

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

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Growth

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