A Novel GH1 Mutation in a Family with Isolated Growth Hormone Deficiency Type II

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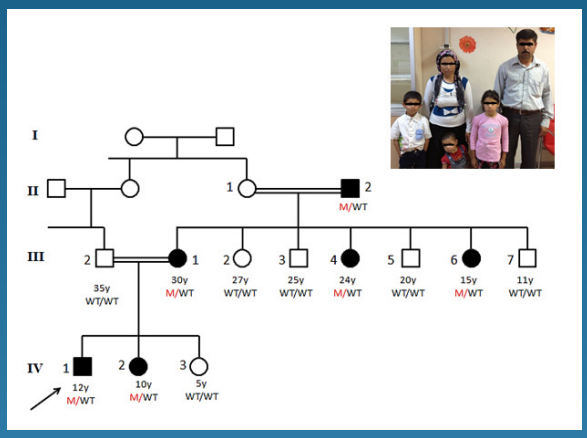
Background:
The familial types of isolated growth hormone deficiency (IGHD) is characterized by a variable degree of growth restriction, low but detectable GH serum concentrations. The recessive type IA and IB, the autosomal-dominant type II, and X-linked recessive type III. The most frequent cause of the IGHD type II are mutations within the first six basepairs of the splice donor site of intron 3 [3] . Phenotype-genotype correlations are notoriously difficult to be established. Herein, we present a child, his sister and mother with a novel GH1 mutation which is likely to lead to IGHD II.

Patients

- The proband (IV-1) was 12 years old boy who presented with short stature at 8 year-9 month. His height was 108.5 cm (-4.15 SDS) and his weight was 14.5 kg (-5.6 SDS), MPH was 164.9 (-1.8 SDS), bone age was six years. Growth velocity: 4.1 cm/year. In laboratory, basal IGF-1: 34.6 ng/ml, IGFBP-3: 0.52 µg/ml. Interestingly, two GH stimulation tests had normal peak GH value of 12.6 ng/ml (with clonidine) and 12.1 ng/ml (with insulin). Other pituitary hormones and magnetic resonance imaging (MRI) of the pituitary region was normal. The proband received recombinant human GH (rhGH) treatment (30 µg/kg/day) and he grew 5.1 cm in six months. IGF-1: 59.3 ng/ml, IGFBP-3:<0.5 µg/ml. Sequence analysis has shown that patient was heterozygous for a novel GH1 gene mutation, p.Q110E (c.328C>G). Proband's mother (III-1), sister (IV-2), two aunts (III-4 and III-6) and grandfather (II-2) were also heterozygous for the GH1 gene mutation.
- The proband's sister (IV-2) was an 8-years old girl who presented with short stature as elder brother. Height: 114.5 cm (-2.2 SDS), weight: 20.2 kg (-1.5 SDS), MPH: 164.9 (-1.8 SDS), bone age was 6 years and growth velocity was4.3 cm/year. In laboratory: Basal IGF-1: 97.2 ng/ml, IGFBP-3: 2.53 µg/ml. GH stimulation tests Peak GH: 6.21 ng/ml (with clonidine), Peak GH: 5.64 ng/ml (with insulin). She received recombinant human GH (rhGH) treatment (30 µg/kg/day).
- The proband's aunt (III-6) was 15 year-2 months old girl who follow up for short stature since age of 13 year. Height: 131 cm (-3.8 SDS), weight: 38.5 kg (-1.0 SDS), MPH: 159.5 (-0.6 SDS), Bone age: 10 year-6 months. Growth velocity: 3.1 cm/year. In laboratory: Basal IGF-1: 42.7 ng/ml, IGFBP-3: 0.55 µg/ml. GH stimulation tests: Peak GH: 0.16 ng/ml (with clonidine), Peak GH: 3.05 ng/ml (with insulin). She received recombinant human GH (rhGH) treatment (30 µg/kg/day). Growth velocity: 5.6 cm/year (first year), 5 cm/year (second year).



	Proband (IV-1)	Sister (IV-2)	Mother (III-1)	Aunt (III-4)	Aunt (III-6)
Gender	M	F	F	F	F
Age (year)	8.7	8	30	24	13
Heigh (cm) & SDS	108.5 (-4.1)	114.5 (-2.2)	142.7 (-3.1)	137 (-4.0)	131 (-3.8)
Weigh (kg) & SDS	14.5 (-5.6)	20.2 (-1.5)	48.4 (-1.2)	51 (-0.8)	38.5 (-1.0)
Bone age (year)	6	6	-	-	10.5
GV (cm/year)	4.1	4.3	-	-	3.1
IGF-1 (ng/ml)	34.6	97.2	93.5	N/A	42.7
IGFBP-3 (µg/ml)	0.52	2.53	2.41	N/A	0.55
1st GHST Peak ng/ml	12.6	6.21	N/A	N/A	0.16
2nd GHST Peak ng/ml	12.1	5.64	N/A	N/A	3.05

Discussion

Familial Types of Isolated Growth hormone deficiency (IGHD) type 2 is characterized by a variable degree of growth restriction, low but detectable GH serum concentrations. So we have detectable normal levels of serum GH concentrations for proband. In somuch that, peak GH levels were >10 ng/ml. But other affected family members had low but detectable levels of serum GH as expected in IGHD type II.