A Novel, Synonymous, Heterozygous, Splicing Variant Affecting the Intracellular Domain of the Growth Hormone Receptor: Causality for Mild Growth Impairment and IGF-I deficiency in an Affected Patient?

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Abstract

Introduction: Although the majority of Growth Hormone insensitivity syndrome (GHIS) cases are classical, the spectrum of clinical phenotypes has expanded to include “atypical” GHIS subjects with milder phenotypes due to very rare heterozygous GHR mutations with dominant negative effects. Case description: A 13 year old pubertal boy was presented with short stature (-1.75SD) and delayed bone age (11 6/12). Final adult height was -1.8 SD, 3SD below his mid-parental height (+1.27SD). His serum IGF-I was low (16ng/ml; reference range: 179-540) with low IGFBP-3 (1.3mg/L; 3.1-9.5), and ALS (565L/ml; 1500-3500). GH stimulation test was normal, and GHBP, increased (6300pmol/L; 240-3000). Methods: The GHR gene analyzed was from genomic DNA. Primary fibroblasts were established to evaluate GHR DNA. Results: A novel synonymous heterozygous GHR: c.945G>A variant in exon 9 (encoding part of the intracellular domain of GHR) was identified. GHR c.945G is the last nucleotide in exon 9 and a substitution from G to A could alter the donor splice site at the junction of exon 9-intron 9. Analysis of the GHR cDNA undertaken revealed heterozygous exonic deletion of exon 9 sequences, consistent with GHR c.945G>A being a splicing defect. The loss of exon 9 generates a predicted truncated GHR protein identical to the dominant-negative heterozygous c.945G>G variant reported by Iida et al. (JCEM, 2008). Conclusion: We describe the first synonymous heterozygous GHR splicing variant in the intracellular domain of GHR associated with mild short stature and very low IGF-I, thus supporting the continuum of genotype, phenotype and biochemistry of GHIS.

Methods:

DNA sequencing, Fibroblast culture, RNA isolation, cDNA production, PCR.

Results

- Parents: Normal GHR DNA
- The last nucleotide of exon 9 is splicing site

Case description

13 yo boy with short stature. Frontal bossing, short neck, Pubertal (8ml tests).

Potential splicing events:
(1) Exon 9 spliced out: predicted p.Ile293Lysfs*4
(2) Read through into intron 9: predicted p.Glu16Valafs*6

The mutation causes heterozygous frameshift at exon 9–10 junction with premature stop at codon 278

Conclusion

We describe the first synonymous heterozygous GHR splicing variant in the intracellular domain of GHR associated with mild short stature and very low IGF-I, thus supporting the continuum of genotype, phenotype and biochemistry of GHIS.