P2-P208

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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We have nothing to disclose

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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 (-1.7SD) 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 (565mU/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* cDNA. **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 excision 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.945+1G>A* 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.

Case description

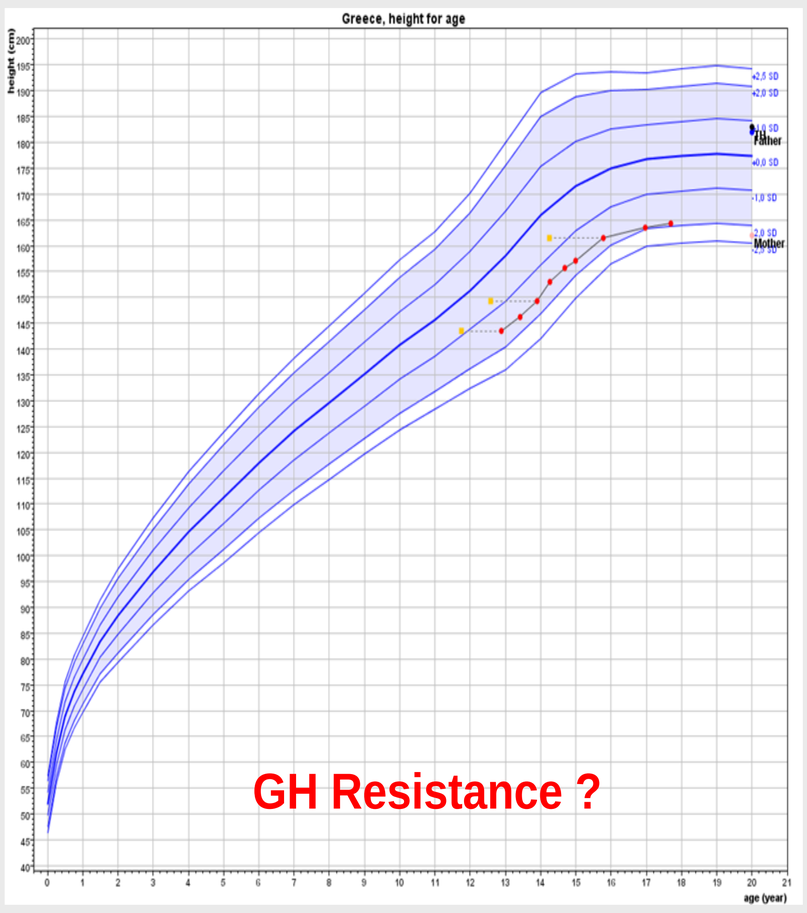
13 yo boy with short stature. Frontal bossing, short neck, Pubertal (8ml testes).

Age	Height SD	Bone Age	Target Height SD
13,06	-1,7	11 9/12	1,05

Short for his MPH: -2.7SD

Basal GH: 2.1ng/ml
Max stimulated GH: 11.9ng/ml

Age	Height SD	Bone Age	IGF-I ng/ml	ALS mU/ml	IGFBP3 mg/L	GHBP pmol/L
13,06	-1,7	11 9/12	16 (179-540)	565 (1500-3500)	1,3 (3.1-9.5)	6300 (240-3000)
17,7	-1,9		20	392	0,68	

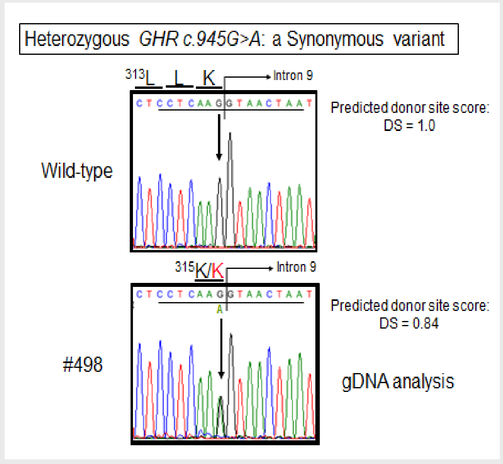


GH Resistance ?

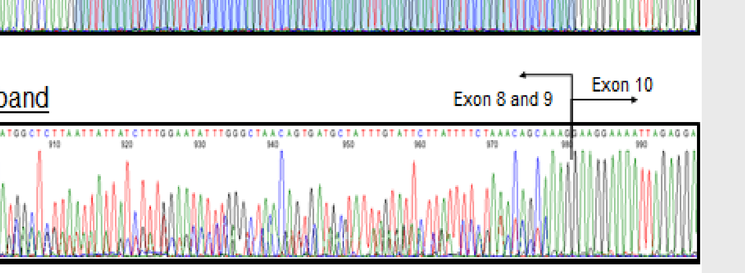
Methods:

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

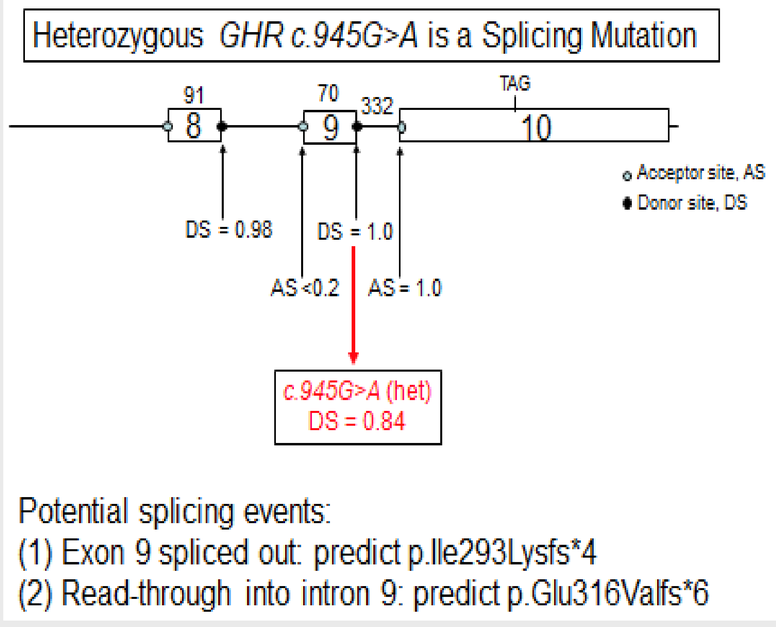
Results



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



Heterozygous *GHR c.945G>A*: Synonymous mutation at the last nucleotide of exon 9.

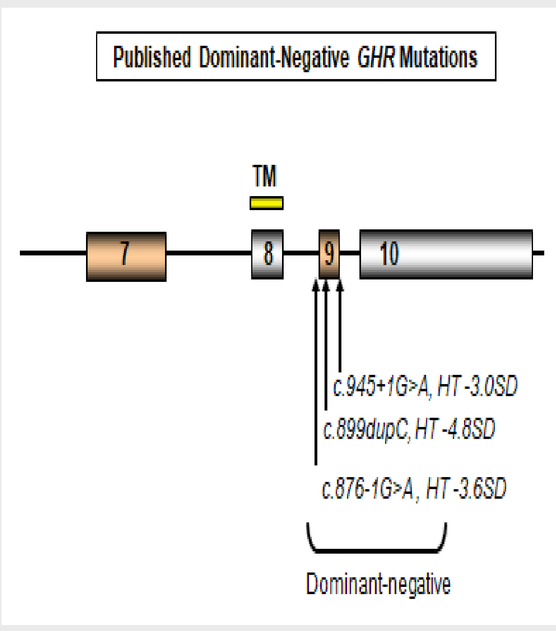


Potential splicing events:
(1) Exon 9 spliced out: predict p.Ile293Lysfs*4
(2) Read-through into intron 9: predict p.Glu316Valfs*6

cDNA analysis: GHR fl allele carries exon 9
GHR d3 allele lacks exon 9

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

- Excision of Exon 9 would result in a predicted truncated GHR, p.Ile293Lysfs*4
- The truncated product is likely to act in a dominant-negative manner, similar to the previously reported heterozygous *c.945+1G>A* (Iida et al, JCEM, 2008), where probands and affected mother had HtSDS -2 to -3.5.



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.