A *GH-1* mutation diagnosed in a preadolescent obese girl with only mild reduced height

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INTRODUCTION

Most of cases of isolated growth hormone deficiency (GHD) detected during childhood are sporadic and inherited. At reevaluation of somatotropic axis at the end of growth, GH secretion is generally normalized. Genetic causes of GHD are questioned when GHD is profound, congenital, inherited or in presence of others pituitary hormone deficiencies with normal pituitary MRI.

Mutations in *GH-1* are classically associated with the autosomal dominant familial isolated GH deficiency phenotype (IGHD type II). IGHD type II includes GH deficiency, possible development of multiple hormone deficiencies and anterior pituitary hypoplasia, with variability in onset, severity and progression, even among members of a same family. The *GH-1* gene consists of five exons that are constitutively spliced to produce a 22kDa protein that accounts for 75% of circulating GH.

Here, we report a case of a *GH-1* mutation identified in a preadolescent girl referred for a mild reduced height contrasting with overweight.

METHODS

The patient was born from non consanguineous parents of French origin. She had no personal nor familial medical history and non evidence of other organic disease. She had two older brothers with normal height. She consulted at 9 years old for short stature and obesity. Her height was at - 1.7 SD and BMI was + 2 SDS (20.8 kg/m²). Her height contrasted with a genetic target size of +1 SD. Bone age was 9 yrs . For these reasons, we performed GH stimulation tests.

Dynamic tests found **profound GH deficiency** and low IGF-1 concentrations.

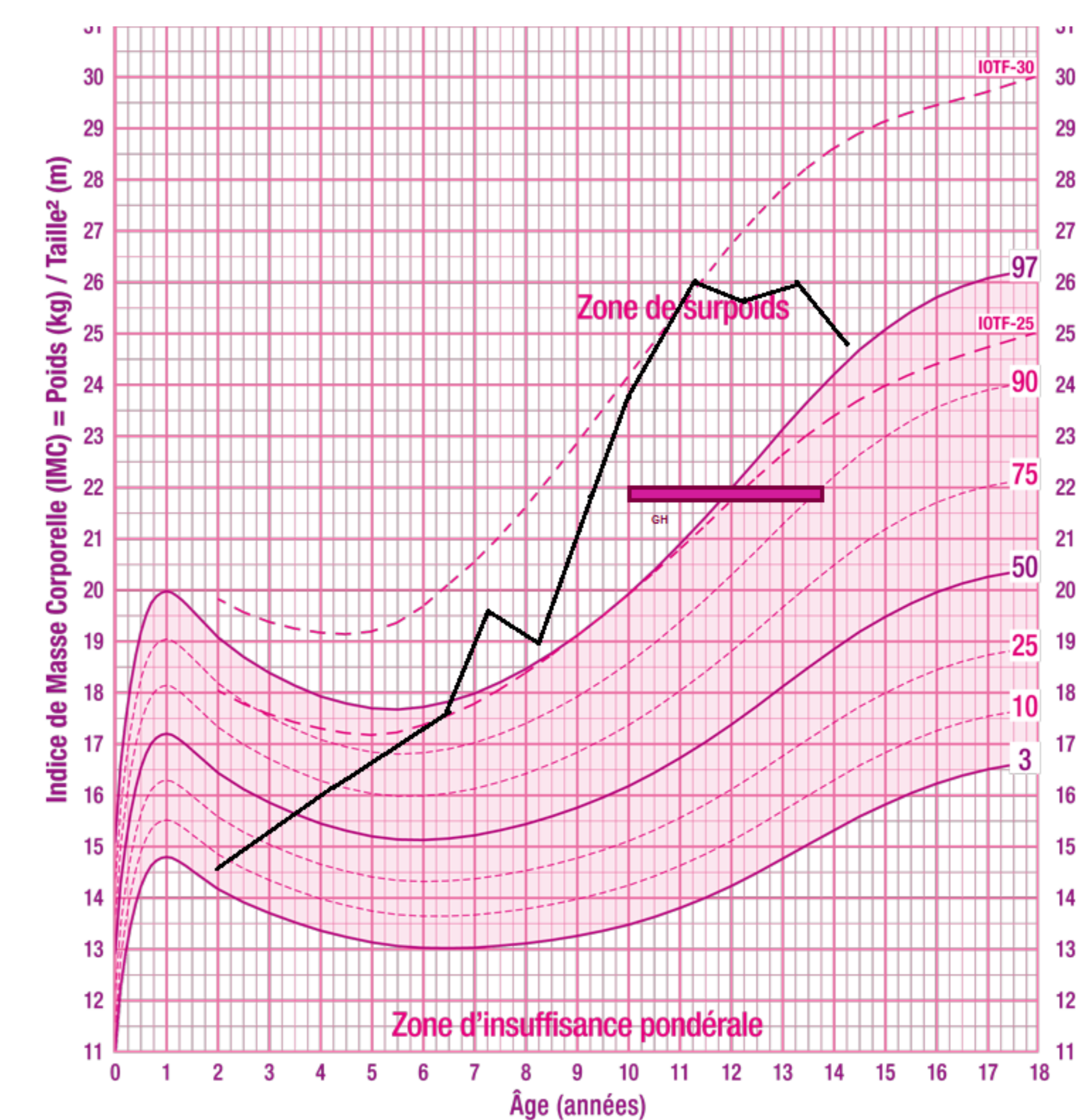|	Insulin tolerance test	Arginin-insulin test
GH peak value (N > 20)	1,1 mUI/L	1,2 mUI/L
IGF1 (N>100 ng/mL)	70 ng/mL	78 ng/mL

Other pituitary hormones were non deficient and the pituitary gland was normal at MRI.

RESULTS

Taking into account the severity of GH deficiency, the discordance between height and target height despite obesity, the diagnosis of GHD was retained, and recombinant human GH treatment was started at dose of 35 µg/kg/day at the age of 10 years. Her height increased from -1.7 SDS to +1 SDS at the age of 13 years, and BMI decreased from + 2 to + 1 SDS.
Final height was 163 cm, and rhGH was stopped at 13.75 years.
At the age of 14, an ITT was performed : GH peak value was 4 mUI/L and circulating IGF1 was 243 ng/mL. (-2SD). Other pituitary hormones were normal
Persistent isolated GHD was therefore confirmed.
An heterozygotous G6664A mutation in *GH-1* causing an Arg183His substitution (R183H) in the GH protein was identified in our patient but not found in her mother and her two brothers. Father DNA was unavailable.
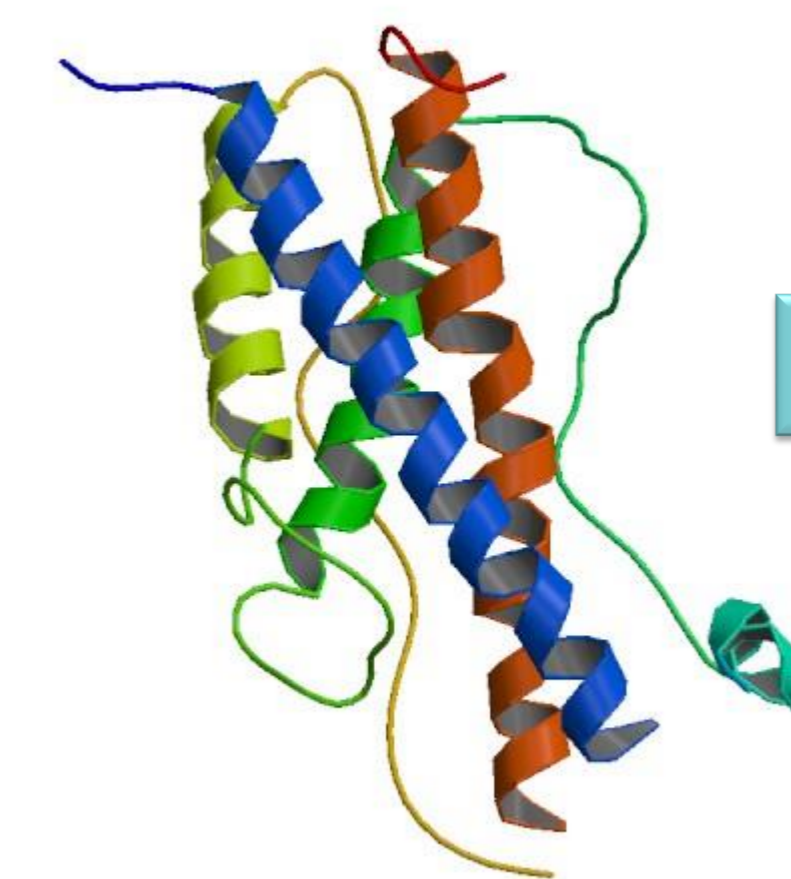

CONCLUSIONS

We described a new case of Arg183His mutation in *GH-1*. Traditionally reported in autosomal dominant IGHD type II, this R183H mutation leads to a dominant negative expression of the *GH-1* gene. Whereas the bioactivity of the mutant protein is equal to those of wild-type, this mutation alters the secretory pathway of GH.
We confirm here the variable expressivity of patients bearing this *GH-1* mutation, reflecting the spectrum of GH deficiency in affected patients, even within families.
This mutation can cause indeed very mild growth retardation. This highlights once again the possibility of profound growth hormone deficiency in overweight children with growth retardation.

Human Growth Hormone structure

References

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