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GH Deficiency with Advanced Bone Age: GHRH Receptor Mutation Detected by Exome Sequencing Associated to Non-Classical Congenital Adrenal Hyperplasia

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Introduction

Isolated Growth Hormone Deficiency (IGHD) is usually associated with a delayed bone age. A genetic cause for IGHD is more frequently found in patients with familial cases and/or consanguineous parents.

Objectives

To diagnose the genetic cause of IGHD and clarify the unusual clinical presentation of advanced bone age in one patient born to consanguineous parents.

Methods

Sanger sequencing of *GH1*, *GHRH*, *GHRH receptor* and *CYP21A2* followed by whole exome sequencing (WES).

Case Report

- Caucasian boy, born to consanguineous parents, presented at 7.5 years with severe short stature (SD-3.7), high-pitched voice, blue sclera and prominent forehead. Pubertal Tanner stage I and delayed bone age (6 years-old).
- Clonidine and combined (insulin, TRH, GnRH) pituitary stimulation tests: GH peak=0.6 ng/ml, cortisol peak=16.1 mcg/dl.
- Normal Pituitary MRI.
- Successfully treated with rGH (33 mcg/kg/day), first year growth velocity of 11.7 cm.

Unusual Progression

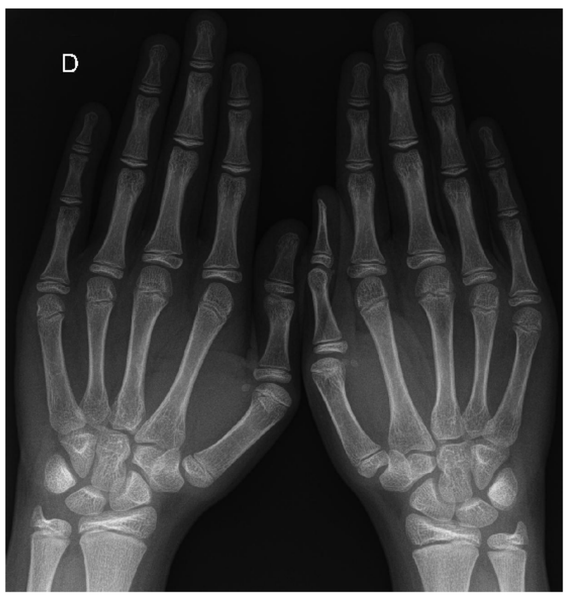

Figure 1 – Advanced bone age (13 yrs) in a 10.8 year-old boy with severe GH deficiency

- At 10.8 years of age: advanced bone age without signs of puberty and with prepubertal serum LH and testosterone levels.

Results

Biochemical Diagnosis

Table 1 – ACTH stimulation test (250 µg)

Hormone	Basal	Peak
Cortisol (mcg/dl)	6.1	18.8
17-OHP (ng/ml)	9.4	52.0
Androstenedione (ng/ml)	1.2	2.0

Genetic Diagnosis of non-classical CAH Sanger and Whole Exome Sequencing

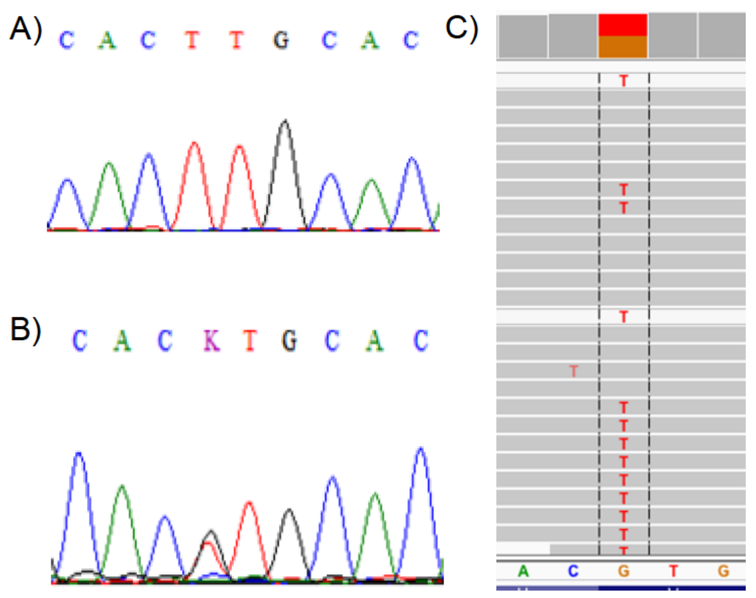

Figure 2 – A) *CYP21A2* Sanger sequencing showing homozygous c.844G>T (p.Val281Leu) mutation in the active gene. B) *CYP21A1P* Sanger sequencing showing heterozygous c.844G>T mutation in the pseudogene. C) WES showed c.844G>T in heterozygous state in the active gene probably due to the high homology of the active and pseudogene.

Genetic Diagnosis of IGHD Sanger and Whole Exome Sequencing

Sanger sequencing of *GH1*, *GHRH* and *GHRH receptor* were performed and no mutations were found. WES showed a homozygous c.431C>T, p.Leu144His mutation in GHRH receptor that was missed in the initial Sanger analysis. This recurrent mutation had been previously identified in Brazilian, Spanish and US patients with IGHD.

Conclusions

Patients born to consanguineous parents might have more than one genetic disease. In this situation unusual clinical presentations can occur. Whole exome sequencing was able to establish the genetic cause of IGHD.

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