SEVERE SHORT STATURE DUE TO A HETEROZYGOUS *IGF1R* MUTATION WITH A GOOD RESPONSE TO rhGH THERAPY: A FAMILY STUDY

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Introduction

The IGF1 resistance syndrome is caused by genomic or genetic defects affecting the ***IGF1R*** *locus* (15q26.3). It is characterized by intrauterine and postnatal growth failure associated with microcephaly and some degree of intellectual retardation, in the face of normal or supranormal IGF1 and IGFBP3 levels.

Case Report

➢ **A 3.5 years old girl,** born at **36.5** weeks by vaginal delivery with birth weight **1.935** g (-**3.2 SDS**), birth length **41 cm (-4.4 SDS)** and cephalic perimeter **(CP) 29 cm (-5.2 SDS)**. She was followed-up in the neuropaediatric clinic because of mild psychomotor retardation**.**

➢ **Exploration at age 3.5 years**:

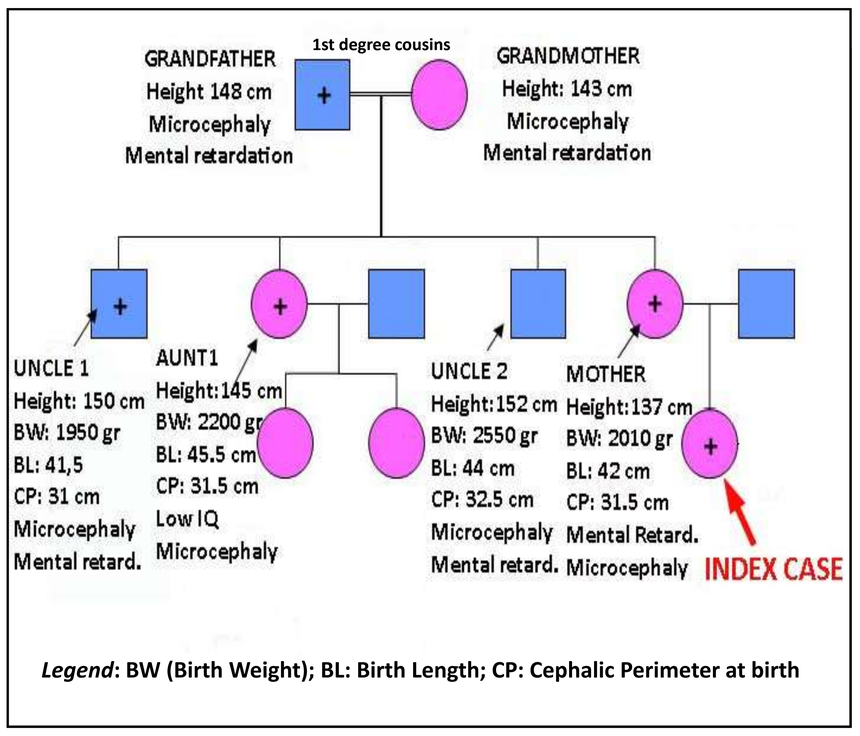
- Normal phenotype. Bone age: **2.5** years.
- **Body Weight:** 10.5 Kg. **(-2.4 SDS);**
- **Height:** 87.4 cm **(-3.0 SDS);** CP: 46.5 cm **(-2.5 SDS)**
- **IGF1:** 95.4 ng/ml (-0.8 SDS);
- IGFBP3: 3 µg/ml (0.51 SDS)
- **GH test (glucagon), peak of: 2.9 ng/ml**
- Further analyses and explorations were normal.

Molecular Studies

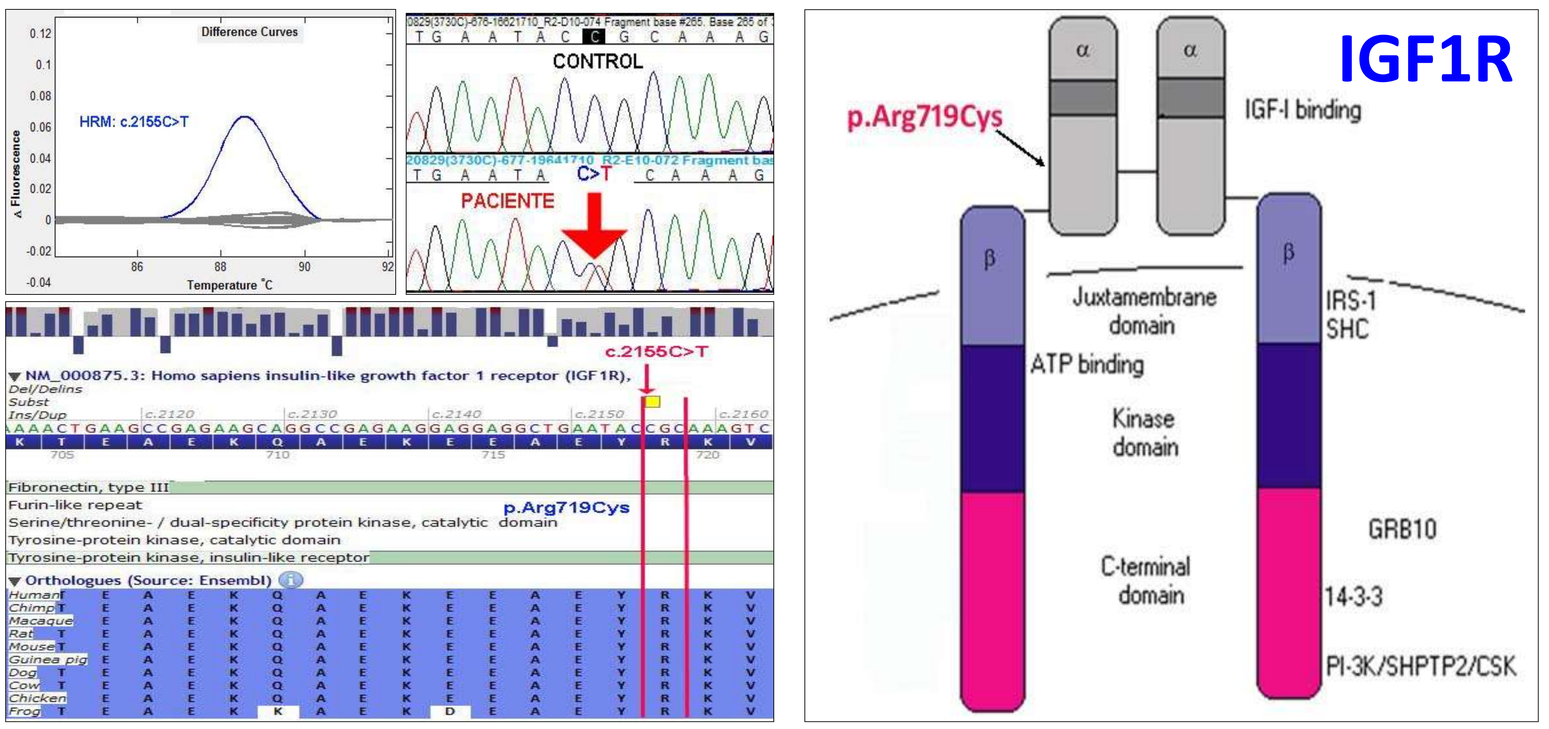
➢ Mutation screening of ***GHR, IGFALS,*** **and** ***IGF1R*** genes by HRM and sequencing.

- A novel point mutation, **c.2155C>T,** was detected in heterozygosis in ***IGF1R*** **exon 10.** The mutation alters a highly phylogenetically conserved residue **p.Arg719Cys**, located in the **fibronectin type III** and **Tyrosine-protein kinase** domains (Fig. 1) .
- The family study was positive for the maternal grandfather, the mother, and two siblings of the mother (Family Pedigree & Table 1).
- This novel mutation, not reported in the literature, was previously detected in our lab in a non-related patient presenting with growth failure from the first year of life, associated with high levels of IGF1 and IGFBP3.

Family Pedigree



Legend: **BW (Birth Weight); BL: Birth Length; CP: Cephalic Perimeter at birth**



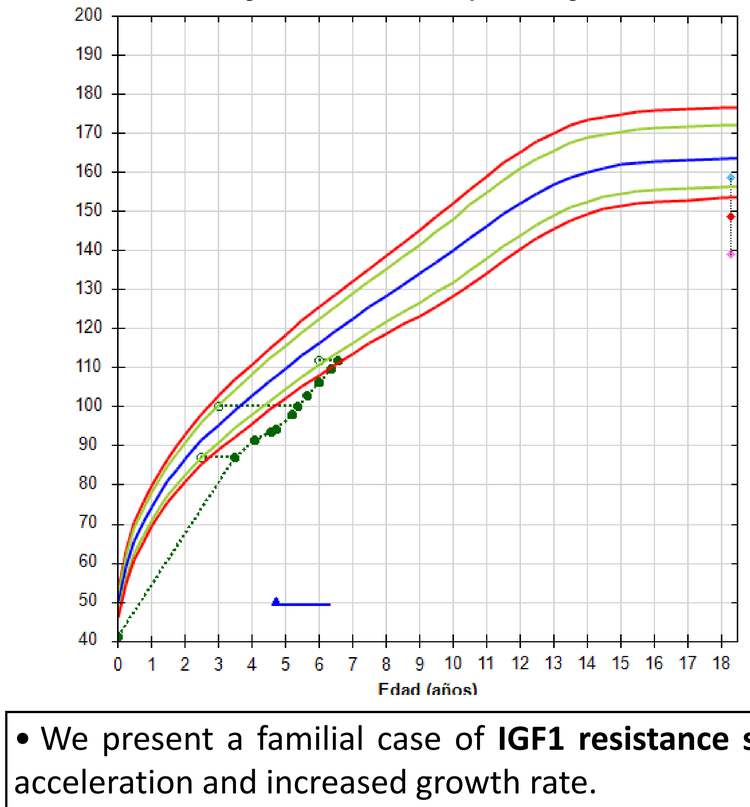
Family History

Family member	*IGF1R* mutation p.R719C	Height (SDS)	Birth BW (SDS)	Birth length (SDS)	Cephalic per. at birth (SDS)	Phenotype
Proband	+	-3	-2.11	-3.47	-2.50	MCF
Father	-	-1.03	NA	NA	NA	-
Mother	+	-4.14*	-3.34	-5.11	-2.43	MCF; low IQ
Grandmother (maternal)	-	-3.22	NA	NA	NA	MCF; low IQ
Grandfather (maternal)	+	-4.65	NA	NA	NA	MCF; low IQ
Uncle 1 (maternal)	+	-4.32	-3.83	-5.41	-3.09	MCF; MR
Uncle 2 (maternal)	-	-3.99*	-2.32	-3.94	-2.43	MCF; MR
Aunt (maternal)	+	-2.91	-3.31	-3.32	-2.63	MCF; low IQ

MCF: microcephaly; MR: Mental Retardation; *: treated with rhGH; NA: not available

Fig.1: Detection by HRM, DNA sequence and domain location of the ***IGF1R*** mutation **c.2155C>T, p.Arg719Cys.**

Index Case Growth Charter

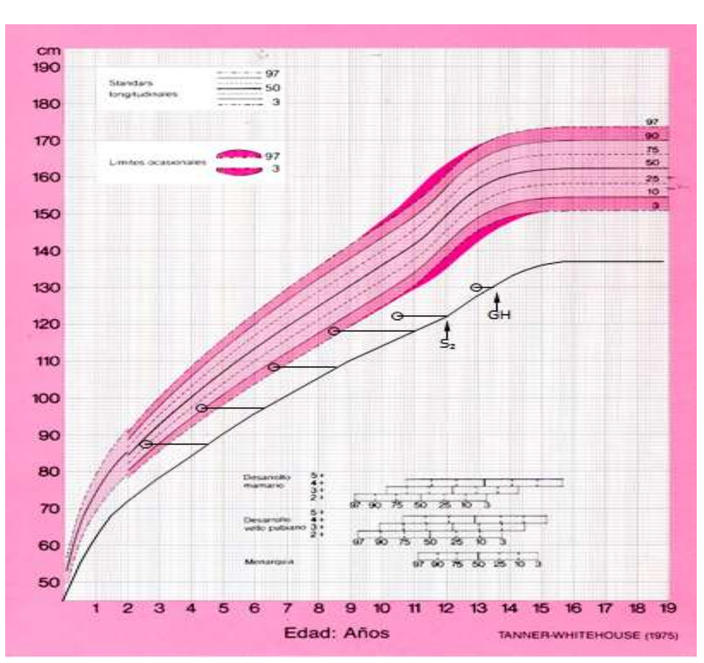


[Estudio Transversal Español 2010]

Index Case follow up

- **rhGH treatment was initiated at a dosage of 0.04 mg/kg/day at age 4 years and 9 months**.
- A good clinical response after 1.5 years rhGH reatment was observed:
- **IGF1**: 254 ng/ml **(+ 1.6 SDS)**.
- **Growth rate**: 10 cm/year **(+ 4.7 SDS)**.
- **Bone age** (after 1.5 yrs treatment)**: 6 years**

Mother Growth Charter



Comments

- We present a familial case of **IGF1 resistance syndrome** due to a novel heterozygous *IGF1R* mutation with good response to rhGH treatment, showing bone age acceleration and increased growth rate.
- It is recommended to screen for *IGF1R* mutations in cases with short stature associated with IUGR, microcephaly and intellectual deficit, especially if there is a familial clustering, and evaluate the indication of rhGH, adjusting or maintaining it according to the observed response.