

SEVERE ISOLATED GROWTH HORMONE DEFICIENCY AND MYOPATHY IN TWO BROTHERS WITH RNPC3 MUTATION

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OBJECTIVES

Isolated growth hormone (GH) deficiency (IGHD) can be caused by mutations in GH1 and other genes involved in pituitary development (as *POUF1*, *PROP1*, *LHX3* and. The molecular basis of a large proportion of patients with familial IGHD remains unknown.

We present two brothers with very distinct phenotype, possibly constituting a novel clinical and genetic entity. The common phenotype included red hair, obesity, myopathy, severe IGHD and, growth without growth hormone.

METHODS

Exome sequencing, alignment, variant call, annotation and filtering.

The sequencing was done using the SeqCapRoche Human Exome V3 capture system (Roche NimbleGen, Madison, WI, USA) and the HiSeq2000 platform (Illumina, San Diego, CA, USA). The initial data processing included alignment to the hg19 reference genome by Novoalign (www.novocraft.com), PCR duplicate removal by Picard tool MarkDuplicates (<http://picard.sourceforge.net/>), and recalibration and variant calling in GATK (DePristo et al. 2011). Variants were annotated by ANNOVAR (Wang et al. 2010), version 23 Aug 2013.

The search for the disease-causing mutation focused on variants with a quality score ≥ 20 and coverage $\geq 4X$, which were located outside of segmental duplications and simple repeats. The search was based on the assumption of rare deleterious variant(s) matching segregation criteria based on the respective hypothesis for AR, XL or *de novo* variant(s).

RESULTS

WES Results:

There was no single homozygous region shared by both siblings that was not also homozygous in any of the parents (other individuals from the group of 12).

Conclusion (WES):

No homozygous "deleterious" candidate variant identified. The variant could be outside the targeted regions or in an exome targeted region that is not covered/ poorly covered by the sequencing (or both alleles are deleted and therefore, not detected by the exome sequencing).

There was a single gene with compound heterozygous variants passing the segregation filter where each parent is heterozygous for one of the variants.

RNPC3:NM_017619:exon6:c.613C>T:p.R205X

RNPC3:NM_017619:exon13:c.1420C>A:p.P474T

	Juhl-1	Juhl-2
initial QC	94,419	93,766
removal of variants with frequency $\geq 1\%$ in public databases	18,384	18,147
deleterious	1,514	1,542
homozygous	107	109
shared homozygous	74	
heterozygous in both parents	3	
in a homozygous region	0	

CONCLUSIONS

Mutations of the RNPC3 gene encoding 65K protein that is a part of the U12-type spliceosome were identified. It is of note that the missense variant detected in our patient is exactly the same, while the non-sense variant is different from those already published. At present it is not clear how the mutations cause this particular phenotype. Additional functional studies and studies in knock out animals will follow.

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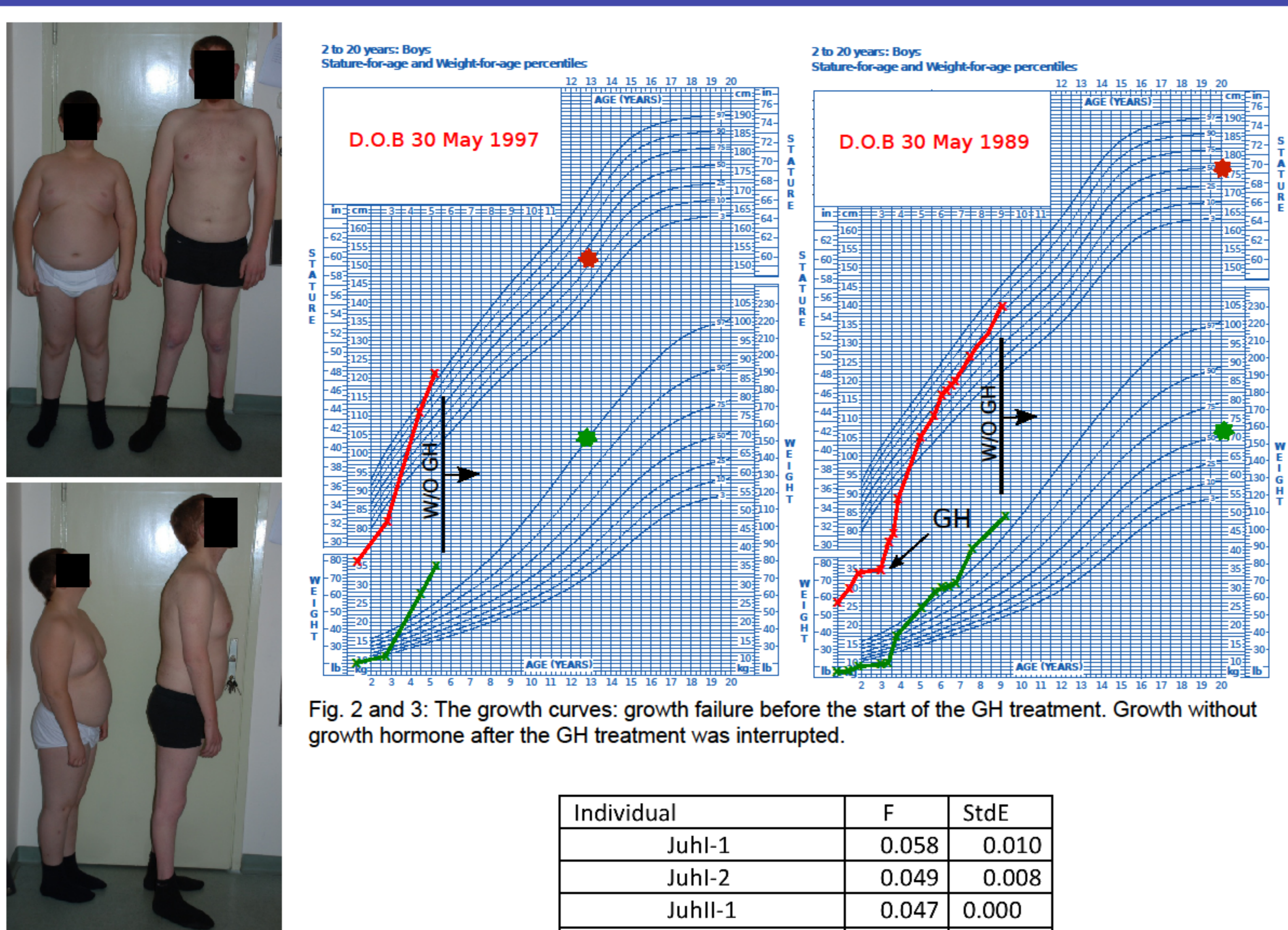


Fig. 2 and 3: The growth curves: growth failure before the start of the GH treatment. Growth without growth hormone after the GH treatment was interrupted.

Individual	F	StdE
Juhl-1	0.058	0.010
Juhl-2	0.049	0.008
Juhl-1	0.047	0.000
Juhl-2	0.049	0.011

Fig. 1: Note the obesity in the young brother, which was also present in the older one until puberty. Note the thinness of the calves in the older patient.

