

Response to rhGH therapy in patients with isolated familial growth hormone deficiency due to *RNPC3* mutations

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Introduction:

- Mutations in *RNPC3* are a novel cause of familial isolated growth hormone deficiency (GHD) and pituitary hypoplasia. *RNPC3* encodes a 65-kDa protein that is a structural component of the U11/U12 small nuclear ribonucleoprotein of the minor spliceosome. Mutations in *RNPC3* lead to structural destabilization of the 65-kDa protein, impaired binding of U12 snRNA and global defects in splicing of U12-type introns.
- To date, the response to recombinant human growth hormone (rhGH) in GHD due to *RNPC3* mutations has not been reported.

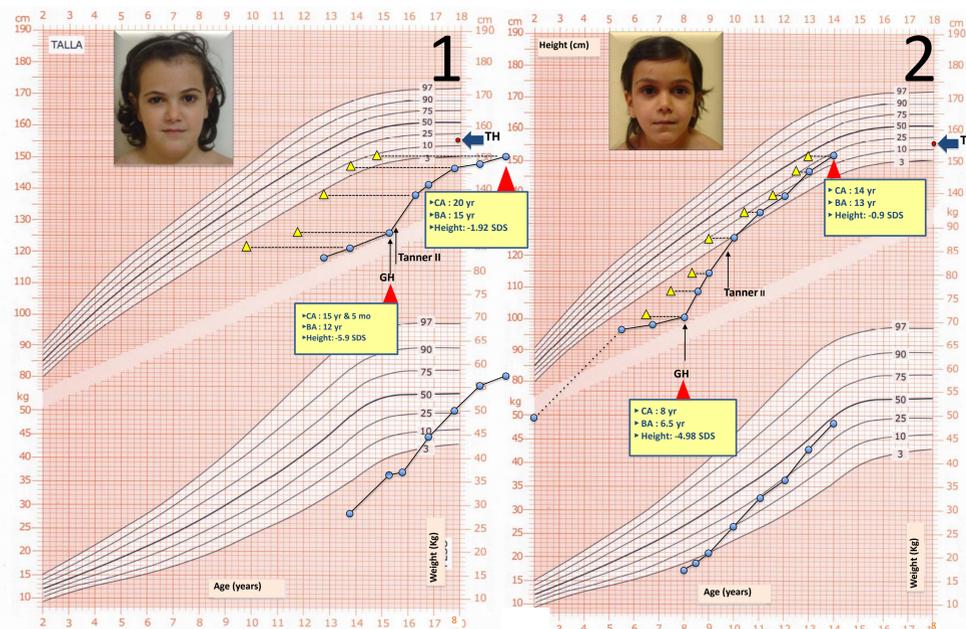
Objective:

We aimed to describe the effects of rhGH therapy in the first three patients identified with isolated GHD and pituitary hypoplasia due to *RNPC3* mutations, analyzing growth, pubertal development, body composition and bone microarchitecture.

Clinical cases:

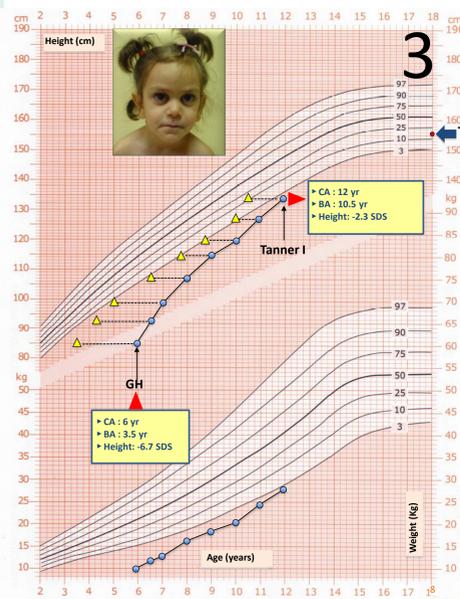
We present 3 sisters, compound heterozygous for mutations in *RNPC3* (c.1504C>T / c.1320C>A), born full term with normal length and weight, to non consanguineous parents (target height (TH): 155.6 cm), heterozygous carriers of the mutations. The patients developed severe postnatal growth failure and typical phenotypic features of GHD.

Case 1 (Figure 1): The patient was 125.5 cm (-5.9 SDS) at age 15.4 years, showed delayed bone age (BA) (3.5 years below chronological age [CA]) and Tanner stage I. Upon rhGH therapy, growth velocity (GV) increased dramatically, particularly during the first 2 years (GV 12.8 and 6 cm/year), achieving 150.3 cm at age 20 (after 4.5 years on rhGH) Puberty started spontaneously, with menarche at age 16.



Case 2 (Figure 2): At treatment onset, she was 8 years and 100.4 cm (-4.98 SDS, BA: 6.5 years), Tanner stage I. She responded even more intensely to rhGH (first 2 years: +14.2 and +11.1 cm/year). At her last visit (age 14.5 years), she was 152.9 cm (+0.7 SDS), close to her target height (155.6 cm). She started puberty at age 9.75 years, progressing to Tanner stage IV, without menarche to her last visit.

Case 3 (Figure 3): The third sibling was 6 years old (BA 3.5 years) and 84.5 cm (-6.7 SDS) at the onset of rhGH. Her growth rate also increased substantially upon treatment, again maximum during the first 2 years on treatment (+14.6 and +8.4 cm/year). She reached the 3rd centile in height at age 12.3 years, remaining prepubertal, with a +4.9 height-SDS increase after 6.5 years on treatment.



Body composition, bone mineral density and trabecular bone structure (Table):

Dual-energy absorptiometry analysis (DXA) was performed in the three patients before (baseline) and after 6 months, 1 year, and 6.5 years from rhGH therapy onset. The first year on rhGH improved lumbar spine bone mineral density (L1-L4 BMD) and normalized trabecular bone structure (TBS) in all patients. BMD Z-score remained unchanged between the 1-y. and the 6.5-year DXAs in patients 2 and 3, but fully normalized in patient 1. An intense lipolytic effect of rhGH treatment was observed in patient 1 after 1 year on rhGH, with body fat decreasing from 44.1% (+2.9 SDS) to 27.2% (+0.1 SDS).

Conclusions:

- The increase in height-SDS after rhGH (+4.0 to +4.9 SDS), is similar to that observed in other causes of severe isolated GHD and suggest that the required receptors and downstream signaling molecules are intact in patients with GHD due to *RNPC3* mutations.
- The height gain observed in the eldest sister (+24.8 cm) despite her advanced age (15.5 years) at therapy onset, next to the better height prediction in her two younger sisters reinforces the importance of the age at treatment onset, but also shows the effect of rhGH treatment in *RNPC3* mutation driven GHD even when it is started at a late age.
- The improvement in BMD and TBS in DXA scans during the first year on therapy suggests that the rhGH-induced rise in IGF-I in these patients has played a major role in the normalization of their bone development.

		Baseline	6 months	1 year	6.5 year
Patient 1	L1-L4 BMD (g/cm ²)	0.6440	0.733	0.781	1.050
	L1-L4 BMD (Z score)	-3.7	-2.7	-2.2	0.4
Patient 2	L1-L4 TBS	1.270	1.940	1.400	N.A.
	L1-L4 BMD (g/cm ²)	0.478	0.515	0.523	0.825
Patient 3	L1-L4 BMD (Z score)	-1.3	-0.7	-1	-1
	L1-L4 TBS	1.260	1.270	1.360	N.A.
Patient 3	L1-L4 BMD (g/cm ²)	0.397	0.446	0.470	0.678
	L1-L4 BMD (Z score)	-2.2	-1.4	-1	-1.1
Patient 3	L1-L4 TBS	1.260	1.270	1.360	N.A.

• Table: Lumbar spine (L1-L4) DXA at baseline and after 6 months, 1 and 6.5 year from therapy onset. Abbreviations: BMD: Bone mineral density; N.A.: Not available; TBS: Trabecular bone structure.