

Impact of Long-term (8 years) High-dose Growth Hormone treatment on growth velocity and final height in two siblings

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Introduction

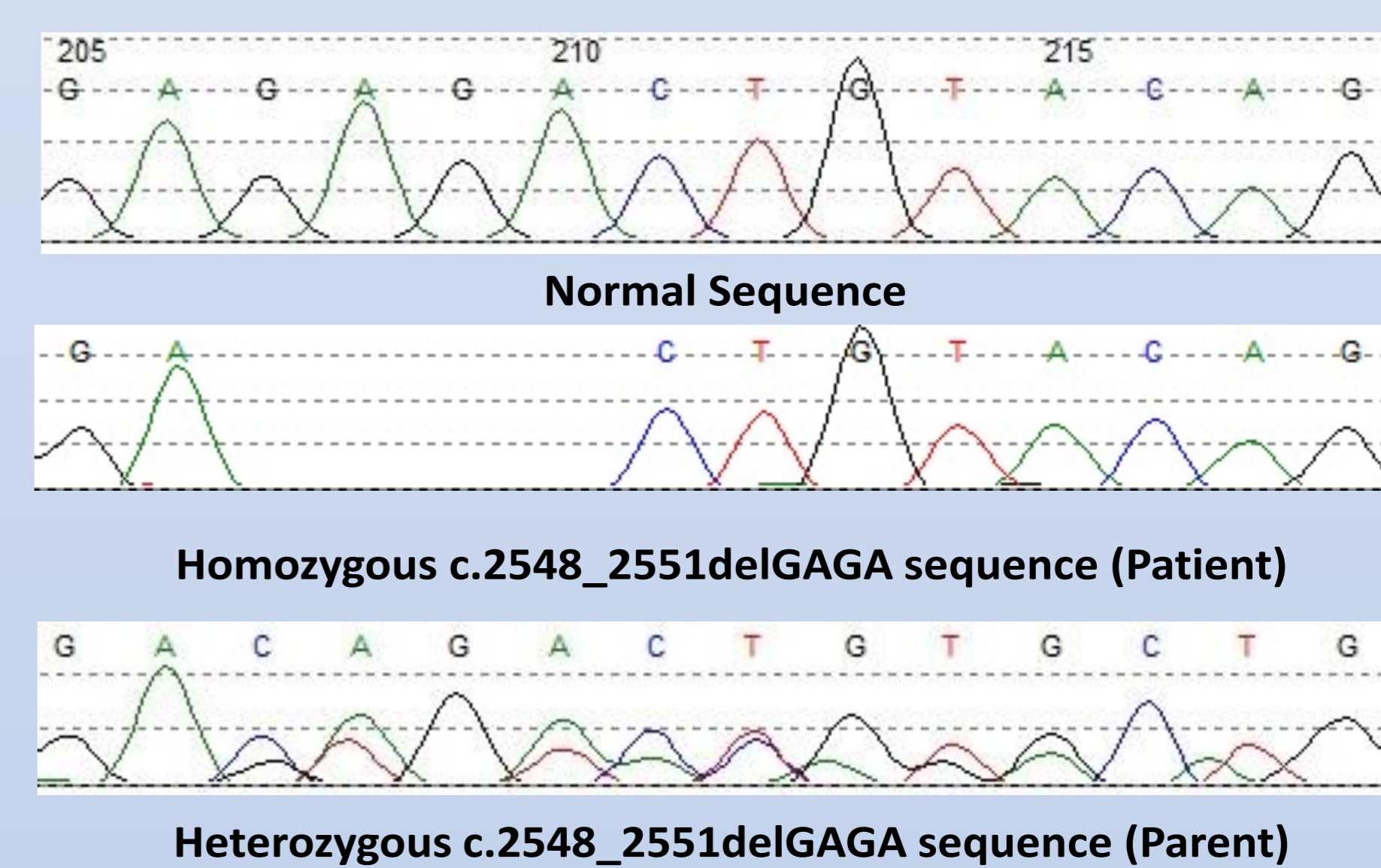
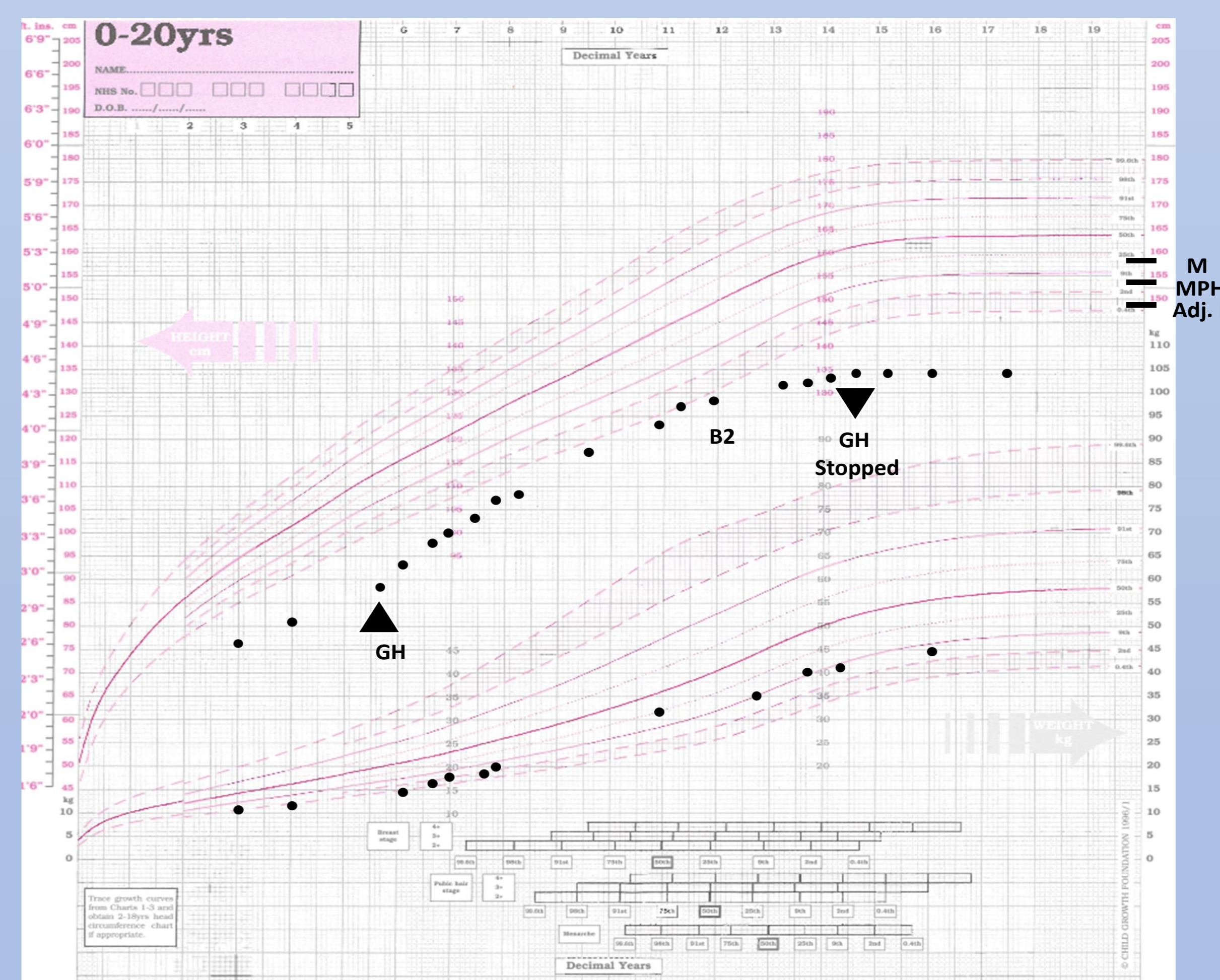
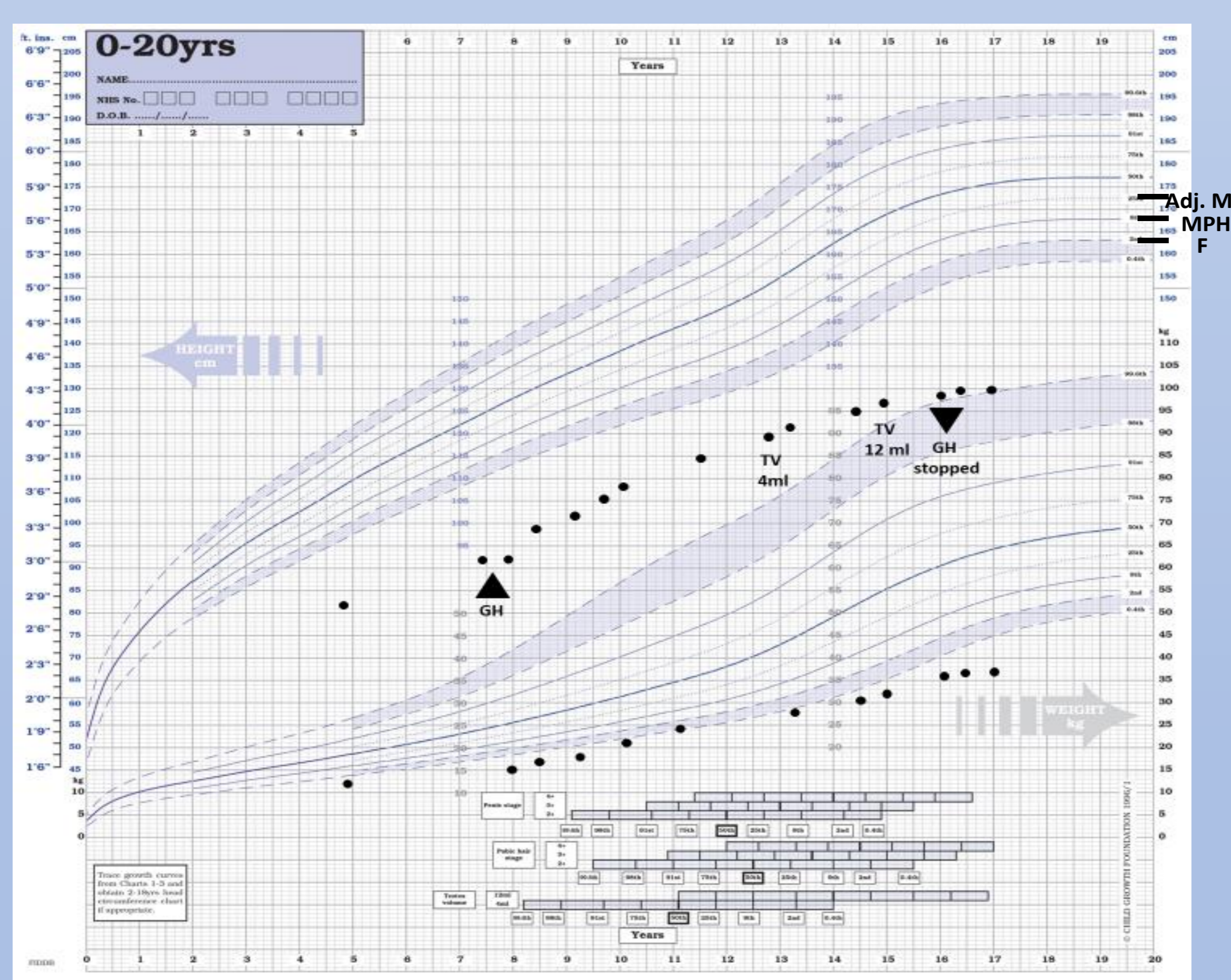
- Acromesomelic dysplasia, type Maroteaux (AMDM) is a rare autosomal recessive skeletal dysplasia, characterized by severe dwarfism (Final Ht 94-123 cm) and disproportionate shortening of the extremities, predominantly affecting middle and distal limb segments¹.
- It results from loss-of-function mutations affecting the C-type natriuretic peptide (CNP) receptor (NPR-B), a transmembrane guanylyl cyclase receptor encoded by the *NPR2* gene².
- Resistance to Growth Hormone (GH) action has been suggested in AMDM³.
- We previously reported an improvement in height velocity over 2 years of high-dose GH in two siblings with AMDM⁴.
- We now present their final height outcomes.

Patients and Methods

- Both siblings (Pt-A male, BW 2.39 kg at term/ Pt-B female, BW 2.52 kg at term) were diagnosed in early childhood/infancy with clinical and radiological features of AMDM. Parents are first cousins of Moroccan origin.
- Subsequent genetic testing identified a homozygous *NPR2* variant (c.2548_2551delGAGA; p.[Glu850fs]) in both siblings.
- GH provocation testing (Glucagon) was suggestive of relative GH resistance (Table 1). High-dose GH (70-75mcg/kg/d s.c.) was started. Pre-GH height velocities were 3.7 (Pt-A) and 4.5 (Pt-B) cm/year. GH dose was adjusted to sustain serum IGF1 levels close to the upper end of reference range for age (Table 2). Annualised height velocities for 1st, 2nd and 3rd year on GH treatment were **7.0, 5.4 and 4.7cm/yr (Pt-A)** and **9.4, 8.0 and 5.9cm/yr (Pt-B)**.
- Puberty onset was at 12.8(Pt-A) and 11.9(Pt-B) yrs. Respective height gain during puberty was only 10.6(Pt-A) and 5.9(Pt-B) cm.
- Final heights after 8.5 yrs of GH treatment were 130.5cm (-6.57SDS, Pt-A) and 134 cm (-4.58SDS, Pt-B).

Glucagon test	GH 0 min mcg/L	GH 20 min mcg/L	GH 60 min mcg/L	GH 90 min mcg/L	GH 120 min mcg/L	GH 150 min mcg/L	GH 180 min mcg/L	IGF-1 nmol/L (NR)	IGFBP3 (mg/L) (NR)
Patient A (7.6 yrs) ♂ Ht -5.6 SDS	21.4	15.8	8.0	7.6	27.3	6.0	6.1	7.8 (8.4 - 45.1)	2.7 (1.6 - 6.5)
Patient B (5.7 yrs) ♀ Ht -4.5 SDS	3.4	7.4	9.4	15.1	7.0	2.9	1.7	4.8 (6.8 - 38.8)	1.8 (1.3 - 5.6)

	Year 1	Year 3	Year 4	Year 5	Year 6	Year 7
Patient A	41.2 (9.6 - 50.7)	60.9 (11.5 - 59.1)	81.3 (14.5-72)	62.6 (18.7 - 90.6)	103.9 (24 - 111)	82.5 (15 - 64.8)
GH dose Pt-A	100	130	105	109	105	98
Patient B	41.5 (7.4 - 41)	78.8 (9.7-50.7)	88.2 (9.7-50.7)	72.7 (11.5 - 59)	75.5 (14.4-71.6)	86.7 (24-66.3)
GH dose Pt-B	103	100	92	81	78	72

Electropherogram showing a fragment of exon 17 of *NPR2* with c.2548_2551delGAGA p.E850fs*32 mutation

Conclusions

- To the best of our knowledge, this is the first report of final height in patients with AMDM after long-term GH treatment.
- Our patients with AMDM had GH/IGF1 profiles consistent with a degree of intrinsic GH resistance.
- GH treatment with doses 3-4 fold higher than conventional GH replacement increased their serum IGF1 levels to upper limit of age- and sex-related reference range, which was associated with increase to greatest height SDS (Pt-A -4.33SDS; Pt-B -2.76SDS) close to onset of puberty.
- Although this early improvement in height SDS enhanced their quality of lives, this was not sustained through puberty and it is uncertain whether this improved final height.
- However, compared with a "GH untreated" AMDM patient (F Ht 116cm) with same mutation and from similar geographic region (Maghreb) their Final heights were significantly better⁵.

References:

- In: Bone dysplasias: An Atlas of Genetic Disorders of Skeletal Development (4 ed.), Oxford University Press. Ch. 13, p. 443.
- Bartels CF et al. Am J Hum Genet. 2004; 75:27-34
- Olney RC et al. J Clin Endocrinol Metab 100: E355-E359, 2015.
- Raj M and Buchanan CR. Horm Res 2009; 72 (suppl 3):104.
- Castro-Feijoo L et al. Horm Res Paediatr 2016;86(suppl 1):444-445

The authors have nothing to disclose

