

Gigantism due two different causes in the same family: AIP mutation-positive acromegaly and Marfan syndrome

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Introduction

- Germline aryl hydrocarbon receptor-interacting protein (AIP) mutations are responsible for 30% of pituitary gigantism cases¹.
- Pathological accelerated growth and/or tall stature can be unrelated to the growth hormone (GH) axis, and may occur in isolation or as part of a syndrome, such as in Klinefelter, Marfan or Sotos syndromes².
- Pseudoacromegaly is a term used to describe patients with gigantism and/or acromegaly features but with no abnormalities in the GH axis³.
- We report a five-generation kindred with two brothers having pituitary gigantism due to AIP mutation-positive GH-secreting pituitary adenomas and their first-cousin coincidentally also having gigantism due to Marfan syndrome.

Case description

The proband (IV.c)

- Presented with accelerated growth at age of 8y
- At the age of 10y, he measured 153 cm (height SDS+2.1)
- Diagnosed with pituitary gigantism due to a 2.5 cm-pituitary adenoma co-expressing GH and prolactin
- Treated unsuccessfully with surgery, cabergoline and octreotide; responded to pegvisomant⁴.
- His final height is 200 cm (Figure 1)

The proband's brother (IV.d)

- Presented a few years later at the age of 16y with accelerated growth, height: 201 cm (SDS+3.9)
- Diagnosed with a somatotropinoma, operated on two occasions
- His final height is 209.5cm

AIP mutation-positive FIPA (familial isolated pituitary adenoma) kindred (Figure 2)

- When the proband's brother was diagnosed with pituitary gigantism, AIP genetic testing was offered to the two affected brothers
- Genetic testing identified a truncating heterozygous nonsense mutation in AIP gene (c.910C>T; R304*), in both brothers
- Eight unaffected family members carry the same AIP mutation, and are currently under surveillance
- A deceased great-uncle had acromegaly based on photographs

Proband's first cousin (IV.h) (Figure 2)

- In the same family, a tall first-cousin was identified, with a height of 208 cm due to Marfan syndrome
- First cousin mother is also tall, and also known to be affected with Marfan syndrome

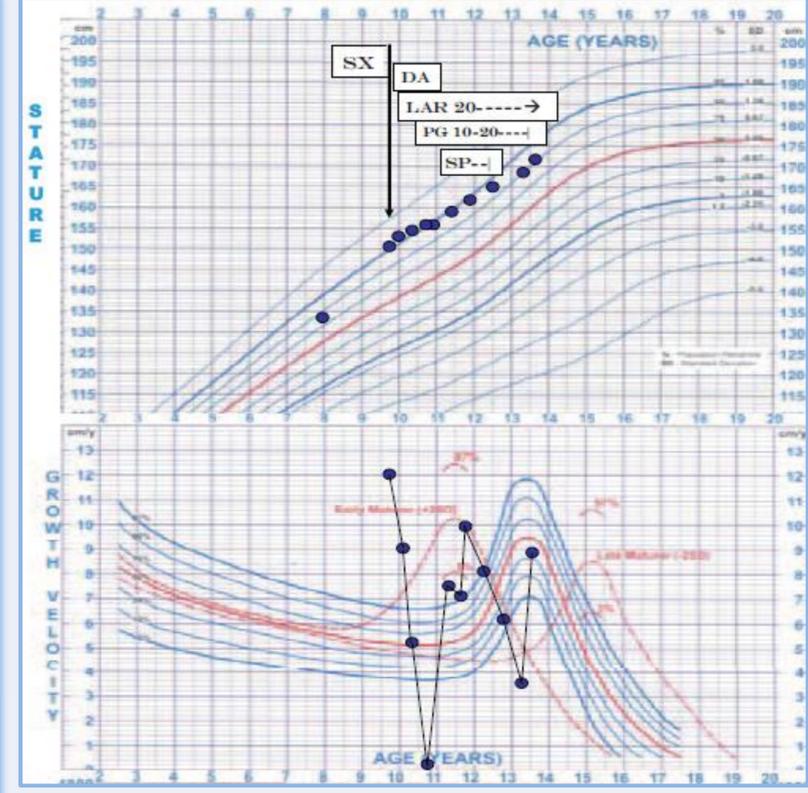


Figure 1: Proband's stature and growth velocity at presentation and throughout the disease course (SX, surgery, DA, dopamine agonist; LAR 20, octreotide LAR 20 mg, PG, pegvisomant, SP, spontaneous puberty)⁴.

Discussion

- Clinical and biochemical exclusion of GH-related pituitary gigantism is usually straightforward¹.
- However, the evaluation of patients with tall stature and/or acromegaly features but no GH axis abnormalities (pseudoacromegaly) may be challenging³, particularly when the classical features of the underlying syndrome are absent, or in case of coexistent acromegaly features (Figure 3).
- In this family, the diagnosis of the two brothers with pituitary gigantism may have been hindered by the presence of extreme tall stature in this family due to Marfan syndrome.
- Marfan syndrome, autosomal dominant disorder caused by loss-of-function variants in *FBN1* gene, mainly affects the skeletal, ocular and cardiovascular systems. Excessive linear growth of long bones resulting in tall stature justifies the assessment of GH axis. However, other features such joint laxity, disproportionate long extremities for trunk size with increased arm span-to-height and lower-to-upper segment ratios, pectus carinatum or excavatum, should lead to an accurate diagnosis of Marfan syndrome².
- Endocrinologists should be aware of clinical conditions masquerading as acromegaly or pituitary gigantism (pseudoacromegaly)^{2,3}, and thus aid in establishing the underlying diagnosis.

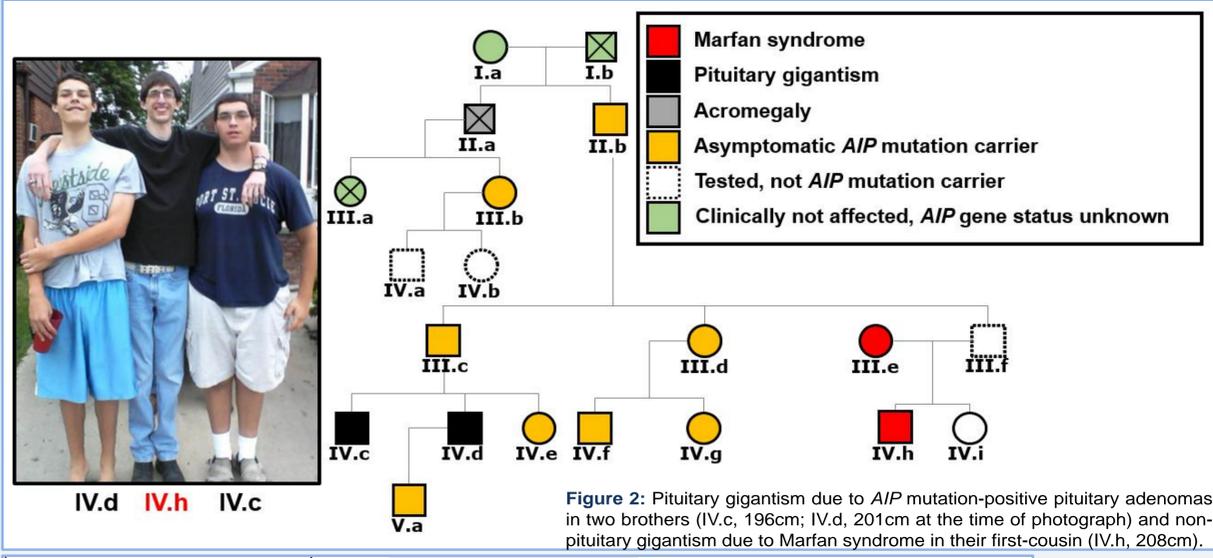


Figure 2: Pituitary gigantism due to AIP mutation-positive pituitary adenomas in two brothers (IV.c, 196cm; IV.d, 201cm at the time of photograph) and non-pituitary gigantism due to Marfan syndrome in their first-cousin (IV.h, 208cm).

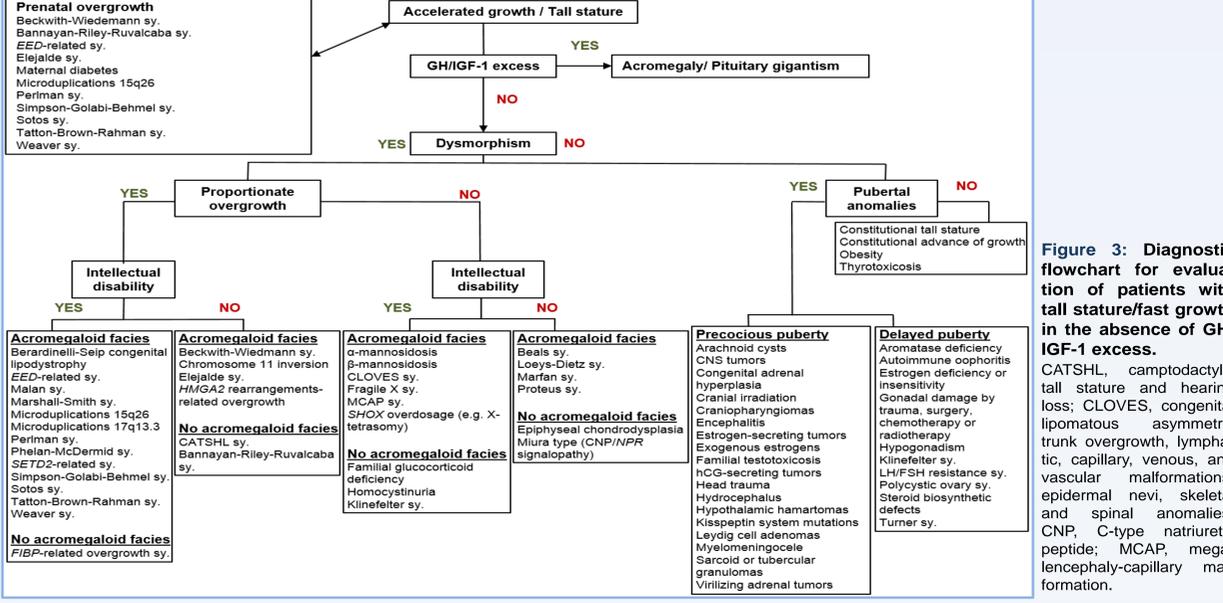


Figure 3: Diagnostic flowchart for evaluation of patients with tall stature/fast growth in the absence of GH/IGF-1 excess. CATSHL, camptodactyly, tall stature and hearing loss; CLOVES, congenital lipomatous asymmetric trunk overgrowth, lymphatic, capillary, venous, and vascular malformations, epidermal nevi, skeletal and spinal anomalies; CNP, C-type natriuretic peptide; MCAP, megalencephaly-capillary malformation.

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