Compound Heterozygosity for two POU1F1 Novel Mutations in Siblings with Isolated Childhood Onset Growth Hormone Deficiency.

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BACKGROUND

- Mutations of POU1F1 have autosomal recessive inheritance, and phenotypically present with small or normal anterior pituitary gland, with normal posterior pituitary and infundibulum without extra pituitary signs
- Patients present with Growth Hormone (GH) and Prolactin (PRL) deficiency with variable presentations of TSH deficiency.
- Children with CO-GHD secondary to genetic mutation are more likely to have persistent GHD in adulthood.

OBJECTIVES

- To describe the clinical course and outcome at of two siblings diagnosed with compound heterozygous novel mutations of the POUF1 gene.
- Both cases have isolated GHD with normal pituitary structure in exon 3 and 4- p.K166E and P.E224K respectively.

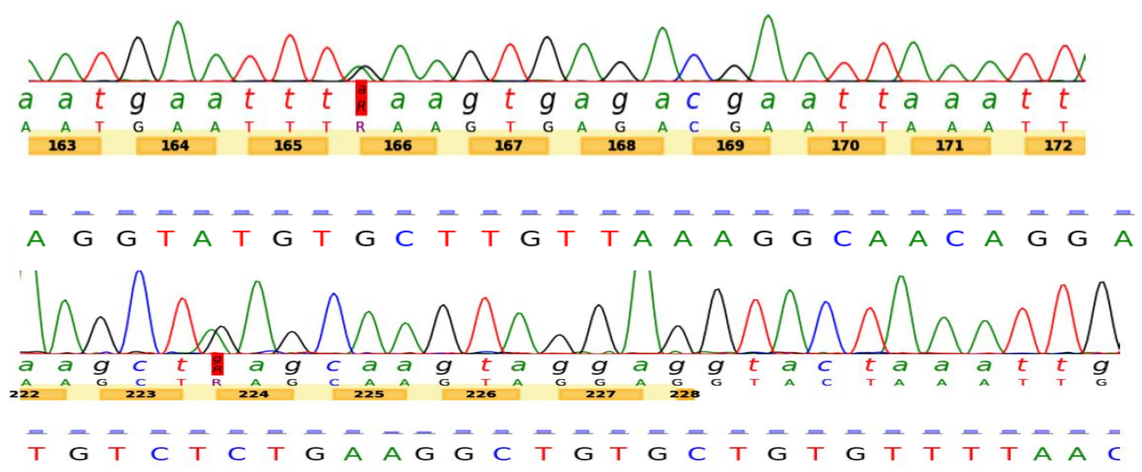

Fig.1 : Genetic sequencing of POU1F1, showing mutation of codon 166 exon 3(above) and codon 224 of exon 4 (below)..

CASE HISTORY

- **Case 1:** Presented with severe growth failure, short stature (SS) and complete isolated GHD at the age of 4 years .
- Low IGF 1 SDS and absence of GH peak on GH stimulation test.
- He had an excellent response to GH treatment.
- At the final height (50th centile), GH status re-evaluation by insulin tolerance test (ITT) revealed persistent severe GHD deficiency.
- **Case 2:** The younger sister presented in the neonatal period with severe hypoglycaemia.
- Diagnosis was confirmed with low IGF 1 SDS, low GH level in neonatal period, clinical growth failure at the age of 2 months and a failed glucagon stimulation test. She has responded well to GH treatment (now 25th centile).

CLINICAL FEATURES

	Case 1	Case 2
Presentation	Severe SS at age of 4 years Ht SDS -4 .0 SD	Neonatal hypoglycaemia Growth failure at 2 months of age Ht SDS -3.35 SD
GH stim. test /IGF-1 SDS	Absence of GH peak to both Glucagon and ITT. IGF-1 SDS -2.2 at age 5.4 years.	GH level in neonatal period 0.1µg/L (critical sample) IGF-1 -2.8 SDS at 2 months of age
MRI pituitary	Normal pituitary structure	Normal pituitary structure
TSH/ACTH/ADH	Normal	Normal
Response to r GH treatment	Height gain SDS +4.5 SD (12 years of rGH treatment) final height of SDS -0.19 SD within genetic target range (SDS 0.2 < mid-parental height).	Height gain SDS + 2.19 following 3 years of rGH treatment.
Outcome	• Attained final height and full pubertal maturation at age of 17 years. • GH discontinued for 2 months. IGF 1 SDS <-2 • ITT revealed severe persistent GHD • rGH recommenced	On going GH treatment with normal growth and development, current Ht SDS is -1.19.

CONCLUSIONS

- Severe GHD and very early presentation are the main pointers to genetic /pathological causes of CO-GHD even in presence of normal pituitary structure.
- This heterozygous mutation in exon 3 and 4 of the POU1F1 gene in this sibling pair is novel.
- The persistence of GHD after attainment of final height in case 1 emphasised the importance of identifying the underlying pathology of CO-GHD. This has facilitated the transition process in this patient and his preparation of the young adults for future possible outcomes.
- A GH level in the neonatal period associated with hypoglycaemia is a useful diagnostic tool of neonatal GHD especially in challenging cases where GHD is isolated and pituitary structure on imaging is normal.

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