

Introduction

Pituitary adenomas are frequent intracranial tumors, particularly in young patients. Familiar isolated pituitary adenomas (FIPA) encompasses the familiar occurrence of isolated pituitary adenomas outside the setting of syndromic conditions such as multiple endocrine neoplasia type 1 and Carney's complex, and comprise about 2-3% of pituitary adenomas. About 20% of FIPA have mutations in the aryl hydrocarbon receptor interacting protein gene (AIP). Interestingly, pituitary adenomas in FIPA are more aggressive and have poor response to treatments.

Objective

To study the presence of AIP gene mutations in 3 patients with clinical features of FIPA.

Case Report

We report the case of two brothers and their mother who presented with isolated pituitary adenoma. Index case was the younger brother, who was referred because of short stature at 13.9 years old. He was a healthy child, who was diagnosed with primary hypothyroidism at 10 years of age. As remarkable family history, his mother and one brother had been diagnosed with no functional pituitary adenomas. The mother had a pituitary microadenoma and the brother, who also had short stature, a pituitary macroadenoma, that was surgically removed years before in another Hospital.

Index Case

Weight: 37 Kg (-1,49 SD)
 Height: 137,2 cm (-2,44 SD)
 Tanner Stage G3, PH2
 Testicular volume 8cc
 Bone Age 12y

Table 1: Pituitary function of the 3 cases

	IGF1 (ng/ml-SD)	BP3 (µg/ml-SD)	PRL (ng/ml)	ACTH (pg/ml)	Cortisol (µg/dl)	TSH (mIU/ml)	T4I (ng/dl)	FSH (mIU/ml)	LH (mIU/ml)
Index Case	330 (-0,14)	5,18 (-0,63)	9,2	12,9	9,1	2,4	1,1	2,07	2,7
Brother	281	4,25	24,4	85	34,2	1,8	1,6		
Mother	86,2	3,36	12,2	18,8	24,9	0,53	1,35		

Growth hormone deficiency was excluded with arginine test (Gh peak 7,6 ng/ml).

Because of his familiar background a MRI was performed.(figures 1,2)

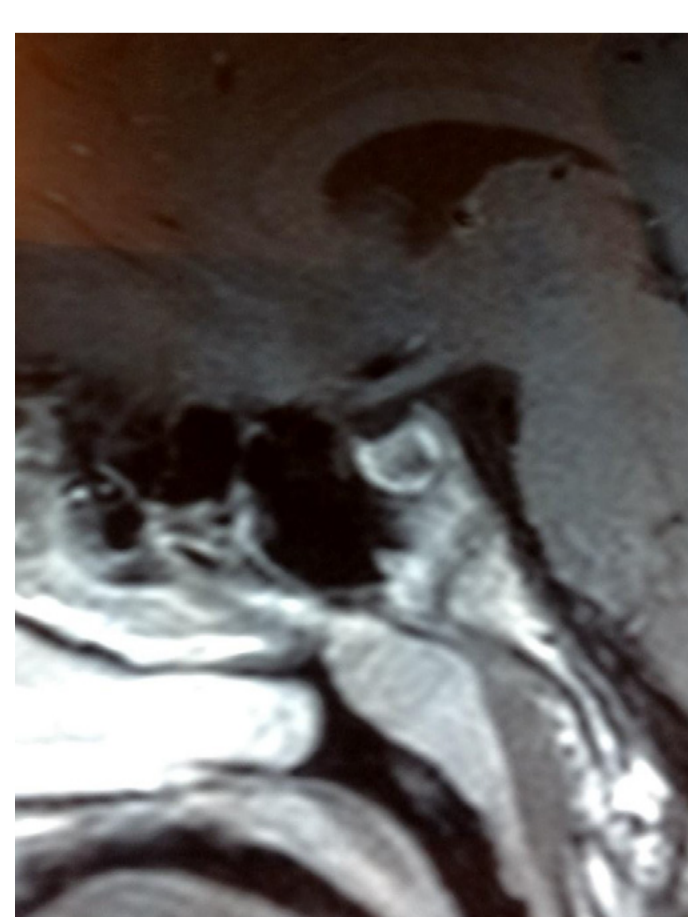


Fig.1: MRI Index Case

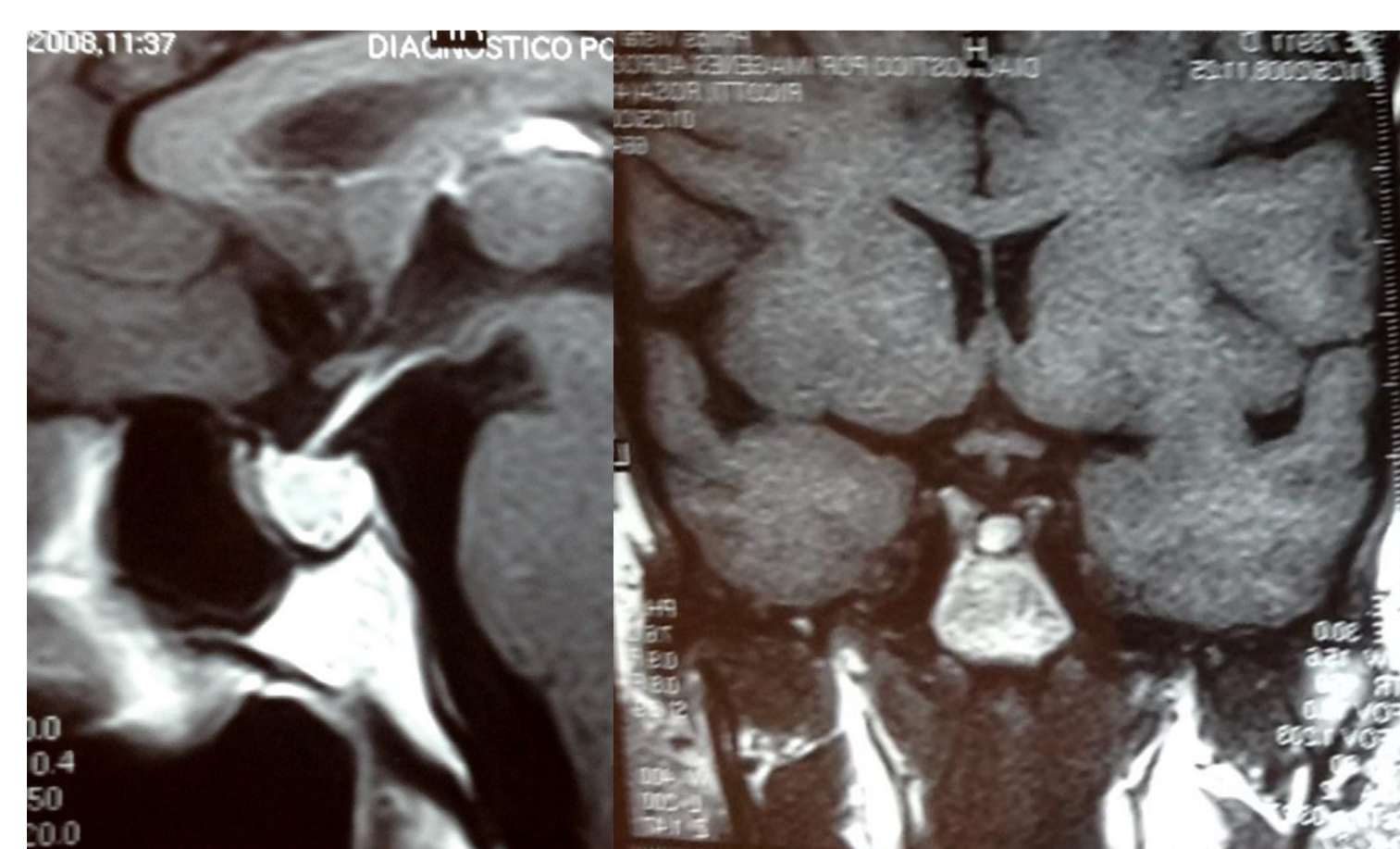


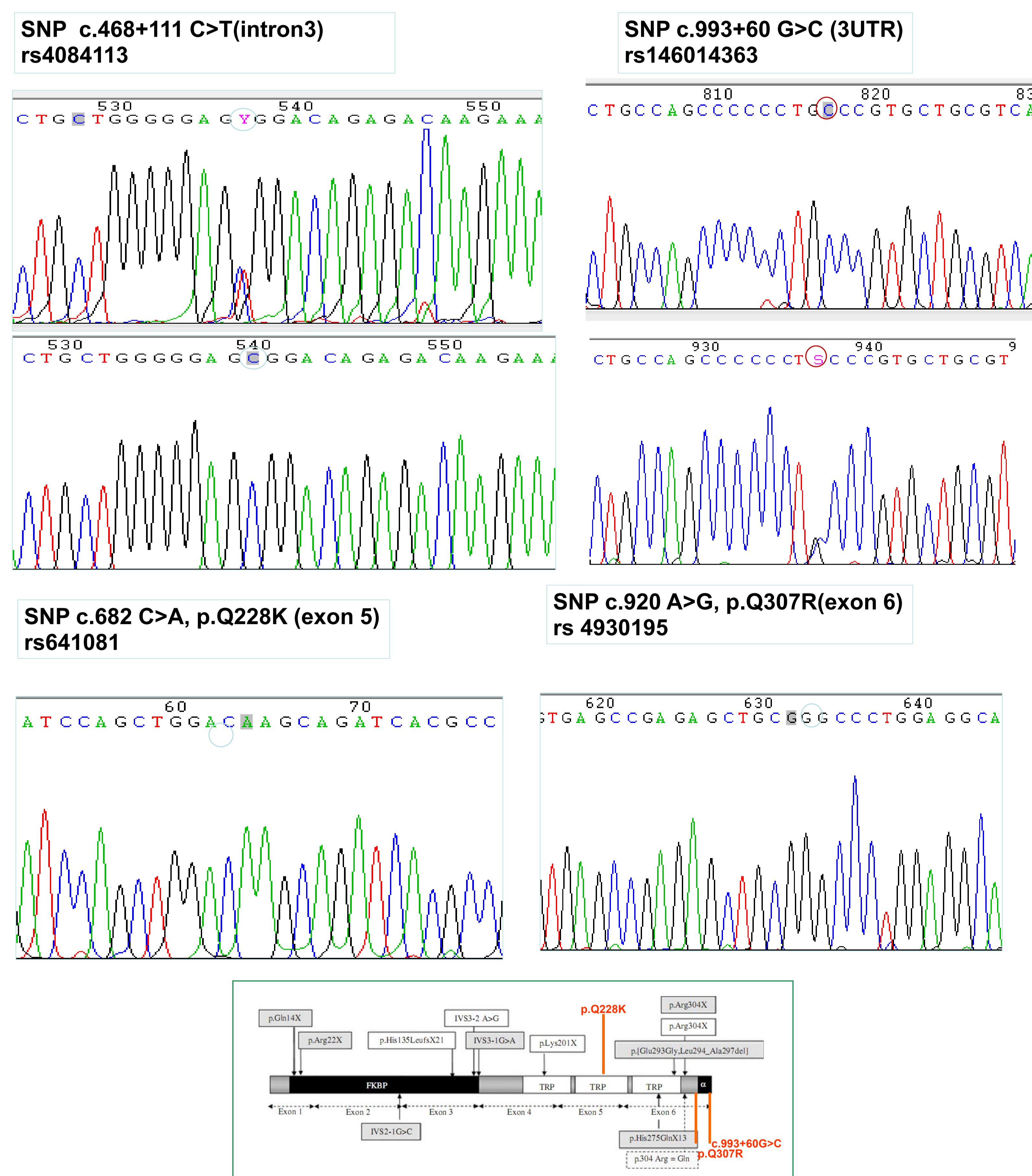
Fig.2: MRI Mother

Methods

Genomic DNA was obtained from peripheral blood leukocytes. The promoter region and exons 1 to 6 and intronic flanking regions of the AIP gene were amplified by PCR using specific primers. The DNA fragments were sequenced by automatic sequencing.

Results

We found the following polymorphisms (SNPs): **c. 468 + 111 C>T**, (intron 3) heterozygous in index patient and mother and homozygous in brother and **c. 993 + 60G >C heterozygous** in 3' UTR and in the three patients. We also found **c.682C>A** (exon 5) homozygous and **c.920A>G** (exon 6) homozygous in three patients.



Conclusions

When a pituitary adenoma is diagnosed a carefully family history should be performed, and if FIPA is detected the AIP gen analysis could allow an early diagnosis and prevent in GH producing adenomas the gigantism phenotype.

Our family genotype has two exonic homozygous missense SNPs in the coding region of AIP gene, c.682C>A and c.920A>G which were significantly increased in patients than in healthy population.

Otherwise, the frequency of c.993+60G>C variant in healthy population is discordant (0,9 to 2%) between published reports and should be studied in argentinian people as well as in unaffected family members.

Finally, the synergism between the SNPs founded cannot be excluded.