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Case report

A novel truncating AIP mutation, p.W279*, in a familial isolated pituitary adenoma (FIPA) kindred

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ABSTRACT

Familial isolated pituitary adenomas (FIPA) constitute 2-3% of pituitary tumours. *AIP* is the most commonly mutated gene in FIPA. We herein report a novel germline mutation of the *AIP* gene in a family with FIPA. We present two patients, a father and his 12-year-old daughter, diagnosed clinically and using laboratory measures with acromegaly-gigantism. Both underwent transsphenoidal hypophyseal surgery for macroadenomas. We initially detected a novel heterozygous germline *AIP* mutation, c.836G>A (p.W279*), in the father's DNA. We then found the same mutation in his affected daughter. Pituitary adenomas associated with *AIP* mutations mostly present as FIPA (68%) at an early age (78% occur at <30 years old). They are often growth hormone (GH) - or prolactin - secreting macroadenomas (88%) that have already extended beyond the sella at the time of diagnosis. Acromegalic cases are resistant to somatostatin analogues and multimodal management is frequently essential to control the disease. Our patients had normalized GH/IGF-1 values soon after surgery, although enough time may not have elapsed to reach final cure. While penetrance of the disease can be as low as 10% in FIPA, especially children and young patients with somatotropinoma and prolactinoma should be surveyed for inactivating mutations or deletions in *AIP*. Determining the causative mutations may be of assistance in early diagnosis, treatment success, and genetic counseling.

Key words: AIP mutation, Familial isolated pituitary adenoma, Gigantism

INTRODUCTION

Hypophyseal (pituitary) adenomas are one of the most common intracranial neoplasms. Most occur sporadically, while 5% of all cases present as a component of inherited syndromes due to germline mutations in different genes, such as *MEN1* (encoding menin), *AIP* (encoding aryl hydrocarbon receptor interacting protein), *PRKAR1A* (encoding protein kinase cAMP-dependent type I regulatory subunit alpha), and *CDKN1B* (encoding cyclin-dependent kinase inhibitor 1B).[1,2] The first isolated familial pituitary tumors,

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which in most cases were familial acromegaly, were identified in 1999.[3] Following reports from the same center, familial isolated pituitary adenoma (FIPA) was identified as a separate clinical entity.[4]

FIPA is characterized by pituitary adenomas occurring in two or more family members and absence of genetic and clinical features of multiple endocrine neoplasia type 1 (MEN-1), multiple endocrine neoplasia type 4 (MEN-4), Carney complex, or other multitumour conditions.[4] FIPA is found in 2-3% of pituitary adenomas.[4] *AIP*, which was first identified as causative of FIPA in 2006, is the most commonly mutated gene.[5,6] We herein report a novel germline mutation of the *AIP* gene in a family with FIPA.

CASE REPORT

A 39-year-old male patient presented to the endocrinology outpatient clinic complaining of multiple skin tags all over his body, especially on the neck and under the armpits. The lesions had progressively increased over several years. He was also suffering from facial and hand edema but denied any change in shoe size. On physical examination, a large number of flesh-colored skin tags measuring 0.2-1.5 cm in size were detected all over the body and especially all over the neck and under the armpits. Acanthosis nigricans was also evident on the neck and under the armpits. He had a blood pressure of 130/80 mmHg, a regular pulse rate of 82bpm, and coarse facial features. Prognatism was absent. He was 186 cm tall and weighed 103kg. He had a body mass index (BMI) of 29.77 kg/m^2 and abdominal obesity. The liver was palpable 2 cm below the costal margin. Physical examination of other organ systems revealed no abnormality. Family history of acromegaly and gigantism was absent. He described his 12-year-old daughter as being taller and heavier than her peers. At his next visit, his daughter was also examined. She had grown 4-5 cm in the last year. She was 178 cm in height (4.3 SDS) and weighed 81 kg (5.3 SDS). Her BMI was 25.56 kg/m^2. She was over the 97th percentile for both height and weight. Acanthosis nigricans was evident under the armpits. She was at Tanner stage 4 (telarche stage 4 and pubarche stage 4) and had been menstruating for 6 months. Examination of other organs revealed no abnormality.

Basal GH and IGF-1 levels were measured due to clinical suspicion of acromegaly-gigantism in both family members. They were higher than the age-matched reference range. GH was measured during the 75g oral glucose tolerance test but was not suppressed below 1 ng/ml. Complete blood count and blood chemistry panel were within normal limits. Other pituitary hormone levels were also normal as shown in Table 1.

The father had a right-sided pituitary mass measuring 13×12×8mm in size, which was isointense on T1 and T2 weighted MRI images and showed no

Table 1. Laboratory data of patients

	Father		**Daughter**	
	Before operation	**After operation** (6th month)	**Before operation**	**After operation** (6th month)
GH (ng/ml)	**9.97** (0.05-3.0)	0.284 (0.05-3.0)	**6.29** (0.05-17.3)	1.07(0.05-17.3)
IGF-1 (ng/ml)	**626** (109-494)	300 (109-494)	**1504** (183-850)	821 (183-850)
PRL (ng/ml) (3.46-19.4)	13.5	13.3	15.9	11.2
ACTH (pg/ml) (7.2-63.3)	41.4	27.4	20.9	59.6
Cortisol (µg/dl) (3.7-19.4)	14.1	18.7	20.29	24.9
FSH (µIU/ml)	3.32 (0.95-11.95)	2.85	3.9 (2.55-16.69)	3.5
LH (µIU/ml)	3.9 (0.57-12.07)	2.1	1.64 (1.8-11.78)	2.03
TSH (µIU/ml) (0.35-4.94)	1.39	1.84	1.94	3.39
Free T4 (ng/dl) (0.7-1.48)	1.06	1.12	1.05	0.94
Calcitonin (pg/ml) (0-10)	<2	-	<2	-

enhancement after intravenous contrast medium administration. Minimal extension into the right cavernous sinus was evident. The optic chiasm was spared and other related structures were normal. His daughter also had a right-sided pituitary mass measuring 12×15×10 mm in size, which was hypointense on T1 weighted images and hyperintense on T2 weighted MRI images; it consisted of cystic areas and demonstrated no enhancement after intravenous contrast medium administration. The lesion extended into the right cavernous sinus and circumvented the cavernous segment of the internal carotid artery medially. The optic chiasm and other related structures were intact. Both patients had normal visual field examination.

Histologic examination of the father's mass revealed negative staining for ACTH and PRL, extensive positive staining for GH, and negative staining for p53. The staining index for Ki-67 was lower than 1%. The histologic examination of the girl's mass revealed a disrupted reticular fibrin network, negative staining for ACTH and PRL, and positive staining for GH and p53. The staining index for Ki-67 was 7%.

Both patients provided written informed consent for genetic analysis and Institutional Review Board approval was obtained. We extracted DNA from whole blood and performed Sanger sequencing of the *AIP* gene (NM_003977.2) with primers covering the exonic sequences as well as the exon-intron junctions. We initially detected a novel heterozygous germline *AIP* mutation, c.836G>A (p.W279*), in the father's DNA. We subsequently found the same mutation in the affected daughter (Figure 1).

Removal of the pituitary adenomas of both family members was performed by endoscopic transsphenoidal surgery. Somatostatin analogues were not administered either before or after surgery. GH and IGF-1 levels of both patients returned to normal 3 months after surgery and were within normal limits at the 6th month control visit.

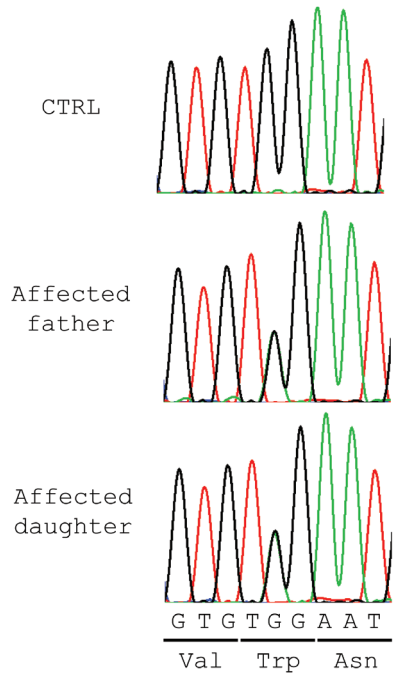

Figure 1. Sequence chromatograms showing the heterozygous *AIP* mutation detected in both patients. A wild-type sequence from a control subject is shown in the top panel. The G>A mutation in the affected patients affects the Tryptophan residue at position 279 by introducing a Stop codon.

DISCUSSION

In families with FIPA, one of the most important genetic causes is related to mutations and deletions in the *AIP* gene. These mutations are often characterized by onset at a young age and GH-and PRL-secreting pituitary adenomas leading to acromegaly or gigantism.[7] Until recently, 91 different variants were reported as disease-causing in the *AIP* gene (HGMD Professional 2016.1 database accessed on 06/2016).

The human *AIP* gene encodes a 37kDa protein of 330 amino acids and consists of an N-terminal immunophilin-like domain and a C-terminal tetratricopeptide repeat (TPR) domain similar to other proteins.[8] Approximately 75% of all *AIP* mutations lead to an impaired C-terminal TPR domain and/or final α-7helix.[9] We herein report the detection of a novel mutation, p.W279*, in the *AIP* gene. This mutation is located within the third motif of the AIP TPR domain and very likely leads to a dysfunctional truncated protein with impaired ability to interact with chaperones and client proteins.[10]

Pituitary adenomas associated with *AIP* mutations have several characteristic features: 1) the most frequent clinical presentation is FIPA (68%); 2) most of

them are somatotropinomas or prolactinomas; early onset ones can lead to gigantism; 3) 78% of patients are less than 30 years old; 4) most of the adenomas (88%) are macroadenomas that have already extended beyond the sella at the time of diagnosis; 5) GH excess is resistant to somatostatin analogues and multimodal management is frequently warranted to control the disease.[11] The features of our cases represent a typical example of those reported in the literature. Although GH/IGF-1 levels were normalized soon after transsphenoidal surgery, sufficient time may not have elapsed to judge cure.

FIPA may be either homogeneous (affected family members having identical pituitary tumor types) or heterogeneous (affected family members having different pituitary tumor types).[4] Our case was an example of homogeneous FIPA due to GH-secreting pituitary adenomas in both members.

The penetrance of FIPA varies between 10 to 50%.[12] Especially children and young patients with somatotropinomas and prolactinomas should be surveyed for inactivating mutations or deletions in *AIP*. Determining the causative mutations may be of benefit in early diagnosis, treatment success, and genetic counseling.

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DECLARATION OF INTEREST

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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