Familial Isolated Pituitary Adenomas: From Genetics to Therapy

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Abstract

According to autopsy and radiological data, pituitary adenomas (PAs) develop in approximately 15% to 20% of the population. The great majority of PAs arise sporadically and affect adults. Rarely they are diagnosed in children and adolescents. Approximately 5% of cases are thought to be familial. Inherited conditions associated with pituitary tumors include multiple endocrine neoplasia type 1 (MEN-1) and type 4 (MEN-4), (CNC) Carney Complex, and familial isolated PA (FIPA) syndrome. FIPA is an autosomal dominant condition, defined by the presence of two or more patients affected by PAs in the same kindred, and no other associated condition. Germline mutations of the aryl hydrocarbon receptor interacting protein gene located on chromosome 11q13 have been reported in 15%–40% of FIPA cases. In the remaining cases, genetic defect are unidentified. This article focuses on FIPA clinical, pathological, genetic features, and therapeutic management. Clin Trans Sci 2011; Volume 4: 55–62

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Introduction

Pituitary adenomas (PAs) are quite common brain neoplasms composed of adenohypophyseal cells.¹ A 2004 meta-analysis¹ reported a mean prevalence of 14.4% and 22.5% in autopsy and radiological series, respectively. More recent population surveys studies detected 72 to 94 clinically relevant cases per 100,000 inhabitants.^{2,3} PAs are more typical of adults. Only 3.5% to 8.5% of all pituitary tumors are diagnosed before age 20,⁴ and only approximately 3% of all intracranial tumors in childhood are PAs.⁴ Although PAs are typically benign, significant morbidity may result due to their hormonal activity, location, mass effect, and interference with normal pituitary hormone function.⁵

Prolactinomas represent the most common type of PAs in adults (39%–50%), followed by nonfunctioning PAs (23%–27%), growth hormone (GH)-secreting adenomas (16%–21%), corticotroph hormone (ACTH)-secreting adenomas (4.7%–16%), thyrotropin-stimulating hormone (TSH)-secreting adenomas (0.4%), luteinizing hormone (LH)- or follicle-stimulating hormone (FSH)-secreting adenomas (0.9%).⁵ ACTH-secreting adenomas are the most common type in early childhood and in prepubescent children, whereas prolactinomas prevail in older children (50%) and adolescents.⁴

PAs are widely considered to be of monoclonal origin⁶ and their development has been associated with several inherited and acquired genetic mutations (*Table 1*), and with altered availability of regulatory factors (including hypothalamic and peripheral hormones, autocrine and paracrine growth factors).⁷

The great majority of PAs are sporadic.⁴ Approximately 5% of cases occur in familial settings and could present in the context of endocrine-related tumor syndromes, as multiple endocrine neoplasia type 1 (MEN-1), type 4 (MEN-4), CNC, or isolated, as in familial isolated PA (FIPA) syndrome.⁸ Different gene mutations have been identified in patients affected by familial PAs and their influence on pituitary tumorigenesis has been investigated in animal models (*Table 2*).

Our review summarizes currently available epidemiologic, genetic, clinical, and therapeutic data on FIPA.

Case Report

A 55-year-old lady was referred for evaluation of recurrent acromegaly. At age 37, she was diagnosed with a 1 cm GH-secreting

adenoma and treated surgically. After 3 years, she was found to have recurrent acromegaly. Her serum growth hormone (GH) and insulin-like growth factor 1 (IGF-1) levels did not respond to cabergoline, and showed only a partial response to a somatostatin analogue (30% decrease in serum IGF-1 without normalization). She did not tolerate the GH receptor antagonist pegvisomant because of lipohypertrophy. At the time of most recent evaluation, her random serum GH level was elevated at 42.7 ng/mL and IGF-1 level was 715 ng/mL (NV 53–287). A pituitary magnetic resonance imaging (MRI) showed a 0.9 cm adenoma. Family history revealed a presence of acromegaly in a paternal cousin, in the daughter of another paternal cousin, in a paternal great-uncle (deceased, but confirmed by obvious acromegaly features on pictures), and in the paternal great-grandfather's brother (deceased, but with historical evidence of acromegaly). A genetic analysis of the aryl hydrocarbon receptor interacting protein gene (AIP) was performed on peripheral blood DNA, showing heterozygous single nucleotide change causing an amino acid substitution in exon 1, previously reported as disease-causing mutation (R16H) (47G>A).⁹ This change was not present in her mother. Genetic analysis was performed in the two living relatives with acromegaly showing normal AIP sequence, suggesting that the R16H amino acid substitution was not related to development of PA, and that this change is more likely to be a rare polymorphism rather than a disease-causing mutation (*Figure 1*).

Definition of FIPA Syndrome

FIPA syndrome is defined as the occurrence of PAs of any type among two or more related family members in the absence of MEN-1 or CNC.¹⁰ It includes the syndrome of isolated familial somatotrophinomas (IFS), defined as two or more cases of acromegaly or gigantism in a family in absence of MEN-1 or CNC.^{11,12}

The first report of familial acromegaly dates back to the biblical giant Goliath, whose father and three brothers were also giants.¹³ The term “acromegaly” was coined in 1886 by Pierre Marie¹⁴ and, in the following years, it became clear that gigantism and acromegaly were both caused by PAs occurring at different stages of life.¹⁴ The Hugo brothers (two famous giants born at the end of the 19th century who toured Europe's circuses) represent the first case of familial acromegaly reported in medical literature.¹⁴ Their

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Gene	Defect
Oncogenes	
<i>GNAS1</i> (20q13.3) ⁵⁰	Somatic mutations in sporadic GH-SA
<i>Cyclin D1</i> (11q13) ⁵¹	Overexpression in NFAPA and GH-SA
<i>PTTG</i> (5q35.1) ⁵²	Increased expression in invasive pituitary tumors
<i>K-RAS</i> (12p12.1), <i>N-RAS</i> (1p13.2), <i>H-RAS</i> (11p15.5) ⁵³	Activating mutations in highly invasive pituitary tumors
<i>PKC</i> (16p11.2) ⁵⁴	Point mutations in invasive pituitary adenomas
<i>Ptd-FGFR4</i> (5q35.1) ⁵⁵	Alternative transcription initiation associated with more invasive tumors in patients with GH-SA
Tumor suppressor genes	
<i>AIP</i> (11q13.3) ^{20,39,40}	Germline mutations in some FIPA families. Rare mutations in sporadic adenomas
<i>BMP-4</i> (14q22-q23) ⁵⁶	Promoting action on PRL-SA. Inhibitory role in ACTH-SA
<i>p27^{Kip-1}</i> (<i>CDKN1B</i>) (12p13.1-p12) ^{57,58}	Germline heterozygous nonsense mutation in MEN-4. Reduced protein expression in sporadic pituitary tumors. No somatic mutations
<i>P16^{INK4A}</i> (<i>CDKN2A</i>) (9p21) ^{59,60}	Down-regulation and hypermethylation of the promoter region in pituitary adenomas
<i>P18^{INK}</i> (<i>CDKN2C</i>) (1p32) ^{57,61}	Germline mutations in MEN-4. LOH and hypermethylation of promoter region in pituitary adenoma
<i>GADD45gamma</i> (9q22.1-q22.2) ⁶²	LOH in pituitary adenomas
<i>MEG3a</i> (14q32) ⁶³	Hypermethylation of promoter region results in loss of expression found in NFAPA and FSH/LH-SA
<i>MEN-1</i> (11q13) ^{64,65}	LOH, inactivating germline mutations, somatic mutations in MEN-1. Rare LOH in sporadic pituitary adenomas
<i>p53</i> (17p13.1) ⁶⁶	Overexpression in pituitary adenomas and carcinomas. Mutations in pituitary carcinomas
<i>PKA</i> (<i>PRKAR1A</i>) (17q23-q24) ⁶⁷	Truncating mutations in CNC
<i>Rb</i> (13q14.2) ⁶⁸	LOH in pituitary adenomas and carcinomas
<i>Wnt pathway inhibitors</i> (<i>WIF</i> , <i>SFRP2</i> , <i>frizzled B</i> = <i>SFRP3</i> (<i>FZDB</i>), <i>SFRP4</i>) ⁶⁹	Reduced expression of all factors and hypermethylation of WIF promoter region in pituitary adenomas (especially NFAPA)
<i>Zac1</i> (6q24-q25) ⁷⁰	High expression and hypermethylation of promoter region in pituitary adenomas (especially NFAPA)
<i>DAPK1</i> (9q34.1) ⁷¹	Loss of DAP kinase expression in invasive adenomas
ACTH-SA: corticotroph hormone secreting adenomas; CNC: Carney Complex; FSH/LH-SA: gonadotropin secreting adenomas; GH-SA: growth hormone secreting adenomas; LOH: loss of heterozygosity; NFAPAs: nonfunctioning pituitary adenomas; PRL-SA: prolactin secreting adenomas.	

Table 1. Genes involved in pituitary adenomas formation.

heights were 2.30 and 2.25 m. The autopsy of the taller brother revealed a large PA, in addition to hypogonadism, frontal bossing, prognathism, adrenal atrophy, and enlarged internal organs. Their parents, three brothers, and two sisters were of normal height.¹⁴

In the following years, several cases of isolated PAs, especially somatotropinomas, occurring in familial settings were reported.^{15,16} Gradually, FIPA became appreciated as a new clinical disease. Currently over 200 FIPA families have been described.¹⁷

Clinical Features

FIPA is an autosomal dominant disease with a low penetrance¹⁸ and a slightly higher prevalence in women (62%).^{17,19} Prolactinomas (41%) and somatotrophinomas (30%) are the most common tumor types, followed by nonsecreting tumors (13%), somatomammotropinomas (7%), gonadotropinomas (4%), ACTH-secreting adenoma (4%), and thyrotropinoma (1%).^{17,19} The majority of affected members are close relatives (first-degree relationship in 75% of cases).^{17,19} The tumor phenotype within individual FIPA kindreds can be homogeneous or heterogeneous.^{17,19} In heterogeneous FIPA kindreds, all tumors phenotypes can occur, but almost invariably at least one prolactinoma or GH-secreting adenoma is seen per family. Usually FIPA patients are younger at diagnosis (on average 4 years) than patients with sporadic

adenomas.¹⁹ When multigenerational families are assessed, patients from the younger generations have a significantly earlier mean age at diagnosis as compared with their forebears (29.0 vs. 50.5 years). This effect could be related to genetic anticipation or to an earlier recognition of the disease due to parents' increased awareness.¹⁹ Overall, tumor sizes and tendency to invade surrounding tissues do not differ between FIPA and sporadic adenoma patients.¹⁹ Patients from heterogeneous FIPA kindreds have a higher incidence of macroadenomas, especially nonsecreting type, than patients from homogeneous kindreds.¹⁹⁻²¹

IFS syndrome is characterized by a slightly male predominance (male-female ratio 1.5) and a much younger age at diagnosis (25 years) when compared to sporadic acromegaly.¹⁹ Tumors usually present as macroadenomas and cause gigantism in the 25% of cases. In more than half of IFS families, the disease is not transmitted to a succeeding generation by an affected individual, probably because the early onset of the tumor and its moderately aggressive behavior lead to loss of gonadotrope function and reproductive potential early in life.²²

FIPA Genetics

The first FIPA-causing genetic mutation has been identified in 2006 in the AIP gene in AIP (OMIM ID 600253, located on

Syndrome	Gene (locus)	Major features	PA prevalence (%)	Type of PA, % of cases	Median age at onset of tumor	Sex prevalence	Other typical PA features	Animal model
MEN-1	MEN-1 (11q13) ⁶⁴	Parathyroid tumors (100%); enteropancreatic endocrine tumors (30%–75%); pituitary adenoma (40%); PRL-SA (60%), NFAPA (15%), GH-SA (10%), ACTH-SA (5%), TSH-SA (rare) More rarely: foregut carcinoid tumors, adrenocortical tumors (usually nonfunctional), pheocromocytomas, facial angiomas, collagenomas, and lipomas ^{72,73}	40 ^{72,73}	PRL-SA (60%); GH-SA (10%); NFAPA (15%); ACTH-SA (5%); TSH-SA (rare) ^{72,74}	34 to 50 ⁷³	F > M ⁷²	85% of PA in MEN-1 are macroadenomas. Often, PA are pluri-hormonal secreting and multiple. PA associated to MEN-1 are also more aggressive than sporadic PA and resistant to dopamine agonists. Pituitary carcinomas are uncommon ^{72–74}	Men-1 (–/–) mice die at embryonic age 75 Men (+/–) mice develop PA, parathyroid, pancreatic, adrenal, and thyroid tumors; Leydig cell tumors, ovary sex cord tumors ^{75,76}
MEN-4*	CDKN1B (12p13) ^{77,78}	Primary hyperparathyroidism; pituitary adenomas; more rarely, renal angiomylipoma, neuroendocrine cervical carcinoma ^{77,78}		GH-SA (50%) ACTH-SA (50%)	-	-	-	MENX rats develop pheocromocytomas, paragangliomas, parathyroid adenomas, thyroid C-cell hyperplasia, endocrine pancreas hyperplasia, and multipituitary hyperplasia, and multifocal PA ⁷⁸ . CDKN1B knockout mice develop intermediate-lobe pituitary tumors ⁷⁹ p27 ^{CK1} mice develop pituitary tumors, adrenal, retinal, spleen, lung, and ovarian hyperplasia and/or tumors ⁷⁹
CNC	PKRKAR1A (17q23–24) ⁸⁰ Locus at 2p16 ⁸⁰	Cushing syndrome secondary to primary pigmented nodular adrenocortical disease, skin lesions (blue nevi, lentigines), myxomas (cardiac and extracardiac), thyroid nodules, psammomatous melanotic Schwann-cell tumors, pituitary adenomas or hyperplasia, testicular tumors ⁸⁰	10 ^{80,81}	GH-SA, PRL-SA (most common types) ^{80,81}	Teen years, early adulthood ^{80,81}	M > F ^{80,81}	Approximately 75% of patients have abnormal GH-secretory and PRL-secretory responses to stimuli; however, clinically evident acromegaly and/or considerably elevated PRL levels or tumor evident on imaging are more rare. Tumors are often multicentric and contain foci of hyperplasia. Slow progression. Good general response to somatostatin analogues ^{80,81}	PKRKAR1A heterozygous mutations do not develop PA82PKRKAR1A (–/–) develop GH-axis abnormalities and PA ⁸²
FIPA	AIP (11q13.3) ^{9,20,39}	Pituitary adenoma ^{9,20,39}	100 (by definition)	GH-SA (41%), PRL-SA (30%), mixed GH and PRL-SA (7%)	20 ^{20,39}	F > M ^{9,20,39}	Great majority are macroadenomas; PA tend to be more aggressive and larger in patients with AIP mutations. Often patients do not respond well to somatostatin analogues therapy ^{9,20,39}	Homozygous AIP mutations are embryonic lethal ⁴³ AIP ^{+/–} mice are extremely susceptible to develop PA, especially GH-SA and present a more aggressive profile ⁴⁵

* To date, only two cases have been reported.

ACTH-SA: corticotroph hormone secreting adenomas; GH-SA: growth hormone secreting adenomas; NFAPA: nonfunctioning pituitary adenomas; PA: pituitary adenomas; PRL-SA: prolactin secreting adenomas.

Table 2. Genes associated with familial pituitary syndromes.

Figure 1. Family pedigree. ● = affected female, ■ = affected male. The index case (IV-3) is indicated by the arrow. DNA from III-2, IV-3, IV-5, and V-3 was available for genetic testing.

chromosome 11q13) by linkage and expression analysis obtained in a three clusters of FIPA kindred from Northern Finland using whole-genome single-nucleotide polymorphism genotyping.⁹

Approximately 20% of FIPA families and 40% of IFS families harbor a mutation in AIP.^{19,23,24} AIP consists of six exons encoding for a 330 amino acids protein, which is part of the aryl hydrocarbon

receptor (AHR) pathway²⁵ (Figure 2). AHR is a ligand-inducible transcription factor that mediates the cellular response to xenobiotic compounds.²⁶ In the absence of ligand, AHR is inactive and localized in the cytoplasm where it forms a complex with X-associated protein-2 (XAP2) or aryl hydrocarbon receptor-associated protein-9 (ARA9), AIP, and HSP90 Co-chaperone p23 (a 90-kDa heat-shock protein).²⁷ Upon ligand binding, AHR is activated by a conformation change that exposes a nuclear localization signal.²⁸ HSP90 is released from the complex and the receptor translocates to the nucleus, where it binds to aryl hydrocarbon receptor nuclear translocator. The heterodimer binds to the xenobiotic response element and regulates gene expression. The activation of AHR by xenobiotic compounds leads to several toxic effects, including carcinogenesis, tumorigenesis, and immunosuppression.^{28,29} AIP was also found to interact with hepatitis B virus X-protein, which plays an important role in viral replication.³⁰

AIP presents two domains: (1) the N-terminal NFKBP domain, which contributes to the stability of AHR-HSP90-AIP complex; (2) the C-terminal domain, which contains three tetratricopeptide repeats (TPR) domains, and is responsible for protein-protein interactions. It preferentially binds to HSP90, but can also interact with other regulatory proteins, including phosphodiesterases,²⁶ surviving,³¹ and RET (ret protein oncogene).³² The five last amino acids of the α -helical C-terminus are essential for AIP binding to AHR.^{25,29}

Inactivating germline mutations and the loss of the normal allele in tumors support its role as a tumor suppressor gene.^{24,33,34}

Indeed, loss of heterozygosity is found in tumors of FIPA patients.^{12,35,36} According to the Knudson two-hit hypothesis,³⁷ the first hit is due to an inherited germline mutation of one allele and the second hit is a somatic deletion of the other allele.

Almost 50 different germline AIP mutations have been demonstrated in the setting of FIPA, with a high incidence in the TPR domain (i.e., R304X and R304O), supporting the fundamental role of this region for AIP action.^{9,38,39} Other nonsense and missense mutations all along the coding sequence have been described (Table 3). Less frequently, germline mutations have been found in sporadic PAs.^{9,38–41} Most of the patients with AIP mutations in the sporadic cohort presented with acromegaly.^{9,38–41}

AIP mutation positive patients are younger at diagnosis than AIP-negative patients. First symptoms occur in children/adolescents in 50% of cases. The youngest patient with a known AIP mutation was diagnosed with a PA at the age of 6 years, the eldest at the age of 66 years.^{18,20,24,39} Tumors usually

Figure 2. Aryl hydrocarbon receptor (AHR) is a ligand inducible transcription factor that controls a variety of physiological events (such as toxin metabolism, response to hypoxia, and hormone receptor function) acting on cellular signaling and interacting with several regulatory and signaling factors, co-activators and receptors.²⁸ Normally, AHR is inactive and localized in the cytoplasm where it forms a complex with HSP90, and XAP2 or ARA9, AIP (gene structure in the callout), and HSP90 Co-chaperone p23.²⁷ Upon ligand binding, AHR is activated by a conformation change that exposes a nuclear localization signal (NLS).²⁸ HSP90 is released from the complex and the receptor translocates to the nucleus, where it binds to aryl hydrocarbon receptor nuclear translocator (ARNT). The heterodimer binds to the xenobiotic response element (XRE) and regulates gene expression. The final result can be a transcriptional activation or inhibition of genes involved in different metabolic processes.²⁸

Mutation type	AIP mutation and reference
Base pair substitution resulting in missense mutation	c.145G > A p.V29M (Val29Met) ⁸³
	c.308A > G p.K103R ⁸⁴
	c.713G > A p.C238Y (Cis238Tyr) ³⁹
	c.721A > G p.K241E ²⁰
	c.769A > G p.I257V ⁸⁵
	c.811C > T p.R271W (Arg271Trp) ^{20,86}
	c.896C > T p.A299V (Ala299Val) ^{18,40}
Base pair substitution resulting in nonsense mutation	c.911G > A p.R304Q (Arg304Gln) ^{18,32,38-40}
	c.40C > T p.Q14X (Gln14X) ^{9,40,87}
	c.64C > T p.R22X (Arg22X) ⁴¹
	c.70G > T p.E24X (Glu24X) ³⁹
	c.241C > T p.R81X (Arg18X) ^{39,88}
	c.424C > T p.Q142X (Gln142X) ²⁰
	c.490C > T p.Q164X ¹⁸
Base pair substitution resulting in nonsense mutation	c.601A > T p.K201X (Lys201X) ³⁸
	c.649C > T p.Q217X (Gln217X) ²⁰
	c.715C > T p.Q239X (Gln239X) ²⁰
	c.721A > T p.K241X ⁸⁴
Frameshift mutation	c.804A > C p.Y268X (Tyr268X) ⁸⁸
	c.910C > T p.R304X (Arg304X) ^{9,18,20,38,39}
	c.74_81delins7 p.L25PfsX130 ¹⁸
	c.286-287delGT p.V96PfsX32 ⁸³
Frameshift mutation	Frameshift mutation in exon 2 ⁸⁹
	Not available p.P114fs ⁸⁴
	c.404delA p.H135LfsX20 ³⁸

Mutation type	AIP mutation and reference
	c.500delC p.P167HfsX3 ⁴⁶
	c.517-521delGAAGA p.E174fsX47 ^{20,90}
	c.542delT p.L181fsX13 ⁴⁰
	c.622dupC p.C208LfsX15 ¹⁸
	c.824-825insA p.H275QfsX12 ⁴⁰
	c.854-857delAGGC p.Q285fsX16 ²⁰
	c.919insC p.Q307RfsX103 ⁸⁴
In-frame deletions	c.66-71delAGGAGA p.G23_E24del ⁴⁰
	c.138-161del24 p.G47_R54del ²⁰
	c.742_744delTAC p.Y248del ⁹¹
	c.878-879AG > GT p.E293G ⁴⁰ c.880-891 del CTGGACCCAGCC p.L294_A297del ⁴⁰
In-frame insertion	c.805_825dup p.F269_H275dup ³⁹
Large gene deletions	c.100-1025_279p357 p.A34_K93 Ex2del ^{18,91}
	c.1104-109_279p578 Ex1_ Ex2del ⁹¹
	Whole gene deletion ¹⁸
	c.1-?_993p?del- Whole gene deletion ¹⁸
Promoter	c.-270-269CG > AA and c.-220G > A ^{18,39}
Splice-site base pair substitution	IVS2-1G > C (c.100 1G > C) ⁴⁰
	c.249G > T p.G83AfsX15 ¹⁸
	IVS3p15C > T (c.468p15C > T) ⁸⁵
	IVS3-1G > A (c.469-1G > A) ⁹
	IVS3-2A > G (c.469-2A > G) ³⁸
	c.807C > T p.F269 = ³⁹

Table 3. AIP mutations.

present as macroadenomas, with a prevalence of GH and GH-PRL secreting adenomas,^{19,38,42} whereas nonsecreting, gonadotrope and corticotrope adenomas are extremely rare.³⁸ In unselected FIPA cohorts, women are in the majority (62%), whereas cases in FIPA kindreds with AIP mutation and among sporadic AIP-mutated adenomas are mostly men (63.6%).⁴² AIP-mutated somatotropinomas are associated with

higher levels of GH secretion in respect with nonmutated somatotropinomas.⁴²

All germline mutations reported to date are heterozygous, suggesting that homozygosity is not compatible with life in humans, as it is seen in recently developed mouse model of FIPA.⁴³ Indeed, mice with homozygous deletion of AIP died of congenital cardiovascular abnormalities during embryonic development,

due to a double-outlet right ventricle, ventricular septal defects and pericardial edema. Hypomorph mice, expressing levels of AIP that are approximately 10% of normal, have patent ductus venosus.⁴⁴ These observations suggest that AIP plays a role in AHR-mediated cardiovascular development.⁴⁴

A very recent study⁴⁵ showed that C57BL/6Rcc heterozygous AIP knockout mice (AIP^{+/-}) do not present any congenital cardiovascular abnormalities, but they are very prone to develop pituitary tumors, whose features modeled human familial PAs. AIP^{+/-} mice are prone to develop multiple primary pituitary tumors already at the age of 6 months, whereas multifocal pituitary tumors were detected among the wild-type (WT) mice only at much older age groups (15–21 months). Indeed, at age 15 months, 94% of the AIP^{+/-} mice developed PAs versus 33% of WT mice. Penetrance reached 100% by age 18 months. The great majority of tumors in AIP^{+/-} animals (88%) are somatotropinomas. Prolactinomas are also relatively frequent, whereas only two mixed GH/PRL-secreting tumors and one ACTH-secreting tumor were detected. In WT mice, 92.6% of tumors were prolactinomas, and 7.4% mixed GH/PRL-secreting adenoma, and no pure GH-secreting adenoma. Moreover, AIP-mutated tumors had a significantly higher proliferation rate compared to WT adenomas. In AIP^{+/-} mice, sex did not influence PAs' formation. Overall, AIP^{+/-} mouse model greatly resembles the human phenotype (complete penetrance was the only major feature distinguishing mice from human adenomas),⁴⁵ suggesting the presence of similar molecular mechanisms underlying pituitary tumorigenesis in humans and mice.^{9,39,40}

In FIPA families with normal AIP, a linkage with loci 2p16,³⁵ 3q28,⁴⁶ 4q32.3–4q33,⁹ 8q12.1,^{9,46} 19q13.4,⁴⁶ and 21q22.1⁴⁶ has been shown, suggesting that mutations in several other genes may be involved in the development of FIPA syndrome. On the other hand, no germline mutations in any of the several oncogenes and oncosuppressors that have been shown to be mutated in sporadic PAs have been observed in FIPA patients (Table 1).

Management

Current management of familial pituitary tumors does not differ substantially from the management of sporadic cases.^{23,42} However, most studies, have pointed out that FIPA PAs, especially AIP-mutated are more resistant to pharmaceutical and surgical treatments compared to sporadic PAs.^{19,24,39,40} Typical features of AIP-mutated somatotropinomas, such as large size, high GH secretion, and rapid growth, impacted treatment efficacy, with resulting overall low rates of cure.^{42,47} Therapy with somatostatin analogues causes significantly lesser reduction in GH and IGF-1 and less pronounced tumor shrinkage.⁴² Low rate of neurosurgical cure has also been reported, hence requiring significantly higher rate of reoperation.⁴² Finally, an increased risk of hypopituitarism is seen in patients with AIP-mutated tumors.⁴² No statistical differences in terms of clinical or therapeutic characteristics were found among patients with different types of AIP mutations.⁴²

Discussion and Conclusions

FIPA is an increasingly recognized syndrome. Recent studies confirmed the key role of AIP mutations in a subset of families, particularly in families with IFS syndrome. Other gene(s) causing FIPA syndrome are likely to be discovered in the near future. Evidence to date also suggests that young patients with aggressive pituitary tumors may be more likely to carry AIP mutations, justifying genetic testing, especially in presence of a family history

of PAs.^{23,38,42} A low penetrance mitigates the consequences of such mutation. Because of FIPA PAs, typical aggressiveness and early occurrence, and the increased risk of developing PAs, there is potential value in performing genetic testing and monitoring carriers of AIP mutations with periodic MRI and hormonal testing. However, the cost-effectiveness of such strategy has not been established, and consensus surveillance strategies have yet to be developed. Finally, genetic studies can also help the differential diagnosis between FIPA and other familial syndromes associated to PAs (i.e., MEN-1) in cases where PA is the presenting feature.

The low prevalence of AIP mutations among FIPA families and low penetrance must be considered when analyzing a pedigree.²³ Furthermore, rare AIP polymorphisms (e.g., R16H change of our case report) and real mutations that affect pituitary tumorigenesis have to be distinguished.

Long-term follow-up of already diagnosed FIPA patients and new molecular and genetic studies on humans and mice could in the future clarify the impact that individual mutations in AIP (or other genes that will likely be discovered) have on PAs development, and their predictive role on tumor behavior and response to the different treatments.^{18,39,48,49}

Disclosure

The authors have nothing to disclose.

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