Pituitary adenomas represent a group of functionally diverse neoplasms with relatively high prevalence in the general population. Most occur sporadically, but inherited genetic predisposing factors are increasingly recognized. Familial isolated pituitary adenoma is a recently defined clinical entity, and is characterized by hereditary presentation of pituitary adenomas in the absence of clinical and genetic features of syndromic disease such as multiple endocrine neoplasia type 1 and Carney complex. Familial isolated pituitary adenoma is inherited in an autosomal dominant manner and accounted for approximately 2–3% of pituitary tumors in some series. Germline mutations in the aryl-hydrocarbon interacting protein gene are identified in around 25% of familial isolated pituitary adenoma kindreds. Pituitary adenomas with mutations of the aryl-hydrocarbon interacting protein gene are predominantly somatotropinomas and prolactinomas, but non-functioning adenomas, Cushing disease, and thyrotrropinoma may also occur. These tumors may present as macroadenomas in young patients and are often relatively difficult to control. Furthermore, recent evidence indicates that aryl-hydrocarbon interacting protein gene mutations occur in >10% of patients with sporadic macroadenomas that occur before 30 years of age, and in >20% of children with macroadenomas. Genetic screening for aryl-hydrocarbon interacting protein gene mutations is warranted in selected high-risk patients who may benefit from early recognition and follow-up.

KEYWORDS: Familial Isolated Pituitary Adenomas; FIPA; AIP Gene; AIP Mutations.

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INTRODUCTION

Pituitary adenomas are one of the most common intracranial neoplasms. Questions regarding their prevalence in the general population were recently addressed by a large cross-sectional study in the province of Liège, Belgium, which revealed 94 cases of pituitary adenomas per 100,000 inhabitants (1). Similar findings were later confirmed in Banbury, UK (2). Despite being generally benign, pituitary adenomas still exert significant influence as they combine symptoms of hormonal dysfunction with signs of local compression, and may require complex and costly management and long-term follow-up. Pituitary adenoma formation is generally considered to be the result of the clonal expansion of a single mutated cell (3) and molecular studies have identified a number of genetic and epigenetic abnormalities that may have a possible causative or facilitatory role in pituitary tumorigenesis. These include somatic mutations in the gsp oncogene, overexpression of the pituitary tumor transforming gene (PTTG), disruptions in cell cycle regulation and intracellular signaling pathways and, rarely, mutations of classic oncogenes (4,5). The vast majority of pituitary adenomas, however, arise sporadically, and inherited germline mutations in different genes are few in number, accounting for approximately 5% of all pituitary tumors (6). Traditionally, familial pituitary adenomas have been associated with some multiple neoplasia syndromes, including multiple endocrine neoplasia type 1 (MEN 1), Carney complex, and the newly defined multiple endocrine neoplasia type 4. By the end of the 20th century, however, only occasional cases of non-syndromic familial pituitary tumors were reported, mostly acromegaly (7). The first single-center study to specifically scout for cases of familial pituitary adenomas unrelated to MEN 1 and Carney complex was performed in Liège, Belgium in the 1990s, and led to the identification of an initial cohort of 27 patients (8). Reports from the same center confirmed the condition as a new clinical entity, and the term familial isolated pituitary adenomas (FIPA) was adopted (9–11). Its definition expanded the search internationally, and by 2011 more than 200 affected families had been reported (12,13). FIPA is currently considered to account for around 2–3% of pituitary adenomas (14).

CLINICAL FEATURES OF PATIENTS WITH FIPA

The syndrome of FIPA is defined as familial presentation of any type of pituitary adenoma in the absence of clinical and genetic evidence for MEN 1 and Carney complex.
(9,11,14,15). Following the initial description of the condition, the clinical characteristics of a large international cohort of 64 families comprising more than 140 patients from 22 tertiary referral centers were reported in 2006 (14). Genealogical information suggested that FIPA is inherited in an autosomal dominant pattern with variable penetrance. Based on the tumor phenotype in the individual families, FIPA can be divided into two almost equal subgroups: homogeneous, when all affected family members experience the same adenoma type, and heterogeneous, with different pituitary tumors within the family. Prolactinomas and somatotropinomas comprise more than 70% of all tumors, and although in heterogeneous FIPA all types of tumors can be seen, there is at least one prolactin- or growth hormone-secreting adenoma in almost all affected families. Females tend to be more frequently affected (62%), which is not unexpected given the fact that prolactinomas are the most common phenotype overall. Prolactin-secreting adenomas comprise 40% of all FIPA tumors, and their characteristics principally match their sporadic counterparts in terms of sexual predisposition, age at presentation, and proportion of microadenomas. In heterogeneous FIPA families, however, these tumors exhibit more aggressive behavior, with significantly higher rates of suprasellar expansion and cavernous sinus invasion compared with sporadic prolactinomas. Growth hormone-secreting adenomas account for 30% of FIPA tumors, and somatotropinomas are responsible for another 7%. They are equally distributed between homogeneous and heterogeneous families but, unlike FIPA prolactinomas, somatotropinomas are more aggressive when occurring in a homogeneous setting. In homogeneous FIPA, acromegaly is usually diagnosed 10 years earlier, with tumors more frequently displaying extrasellar growth, compared with heterogeneous relatives and sporadic populations (14). Acromegaly in patients with FIPA also appears to respond poorly to somatostatin analog therapy (16). Non-secreting adenomas, predominantly associated with heterogeneous families, arise in 13% of patients with FIPA and are also characterized by more aggressive evolution, being diagnosed earlier and exhibiting more invasive properties than sporadic adenomas. Gonadotropinomas, corticotropinomas, and thyrotropinomas are rare, and account for 4%, 4%, and 1% of FIPA tumors, respectively. They are usually associated with other adenoma types in heterogeneous families, although individual families with homogeneous presentation have been reported (14). The descendants in FIPA families with multiple affected generations are diagnosed considerably earlier than their parents/grandparents.

**MOLECULAR GENETICS OF FIPA**

The elucidation of the responsible genetic causes of FIPA started with the identification of loss of heterozygosity in locus 11q13 in relatives with familial acromegaly who lacked mutations in the MEN1 gene (17,18). Separate research for potential genes in a Finnish cohort of patients with familial pituitary tumors revealed inactivating mutations in the gene for aryl-hydrocarbon receptor interacting protein (AIP) (19). The causative role of AIP in FIPA was confirmed with the discovery of several new germline mutations in a large series of 73 families (20). Loss of heterozygosity in tumor tissues suggests a tumor suppressor function for AIP, but the exact molecular mechanisms leading to pituitary tumorigenesis are not known. Homozygous AIP+/– knockout mice die in the early embryonic period as a result of severe cardiovascular abnormalities, suggesting that AIP may play a role in cardiovascular development (21). Heterozygous AIP+/– animals, however, develop a phenotype that is very similar to human pituitary disease with the majority of the mice presenting with aggressive somatotropinomas (22). The AIP gene consists of six exons and codes for a 330-amino-acid protein, the sequence of which is highly conserved between different species. It shares a structural homology with immunophilin proteins because of the presence of a peptidyl-prolyl cis-trans isomerase-like domain, but does not function as such (23,24). Instead, AIP takes part in numerous protein–protein interactions, mediated through its C-terminal, which houses three tetratricopeptide repeats and a final z-helix. Among the first identified partners of AIP is the aryl hydrocarbon receptor (AhR), a ligand-inducible transcription factor that modulates cellular responses to various xenobiotic toxins, such as dioxins, as well as some endogenous compounds such as cAMP (25). In the absence of ligands, the AhR binds to two molecules of the 90-kDa heat-shock protein, acting as chaperone, and to AIP and p23 proteins, acting as co-chaperones, to form a multiprotein complex in the cytoplasm (26). The activation of this complex by its xenobiotic ligand results in nuclear translocation, where AhR binds to the aryl hydrocarbon receptor nuclear translocator and promotes the transcription of specific genes coding various drug metabolizing enzymes as well as other proteins (24). The effect of AIP on the functional status of AhR is still a matter of debate because conflicting results have been reported, but it seems that it maintains the stability of the complex by protecting AhR from ubiquitin-dependent degradation (27). Reduced AIP levels in AIP-mutated pituitary adenomas are associated with a lack of nuclear AhR immunostaining, suggesting that down-regulation of AhR may be involved in pituitary tumorigenesis (28). Consistent with this finding, over-expression of wild-type AIP in pituitary and hepatic cell cultures slows down cell proliferation (16). AIP is also thought to interact with two subtypes of phosphodiesterasers: PDE4A5 and PDE2A (29,30). These enzymes participate in the regulation of numerous signaling cascades that use cAMP as a second messenger, including the growth hormone-releasing hormone receptor pathway in pituitary cells. Disruptions in signal transduction, which lead to abnormally high cAMP concentrations, are associated with pituitary hyperplasia and adenoma formation in some conditions, such as Carney complex and McCune–Albright syndrome (31). AIP binding to PDE4A5 reduces its catalytic activity, and it is not clear if this interaction plays a role in pituitary tumorigenesis, as loss of AIP would presumably result in low cAMP levels. The interaction with PDE2A does not alter the enzyme activity, and the local reduction of cAMP may impede the nuclear translocation of the AhR complex (30). Recently, AIP was shown to interact with the tyrosine kinase receptor, encoded by the RET proto-oncogene, and the inhibitor of apoptosis, survivin, and therefore to have a potential role in cell cycle regulation. Binding to survivin maintains its stability and promotes cell survival by elevating the anti-apoptotic threshold. On the other hand, the interaction with RET prevents the formation of the AIP–survivin
complex, resulting in subsequent survivin degradation and increase in apoptosis (32). These effects, however, are contrary to the proposed tumor-suppressor role of AIP. Apart from stabilizing the AhR complex, AIP may also bind to a set of nuclear receptors including peroxisome proliferator-activated receptor γ, the glucocorticoid receptor, and β-thyroid hormone receptor 1. Furthermore, a role has been proposed for AIP in virus-induced tumorigenesis as a potential partner of hepatitis B virus X antigen and Epstein–Barr virus-encoded nuclear antigen 3 (24).

Over 50 different mutations in the AIP sequence have been identified in FIPA families from all over the world, and these mutations are spread through the entire length of the gene (23,33). Most of them affect the C-terminal end and the tetratricopeptide repeat motifs supporting their essential role in AIP function. Nonsense and frameshift mutations lead to premature stop codons with a resultant truncated protein, whereas missense mutations tend to affect the tetratricopeptide repeat domains and the terminal α-helix. Whole gene deletions have also been identified, suggesting the use of a multiple ligation-dependent probe amplification method for patients with FIPA in whom sequencing fails to identify abnormalities (34,35,36). Mutations in codons R304, R271, and R81 have been reported in independent families with FIPA, indicating possible hotspots. No genotype–phenotype correlations have been observed to date in patients with AIP-mutated FIPA (37).

Mutations in the AIP gene, however, are found in only approximately 25% of all patients with FIPA, and in 40–50% of patients in the subgroup with acromegaly from homogeneous FIPA families (12). The genetic cause for the rest of the cases is still unknown, but several other loci, such as 2p16, 3q28, 4q32, 8q12, 19q13, and 21q22, may be involved in the development of the syndrome although no particular genes have been identified (38). On the other hand, the penetrance of AIP mutations is estimated to be approximately 30% in the largest reported families (15,19,35,39), suggesting the possible existence of genetic or environmental modifying factors (Figure 1).

**CLINICAL CHARACTERISTICS OF PATIENTS WITH AIP-MUTATED FIPA**

Patients with AIP-related pituitary adenomas have also been shown to exhibit some specific clinical features that differentiate them from patients with wild-type AIP alleles (37). In contrast to the overall female predominance in FIPA, male sex is significantly more common in the subgroup of patients harboring AIP mutations. All types of pituitary tumors may occur in association with mutated AIP, but growth hormone-secreting adenomas largely predominate, arising in about 80% of patients, and co-secretion of prolactin is observed in more than 50% of these. A direct comparison of 75 patients with AIP-mutated somatotropinomas with 232 genetically negative control subjects with acromegaly revealed that AIP anomalies are associated with much earlier onset and more aggressive evolution of the disease (Table 1). Invasive macroadenomas are manifested in childhood or adolescence in more than half of patients with AIP mutations, and almost a third of patients with somatotropinomas present with gigantism. Disease control is also harder to achieve and maintain, because somatostatin analogs are less effective for lowering growth hormone and insulin-like growth factor levels and inducing tumor shrinkage in acromegaly caused by AIP mutations. Moreover, these patients have significantly worse long-term therapeutic control although they frequently undergo multiple surgeries and radiotherapy. Patients with AIP-mutated prolactinomas also present with large tumor size and invasive features. Resistance to dopamine agonists may be observed in 50% of these, raising the need for surgery and/or radiotherapy.

**CLINICAL IMPLICATIONS AND MANAGEMENT**

Similar to the other familial presentations of pituitary tumors in MEN 1 and Carney complex, the treatment of FIPA does not differ substantially from the management of sporadic adenomas in terms of indications and therapeutic modalities. However, the aggressive nature of FIPA tumors, especially in patients with AIP mutations requires increased attention from medical specialists. Detailed physical

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**Figure 1** - Genealogical tree of a familial isolated pituitary adenoma (FIPA) family with E174 frameshift aryl-hydrocarbon receptor interacting protein gene (AIP) mutation. Filled black symbols indicate mutation-positive patients with pituitary tumors. (+) symbols show patients with AIP mutation without clinical, hormonal or radiological evidence for pituitary pathology. (-) is used for patients with wild-type AIP. Subjects marked with (?) did not undergo genetic analysis but had no clinical signs of pituitary disease. Subjects with AIP mutation and elevated insulin-like growth factor-1 levels are shown by a symbol with a filled upper right corner, and an AIP-mutation positive girl with premature telarche, ovarian enlargement and advanced bone age is indicated by a symbol with a filled lower left corner. Adapted by the author Naves LA (39).
examination should be performed for exclusion of extra-pituitary pathology that may imply syndromic disease, and a comprehensive family history taken before referring patients to genetic screening. Genetic testing in relatives of patients with AIP mutations can be especially beneficial in terms of early diagnosis, which may yield better outcomes from treatment. Although no consensus protocols for management of patients with AIP-mutated FIPA currently exist, it may be appropriate to start regular magnetic resonance imaging monitoring and hormonal evaluation from early childhood because macroadenomas and gigantism have been diagnosed in patients as young as 6–8 years (34,36). Widespread screening for AIP mutations among apparently sporadic pituitary adenomas may not be warranted, as the prevalence of AIP alterations is low in such populations. However, AIP mutations are discovered in approximately 12% of young patients (aged <30 years) and in 20% of pediatric patients, most often presenting with growth hormone-secreting or prolactin-secreting macroadenomas, suggesting that focused screening in this patient group may provide valuable clinical information (33,40).

The definition of FIPA has further widened the spectrum of familial pituitary pathology in addition to the well-known MEN 1 and Carney complex. The identification of the AIP gene as a causative factor in a subset of patients with FIPA has also provided some new insights into pituitary tumorigenesis. Genetic testing can now be offered to at-risk subjects in affected families, allowing for earlier diagnosis and more successful treatment. Consensus guidelines concerning the management and follow-up of patients with FIPA will hopefully be developed with the accumulation of data from large international cohorts and long-term monitoring studies. However, much remains to be done, as the low prevalence and the uncertain penetrance of AIP mutations suggests that other predisposing or modifying genes are to be expected. It is also unclear whether patients with FIPA additionally have a predisposition for other endocrine or non-endocrine tumors, which could expand its definition beyond the pituitary. Further studies will help to clarify these issues and provide more information on the genetic and molecular basis for the development of pituitary adenomas.

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