

## Familial Isolated Pituitary Adenomas

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DOI: 10.17925/USE.2009.05.1.55

### Abstract

Over the last century several families have been described with familial isolated pituitary adenomas (FIPAs). Most commonly, family members have acromegaly or prolactinoma, but other types of pituitary adenomas can also occur. Recently, mutations in the *AIP* (aryl hydrocarbon receptor interacting protein) gene have been found to occur in 30–50% of FIPA patients, while for the rest of the patients the gene causing the disease is currently unknown and is a topic of intense research. Tumours in patients with *AIP* mutations are diagnosed at significantly younger ages and tend to be larger. Often the response to medical therapy in these patients is poor. This article discusses the clinical and genetic characteristics of this relatively recently recognised disease.

### Keywords

Pituitary tumour, familial disease, *AIP*, tumour suppressor gene

**Disclosure:** The authors have no conflicts of interest to declare.

**Acknowledgements:** We are very grateful for the helpful advice on the manuscript from one of our patients with familial isolated pituitary adenoma.

**Received:** 25 April 2009 **Accepted:** 6 July 2009

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Pituitary adenomas are common intracranial tumours, and clinically relevant pituitary adenomas have been estimated to occur in about one in every 1,000 of the population.<sup>1</sup> The vast majority of these adenomas are sporadic; however, there is increasing recognition that pituitary adenomas may also occur in a familial setting, and a recent estimate suggests that 5% of pituitary adenomas are familial in origin.<sup>2</sup> Familial pituitary adenomas can form part of the classic syndromes of multiple endocrine neoplasia type 1 (MEN1) and Carney complex. However, a number of families have been identified to have isolated familial pituitary tumours and show an autosomal dominant inheritance with incomplete penetrance (the proportion of individuals with the inherited mutation who develop the disease), without the clinical features or genetic abnormalities of the MEN1 syndrome and Carney complex. Over the last decade, these individuals have been classified as having isolated familial somatotropinoma (IFS),<sup>3,4</sup> familial isolated pituitary adenoma (FIPA)<sup>5,6</sup> or pituitary adenoma predisposition (PAP),<sup>7</sup> covering overlapping entities.

The first documented report of families with several members affected by acromegaly occurred over 100 years ago (see *Figure 1*).<sup>8</sup> However, the genetic basis of this condition was unknown until 2006, when a Finnish group identified germline mutations in a gene known as *AIP* (aryl hydrocarbon receptor interacting protein; see *Figure 2*) while studying large families with acromegaly and prolactinoma in northern Finland.<sup>7</sup> Subsequent work focused on determining the prevalence of *AIP* mutations in FIPA families and studying the relevance in sporadic pituitary tumours.

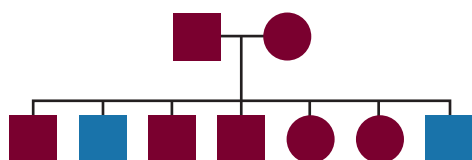
FIPA is an autosomal dominant disease with low or variable penetrance (see *Figure 3*) characterised by a heterogeneous

genetic background. FIPA has been identified in more than 170 families, with over 400 individuals described in the literature, including 86 families having familial acromegaly. Within FIPA families there is a heterogeneity of pituitary tumours (see *Figure 4*),<sup>2,6,7,9–11</sup> with somatotroph (growth-hormone-secreting) and lactotroph (prolactin-secreting) adenomas being the most common, although other combinations involving non-functioning adenomas, corticotroph (ACTH-secreting) and gonadotroph (gonadotropin-secreting) adenomas have also been reported.<sup>2,12</sup> Patients with familial disease are on average four to six years younger at diagnosis than sporadic patients. Patients from later generations tend to be significantly younger at diagnosis compared with earlier generations, probably because of increased pituitary disease recognition and surveillance among later generations.

### Clinical Characteristics of *AIP* Mutation Patients versus Those with No *AIP* Mutation

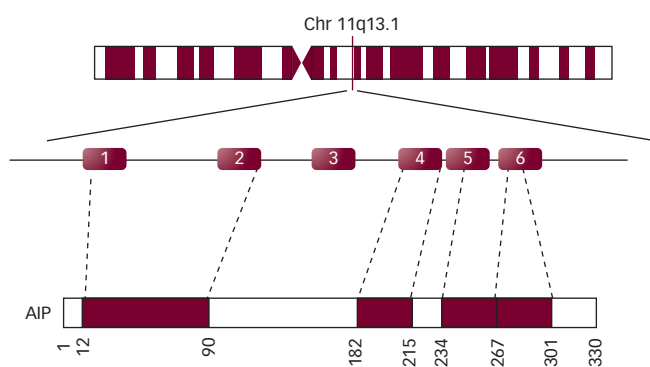
About 30–50% of families with FIPA have a mutation in the *AIP* gene. Some early-onset – often childhood-onset – acromegaly patients are also positive for *AIP* mutations. Mutations of *AIP* have mainly been found in families with either pure somatotroph adenomas or families with mixed somatotroph and lactotroph adenomas. Interestingly, none of the pure prolactinoma families have *AIP* mutations, and no *AIP* mutation has been found in a known FIPA family with at least one member not having either a somatotroph or lactotroph adenoma. Pituitary adenoma tissue has also been studied for *AIP* mutations in cases where the DNA extracted from blood (germline) is negative, but has never revealed any *AIP* mutations.<sup>9,13</sup>

**Figure 1: Familial Acromegaly in Two French Brothers**



Two brothers, 226cm (1887–1914) and 231cm (1876–1916) tall, are shown with their siblings and their family tree. Source: Dr WW de Herder.

**Figure 2: AIP Gene and AIP Protein**



The AIP gene is located on the long arm of the 11th chromosome at the band named 11q13.1. The gene consists of so-called exons, which will be translated to a protein of 330 amino acids.

Tumours with AIP mutations are diagnosed in subjects at significantly younger ages, and are larger than those found in FIPA patients without AIP mutations, as well as those found in patients with sporadic tumours.<sup>9,10,12</sup> Patients with an AIP mutation have a mean age of diagnosis of 25 years compared with 40 years for those without AIP mutations.<sup>9,10,12</sup> The youngest patient described as having AIP mutations is six years old (unpublished data), and around two-thirds of patients with AIP mutations are diagnosed at 25 years of age or under.<sup>9,10,12</sup> AIP mutation patients have larger pituitary tumours, suggesting more aggressive disease.<sup>10</sup> In our cohort, a poor biochemical response to somatostatin analogues (<50% reduction in growth hormone [GH]/insulin-like growth factor 1 [IGF-I]) occurred in eight of the 15 patients with familial acromegaly.

Due to limited genealogical data, the exact penetrance (proportion of individuals with the mutation who develop the disease) of pituitary tumours is difficult to calculate accurately. However, a best estimate emerges from the largest well-studied family with an AIP mutation: one-third of individuals (three of nine subjects with AIP mutations) developed pituitary tumours at the time of the study.<sup>14</sup> We find similar penetrance in our largest family with AIP mutations.

## AIP Mutations Described

The AIP protein was thought to be associated with the receptor of an environmental toxin and with a protein important in cAMP degradation (a second messenger signalling molecule in the cell). Currently, it is unclear which mechanism leads to pituitary tumorigenesis in patients with AIP mutations. Forty-one AIP mutations have been identified to date, including deletions, insertions, segmental duplications, non-sense and missense mutations and large deletions. Mutations usually disrupt the structure of the end of the protein molecule that plays a key role in the functioning of the molecule. Most studies have used sequencing methods with AIP primers covering just the exons and the area around them. However, a new technique called multiplex ligation-dependent probe amplification (MLPA) reveals large genomic rearrangements in families who previously may have tested negative for germline AIP mutations by conventional sequencing.<sup>15</sup>

## Prevalence of AIP Mutations in Familial Isolated Pituitary Adenoma Families

Out of more than 170 FIPA families described in the literature, 30 families have been reported as having 24 different types of AIP mutations. However, the prevalence of AIP mutations is difficult to assess because not all of the reported FIPA families have been sequenced for AIP mutations, and the vast majority were not tested using MLPA. A best estimate is provided by the three largest FIPA family cohorts.<sup>7,9-12</sup> Out of all 136 FIPA families sequenced for AIP, there are 27 (20%) families with AIP mutations. Looking only at families with acromegaly, 21 of 53 (40%) families have an AIP mutation.

## Prevalence of AIP Mutations in 'Apparently' Sporadic Patients

Several studies have searched for AIP mutations in sporadic pituitary adenoma patients, i.e. in patients with no family history of pituitary disease.<sup>7,9,11,13,16-24</sup> About 2% of these patients have an AIP mutation in their DNA (27 of 1,100 sporadic pituitary adenoma

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patients). When the tumour tissue itself is studied in pituitary adenoma samples, no somatic AIP mutations are found, i.e. no changes in the tumour itself.<sup>9,13</sup> Most patients with AIP mutations in the 'apparently' sporadic cohort have a diagnosis of acromegaly, but there are two reported cases of mutations in patients with Cushing's disease.<sup>11,19</sup>

### Other Tumours in Familial Isolated Pituitary Adenoma Patients

In our cohort of FIPA families, non-pituitary tumours occur in seven families with affected patients or obligate *AIP* mutation carriers: lipomas, breast, thyroid, testicular, renal and bone marrow tumours, ependymomas, anaplastic astrocytomas and primitive neuroectodermal tumours<sup>9</sup> (also unpublished data). The association of FIPA with adrenal carcinoma<sup>25,26</sup> or ependymoma<sup>15</sup> has also been reported. However, it is unclear whether any of these tumours

*Genetic testing of relatives of patients with AIP mutations, with regular biochemical and occasional imaging screening, may lead to earlier pituitary tumour detection, thus allowing treatment at an earlier stage.*

are part of the FIPA syndrome as the FIPA cohort is too small, not all the studies reported on second tumours and the tumour types are variable.

### AIP Mutations in Other Tissues

The role of somatic *AIP* mutations has been studied in the pathogenesis of common cancers (373 colorectal cancers, 82 breast cancers and 44 prostate tumour samples)<sup>27</sup> and 79 endocrine tumours (26 thyroid lesions, 19 adrenal lesions, 16 carcinoids, eight parathyroid lesions, four paragangliomas, four pancreatic endocrine tumours and two adenocarcinoids).<sup>21</sup> No somatic mutations were found, suggesting that *AIP* is not strongly involved in tumorigenesis in these tumour types.

### Tumour-suppressor Role for AIP

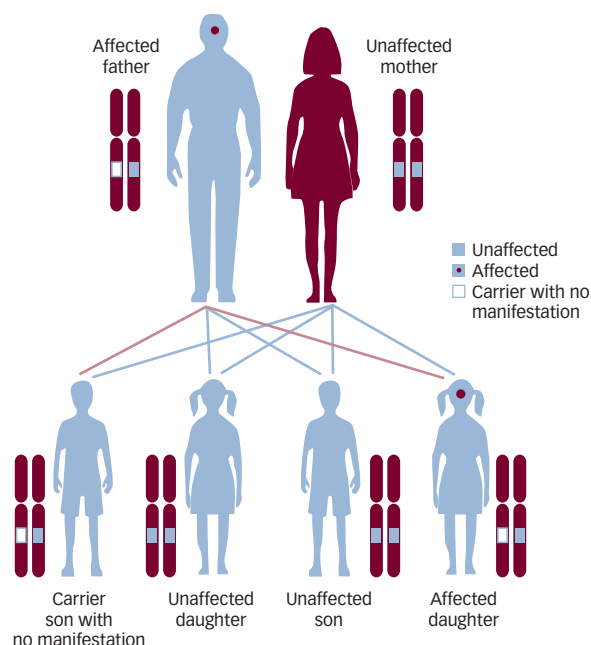
Based on clinical data, it has been suggested that FIPAs are caused by a heterozygous germline mutation in a tumour-suppressor gene. Our group has recently captured unique functional data on *AIP* consistent with a tumour-suppressor role for *AIP*.<sup>9</sup> Cells were transfected with the *AIP* gene and showed reduced proliferation. On the other hand, when the cell's own *AIP* was knocked out, cell proliferation increased.

### Practical Relevance to the Clinical Endocrinologist of These Emerging Data About Familial Isolated Pituitary Adenomas

Identifying *AIP* mutations in patients and carriers is of great clinical importance. Patients with *AIP* mutations tend to have a more aggressive disease, and treatment can be extremely challenging if diagnosis is late. Genetic testing of relatives of patients with *AIP* mutations, with regular biochemical and occasional imaging screening, may lead to earlier pituitary tumour detection, thus allowing treatment at an earlier stage. All patients with a family history of pituitary adenoma and no suspicion of MEN1 and Carney complex should undergo genetic counselling and testing for *AIP*.

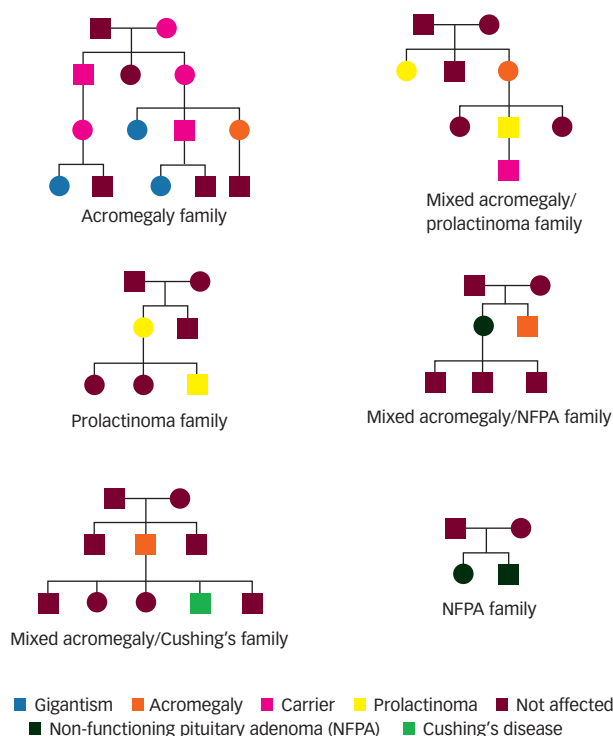
If a mutation is found, family members should be screened for the mutation. Carriers should be tested regularly for clinical symptoms and signs, and should undergo biochemical and (if necessary)

**Figure 3: Inheritance of Familial Isolated Pituitary Adenoma**



Patients with familial isolated pituitary adenoma inherit an abnormal copy of the gene causing the disease from one of their parents. In some patients this will result in the development of a pituitary adenoma (the disease is manifested), while in others it will not cause any disease, but the gene can be passed on to the next generation.

**Figure 4: Example of Familial Isolated Pituitary Adenoma Family Trees**



Heterogeneity of pituitary tumours is found in families with familial isolated pituitary adenoma. The most common tumour types seen are somatotroph and lactotroph adenomas.

imaging investigations, given that heterologous tumours can occur within families and also that incidental tumours of the pituitary are common. Early-onset sporadic pituitary adenomas, especially

somatotroph adenomas, have an increased chance of harbouring germline *AIP* mutations, so genetic testing should be considered in these index cases. If no *AIP* mutation is found, all family members with a 50% chance of inheriting the disease should be regularly tested. Currently, we are searching for gene(s) causing the disease in *AIP*-negative families and would like patients with a family history of pituitary adenomas to contact us if they are interested in taking part in the study.

## Conclusions

*AIP* has been identified as a novel gene involved in the development of FIPA, especially in those cases involving growth-hormone-secreting tumours, and is probably a tumour-suppressor gene. Mutations in *AIP* have been found in ~15–40% of families with FIPA. This number will likely increase if all families are tested for large gene deletions. Patients with *AIP* mutations are diagnosed at younger ages, and their pituitary tumours tend to be larger and more aggressive and respond less well to somatostatin analogues.

To assess the penetrance of the disease in patients with *AIP* mutations, apparently unaffected relatives who are carriers need full clinical and biochemical investigation.<sup>2</sup> Germline *AIP* mutations have been found in 'apparently' sporadic tumours. As the majority of FIPA patients do not harbour *AIP* mutations, and the clinical phenotype (primarily the age at onset and the pituitary tumour type) is different in the *AIP*-mutation-negative families, we think there is a strong possibility that another gene, or genes, may be involved in the pathogenesis of these FIPA cases. ■



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