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AIP Familial Isolated Pituitary Adenomas

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Summary

Clinical characteristics

AIP familial isolated pituitary adenoma (*AIP*-FIPA) is defined as the presence of an *AIP* germline pathogenic variant in an individual with a pituitary adenoma (regardless of family history).

The most commonly occurring pituitary adenomas in this disorder are growth hormone-secreting adenomas (somatotropinoma), followed by prolactin-secreting adenomas (prolactinoma), growth hormone and prolactin co-secreting adenomas (somatomammotropinoma), and nonfunctioning pituitary adenomas (NFPA). Rarely TSH-secreting adenomas (thyrotropinomas) are observed. Clinical findings result from excess hormone secretion, lack of hormone secretion, and/or mass effects (e.g., headaches, visual field loss). Within the same family, pituitary adenomas can be of the same or different type. Age of onset in *AIP*-FIPA is usually in the second or third decade.

Diagnosis/testing

The diagnosis of *AIP*-FIPA is established in a proband with a pituitary adenoma by identification of a heterozygous germline pathogenic variant in *AIP* by molecular genetic testing.

Management

Treatment of manifestations: Pituitary adenomas identified in those with *AIP*-FIPA are generally treated in the same manner as pituitary adenomas of unknown cause: they can be treated by medical therapy (somatostatin analogs, growth hormone receptor antagonists, and dopamine agonists), surgery, and/or radiotherapy. Although surgery is usually performed in persons with *AIP*-FIPA, it often does not fully control the tumor; thus, medical therapy and radiotherapy following surgery may be required to control hormone output and tumor growth. *AIP*-FIPA adenomas often do not respond well to first-generation somatostatin analog, while data suggest that they may respond better to second-generation multi-ligand agonists. Prolactinomas are treated with dopamine

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agonist therapy or surgery and can be aggressive and difficult to treat. NFPA is treated with surgery and if necessary radiotherapy.

Prevention of secondary complications: Expert management for hypopituitarism which can be due to tumor size, surgery, or radiotherapy. Persons on glucocorticoid replacement therapy need to increase their steroid dose when ill or stressed.

Surveillance: In asymptomatic individuals: annual growth assessment and evaluation for signs/symptoms of pituitary adenoma and pubertal development from age four years until adulthood. Continue annual evaluation for signs and symptoms of pituitary adenoma until age 30 years and then every five years between ages 30 and 50 years. Annual pituitary function tests (serum IGF-1, prolactin, estradiol/testosterone, LH, FSH, TSH, free T4) beginning at age four years until age 30; pituitary MRI at age ten years and repeated (every 5 years has been suggested) or as necessary based on clinical and biochemical parameters until age 30 years. Starting at age 30 to 50 years surveillance can be relaxed.

In symptomatic individuals: annual clinical assessment and pituitary function tests (serum IGF-1, spot growth hormone, prolactin, estradiol/testosterone, LH, FSH, TSH, free T4, and morning cortisol); if indicated annual dynamic testing to evaluate for hormone excess or deficiency (e.g., glucose tolerance test, insulin tolerance test); pituitary MRI with frequency depending on clinical status, previous extent of the tumor, and treatment modality. Clinical monitoring of secondary complications of the tumor and/or its treatment (e.g., diabetes mellitus, hypertension, osteoarthritis, hypogonadism, osteoporosis); in those with acromegaly, colonoscopy at age 40 years and repeated every three to ten years depending on the number of colorectal lesions and IGF-1 levels.

Evaluation of relatives at risk: Family members at risk for *AIP*-FIPA warrant molecular genetic testing for the family-specific pathogenic variant to identify those who harbor the variant and thus require surveillance for pituitary adenomas.

Genetic counseling

AIP-FIPA is inherited in an autosomal dominant manner. Each child of an individual with *AIP*-FIPA has a 50% chance of inheriting the pathogenic variant. Prenatal testing for a pregnancy at increased risk is possible if the *AIP* pathogenic variant of an affected family member has been identified; however, because *AIP*-FIPA demonstrates reduced penetrance, the finding of an *AIP* pathogenic variant prenatally does not allow accurate prediction of whether a tumor will develop, or the type of adenoma, age of onset, prognosis, or availability and/or outcome of treatment.

Diagnosis

Suggestive Findings

AIP familial isolated pituitary adenoma (*AIP*-FIPA) **should be suspected** in individuals with the following:

- A pituitary adenoma diagnosed before age 18 years, especially a growth hormone-secreting pituitary adenoma, regardless of family history
- A pituitary macroadenoma (tumor >10 mm in diameter) diagnosed before age 30 years, especially a growth hormone-secreting pituitary adenoma, regardless of family history
- A prolactin-secreting pituitary macroadenoma (tumor >10 mm in diameter) diagnosed before age 30 years, regardless of family history

  Note: (1) A germline *AIP* pathogenic variant is identified in approximately 20% of simplex cases of childhood-onset growth hormone-secreting pituitary adenomas [Chahal et al 2010, Cazabat et al 2011,

Tichomirowa et al 2011]. (2) A germline *AIP* pathogenic variant is identified in 11% of simplex cases of young-onset (age <30 years) pituitary macroadenomas [Tichomirowa et al 2011].

- A family history of more than one individual with a pituitary adenoma

  Note: (1) A germline *AIP* pathogenic variant is identified in approximately 20% of families with FIPA [Chahal et al 2010] and in 40% of families in which somatotropinomas are the only tumor type observed. (2) To date, *AIP* pathogenic variants have not been identified in families with two adults with microprolactinomas (prolactin secreting tumors <10 mm in diameter); therefore, the probability of identifying an *AIP* pathogenic variant in such a family is low.

- Absence of clinical features of other disorders associated with pituitary adenomas such as multiple endocrine neoplasia type 1 or type 4 (MEN1 or MEN4) or Carney complex

The **pituitary adenomas** in individuals with *AIP*-FIPA can include:

- Growth hormone-secreting (somatotropinoma)

  Note: Somatotroph (growth hormone-secreting) cell hyperplasia has also been described in individuals with *AIP*-FIPA, although it is extremely rare.

- Prolactin-secreting (prolactinoma)
- Growth hormone and prolactin co-secreting (somatomammotropinoma)
- Nonfunctioning pituitary adenoma (NFPA)

  Note: Most *AIP*-related NFPAs show growth hormone and/or prolactin immunostaining in tumor tissue.

- Thyrotropinoma (TSH-secreting) (rare; 1 thyrotropinoma described)
- Multihormonal (i.e., secreting >1 pituitary hormone) (extremely rare apart from tumors secreting growth hormone and prolactin)

No unequivocal cases of corticotropinomas have been described.

Establishing the Diagnosis

The diagnosis of *AIP*-FIPA **is established** in a proband with a pituitary adenoma(s) by identification of a heterozygous germline pathogenic variant in *AIP* by molecular genetic testing (see Table 1).

Molecular genetic testing approaches can include a combination of **gene-targeted testing** (single-gene testing and multigene panel) and **comprehensive genomic testing** (exome sequencing, exome array, genome sequencing) depending on the phenotype.

Gene-targeted testing requires that the clinician determine which gene(s) are likely involved, whereas genomic testing does not. Because the phenotype of *AIP*-FIPA can occur with other disorders, individuals with the distinctive findings described in Suggestive Findings are likely to be diagnosed using gene-targeted testing (see Option 1), whereas those with a phenotype indistinguishable from other inherited disorders with pituitary tumors are more likely to be diagnosed using comprehensive genomic testing (see Option 2).

Option 1

When the phenotypic and laboratory findings suggest the diagnosis of *AIP*-FIPA, molecular genetic testing approaches can include **single-gene testing** (or concurrent or serial single-gene testing) or use of a **multigene panel**:

- **Single-gene testing.** Sequence analysis of *AIP* detects small intragenic deletions/insertions and missense, nonsense, and splice site variants; typically, exon or whole-gene deletions/duplications are not detected. Perform sequence analysis first. If no pathogenic variant is found perform gene-targeted deletion/duplication analysis to detect intragenic deletions or duplications.
- **A multigene panel** that includes *AIP* and other genes of interest (see Differential Diagnosis) is most likely to identify the genetic cause of the condition at the most reasonable cost while limiting identification of variants of uncertain significance and pathogenic variants in genes that do not explain the underlying phenotype. Note: (1) The genes included in the panel and the diagnostic sensitivity of the testing used for each gene vary by laboratory and are likely to change over time. (2) Some multigene panels may include genes not associated with the condition discussed in this *GeneReview*. (3) In some laboratories, panel options may include a custom laboratory-designed panel and/or custom phenotype-focused exome analysis that includes genes specified by the clinician. (4) Methods used in a panel may include sequence analysis, deletion/duplication analysis, and/or other non-sequencing-based tests. For this disorder a multigene panel that also includes deletion/duplication analysis is recommended (see Table 1).

  For an introduction to multigene panels click here. More detailed information for clinicians ordering genetic tests can be found here.

Option 2

When the phenotype is indistinguishable from other inherited disorders characterized by pituitary tumors, **comprehensive genomic testing** (which does not require the clinician to determine which gene[s] are likely involved) is a possible option. **Exome sequencing** is most commonly used; **genome sequencing** is also possible.

If exome sequencing is not diagnostic – and particularly when evidence supports autosomal dominant inheritance – **exome array** (when clinically available) may be considered to detect (multi)exon deletions or duplications that cannot be detected by sequence analysis.

For an introduction to comprehensive genomic testing click here. More detailed information for clinicians ordering genomic testing can be found here.

Table 1. Molecular Genetic Testing Used in *AIP*-FIPA

Gene [1]	Method	Proportion of Probands with a Pathogenic Variant [2] Detectable by Method
AIP	Sequence analysis [3]	~95% [4, 5]
	Gene-targeted deletion/duplication analysis [6]	~5% [7]

1. See Table A. Genes and Databases for chromosome locus and protein.
2. See Molecular Genetics for information on allelic variants detected in this gene.
3. Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or pathogenic. Variants may include small intragenic deletions/insertions and missense, nonsense, and splice site variants; typically, exon or whole-gene deletions/duplications are not detected. For issues to consider in interpretation of sequence analysis results, click here.
4. Georgitsi et al [2008]; Igreja et al [2010]; Hernández-Ramírez et al [2015]; Author, personal observation
5. One promoter variant has been reported (see Molecular Genetics).
6. Gene-targeted deletion/duplication analysis detects intragenic deletions or duplications. Methods used may include quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification (MLPA), and a gene-targeted microarray designed to detect single-exon deletions or duplications.
7. To date, four individuals/families with exon or multiexon deletions and two families with whole-gene deletions have been identified [Georgitsi et al 2008, Igreja et al 2010, Hernández-Ramírez et al 2015, Marques et al 2020].

Clinical Characteristics

Clinical Description

To date, more than 300 individuals with a germline pathogenic variant in *AIP* have been identified [Beckers et al 2013, Hernández-Ramírez et al 2015]. The following description of the phenotypic features associated with this condition is based on these reports.

Table 2. Pituitary Adenomas in Individuals with *AIP*-FIPA

Type of Pituitary Adenoma	% of Persons w/Type of Adenoma	Reference
Somatotropinoma (growth hormone-secreting)	70%	Hernández-Ramírez et al [2015]
Somatomammotropinoma (growth hormone- and prolactin-secreting)	10%	
Prolactinoma	10%	
Nonfunctioning pituitary adenoma	8%	
Thyrotropinoma (TSH-secreting)	Rare	

The median age of diagnosis of *AIP* familial isolated pituitary adenoma (*AIP*-FIPA) is 23 years. The earliest age of diagnosis of a pituitary adenoma in a person with an *AIP* pathogenic variant is four years [Dutta et al 2019].

Hormone Dysfunction

Somatotropinoma (growth hormone-secreting pituitary adenoma)

- **Acromegaly.** Approximately 80% of persons with *AIP*-FIPA have acromegaly. Persons with acromegaly have excess growth hormone secretion resulting in enlargement of hands and feet, and coarse facial appearance with prognathism and malocclusion of teeth. They may have headaches, joint pain, carpal tunnel syndrome, sleeping difficulties, excessive sweating, hypertension, diabetes mellitus, and muscle weakness. Individuals with longstanding acromegaly often have cardiovascular and rheumatologic/orthopedic complications, which need to be treated accordingly. Individuals with acromegaly of any cause are at increased risk for colon cancer.

  If acromegaly starts in childhood/adolescence it can lead to pituitary gigantism.

- **Pituitary gigantism.** Excessive growth hormone secretion before fusion of the growth plates results in pituitary gigantism. Exceptionally tall stature results from a combination of high growth hormone levels and delayed onset of puberty due to suppression of LH/FSH secretion by mass effect of the tumor and/or, when present, the direct effect of high prolactin levels.

  One third of all individuals with a germline *AIP* pathogenic variant and 40%-50% of individuals with *AIP*-FIPA with a somatotropinoma have pituitary gigantism [Daly et al 2010].

Prolactinomas. Approximately 10% of persons with an *AIP* pathogenic variant have a prolactinoma [Daly et al 2010, Igreja et al 2010]. Prolactinomas result in signs and symptoms of prolactin excess (i.e., amenorrhea, sexual problems, galactorrhea, and infertility) and can also cause mass effects (e.g., visual field defects, headaches).

Almost all *AIP*-related prolactinomas are macroadenomas with male predominance [Daly et al 2010, Igreja et al 2010].

Nonfunctioning pituitary adenomas (NFPAs). NFPAs are seen in 4%-7% of persons with an *AIP* pathogenic variant.

NFPAs are usually diagnosed due to the local effects of the tumor, such as bitemporal hemianopia or hypogonadism. It is unclear why these silent adenomas do not release hormones at a clinically recognizable level; however, there is likely to be a continuum between fully functional and completely silent adenomas [Drummond et al 2019]. Distinguishing NFPA from prolactinomas can occasionally be difficult due to the stalk effect (pituitary stalk compression resulting in increased prolactin levels in the absence of a prolactin-secreting adenoma).

In *AIP*-FIPA, NFPAs that have been resected are often (but not always) silent somatotropinoma or lactotroph adenomas [Igreja et al 2010, Villa et al 2011]. In families with *AIP*-FIPA, NFPAs are identified at a younger age than NFPAs in persons without a germline pathogenic variant [Daly et al 2010]. Screening of clinically unaffected *AIP* heterozygotes can identify small nonfunctioning pituitary lesions, equivalent to incidentalomas in the general population [Caimari et al 2018].

Thyrotropinomas (TSH-secreting adenomas causing hyperthyroidism) are rarely seen in *AIP*-FIPA.

A single individual with *AIP*-FIPA and a thyrotropinoma has been described [Daly et al 2007].

AIP-FIPA does not appear to increase the risk of corticotropinoma. The individuals with FIPA previously reported with Cushing disease were subsequently found to have likely benign variants in *AIP*, variants of uncertain significance [Beckers et al 2013], or no loss of heterozygosity identified in the tumor [Cazabat et al 2012].

Subfertility is common in persons with pituitary tumors. No data are available specifically regarding subfertility in *AIP*-FIPA.

Mass effects. Large pituitary adenomas can be associated with deficiencies of other pituitary hormones that result in subfertility, hypothyroidism, hypoadrenalism, low levels of growth hormone, and panhypopituitarism.

Macroadenomas (>10 mm in diameter) may also press on the optic chiasm and optic tracts, causing bitemporal hemianopia. The tumor may invade the adjacent cavernous sinus. Headache can be present in any type of adenoma but is especially common in acromegaly; the mechanism for the increased frequency is unknown.

Larger pituitary tumors may autoinfarct, resulting in pituitary apoplexy (sudden-onset severe headache, visual disturbance, cranial nerve palsies, hypoglycemia, and hypotensive shock). Pituitary apoplexy has been described in individuals with *AIP*-FIPA [Chahal et al 2011].

Pituitary carcinoma. To date pituitary carcinoma has not been described in an individual with *AIP*-FIPA.

Other, non-pituitary tumors have been observed in some families with *AIP*-FIPA; however, because the background population risk for tumors is fairly high and because no consistent pattern has been observed, at present there is no conclusive evidence that an *AIP* germline pathogenic variant increases the risk for any other tumors. In addition, non-pituitary tumors from *AIP* heterozygotes have been analyzed for loss of heterozygosity at the AIP locus, and no abnormality was found [Hernández-Ramírez et al 2015].

Genotype-Phenotype Correlations

Individuals with *AIP* truncating pathogenic variants may have a slightly earlier age of onset and diagnosis compared to those with non-truncating pathogenic variants [Hernández-Ramírez et al 2015].

Penetrance

Studies on large families with *AIP* pathogenic variants show a clinical penetrance of pituitary adenomas of approximately 23% (range 15%-30%) [Vierimaa et al 2006, Naves et al 2007, Williams et al 2014, Hernández-Ramírez et al 2015]. Although some families with *AIP*-FIPA can show high penetrance, the higher levels of

penetrance initially reported in some families is probably ascertainment bias due to insufficient information on all at-risk family members (e.g., lack of medical records, information on pituitary hormone testing, and/or imaging studies) [Daly et al 2007, Leontiou et al 2008].

The factors influencing penetrance are not known; the possibility of a second locus has been investigated but not confirmed [Khoo et al 2009, Hernández-Ramírez et al 2015].

Nomenclature

Previously, pituitary adenoma predisposition (PAP) syndrome was used to refer to individuals who had an *AIP* pathogenic variant; the term is not used widely.

Prevalence

The exact prevalence of *AIP*-FIPA is not known. To date, about 150 families and about 150 simplex cases (i.e., a single occurrence in a family) of *AIP*-FIPA have been identified [Daly et al 2010, Hernández-Ramírez et al 2015, Caimari et al 2018].

Genetically Related (Allelic) Disorders

No phenotypes other than those discussed in this *GeneReview* are known to be associated with germline pathogenic variants in *AIP*.

Differential Diagnosis

In children more often than in adults, pituitary adenomas may be a manifestation of a genetic condition. Pituitary adenomas of genetic origin can be divided into isolated and syndromic categories.

Familial Isolated Pituitary Adenomas (FIPA)

FIPA is defined as a hereditary condition associated with pituitary adenomas and no other features of a syndrome known to be associated with pituitary adenomas.

X-linked acrogigantism (XLAG), a second genetically characterized type of FIPA, is caused by duplication of *GPR101*. XLAG, a highly penetrant disorder, is associated with pituitary hyperplasia or adenoma resulting in growth hormone excess with onset in infancy, usually with associated hyperprolactinemia [Trivellin et al 2014]. Most individuals with XLAG have a *de novo* somatic mosaic genetic alteration not inherited from a parent.

Families with FIPA of known or unknown cause can have homogeneous pituitary adenoma phenotypes (i.e., pituitary tumors of the same type) or heterogeneous phenotypes (i.e., pituitary tumors of different types).

Aspects of FIPA that tend to differ between families in which a germline *AIP* pathogenic variant has been identified and those in which no germline *AIP* pathogenic variant has been identified include: age of onset, number of persons affected in the family, male-to-female ratio, and typical adenoma types. Tumor variables may also include: size, aggressiveness, and response to treatment [Hernández-Ramírez et al 2015] (see Table 3).

Table 3. Comparison of Findings in Persons with Isolated Pituitary Adenomas by Family History and Presence/Absence of a Germline *AIP* Pathogenic Variant

Characteristics		Familial Isolated Pituitary Adenoma			Simplex Somatotropinoma [1]
		AIP-FIPA	XLAG	FIPA of unknown cause	
Clinical features	Age of onset [2]	4-24 yrs	Infancy / early childhood	40 yrs	43 yrs
	Average # of affected family members [3]	3-4	1	2-3	NA
	Male-to-female ratio [4]	1:1 to 2:1	1:2	1:1	1:1
Adenoma features	Somatotropinomas / somatomammotropinomas	70%-80%	~100%	~50%	NA
	Size	Macroadenomas in vast majority	Pituitary hyperplasia-macroadenoma	Majority macroadenoma [5]	Smaller
	Aggressiveness	More	Variable	More	Less
	Response to treatment	Poorer	Poorer	Poorer	Better

FIPA = familial isolated pituitary adenoma; NA = not applicable
1. Simplex case = a single occurrence in a family
2. Daly et al [2010], Igreja et al [2010], Hernández-Ramírez et al [2015], Daly et al [2016]
3. Igreja et al [2010]
4. Cazabat et al [2009], Daly et al [2010], Igreja et al [2010]
5. Marques et al [2020]

Syndromes Associated with Pituitary Tumors

Table 4. Syndromes Associated with Pituitary Tumors

Gene(s)	Disorder	MOI	Pituitary Tumor Features	Other Features
MEN1	Multiple endocrine neoplasia type 1 (MEN1)	AD	Pituitary tumors occur in ~40% of affected individuals, most often prolactinomas	• Gastro-entero-pancreatic tract tumors • Parathyroid adenoma w/ hypercalcemia • Other manifestations
CDKN1A *CDKN1B* *CDKN2B* *CDKN2C*	MEN1-like syndrome [1]	AD	Pituitary tumors occur in ~40% of affected individuals, most often somatotropinomas	• Rare disorder • Clinical findings similar to those of MEN1
PRKAR1A *PRKACB* [2]	Carney complex	AD	~80% of affected individuals have somatotroph cell hyperplasia or small pituitary adenoma	• Skin pigmentary abnormalities • Myxomas of the organs • Schwannomas • Primary pigmented nodular adrenocortical disease • Large-cell calcifying Sertoli cell tumors • Thyroid nodules • Acromegaly

Table 4. continued from previous page.

Gene(s)	Disorder	MOI	Pituitary Tumor Features	Other Features
GNAS	McCune-Albright syndrome	NA (somatic)	• ~30% of affected individuals have pituitary disease • Pituitary adenomas w/↑ secretion of growth hormone • Hyperplasia of somatomammotroph cells w/prolactinemia	• Polyostotic fibrous dysplasia • Café au lait patches • Multiple endocrine disorders (e.g., multinodular goiters, multinodular adrenal hyperplasia, & precocious puberty)
MAX *SDHA* *SDHB* *SDHC* *SDHD* *RET*	Hereditary paraganglioma-pheochromocytoma syndromes	AD	• Low penetrance of pituitary disease • Pituitary carcinoma described, vacuolated histology picture	• Paragangliomas • Pheochromocytoma • GIST • Kidney tumors
DICER1	*DICER1* syndrome	AD	• Low penetrance of pituitary disease • ACTH-secreting pituitary blastoma	Manifests before age 2 yrs
MSH2 *MSH6* *MLH1* *?PMS2*	Lynch syndrome	AD	• Low penetrance of pituitary disease • ACTH-secreting macroadenomas	Colorectal, endometrial, ovarian, & other carcinomas
USP8	Pituitary adenoma 4 (OMIM 219090)	AD	1 individual w/pituitary adenoma	Developmental delay

AD = autosomal dominant; GIST = gastrointestinal stromal tumor; MEN1 = multiple endocrine neoplasia type 1; MOI = mode of inheritance

1. Agarwal et al [2009]

2. One individual with Carney complex (<1% of families with Carney complex) had a germline rearrangement resulting in four copies of *PRKACB* [Forlino et al 2014]. *PRKACB* encodes the catalytic subunit Cβ of the cyclic AMP-dependent protein kinase A (PKA). Levels of Cβ and PKA activity were increased in the individual's lymphoblasts and fibroblasts; the authors propose that this is a Carney complex-causing gain-of-function variant.

Note: Autopsy and radiologic studies suggest that 14%-22% of the population may harbor a pituitary adenoma, most of these being asymptomatic [Ezzat et al 2004]. Thus, it is possible for two pituitary adenomas, especially prolactinomas, to occur sporadically in a family by chance.

Other Space-Occupying Lesions

In addition to pituitary adenomas, numerous space-occupying lesions can occur in the pituitary fossa [Saeger et al 2007]. The most common space-occupying lesions after pituitary adenomas are craniopharyngiomas, which cause symptoms by compressing the normal pituitary, resulting in hormonal deficiencies and mass effects on the surrounding tissues and brain [Zacharia et al 2012].

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs of an individual with *AIP* familial isolated pituitary adenoma (*AIP*-FIPA), the evaluations in Table 5 are recommended (for details see Katznelson et al [2011]).

Table 5. Recommended Evaluations Following Initial Diagnosis in Individuals with *AIP*-FIPA

System/Concern	Evaluation	Comment
Pituitary adenoma	• LH, FSH, testosterone/estradiol • Visual field eval • Consultation w/endocrinologist	• If adenoma suspected: pituitary MRI to detect size & extent • DXA scan in those w/hypogonadism
Somatotropinoma (growth hormone-secreting)	• Evaluate for signs/symptoms (e.g., stature, change in facial appearance, change in shoe size, problems w/ring sizes, headache, excessive sweating, joint pains, carpal tunnel syndrome). • Spot serum growth hormone, IGF-1	Include: • Review of serial photographs for acromegalic changes • Measurement of parental heights • GTT in persons w/findings of acromegaly • Assess ACTH reserve if needed.
Prolactinoma	• Evaluate for signs/symptoms (e.g., menstrual history, galactorrhea, infertility, low libido, impotence). • Serum prolactin	Note: (1) High prolactin levels can be due to stalk effect; (2) There are many non-pituitary causes of hyperprolactinemia.
NFPAs	Evaluate for signs/symptoms (e.g., headache, lack of other pituitary hormones, visual field problems).	Many nonfunctioning adenomas are identified incidentally w/no clinical or biochemical associations.
Thyrotropinoma	TSH, free T4	Consider other causes of thyroid hormone resistance.
Other	Consultation w/clinical geneticist &/or genetic counselor	

GTT = glucose tolerance test; NFPAs = nonfunctioning pituitary adenomas

Treatment of Manifestations

While there is experience with treating pituitary adenomas in symptomatic persons with FIPA, the experience of management and treatment of persons identified prospectively through clinical screening due to family history of FIPA and/or presence of a heterozygous germline *AIP* pathogenic variant is relatively recent. However, the age of detection in the *AIP*-FIPA is earlier and the prognosis generally better. Given the prevalence of incidental pituitary adenomas, it is important to remember that such a tumor may arise in an individual with an *AIP* pathogenic variant, completely by chance. The following recommendations are based on those of Katznelson et al [2011], Melmed et al [2011], Williams et al [2014], and Hernández-Ramírez et al [2015].

Table 6. Treatment of Manifestations in Individuals with *AIP*-FIPA

Manifestation/Concern	Treatment	Considerations/Other
Pituitary microadenomas	Medical therapy (e.g., somatostatin analogs, growth hormone receptor antagonists, & dopamine agonists), surgery &/or radiotherapy	Monitor microadenomas w/normal clinical & biochemistry findings closely.
Pituitary macroadenomas	Transsphenoidal surgery, medical therapy, &/or radiotherapy	Surgery often does not fully control the tumor; large recurring tumors may require radiotherapy if tumor invades neighboring anatomic structures (e.g., cavernous sinus).
Somatotropinomas	• Radiotherapy (conventional or radiosurgery) for growing adenomas, for which repeat surgery is unlikely to control hormone levels • Standard treatment of cardiovascular & rheumatologic/orthopedic complications for those w/acromegaly	Tumors often do not respond to medical therapy w/1st-generation somatostatin analogs; [1] 2nd-generation may have more effect. [2]

Table 6. continued from previous page.

Manifestation/Concern	Treatment	Considerations/Other
Prolactinomas	• Dopamine agonist therapy (e.g., cabergoline) • Surgical treatment often used for macroprolactinoma (diameter >10 mm)	Prolactinomas in *AIP*-FIPA can be aggressive & difficult to treat. [1]
Nonfunctioning pituitary adenomas	Surgery & (if necessary) radiotherapy	Usually do not respond to traditional somatostatin analogs

1. Daly et al [2010]
2. Daly et al [2019]

Prevention of Secondary Complications

Tumor size, surgery, and/or radiotherapy can cause hypopituitarism, which requires careful expert follow up.

Persons on glucocorticoid replacement therapy need to increase their steroid dose when ill or stressed.

Surveillance

No formal guidelines regarding surveillance of persons with *AIP*-FIPA have been established. The following recommendations are based on expert opinion from the literature and on the authors' personal experience with more than 200 persons with symptomatic or asymptomatic *AIP*-FIPA.

Table 7. Recommended Surveillance for Individuals with *AIP*-FIPA

System/Concern	Evaluation	Frequency
Pituitary adenoma	• Measure height & weight; calculate height velocity. • Evaluate for signs/symptoms & evaluate pubertal development.	Annually beginning at age 4 yrs until adulthood [1]
	Evaluate for signs/symptoms.	Annually until age 30 yrs & every 5 yrs between ages 30 & 50 yrs, earlier if symptomatic
	Serum IGF-1, prolactin, estradiol/ testosterone, LH, FSH, TSH, free T4	Annually from age 4 yrs to 30 yrs; to date, no secreting pituitary adenomas have developed after age 30 in those w/normal findings at age 30 yrs. Blood tests if symptomatic after age 30 yrs.
	Pituitary MRI	• Baseline at age 10 yrs unless indicated earlier due to clinical findings • Repeat MRI every 5 yrs until age 30 yrs (if clinical & pituitary function tests remain normal) • If clinical or biochemical abnormality between ages 30 & 50 yrs

1. In children between ages four and ten years, it may be difficult to get annual blood samples. In these cases, monitoring symptoms and growth may be an acceptable alternative, as non-growth hormone-secreting adenomas before age ten years are rare.

Table 8. Recommended Additional Surveillance for Symptomatic Individuals with *AIP*-FIPA

System/Concern	Evaluation	Frequency
History of pituitary adenoma	• Clinical assessment • Serum IGF-1, spot growth hormone, prolactin, estradiol/testosterone, LH, FSH, TSH, free T4, morning cortisol • If necessary dynamic testing (e.g., glucose tolerance test, insulin tolerance test) to evaluate for hormone excess or deficiency	Annually
	Pituitary MRI	Frequency depends on clinical status, previous extent of tumor, & treatment modality.
Osteoporosis in those w/hypogonadism	DXA eval	Per established guidelines
Complications of acromegaly	Monitor for diabetes mellitus, hypertension, hypogonadism, & osteoarthritis.	Per established guidelines
	Colonoscopy	• At age 40 yrs • Repeat every 3 to 10 yrs depending on # of colorectal lesions on initial colonoscopy & IGF-1 levels. [1]

1. Cairns et al [2010]

Evaluation of Relatives at Risk

It is appropriate to clarify the genetic status of apparently asymptomatic at-risk relatives of an affected individual by molecular genetic testing for the familial *AIP* pathogenic variant so that morbidity and mortality can be reduced by early diagnosis and treatment. Identification of at-risk family members may also reduce the need for costly screening procedures in those family members who have not inherited a pathogenic variant.

See Genetic Counseling for issues related to testing of at-risk relatives for genetic counseling purposes.

Pregnancy Management

Pregnancy may increase the size of a growth hormone-secreting adenoma or a prolactin-secreting adenoma (especially macroadenomas); thus, a pregnant woman with pituitary macroadenoma is at risk of developing visual field defects. In each trimester it is appropriate to inquire about headaches and perform visual field testing. Medical therapies are stopped during pregnancy.

See MotherToBaby for further information on medication use during pregnancy.

Therapies Under Investigation

A study that is actively ascertaining individuals with FIPA or childhood-onset pituitary adenoma is listed in ClinicalTrials.gov.

Growth hormone receptor antagonists block the action of endogenous growth hormone, thereby controlling disease manifestations such as headaches, soft tissue enlargement, diabetes mellitus, hypertension, and high IGF-1 levels. A growth hormone receptor antagonist has been used successfully in persons with *AIP*-FIPA and acromegaly and pituitary gigantism [Goldenberg et al 2008]. In two individuals with *AIP*-related pituitary tumors resistant to treatment with first-generation somatostatin analogs, pasireotide, a second-generation multi-ligand somatostatin analog with affinity to multiple somatostatin receptors, was shown to achieve long-term control of disease [Daly et al 2019]. Although growth hormone receptor antagonists are currently not licensed

for pediatric use, several case reports have shown their effectiveness, especially when IGF-1 levels need to be reduced immediately to prevent abnormally rapid growth [Higham et al 2010, Dutta et al 2019].

Search ClinicalTrials.gov in the US and EU Clinical Trials Register in Europe for access to information on clinical studies for a wide range of diseases and conditions.

Genetic Counseling

Genetic counseling is the process of providing individuals and families with information on the nature, mode(s) of inheritance, and implications of genetic disorders to help them make informed medical and personal decisions. The following section deals with genetic risk assessment and the use of family history and genetic testing to clarify genetic status for family members; it is not meant to address all personal, cultural, or ethical issues that may arise or to substitute for consultation with a genetics professional. —ED.

Mode of Inheritance

AIP familial isolated pituitary adenoma (*AIP*-FIPA) is inherited in an autosomal dominant manner with reduced penetrance.

Risk to Family Members

Parents of a proband

- Almost all individuals reported to date with *AIP*-FIPA have a parent who is also heterozygous for the *AIP* pathogenic variant [Hernández-Ramírez et al 2015]. Because of reduced penetrance, the parent may or may not be affected.
- Reports of unequivocally *de novo* pathogenic variants are rare [Ramírez-Rentería et al 2016]. As not all simplex *AIP*-FIPA cases (i.e., a single occurrence in a family) have been evaluated sufficiently to determine if the pathogenic variant occurred *de novo* in the proband, the proportion of *AIP*-FIPA resulting from a *de novo AIP* pathogenic variant is unknown.
- Molecular genetic testing is recommended for the parents of a proband with an apparently negative family history of the disease and a pathogenic *AIP* variant.
- If the *AIP* pathogenic variant found in the proband cannot be detected in the leukocyte DNA of either parent, possible explanations include a *de novo* pathogenic variant in the proband or germline mosaicism in a parent.* Although no instances of germline mosaicism have been reported, it remains a possibility.

  * Misattributed parentage can also be explored as an alternative explanation for an apparent *de novo* pathogenic variant.
- The family history of some individuals diagnosed with *AIP*-FIPA may appear to be negative because of failure to recognize the disorder in family members due to a milder phenotypic presentation or reduced penetrance. Therefore, an apparently negative family history cannot be confirmed unless molecular genetic testing has been performed on the parents of the proband.

Sibs of a proband. The risk to the sibs of the proband depends on the genetic status of the proband's parents:

- If a parent of the proband is affected or is known to have the *AIP* pathogenic variant, the risk to the sibs of inheriting the pathogenic variant is 50%. Because the clinical penetrance of pituitary tumors in *AIP*-FIPA is approximately 15%-30%, sibs who inherit an *AIP* pathogenic variant may or may not develop a pituitary adenoma (see Penetrance).

- If the pathogenic variant found in the proband cannot be detected in the leukocyte DNA of either parent, the recurrence risk to sibs is estimated to be 1% because of the theoretic possibility of parental germline mosaicism [Rahbari et al 2016].
- The sibs of a proband with clinically unaffected parents are still at increased risk of inheriting the *AIP* pathogenic variant because of the possibility of reduced penetrance in a heterozygous parent or the theoretic possibility of parental germline mosaicism.

Offspring of a proband. Each child of an individual heterozygous for an *AIP* pathogenic variant has a 50% chance of inheriting the *AIP* pathogenic variant.

Other family members. The risk to other family members depends on the status of the proband's parents; if a parent is heterozygous for an *AIP* pathogenic variant, his or her family members may be at risk for *AIP*-FIPA.

Related Genetic Counseling Issues

See Management, Evaluation of Relatives at Risk for information on evaluating at-risk relatives for the purpose of early diagnosis and treatment.

Family planning

- The optimal time for determination of genetic risk and discussion of the availability of prenatal/preimplantation genetic testing is before pregnancy.
- It is appropriate to offer genetic counseling (including discussion of potential risks to offspring and reproductive options) to young adults who are affected or at risk.

DNA banking is the storage of DNA (typically extracted from white blood cells) for possible future use. Because it is likely that testing methodology and our understanding of genes, allelic variants, and diseases will improve in the future, consideration should be given to banking DNA of affected individuals.

Prenatal Testing and Preimplantation Genetic Testing

Once the *AIP* pathogenic variant has been identified in the family, prenatal and preimplantation genetic testing for *AIP*-FIPA are possible. As *AIP*-FIPA demonstrates reduced penetrance, the finding of a pathogenic variant in *AIP* prenatally does not allow accurate prediction of a tumor, the adenoma type, age of onset, prognosis, or availability and/or outcome of treatment.

Differences in perspective may exist among medical professionals and within families regarding the use of prenatal testing, particularly if the testing is being considered for the purpose of pregnancy termination rather than early diagnosis. While use of prenatal testing is a personal decision, discussion of these issues may be helpful.

Resources

GeneReviews staff has selected the following disease-specific and/or umbrella support organizations and/or registries for the benefit of individuals with this disorder and their families. GeneReviews is not responsible for the information provided by other organizations. For information on selection criteria, click here.

- **FIPA Patients**

  Familial Isolated Pituitary Adenoma

  Email: info@fipapatients.org

  www.qmul.ac.uk/fipa-patients

- **AMEND Research Registry**

  Association for Multiple Endocrine Neoplasia Disorders

  United Kingdom

  Email: jo.grey@amend.org.uk

  UK National MEN1 & PNET Research Registry

- **FIPA Consortium Registry**

  Patients with familial pituitary adenoma or childhood onset pituitary disease and their families are encouraged to contact the registry.

  Email: info@fipapatients.org

  www.fipapatients.org/contact

Molecular Genetics

Information in the Molecular Genetics and OMIM tables may differ from that elsewhere in the GeneReview: tables may contain more recent information. —ED.

Table A. AIP Familial Isolated Pituitary Adenomas : Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
AIP	11q13.2	AH receptor-interacting protein	AIP database AIP Gene Mutations	AIP	AIP

Data are compiled from the following standard references: gene from HGNC; chromosome locus from OMIM; protein from UniProt. For a description of databases (Locus Specific, HGMD, ClinVar) to which links are provided, click here.

Table B. OMIM Entries for AIP Familial Isolated Pituitary Adenomas (View All in OMIM)

102200	PITUITARY ADENOMA 1, MULTIPLE TYPES; PITA1
605555	ARYL HYDROCARBON RECEPTOR-INTERACTING PROTEIN; AIP

Molecular Pathogenesis

AIP encodes AIP, a co-chaperone with several interacting partners. In the context of pituitary adenomas, AIP behaves as a tumor suppressor gene [Leontiou et al 2008]. AIP, previously known as hepatitis B virus (HBV) X-associated protein (XAP2) or aryl hydrocarbon receptor (AhR)-associated protein (ARA9), is a 330-amino acid 37-kd protein [Kuzhandaivelu et al 1996, Carver & Bradfield 1997]. The C-terminal end of the protein has three tetratricopeptide repeats (TPRs) and a final alpha-helix. The three TPR domains are degenerate sequences of 34 amino acids comprising two antiparallel helices that play a crucial role in mediating the protein-protein interactions of AIP [Kazlauskas et al 2002].

Mechanism of disease causation. The majority (75%) of *AIP* pathogenic variants result in, or predict, a truncated protein. Many of the pathogenic missense variants affect structurally important conserved amino acids of the TPR structure [Vargiolu et al 2009, Igreja et al 2010, Cai et al 2011]. Clinical data and functional studies both indicate a tumor suppressor role for AIP.

Of note, truncating variants have been reported throughout the protein. Some are predicted to cause nonsense-mediated decay, while others lose the functionally important C-terminal alpha helix. In addition, truncating variants may result in protein with a shortened half-life. Shortened protein half-life has also been shown for many of the pathogenic missense variants [Hernández-Ramírez et al 2016].

Table 9. Notable *AIP* Pathogenic Variants

Reference Sequences	DNA Nucleotide Change	Predicted Protein Change	Comment [Reference]
NM_003977.3 NP_003968.3	c.40C>T	p.Gln14Ter	Finnish founder variant [Vierimaa et al 2006]
	c.241C>T	p.Arg81Ter	Mutational hot spot identified in apparently independent families from Brazil, USA, India, & UK [Chahal et al 2010, Beckers et al 2013]
	c.805_825dup	p.Phe269_His275dup	English/European founder variant [Salvatori et al 2017]
	c.910C>T	p.Arg304Ter	The most common mutational hot spot; Irish, Romanian, English, Italian, Indian & Mexican families described; a founder effect in some regions (e.g., Ireland) [Chahal et al 2010, Beckers et al 2013]

Variants listed in the table have been provided by the authors. *GeneReviews* staff have not independently verified the classification of variants.
GeneReviews follows the standard naming conventions of the Human Genome Variation Society (varnomen.hgvs.org). See Quick Reference for an explanation of nomenclature.

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Chapter Notes

Author Notes

Website: www.fipapatients.org

The FIPA Patients website, established by Dr Korbonits in collaboration with the FIPA Consortium, is an information resource for patients and families with familial isolated pituitary adenoma. It also provides general information for medical professionals on research in the field of FIPA, including links to relevant publications.

The authors welcome comments and inquiries: info@fipapatients.org.

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