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NLM Citation: Korbonits M, Hernández-Ramírez LC. *AIP* Familial Isolated Pituitary Adenomas. 2012 Jun 21 [Updated 2025 Jan 16]. In: Adam MP, Feldman J, Mirzaa GM, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2025.
Bookshelf URL: https://www.ncbi.nlm.nih.gov/books/

AIP Familial Isolated Pituitary Adenomas

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Created: June 21, 2012; Updated: January 16, 2025.

Summary

Clinical characteristics

AIP familial isolated pituitary adenoma (*AIP*-FIPA) is characterized by an increased risk of pituitary neuroendocrine tumors (PitNETs, also known as pituitary adenomas), including growth hormone (GH)-secreting PitNETs (somatotropinomas), prolactin-secreting PitNETs (prolactinomas), GH and prolactin cosecreting PitNETs (somatomammotropinomas), and clinically nonfunctioning PitNETs (NF-PitNETs). Rarely, thyroid-stimulating hormone (TSH)-secreting PitNETs (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, PitNETs can be of the same or different type. Age of diagnosis 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 PitNET by identification of a heterozygous germline pathogenic variant in *AIP* by molecular genetic testing.

Management

Treatment of manifestations: AIP-associated pituitary tumors are usually treated in the same manner as those of unknown genetic cause. Standard treatment of GH-producing microadenomas includes medical therapy (somatostatin receptor ligands [SRLs], GH receptor antagonists, and dopamine agonists), surgery, and/or radiotherapy. Large somatotropinomas are treated with transsphenoidal surgery, medical therapy, and/or radiotherapy. Cardiovascular and rheumatologic/orthopedic complications for individuals with acromegaly are managed as in other individuals with acromegaly. Prolactinomas are treated with dopamine agonist therapy or surgery. NF-PitNETs are treated with surgery and, if necessary, radiotherapy. Management of hypopituitarism (due to tumoral compression, surgery, or radiotherapy) should follow standard guidelines for endocrine care. Persons on glucocorticoid replacement therapy need to increase their steroid dose when ill or stressed.

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Surveillance: In asymptomatic individuals: annual growth assessment and evaluation for signs/symptoms of PitNETs and pubertal development from age four years until adulthood. Although development of new disease in a previously clinically screened person has not been observed in individuals age >30 years, 11 percent of individuals have been diagnosed at age >30 years. Therefore, annual evaluation for signs and symptoms of PitNETs should be carried out 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, thyroxine) 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. Pituitary MRI can be done in those with clinical or biochemical abnormality from age 30 to 50 years, but screening can be less frequent if laboratory tests are normal.

In symptomatic individuals: annual clinical assessment and pituitary function tests (serum IGF-1, spot GH, prolactin, estradiol/testosterone, LH, FSH, TSH, thyroxine, 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: Molecular genetic testing for the familial *AIP* pathogenic variant is appropriate for all at-risk relatives. Apparently asymptomatic individuals found to be heterozygous for a familial *AIP* pathogenic variant seem to benefit from targeted surveillance: PitNETs identified in asymptomatic individuals are significantly less invasive and are associated with better outcomes compared with PitNETs diagnosed in symptomatic individuals.

Genetic counseling

AIP-FIPA is inherited in an autosomal dominant manner with reduced penetrance. Almost all individuals reported to date with *AIP*-FIPA have a parent who is also heterozygous for the *AIP* pathogenic variant; because clinical penetrance of PitNETs in individuals with *AIP* pathogenic variants is approximately 15%-30%, a heterozygous parent may or may not be affected. Each child of an individual who is heterozygous for an *AIP* pathogenic variant has a 50% chance of inheriting the pathogenic variant. Once the *AIP* pathogenic variant has been identified in an affected family member, prenatal and preimplantation genetic testing are possible. As *AIP*-FIPA demonstrates reduced penetrance, the finding of an *AIP* pathogenic variant prenatally does not allow accurate prediction of a tumor, the PitNET type, 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 probands with the following:

- A pituitary neuroendocrine tumor (PitNET) diagnosed before age 18 years, especially a growth hormone (GH)-secreting PitNET, regardless of family history
- A pituitary macroadenoma (tumor >10 mm in diameter) diagnosed before age 30 years, especially a GH-secreting PitNET, regardless of family history
- A prolactin-secreting pituitary macroadenoma (tumor >10 mm in diameter) diagnosed before age 30 years, regardless of family history. A single individual with clinically presenting childhood-onset microadenoma (tumor <10 mm) has been identified in this setting [Marques et al 2020].

Note: (1) A germline *AIP* pathogenic variant is identified in approximately 20% of simplex cases of childhood-onset GH-secreting PitNETs [Tichomirowa et al 2011, Cazabat et al 2012, Iacovazzo et al 2016b]. (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 PitNET.

Note: (1) A germline *AIP* pathogenic variant is identified in approximately 10%-15% of families with FIPA and in 40% of families in which somatotropinomas are the only tumor type observed [Daly et al 2007, Marques et al 2020]. (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 syndromic disorders associated with PitNETs such as multiple endocrine neoplasia type 1 or type 4 (MEN1 or MEN4) or Carney complex.

The **PitNETs** in individuals with *AIP*-FIPA can include:

- GH secreting (somatotropinoma)

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

- Prolactin secreting (prolactinoma)
- GH and prolactin cosecreting (somatomammotropinoma)
- Clinically nonfunctioning PitNETs (NF-PitNETs)

  Note: Most *AIP*-related NF-PitNETs show GH and/or prolactin immunostaining in tumor tissue.

- Thyrotropinoma (thyroid-stimulating hormone [TSH] secreting) (rare; 1 individual described)
- Multihormonal (i.e., secreting >1 pituitary hormone) (extremely rare apart from tumors secreting GH and prolactin)

Note: No unequivocal cases of corticotropinomas have been described in individuals with *AIP*-FIPA.

Establishing the Diagnosis

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

Note: (1) Per ACMG/AMP variant interpretation guidelines, the terms "pathogenic variant" and "likely pathogenic variant" are synonymous in a clinical setting, meaning that both are considered diagnostic and can be used for clinical decision making [Richards et al 2015]. Reference to "pathogenic variants" in this *GeneReview* is understood to include likely pathogenic variants. (2) Identification of a heterozygous *AIP* variant of uncertain significance does not establish or rule out the diagnosis.

Molecular genetic testing approaches can include a combination of **gene-targeted testing** (single gene testing, multigene panel) and **comprehensive genomic testing** (exome sequencing, genome sequencing). Gene-targeted testing requires that the clinician determine which gene(s) are likely involved (see Option 1), whereas comprehensive genomic testing does not (see Option 2).

Option 1

Single-gene testing. Sequence analysis of *AIP* is performed first to detect missense, nonsense, and splice site variants and small intragenic deletions/insertions. Note: Depending on the sequencing method used, single-exon, multiexon, or whole-gene deletions/duplications may not be detected. If no variant is detected by the sequencing method used, the next step is to perform gene-targeted deletion/duplication analysis to detect exon and whole-gene deletions or duplications.

Note: Targeted analysis for pathogenic variants can be performed first in individuals of Finnish ancestry (see Table 9).

A multigene panel that includes *AIP* and other genes of interest (see Differential Diagnosis) may be considered to identify the genetic cause of the condition 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 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** does not require the clinician to determine which gene is likely involved. **Exome sequencing** is most commonly used; **genome sequencing** is also possible. To date, the majority of FIPA-related *AIP* pathogenic variants reported (e.g., missense, nonsense) are within the coding region and are likely to be identified on exome sequencing. Deep intronic variants within *AIP* have been reported in ClinVar, but not in association with *AIP*-FIPA. Large *AIP* deletions are less common, although these structural variants may not be identified by all molecular diagnostic laboratories.

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*-Familial Isolated Pituitary Adenoma

Gene [1]	Method	Proportion of Pathogenic Variants [2] Identified by Method
AIP	Sequence analysis [3]	~91.5% [4, 5]
	Gene-targeted deletion/duplication analysis [6]	~8.5% [7]

1. See Table A. Genes and Databases for chromosome locus and protein.
2. See Molecular Genetics for information on 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 missense, nonsense, and splice site variants and small intragenic deletions/insertions; 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]; Landrum et al [2014]; Hernández-Ramírez et al [2015]; Hernández-Ramírez [2021]; Detomas et al [2023]; Gaspar et al [2023]; Lamback et al [2024]; Xiang et al [2024]; M Korbonits & LC Hernández-Ramírez, personal observations
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 a range of techniques such as quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification (MLPA), and gene-targeted array-based comparative genomic hybridization assays designed to detect single-exon deletions or duplications. Short read-based NGS panels and exome and genome sequencing may be able to detect deletions/duplications using read depth; however, sensitivity is variable and might be lower than that of other methods.
7. To date, five individuals/families with exon or multiexon deletions and two families with whole-gene deletions have been reported in the literature. Five more intragenic large deletions have been reported by clinical laboratories in ClinVar [Georgitsi et al 2008, Igreja et al 2010, Landrum et al 2014, Hernández-Ramírez et al 2015, Marques et al 2020, Hernández-Ramírez 2021].

Clinical Characteristics

Clinical Description

AIP familial isolated pituitary adenoma (*AIP*-FIPA) is characterized by an increased risk of pituitary neuroendocrine tumors (PitNETs), including growth hormone (GH)-secreting PitNETs (somatotropinomas), prolactin-secreting PitNETs (prolactinomas), GH and prolactin cosecreting PitNETs (somatomammotropinomas), and nonfunctioning PitNETs (NF-PitNETs). Rarely, thyroid-stimulating hormone (TSH)-secreting adenomas (thyrotropinomas) are observed. To date, more than 300 individuals with a germline pathogenic variant in *AIP* have been reported in research articles, and there are more than 60 entries from molecular diagnostic laboratories included in ClinVar [Beckers et al 2013, Landrum et al 2014, Marques et al 2020]. The following description of the phenotypic features associated with this condition is based on these reports.

Table 2. Pituitary Neuroendocrine Tumors in Individuals with *AIP* Familial Isolated Pituitary Adenoma

Type of PitNET	% of Persons w/Type of PitNET
Somatotropinoma (GH secreting)	~51%
Prolactinoma (prolactin secreting)	10%
Somatomammotropinoma (GH & prolactin secreting)	~31%
Nonfunctioning PitNET	8%
Thyrotropinoma (TSH secreting)	Rare

Based on Marques et al [2020]
GH = growth hormone; PitNET = pituitary neuroendocrine tumor; TSH = thyroid-stimulating hormone

Onset. The median age of diagnosis of *AIP* familial isolated pituitary adenoma (*AIP*-FIPA) is 23 years [Hernández-Ramírez et al 2015]. The earliest age of diagnosis of a pituitary tumor in a person with an *AIP* pathogenic variant is four years [Dutta et al 2019].

Somatotropinoma (GH-secreting PitNET)

- **Acromegaly.** Approximately 80% of persons with *AIP*-FIPA have acromegaly [Marques et al 2020]. Persons with acromegaly have excess GH 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 long-standing 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 [Katznelson et al 2014].

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

- **Pituitary gigantism.** Excessive GH secretion before fusion of the growth plates results in pituitary gigantism. Exceptionally tall stature results from a combination of high GH levels and delayed onset of puberty due to suppression of luteinizing hormone (LH) / follicle-stimulating hormone (FSH) secretion by mass effect of the tumor and/or, when present, the direct effect of high prolactin levels [Korbonits et al 2024b].

  One third of all individuals with a germline *AIP* pathogenic variant and one half of individuals with *AIP*-FIPA with a somatotropinoma have pituitary gigantism [Daly et al 2010, Hernández-Ramírez et al 2015, Iacovazzo et al 2016b].

Prolactinomas. Approximately 10% of persons with *AIP* pathogenic variants have a prolactinoma [Marques et al 2020]. Prolactinomas result in manifestations of prolactin excess (e.g., amenorrhea, sexual problems, galactorrhea, and infertility) and can also cause mass effects (e.g., visual field defects and headaches).

AIP-related prolactinomas exhibit male predominance, younger age at onset, increased invasiveness, and larger diameter compared with unselected tumors. Around 60% of these tumors respond adequately to standard medical treatment [Carty et al 2021, Vroonen et al 2023]. One family has been described with all affected family members having prolactinoma and none having GH-secreting tumors [Carty et al 2021].

Nonfunctioning PitNETs (NF-PitNETs). Clinically NF-PitNETs are seen in 8% of persons with an *AIP* pathogenic variant [Marques et al 2020].

NF-PitNETs are usually diagnosed due to the local effects of the tumor, such as bitemporal hemianopia or hypogonadism. It is unclear why these silent tumors do not release hormones at a clinically recognizable level; however, there is likely to be a continuum between fully functional and completely silent PitNETs [Drummond et al 2019]. Distinguishing NF-PitNETs 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 PitNET).

In *AIP*-FIPA, NF-PitNETs that have been resected are often (but not always) silent somatotropinoma or lactotroph PitNETs [Hernández-Ramírez et al 2015]. In families with *AIP*-FIPA, NF-PitNETs are identified at a younger age than NF-PitNETs 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 [Marques et al 2020].

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].

Note regarding corticotropinomas. *AIP* defects do not appear to increase the risk of corticotropinoma. One case of a mixed adrenocorticotropic hormone (ACTH)- and prolactin-secreting PitNET associated with a germline loss-of-function *AIP* variant has been reported [Cazabat et al 2012]. Other individuals with corticotropinomas associated with *AIP* defects reported in the literature had benign or likely benign variants or

variants of uncertain significance [Georgitsi et al 2007, Stratakis et al 2010, Beckers et al 2013, Hernández-Ramírez et al 2015, Nguyen et al 2024].

Subfertility is common in persons with pituitary tumors, usually due to hypogonadotropic hypogonadism secondary to compromise of normal gonadotrophs, hyperprolactinemia, surgery, or radiotherapy. Although no data are available specifically regarding subfertility in individuals with *AIP*-FIPA, the risk for this complication is increased in individuals with young-onset PitNETs, particularly prolactinomas [Marques & Boguszewski 2020].

Mass effects. Large pituitary adenomas can be associated with deficiencies of other pituitary hormones that result in subfertility, hypothyroidism, hypoadrenalism, low GH concentration, 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 individuals with acromegaly; the mechanism for the increased frequency is unknown [Melmed 2020].

Larger pituitary tumors may autoinfarct, resulting in pituitary apoplexy (sudden onset of severe headache, visual disturbance, cranial nerve palsies, hypoglycemia, and hypotensive shock). Pituitary apoplexy has been described in individuals with *AIP*-FIPA and is more common in children with *AIP*-FIPA [Chahal et al 2011, Xekouki et al 2013, Dutta et al 2019, Marques et al 2020].

Metastatic PitNET. To date, metastatic PitNET has not been described in an individual with *AIP*-FIPA.

Other, non-pituitary tumors have been observed in some families with *AIP*-FIPA; however, the background population risk for tumors is fairly high and no consistent pattern has been observed. Therefore, at present there is no conclusive evidence that an *AIP* germline pathogenic variant increases the risk for any other tumors. Non-pituitary tumors from *AIP* heterozygotes usually retain heterozygosity at the variant locus, although loss of heterozygosity at the *AIP* locus has been demonstrated in one individual with differentiated thyroid carcinoma and one with adrenocortical carcinoma [Toledo et al 2010, Hernández-Ramírez et al 2015, Coopmans et al 2020].

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 PitNETs 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 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].

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 [Beckers et al 2013, Marques et al 2020].

Genetically Related (Allelic) Disorders

Children with biallelic germline pathogenic *AIP* variants develop a rare (only five individuals reported) pediatric phenotype, including poor weight gain, hyperthermia, tachycardia, hypercalcemia, and diarrhea. Inability to gain weight and early demise is reported. Disruptions in molecular pathways regulating autophagy and protein quality control underlie this clinical presentation [Korbonits et al 2024c].

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

Sporadic tumors. Somatic *AIP* pathogenic variants have been identified in two somatotroph tumors; one occurred with a *GNAS* variant [Chasseloup et al 2024].

Somatic pathogenic *AIP* variants have also rarely been found in malignant melanoma, gastric, colorectal, lung, and breast neoplasms, although their biological relevance is unclear in this context [Sondka et al 2024]. In contrast, *AIP* overexpression promotes tumorigenesis in diffuse large B-cell lymphoma, cholangiocarcinoma, and colorectal cancer [Haworth & Korbonits 2022].

Differential Diagnosis

In children more often than in adults, pituitary neuroendocrine tumors (PitNETs) may be a manifestation of a genetic condition. PitNETs 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 PitNETs and no other features of a syndrome known to be associated with these tumors.

X-linked acrogigantism (X-LAG), a second genetically characterized type of FIPA, is caused by duplication of *GPR101*. X-LAG, a highly penetrant disorder with female preponderance, is associated with pituitary hyperplasia or PitNET resulting in infant-onset growth hormone (GH) excess usually associated with hyperprolactinemia. Most individuals with X-LAG have a *de novo* duplication which is typically mosaic in males. Female-to-male transmission has been observed.

Proposed associations requiring further validation. A single study reported germline heterozygous *CDH23* variants in one third of families with FIPA and 12% of individuals with sporadic PitNETs from a single cohort. Cosegregation with the phenotype was proven in one family, but the variants were not functionally tested, and the findings have not been replicated in other cohorts [Zhang et al 2017]. More recently, germline missense *PAM* variants were detected in a family with gigantism with reduced penetrance and were found to be overrepresented in individuals with sporadic PitNETs from two different cohorts [De Sousa et al 2023, Trivellin et al 2023]. Loss of function was demonstrated in vitro for multiple variants [Trivellin et al 2023].

Families with FIPA of known or unknown cause can have homogeneous PitNET 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 with or without germline *AIP* pathogenic variant 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 PitNETs by Family History and Presence/Absence of a Germline *AIP* Pathogenic Variant

Characteristics		Familial Isolated Pituitary Adenoma (FIPA)			Simplex Somatotropinoma [1]
		AIP-FIPA	X-LAG	FIPA of unknown cause	
Clinical features	Typical age of onset (range) [2]	Adolescence (age 4-24 yrs)	Early childhood (age <4 yrs; typically in first 2 yrs of life)	40 yrs	43 yrs
	Average number of affected family members [3]	3-4	Usually simplex cases, but 3 families w/2-3 affected members have been described	2-3	NA
	Male-to-female ratio [4]	1:1 to 2:1	1:3	1:1	1:1
Adenoma features	Somatotropinomas/ somatomammotropinomas[4]	70%-80%	~100%	~50%	NA
	Size [4]	Macroadenomas in vast majority	Usually macroadenomas; less frequently, pituitary hyperplasia or a combination of PitNET & hyperplasia	Majority macroadenomas	Smaller
	Aggressiveness [4]	More	Variable	More	Less
	Response to standard treatment [4]	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], Hernández-Ramírez et al [2015], Daly et al [2016], Daly & Beckers [2024]
3. Igreja et al [2010], Daly & Beckers [2024]
4. Daly et al [2010], Marques et al [2020], Daly & Beckers [2024]
5. Marques et al [2020]

Genetic Syndromes Associated with Pituitary Tumors

Table 4. Genetic 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 30%-40% of affected persons, most often prolactinomas.	Parathyroid adenoma w/ hypercalcemia; well-differentiated neuroendocrine neoplasms of pancreas, gastrointestinal tract & other locations; adrenocortical tumors; non-endocrine tumors
CDKN1B	Multiple endocrine neoplasia type 4 (MEN4)	AD	Pituitary tumors occur in 45%. [1]	Rare disorder; clinical findings similar to those of MEN1

Table 4. continued from previous page.

Gene(s)	Disorder	MOI	Pituitary Tumor Features	Other Features
PRKAR1A *PRKACB* [2]	Carney complex	AD	≤75% of affected persons have somatotroph hyperplasia / GH-producing adenoma.	Skin pigmentary abnormalities; cardiac, skin, breast, & female genital tract myxomas; schwannomas; primary pigmented nodular adrenocortical disease; large cell calcifying Sertoli cell tumors; thyroid nodules; acromegaly
GNAS	Fibrous dysplasia / McCune-Albright syndrome	NA (postzygotic somatic activating pathogenic variant)	~15%-20% have *GNAS* pathogenic variants in anterior pituitary that can lead to autonomous GH production; ~80% of persons w/ autonomous GH production also have hyperprolactinemia.	Polyostotic fibrous dysplasia; hyperpigmented skin macules; multiple endocrine disorders (e.g., multinodular goiter, multinodular adrenal hyperplasia, & precocious puberty)
MAX *SDHA* *SDHB* *SDHC* *SDHD* *RET* [3]	Hereditary paraganglioma-pheochromocytoma syndromes	AD	Rarely assoc w/PitNETs; [4] metastatic PitNET described, vacuolated histology picture	Paragangliomas; pheochromocytomas; gastrointestinal stromal tumors; clear cell renal cell carcinoma
DICER1	*DICER1* tumor predisposition	AD	ACTH-secreting pituitary blastoma (rare)	↑ risk for pleuropulmonary blastoma, which typically presents in infants & children age <6 yrs
MLH1 *MSH2* *MSH6* *PMS2* [5]	Lynch syndrome	AD	Low penetrance of pituitary disease; ACTH-secreting macroadenomas	Colorectal, endometrial, ovarian, & other carcinomas
USP8	Pituitary adenoma 4 (OMIM 219090)	Most often due to somatic pathogenic variants; one germline *de novo* pathogenic variant reported [6]	Small corticotropinoma w/high ACTH secretion, predominantly occurring in young females	Developmental delay; dysmorphic features; ichthyosiform hyperkeratosis; chronic lung disease; chronic kidney disease; hyperglycemia; dilated cardiomyopathy; hyperinsulinism; partial GH deficiency reported in assoc w/germline pathogenic variant

ACTH = adrenocorticotropic hormone; AD = autosomal dominant; GH = growth hormone; MOI = mode of inheritance

1. Reviewed in Singeisen et al [2023]

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.

3. Hereditary paraganglioma-pheochromocytoma syndromes are also caused by pathogenic variants in *SDHAF2* and *TMEM127*. These genes are not listed in Table 4 because there are no reports of PitNETs associated with *SDHAF2* or *TMEM127* germline pathogenic variants.

4. Reviewed in Hernández-Ramírez et al [2024], Ramírez-Rentería & Hernández-Ramírez [2024]

5. Lynch syndrome is also caused by deletions in *EPCAM*. This gene is not listed in Table 4 because there are no reports of PitNETs associated with *EPCAM* germline pathogenic variants.

6. Cohen et al [2019]

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

Other Space-Occupying Lesions

In addition to PitNETs, numerous space-occupying lesions can occur in the pituitary fossa, including germ cell tumors, hamartomas, Rathke cleft cysts, arachnoid cysts, meningiomas, optic pathway gliomas, sellar lymphomas, metastatic lesions, cavernous sinus venous malformations, aneurysms, and craniopharyngiomas, among others [Ugga et al 2023]. The latter account for the most common space-occupying lesions after PitNETs and cause symptoms by compressing the normal pituitary, resulting in hormonal deficiencies and mass effects on the surrounding tissues and brain [Gan et al 2023].

Management

Recent clinical practice guidelines for pediatric pituitary neuroendocrine tumors (PitNETs), as well as acromegaly and prolactinoma, include management suggestions for hereditary pituitary tumors [Katznelson et al 2014, Petersenn et al 2023, Korbonits et al 2024a, Korbonits et al 2024b]. Nevertheless, as no specific familial isolated pituitary adenoma (FIPA) guideline exists, the following recommendations also include the authors' personal experience managing individuals with this disorder.

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs of an individual diagnosed with *AIP*-FIPA, the evaluations summarized in Table 5 (if not performed as part of the evaluation that led to the diagnosis) are recommended (for details, see Giustina et al [2024]).

Table 5. *AIP* Familial Isolated Pituitary Adenoma: Recommended Evaluations Following Initial Diagnosis

System/Concern	Evaluation	Comment
PitNET	• LH, FSH, testosterone/estradiol • Visual field eval • Consultation w/endocrinologist	DXA scan in those w/hypogonadism
	Pituitary MRI	Beginning at age 10 yrs, or younger if PitNET is suspected
Somatotropinoma (GH secreting)	• Evaluate for signs/symptoms of GH excess (e.g., stature, change in facial appearance, change in shoe size, ↑ ring size, headache, excessive sweating, joint pains, carpal tunnel syndrome). • Spot serum GH, IGF-1	• Review of serial photographs for acromegalic changes • Measurement of parental heights • OGTT in persons w/findings of acromegaly • ACTH reserve if needed
Prolactinoma	• Evaluate for manifestations of prolactin excess (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.
Clinically NF-PitNET	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 thyroxine	Consider other causes of thyroid hormone resistance.

Table 5. continued from previous page.

System/Concern	Evaluation	Comment
Genetic counseling	By medical geneticist, certified genetic counselor, certified advanced genetic nurse	To obtain a pedigree & inform affected persons & their families re nature, MOI, & implications of *AIP*-FIPA to facilitate medical & personal decision making

ACTH = adrenocorticotropic hormone; DXA = dual-energy x-ray absorptiometry; FIPA = familial isolated pituitary adenoma; FSH = follicle-stimulating hormone; GH = growth hormone; IGF-1 = insulin-like growth factor 1; LH = luteinizing hormone; OGTT = oral glucose tolerance test; MOI = mode of inheritance; NF = nonfunctioning; PitNET = pituitary neuroendocrine tumor; TSH = thyroid-stimulating hormone

Treatment of Manifestations

Recommendations for treatment for *AIP*-FIPA have been included in pediatric pituitary adenoma guidelines [Korbonits et al 2024a, Korbonits et al 2024b]. Although management is usually based on general treatment guidelines for PitNETs, two particular aspects should be taken into consideration. First, multiple authors have shown that outcomes for surgical excision and standard medical treatment of clinically presenting somatotropinomas in *AIP*-FIPA are often suboptimal [Beckers et al 2013]. These findings are due to large tumor size and an apparent partial resistance to first-generation somatostatin receptor ligands (SRLs; octreotide and lanreotide), which might be *AIP* dependent [Iacovazzo et al 2016a]. Therefore, these individuals most often require multimodal treatment [Hernández-Ramírez et al 2015, Marques et al 2020]. Second, while there is experience with treating PitNETs in symptomatic persons with FIPA, the approach to management and treatment of prospectively identified individuals is relatively recent. This refers to persons identified through clinical screening due to a family history of FIPA and/or presence of a heterozygous germline *AIP* pathogenic variant. The age of detection of *AIP*-FIPA in these individuals is earlier than in clinically presenting cases, likely due to directed screening, but their prognosis is generally better. Given the prevalence of incidental PitNETs, 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 [2014], Williams et al [2014], Hernández-Ramírez et al [2015], Marques et al [2020], Petersenn et al [2023], Korbonits et al [2024a], Korbonits et al [2024b].

Table 6. *AIP* Familial Isolated Pituitary Adenoma: Treatment of Manifestations

Manifestation/Concern	Treatment	Considerations/Other
Pituitary microadenoma	Medical therapy (e.g., SRLs, GH receptor antagonists, & dopamine agonists), surgery, &/or radiotherapy	Monitor microadenomas w/normal clinical & biochemistry findings closely.
Pituitary macroadenoma	Transsphenoidal surgery, medical therapy, &/or radiotherapy	Surgery often does not fully control tumor; large recurring tumors may require radiotherapy if tumor invades neighboring anatomic structures (e.g., cavernous sinus).
Somatotropinoma & somatomammotropinoma	• Radiotherapy (conventional or radiosurgery) for large tumors, 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 SRLs; [1] 2nd-generation SRLs may have better efficacy. [2]

Table 6. continued from previous page.

Manifestation/Concern	Treatment	Considerations/Other
Prolactinoma	• Dopamine agonist therapy (e.g., cabergoline) • Surgical treatment often used for macroprolactinoma (diameter >10 mm)	Prolactinomas assoc w/*AIP*-FIPA can be aggressive & difficult to treat. [1]
NF-PitNET	Surgery & (if necessary) radiotherapy	Usually do not respond to traditional SRLs
Hypopituitarism	Mgmt per endocrinologist	Can be due to tumor size, surgery, &/or radiotherapy
	Persons on glucocorticoid replacement therapy need to increase their steroid dose when ill or stressed.	

GH = growth hormone; NF = nonfunctioning; PitNETs = pituitary neuroendocrine tumors; SRLs = somatostatin receptor ligands
1. Daly et al [2010]
2. Daly et al [2019]

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 400 persons with symptomatic or asymptomatic *AIP*-FIPA.

Table 7. *AIP* Familial Isolated Pituitary Adenoma: Recommended Surveillance

System/Concern	Evaluation	Frequency
PitNET	• Measure height & weight; calculate height velocity. • Evaluate for signs/symptoms of PitNET & evaluate pubertal development.	Annually beginning at age 4 yrs until adulthood [1]
	Evaluate for signs/symptoms of PitNET.	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 thyroxine	• Annually from age 4 to 30 yrs; to date, no secreting PitNETs 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: MRI can be performed between ages 30 & 50 yrs

FSH = follicle-stimulating hormone; IGF-1 = insulin-like growth factor 1; LH = luteinizing hormone; PitNETs = pituitary neuroendocrine tumors; TSH = thyroid-stimulating hormone
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-GH-secreting PitNETs before age ten years are rare.

Table 8. *AIP* Familial Isolated Pituitary Adenoma: Recommended Additional Surveillance for Symptomatic Individuals

System/Concern	Evaluation	Frequency
History of PitNET	• Clinical assessment • Serum IGF-1, spot GH, prolactin, estradiol/testosterone, LH, FSH, TSH, free thyroxine, 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 3-10 yrs depending on # of colorectal lesions on initial colonoscopy & IGF-1 levels. [1]

DXA = dual-energy x-ray absorptiometry; FSH = follicle-stimulating hormone; GH = growth hormone; IGF-1 = insulin-like growth factor 1; LH = luteinizing hormone; PitNETs = pituitary neuroendocrine tumors; TSH = thyroid-stimulating hormone
1. Giustina et al [2020], Petersenn et al [2023], Korbonits et al [2024a], Korbonits et al [2024b]

Evaluation of Relatives at Risk

It is appropriate to clarify the genetic status of all at-risk relatives of an affected individual by molecular genetic testing for the familial *AIP* pathogenic variant. The use of molecular genetic testing for early identification of at-risk family members improves diagnostic certainty and reduces the need for screening procedures (see Surveillance) in those at-risk family members who have not inherited the pathogenic variant.

Apparently asymptomatic individuals found to be heterozygous for a familial *AIP* pathogenic variant seem to benefit from targeted surveillance (see Table 7). PitNETs identified in asymptomatic individuals are significantly less invasive and are associated with better outcomes compared with PitNETs diagnosed in symptomatic individuals [Marques et al 2020].

As PitNET surveillance for those at risk for *AIP*-FIPA is suggested to begin at age four years, molecular genetic testing is generally offered to children at risk for *AIP*-FIPA by that age or earlier if clinically indicated. Parents may want to know the genetic status of their children prior to initiating surveillance in order to avoid unnecessary procedures in a child who has not inherited the 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 (GH)-secreting PitNET or a prolactin-secreting PitNET (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

The Genetics of Endocrine Tumours - Familial Isolated Pituitary Adenoma – FIPA study is actively recruiting individuals with FIPA or childhood-onset PitNET (NCT00461188).

GH receptor antagonists block the action of endogenous GH, thereby controlling disease manifestations such as headaches, soft tissue enlargement, diabetes mellitus, hypertension, and high insulin-like growth factor 1 (IGF-1) levels. In two individuals with *AIP*-related PitNETs resistant to treatment with first-generation somatostatin receptor ligands (SRLs), pasireotide, a second-generation multiligand SRL with affinity to multiple somatostatin receptors, was shown to achieve long-term control of disease [Daly et al 2019]. However, in another individual, a somatotropinoma showed resistance to both first- and second-generation SRLs, as well as to the dopamine receptor agonist cabergoline [van Santen et al 2021].

The GH receptor antagonist pegvisomant has been used in at least eight persons with acromegaly and pituitary gigantism and confirmed *AIP*-FIPA [van Santen et al 2021, García-de-la-Torre et al 2023, MacFarlane & Korbonits 2024]. Although pegvisomant is currently not licensed for pediatric use, this drug has proven effective in most of the individuals (both adults and children) so far reported, especially when IGF-1 levels need to be reduced immediately to prevent abnormally rapid growth.

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, Marques et al 2020]. Because clinical penetrance of pituitary neuroendocrine tumors (PitNETs) in individuals with an *AIP* pathogenic variant is approximately 15%-30%, the heterozygous parent may or may not be affected.
- Reports of unequivocally *de novo* pathogenic variants are rare [Ramírez-Rentería et al 2016]. The proportion of individuals who have *AIP*-FIPA as the result of a *de novo AIP* pathogenic variant is unknown.
- If the proband appears to be the only affected family member (i.e., a simplex case), molecular genetic testing is recommended for the parents of the proband to evaluate their genetic status, inform recurrence risk assessment, and assess their need for PitNET surveillance. Note: A proband may appear to be the only affected family member because of failure to recognize the disorder in family members due to a milder phenotypic presentation or reduced penetrance. Therefore, *de novo* occurrence of a *AIP* pathogenic

variant in the proband cannot be confirmed unless molecular genetic testing has demonstrated that neither parent has the *AIP* pathogenic variant
- If the pathogenic variant identified in the proband is not identified in either parent and parental identity testing has confirmed biological maternity and paternity, the following possibilities should be considered:
  - The proband has a *de novo* pathogenic variant.
  - The proband inherited a pathogenic variant from a parent with gonadal (or somatic and gonadal) mosaicism. Note: Testing of parental leukocyte DNA may not detect all instances of somatic mosaicism and will not detect a pathogenic variant that is present in the germ (gonadal) cells only.

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 PitNET (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 possibility of parental gonadal mosaicism [Rahbari et al 2016].
- If the parents have not been tested for the *AIP* pathogenic variant but are clinically unaffected, sibs are still presumed to be at increased risk for *AIP*-FIPA because of the possibility of reduced penetrance in a heterozygous parent or parental gonadal 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, the parent's 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.

Prenatal Testing and Preimplantation Genetic Testing

Once the *AIP* pathogenic variant has been identified in an affected family member, 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 PitNET 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 and preimplantation genetic testing. While use of prenatal and preimplantation genetic 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.

- **Familial Isolated Pituitary Adenoma (FIPA) Patients**
  United Kingdom
  Email: info@fipapatients.org
  qmul.ac.uk/fipa-patients
- **AMEND Research Registry**
  Association for Multiple Endocrine Neoplasia Disorders
  United Kingdom
  amend.org.uk
- **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
  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 aryl-hydrocarbon receptor-interacting protein (AIP), a co-chaperone with several interacting partners. In the context of pituitary neuroendocrine tumors (PitNETs), AIP behaves as a tumor suppressor [Leontiou et al 2008]. The C-terminal end of the protein has three tetratricopeptide repeat (TPR) domains 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 protein-protein interactions [Kazlauskas et al 2002].

The majority (75%) of *AIP* pathogenic variants result in, or predict, a truncated protein. 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. Many of the pathogenic missense variants affect structurally important conserved amino acids of the TPR structure, but missense variants can be scattered throughout the protein [Vargiolu et al 2009, Igreja et al 2010, Cai et al 2011]. Shortened protein half-life has also been shown for many of the pathogenic missense variants [Hernández-Ramírez et al 2016].

Mechanism of disease causation. Loss of function

Table 9. *AIP* Pathogenic Variants Referenced in This *GeneReview*

Reference Sequences	DNA Nucleotide Change	Predicted Protein Change	Comment [Reference]
NM_003977.4 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.811C>T	p.Arg271Trp	Mutational hot spot identified in apparently independent families from several countries (UK, New Zealand, Algeria, Germany, & Spain) [Chahal et al 2010, Beckers et al 2013, Marques et al 2020]
	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, Polish, & Mexican families described; a founder effect has been seen in some regions (e.g., Ireland, Italy) [Chahal et al 2010, Beckers et al 2013, Ramírez-Rentería et al 2016]

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.

Chapter Notes

Author Notes

Website: www.qmul.ac.uk/fipa-patients

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

Acknowledgments

We are grateful to referring colleagues and patients for providing information on this disease. Our research is supported by departmental funding from the Coordination of Scientific Research from the National Autonomous University of Mexico (UNAM), and grants from UNAM's Support Program for Research Projects and Technological, the Mexican Society of Nutrition and Endocrinology, and the United Kingdom's Society for Endocrinology as well as UK's Medical Research Council, Barts Charity, and the Rosehills Trust.

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Revision History

- 16 January 2025 (sw) Comprehensive update posted live
- 16 April 2020 (sw) Comprehensive update posted live
- 21 June 2012 (me) Review posted live
- 3 February 2011 (mk) Original submission

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