

REVIEW

Clinical and genetic aspects of familial isolated pituitary adenomas

Vladimir Vasilev,^{1,||} Adrian Daly,¹ Luciana Naves,^{||} Sabina Zacharieva,^{||} Albert Beckers¹

¹University of Liège, Centre Hospitalier Universitaire de Liège, Department of Endocrinology, Belgium. ^{||}Medical University, Sofia, Clinical Centre of Endocrinology and Gerontology, Bulgaria. ^{||}University of Brasilia, Internal Medicine, Department of Endocrinology, Brasilia/DF, Brazil.

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

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

Vasilev V, Daly A, Naves L, Zacharieva S, Beckers A. Clinical and genetic aspects of familial isolated pituitary adenomas. Clinics. 2012;67(S1):37-41.

E-mail: Albert.Beckers@chu.ulg.ac.be

Tel.: 0032 4 3667084

INTRODUCTION

Pituitary adenomas are one of the most common intracranial neoplasms. Questions regarding their prevalence in the general population were recently addressed by a large cross-sectional study in the province of Liège, Belgium, which revealed 94 cases of pituitary adenomas per 100,000 inhabitants (1). Similar findings were later confirmed in Banbury, UK (2). Despite being generally benign, pituitary adenomas still exert significant influence as they combine symptoms of hormonal dysfunction with signs of local compression, and may require complex and costly management and long-term follow-up. Pituitary adenoma formation is generally considered to be the result of the clonal expansion of a single mutated cell (3) and molecular studies have identified a number of genetic and epigenetic abnormalities that may have a possible causative or facilitatory role in pituitary tumorigenesis. These include somatic mutations in the *gsp* oncogene, overexpression of the pituitary tumor transforming gene (*PTTG*), disruptions in cell cycle regulation and intracellular signaling pathways

and, rarely, mutations of classic oncogenes (4,5). The vast majority of pituitary adenomas, however, arise sporadically, and inherited germline mutations in different genes are few in number, accounting for approximately 5% of all pituitary tumors (6). Traditionally, familial pituitary adenomas have been associated with some multiple neoplasia syndromes, including multiple endocrine neoplasia type 1 (MEN 1), Carney complex, and the newly defined multiple endocrine neoplasia type 4. By the end of the 20th century, however, only occasional cases of non-syndromic familial pituitary tumors were reported, mostly acromegaly (7). The first single-center study to specifically scout for cases of familial pituitary adenomas unrelated to MEN 1 and Carney complex was performed in Liège, Belgium in the 1990s, and led to the identification of an initial cohort of 27 patients (8). Reports from the same center confirmed the condition as a new clinical entity, and the term familial isolated pituitary adenomas (FIPA) was adopted (9–11). Its definition expanded the search internationally, and by 2011 more than 200 affected families had been reported (12,13). FIPA is currently considered to account for around 2–3% of pituitary adenomas (14).

CLINICAL FEATURES OF PATIENTS WITH FIPA

The syndrome of FIPA is defined as familial presentation of any type of pituitary adenoma in the absence of clinical and genetic evidence for MEN 1 and Carney complex

Copyright © 2012 CLINICS – This is an Open Access article distributed under the terms of the Creative Commons Attribution Non-Commercial License (<http://creativecommons.org/licenses/by-nc/3.0/>) which permits unrestricted non-commercial use, distribution, and reproduction in any medium, provided the original work is properly cited.

No potential conflict of interest was reported

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

MOLECULAR GENETICS OF FIPA

The elucidation of the responsible genetic causes of FIPA started with the identification of loss of heterozygosity in locus 11q13 in relatives with familial acromegaly who lacked mutations in the *MEN1* gene (17,18). Separate research for potential genes in a Finnish cohort of patients with familial pituitary tumors revealed inactivating mutations in the gene for aryl-hydrocarbon receptor interacting protein (AIP) (19). The causative role of *AIP* in FIPA was confirmed with the discovery of several new germline mutations in a large series of 73 families (20). Loss of heterozygosity in tumor tissues suggests a tumor suppressor function for *AIP*, but the exact molecular

mechanisms leading to pituitary tumorigenesis are not known. Homozygous *AIP*^{-/-} knockout mice die in the early embryonic period as a result of severe cardiovascular abnormalities, suggesting that AIP may play a role in cardiovascular development (21). Heterozygous *AIP*^{+/-} animals, however, develop a phenotype that is very similar to human pituitary disease with the majority of the mice presenting with aggressive somatotropinomas (22). The *AIP* gene consists of six exons and codes for a 330-amino-acid protein, the sequence of which is highly conserved between different species. It shares a structural homology with immunophilin proteins because of the presence of a peptidyl-prolyl *cis-trans* isomerase-like domain, but does not function as such (23,24). Instead, AIP takes part in numerous protein-protein interactions, mediated through its C-terminal, which houses three tetratricopeptide repeats and a final α -helix. Among the first identified partners of AIP is the aryl hydrocarbon receptor (AhR), a ligand-inducible transcription factor that modulates cellular responses to various xenobiotic toxins, such as dioxins, as well as some endogenous compounds such as cAMP (25). In the absence of ligands, the AhR binds to two molecules of the 90-kDa heat-shock protein, acting as chaperone, and to AIP and p23 proteins, acting as co-chaperones, to form a multiprotein complex in the cytoplasm (26). The activation of this complex by its xenobiotic ligand results in nuclear translocation, where AhR binds to the aryl hydrocarbon receptor nuclear translocator and promotes the transcription of specific genes coding various drug metabolizing enzymes as well as other proteins (24). The effect of AIP on the functional status of AhR is still a matter of debate because conflicting results have been reported, but it seems that it maintains the stability of the complex by protecting AhR from ubiquitin-dependent degradation (27). Reduced AIP levels in *AIP*-mutated pituitary adenomas are associated with a lack of nuclear AhR immunostaining, suggesting that down-regulation of AhR may be involved in pituitary tumorigenesis (28). Consistent with this finding, over-expression of wild-type AIP in pituitary and hepatic cell cultures slows down cell proliferation (16). AIP is also thought to interact with two subtypes of phosphodiesterases: PDE4A5 and PDE2A (29,30). These enzymes participate in the regulation of numerous signaling cascades that use cAMP as a second messenger, including the growth hormone-releasing hormone receptor pathway in pituitary cells. Disruptions in signal transduction, which lead to abnormally high cAMP concentrations, are associated with pituitary hyperplasia and adenoma formation in some conditions, such as Carney complex and McCune-Albright syndrome (31). AIP binding to PDE4A5 reduces its catalytic activity, and it is not clear if this interaction plays a role in pituitary tumorigenesis, as loss of AIP would presumably result in low cAMP levels. The interaction with PDE2A does not alter the enzyme activity, and the local reduction of cAMP may impede the nuclear translocation of the AhR complex (30). Recently, AIP was shown to interact with the tyrosine kinase receptor, encoded by the *RET* proto-oncogene, and the inhibitor of apoptosis, survivin, and therefore to have a potential role in cell cycle regulation. Binding to survivin maintains its stability and promotes cell survival by elevating the anti-apoptotic threshold. On the other hand, the interaction with *RET* prevents the formation of the AIP-survivin

complex, resulting in subsequent survivin degradation and increase in apoptosis (32). These effects, however, are contrary to the proposed tumor-suppressor role of AIP. Apart from stabilizing the AhR complex, AIP may also bind to a set of nuclear receptors including peroxisome proliferator-activated receptor α , the glucocorticoid receptor, and β -thyroid hormone receptor 1. Furthermore, a role has been proposed for AIP in virus-induced tumorigenesis as a potential partner of hepatitis B virus X antigen and Epstein-Barr virus-encoded nuclear antigen 3 (24).

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

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

CLINICAL CHARACTERISTICS OF PATIENTS WITH AIP-MUTATED FIPA

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

CLINICAL IMPLICATIONS AND MANAGEMENT

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

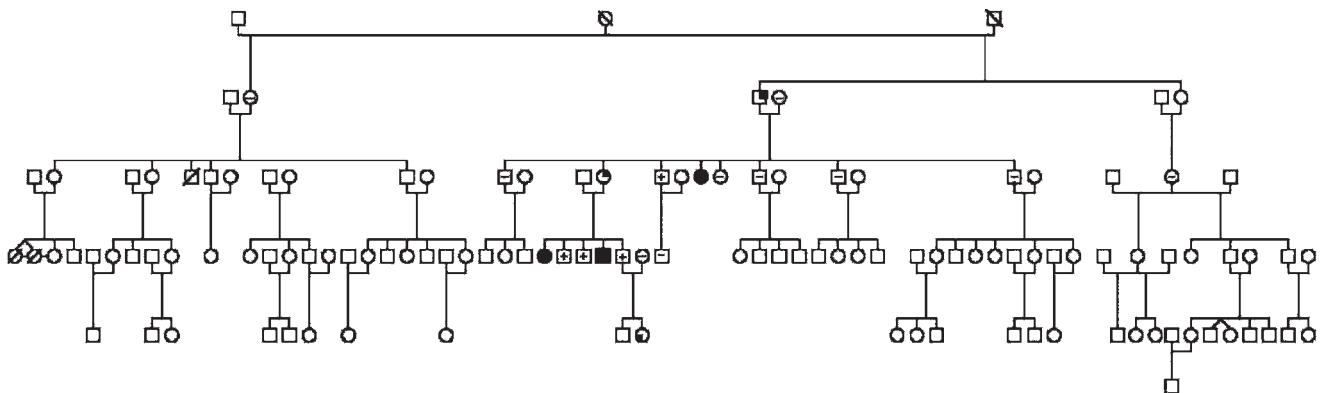


Figure 1 - Genealogical tree of a familial isolated pituitary adenoma (FIPA) family with E174 frameshift aryl-hydrocarbon receptor interacting protein gene (AIP) mutation. Filled black symbols indicate mutation-positive patients with pituitary tumors. (+) symbols show patients with AIP mutation without clinical, hormonal or radiological evidence for pituitary pathology. (-) is used for patients with wild-type AIP. Subjects marked with (?) did not undergo genetic analysis but had no clinical signs of pituitary disease. Subjects with AIP mutation and elevated insulin-like growth factor-1 levels are shown by a symbol with a filled upper right corner, and an AIP-mutation positive girl with premature telarche, ovarian enlargement and advanced bone age is indicated by a symbol with a filled lower left corner. Adapted by the author Naves LA (39).

Table 1 - Comparison of some demographic and clinical features of acromegaly patients with and without *AIP* mutations.

	<i>AIP</i> mutated group	Control group
Number of patients	75	232
Males*	61.3%	46.5%
Age at diagnosis, years*	22	43
Macroadenomas*	90.1%	80.8%
Extrasellar expansion	65.1%	49.8%
Invasion*	51.7%	38.8%
Gigantism*	32%	6.5%

Significant difference is marked with an *. Adapted from Daly et al. (37). *AIP*: aryl-hydrocarbon receptor interacting protein gene.

examination should be performed for exclusion of extra-pituitary pathology that may imply syndromic disease, and a comprehensive family history taken before referring patients to genetic screening. Genetic testing in relatives of patients with *AIP* mutations can be especially beneficial in terms of early diagnosis, which may yield better outcomes from treatment. Although no consensus protocols for management of patients with *AIP*-mutated FIPA currently exist, it may be appropriate to start regular magnetic resonance imaging monitoring and hormonal evaluation from early childhood because macroadenomas and gigantism have been diagnosed in patients as young as 6–8 years (34,36). Widespread screening for *AIP* mutations among apparently sporadic pituitary adenomas may not be warranted, as the prevalence of *AIP* alterations is low in such populations. However, *AIP* mutations are discovered in approximately 12% of young patients (aged <30 years) and in 20% of pediatric patients, most often presenting with growth hormone-secreting or prolactin-secreting macroadenomas, suggesting that focused screening in this patient group may provide valuable clinical information (33,40).

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

ACKNOWLEDGMENTS

The authors would like to thank the assistance of Prof. Albert Beckers from the FIRS of the Centre Hospitalier Universitaire de Liège and from Pfizer.

AUTHOR CONTRIBUTIONS

All the authors participated in data analysis. Vasilev V, Daly A and Beckers A were responsible for the manuscript writing. All the authors approved the final version of the manuscript.

REFERENCES

- Daly AF, Rixhon M, Adam C, Dempegioti A, Tichomirowa MA, Beckers A. High prevalence of pituitary adenomas: a cross-sectional study in the province of Liege, Belgium. *J Clin Endocrinol Metab.* 2006;91(12):4769-75, <http://dx.doi.org/10.1210/jc.2006-1668>.
- Fernandez A, Karavitaki N, Wass JA. Prevalence of pituitary adenomas: a community-based, cross-sectional study in Banbury (Oxfordshire, UK). *Clin Endocrinol (Oxf).* 2010;72(3):377-82, <http://dx.doi.org/10.1111/j.1365-2265.2009.03667.x>.
- Herman V, Fagin J, Gonsky R, Kovacs K, Melmed S. Clonal origin of pituitary adenomas. *J Clin Endocrinol Metab.* 1990;71(6):1427-33, <http://dx.doi.org/10.1210/jcem-71-6-1427>.
- Dworakowska D, Grossman AB. The pathophysiology of pituitary adenomas. *Best Pract Res Clin Endocrinol Metab.* 2009;23(5):525-41, <http://dx.doi.org/10.1016/j.beem.2009.05.004>.
- Vandeva S, Jaffrain-Rea ML, Daly AF, Tichomirowa M, Zacharieva S, Beckers A. The genetics of pituitary adenomas. *Best Pract Res Clin Endocrinol Metab.* 2010;24(3):461-76, <http://dx.doi.org/10.1016/j.beem.2010.03.001>.
- Daly AF, Tichomirowa MA, Beckers A. The epidemiology and genetics of pituitary adenomas. *Best Pract Res Clin Endocrinol Metab.* 2009;23(5):543-54, <http://dx.doi.org/10.1016/j.beem.2009.05.008>.
- Verloes A, Stevenaert A, Teh BT, Petrossians P, Beckers A. Familial acromegaly: case report and review of the literature. *Pituitary.* 1999;1(3-4):273-7, <http://dx.doi.org/10.1023/A:1009958510378>.
- Valdes Socin H, Poncin J, Stevens V, Stevenaert A, Beckers A. Adenomes hypophysiaires familiaux isolés non liés avec la mutation somatique NEM-1. Siuvi de 27 patients. *Ann Endocrinol-Paris.* 2000;61:301.
- Valdes Socin H, Poncin J, Vanbellinghen J, Stevens V, Jaffrain-Rea M, Tamburrano G, et al. Familial isolated pituitary adenomas not related to the MEN1 syndrome. 5th European Congress of Endocrinology; 2001 9-13 June.
- Valdes Socin H, Jaffrain Réa M, Tamburrano G, Cavagnini F, Cicarelli E, Colao A, et al. Familial isolated pituitary adenomas: clinical and molecular studies in 80 patients. *The Endocrine Society's 84th Annual Meeting; 2002 19-22 June; San Francisco.*
- Beckers A. Familial isolated pituitary adenomas. *J Intern Med.* 2004;255(6):698.
- Vasilev V, Daly AF, Petrossians P, Zacharieva S, Beckers A. Familial pituitary tumor syndromes. *Endocr Pract.* 2011;17(Suppl 3):41-6.
- Chahal HS, Chapple JP, Frohman LA, Grossman AB, Korbonits M. Clinical, genetic and molecular characterization of patients with familial isolated pituitary adenomas (FIPA). *Trends Endocrinol Metab.* 2010;21(7):419-27, <http://dx.doi.org/10.1016/j.tem.2010.02.007>.
- Daly AF, Jaffrain-Rea ML, Ciccarelli A, Valdes-Socin H, Rohmer V, Tamburrano G, et al. Clinical characterization of familial isolated pituitary adenomas. *J Clin Endocrinol Metab.* 2006;91(9):3316-23, <http://dx.doi.org/10.1210/jc.2005-2671>.
- Beckers A, Daly AF. The clinical, pathological, and genetic features of familial isolated pituitary adenomas. *Eur J Endocrinol.* 2007;157(4):371-82, <http://dx.doi.org/10.1530/EJE-07-0348>.
- Leontiou CA, Gueorguiev M, van der Spuy J, Quinton R, Lolli F, Hassan S, et al. The role of the aryl hydrocarbon receptor-interacting protein gene in familial and sporadic pituitary adenomas. *J Clin Endocrinol Metab.* 2008;93(6):2390-401, <http://dx.doi.org/10.1210/jc.2007-2611>.
- Yamada S, Yoshimoto K, Sano T, Takada K, Itakura M, Usui M, et al. Inactivation of the tumor suppressor gene on 11q13 in brothers with familial acrogigantism without multiple endocrine neoplasia type 1. *J Clin Endocrinol Metab.* 1997;82(1):239-42, <http://dx.doi.org/10.1210/jc.82.1.239>.
- Gadelha MR, Prezant TR, Une KN, Glick RP, Moskal SF, 2nd, Vaisman M, et al. Loss of heterozygosity on chromosome 11q13 in two families with acromegaly/gigantism is independent of mutations of the multiple endocrine neoplasia type I gene. *J Clin Endocrinol Metab.* 1999;84(1):249-56, <http://dx.doi.org/10.1210/jc.84.1.249>.
- Vierimaa O, Georgitsi M, Lehtonen R, Vahteristo P, Kokko A, Raitila A, et al. Pituitary adenoma predisposition caused by germline mutations in the *AIP* gene. *Science.* 2006;312(5777):1228-30, <http://dx.doi.org/10.1126/science.1126100>.
- Daly AF, Vanbellinghen JF, Khoo SK, Jaffrain-Rea ML, Naves LA, Guitelman MA, et al. Aryl hydrocarbon receptor-interacting protein gene mutations in familial isolated pituitary adenomas: analysis in 73 families. *J Clin Endocrinol Metab.* 2007;92(5):1891-6, <http://dx.doi.org/10.1210/jc.2006-2513>.
- Lin BC, Sullivan R, Lee Y, Moran S, Glover E, Bradfield CA. Deletion of the aryl hydrocarbon receptor-associated protein 9 leads to cardiac

- malformation and embryonic lethality. *J Biol Chem.* 2007;282(49):35924-32, <http://dx.doi.org/10.1074/jbc.M705471200>.
22. Raitila A, Lehtonen HJ, Arola J, Heliövaara E, Ahlsten M, Georgitsi M, et al. Mice with inactivation of aryl hydrocarbon receptor-interacting protein (Aip) display complete penetrance of pituitary adenomas with aberrant ARNT expression. *Am J Pathol.* 2010;177(4):1969-76, <http://dx.doi.org/10.2353/ajpath.2010.100138>.
 23. Ozfirat Z, Korbonits M. AIP gene and familial isolated pituitary adenomas. *Mol Cell Endocrinol.* 2010;326(1-2):71-9, <http://dx.doi.org/10.1016/j.mce.2010.05.001>.
 24. Trivellin G, Korbonits M. AIP and its interacting partners. *J Endocrinol.* 2011;210(2):137-55, <http://dx.doi.org/10.1530/JOE-11-0054>.
 25. Oesch-Bartlomowicz B, Huelster A, Wiss O, Antoniou-Lipfert P, Dietrich C, Arand M, et al. Aryl hydrocarbon receptor activation by cAMP vs. dioxin: divergent signaling pathways. *Proc Natl Acad Sci U S A.* 2005;102(26):9218-23, <http://dx.doi.org/10.1073/pnas.0503488102>.
 26. Kazlauskas A, Poellinger L, Pongratz I. Evidence that the co-chaperone p23 regulates ligand responsiveness of the dioxin (Aryl hydrocarbon) receptor. *J Biol Chem.* 1999;274(19):13519-24, <http://dx.doi.org/10.1074/jbc.274.19.13519>.
 27. Kazlauskas A, Poellinger L, Pongratz I. The immunophilin-like protein XAP2 regulates ubiquitination and subcellular localization of the dioxin receptor. *J Biol Chem.* 2000;275(52):41317-24, <http://dx.doi.org/10.1074/jbc.M007765200>.
 28. Jaffrain-Rea ML, Angelini M, Gargano D, Tichomirowa MA, Daly AF, Vanbellinghen JF, et al. Expression of aryl hydrocarbon receptor (AHR) and AHR-interacting protein in pituitary adenomas: pathological and clinical implications. *Endocr Relat Cancer.* 2009;16(3):1029-43, <http://dx.doi.org/10.1677/ERC-09-0094>.
 29. Bolger GB, Peden AH, Steele MR, MacKenzie C, McEwan DG, Wallace DA, et al. Attenuation of the activity of the cAMP-specific phosphodiesterase PDE4A5 by interaction with the immunophilin XAP2. *J Biol Chem.* 2003;278(35):33351-63, <http://dx.doi.org/10.1074/jbc.M303269200>.
 30. de Oliveira SK, Hoffmeister M, Gambaryan S, Muller-Esterl W, Guimaraes JA, Smolenski AP. Phosphodiesterase 2A forms a complex with the co-chaperone XAP2 and regulates nuclear translocation of the aryl hydrocarbon receptor. *J Biol Chem.* 2007;282(18):13656-63, <http://dx.doi.org/10.1074/jbc.M610942200>.
 31. Horvath A, Stratakis CA. Clinical and molecular genetics of acromegaly: MEN1, Carney complex, McCune-Albright syndrome, familial acromegaly and genetic defects in sporadic tumors. *Rev Endocr Metab Disord.* 2008;9(1):1-11, <http://dx.doi.org/10.1007/s11154-007-9066-9>.
 32. Vargiolu M, Fusco D, Kurelac I, Dirnberger D, Baumeister R, Morra I, et al. The tyrosine kinase receptor RET interacts in vivo with aryl hydrocarbon receptor-interacting protein to alter survivin availability. *J Clin Endocrinol Metab.* 2009;94(7):2571-8, <http://dx.doi.org/10.1210/jc.2008-1980>.
 33. Jaffrain-Rea M-L, Daly AF, Angelini M, Petrossians P, Bours V, Beckers A. Genetic susceptibility in pituitary adenomas: from pathogenesis to clinical implications. *Exp Rev Endocrinol Metab.* 2011;6(2):195-214, <http://dx.doi.org/10.1586/eem.10.87>.
 34. Barlier A, Vanbellinghen JF, Daly AF, Silvy M, Jaffrain-Rea ML, Trouillas J, et al. Mutations in the aryl hydrocarbon receptor interacting protein gene are not highly prevalent among subjects with sporadic pituitary adenomas. *J Clin Endocrinol Metab.* 2007;92(5):1952-5, <http://dx.doi.org/10.1210/jc.2006-2702>.
 35. Igreja S, Chahal HS, King P, Bolger GB, Srirangalingam U, Guasti L, et al. Characterization of aryl hydrocarbon receptor interacting protein (AIP) mutations in familial isolated pituitary adenoma families. *Hum Mutat.* 2010;31(8):950-60, <http://dx.doi.org/10.1002/humu.21292>.
 36. Georgitsi M, Heliövaara E, Paschke R, Kumar AV, Tischkowitz M, Vierimaa O, et al. Large genomic deletions in AIP in pituitary adenoma predisposition. *J Clin Endocrinol Metab.* 2008;93(10):4146-51, <http://dx.doi.org/10.1210/jc.2008-1003>.
 37. Daly AF, Tichomirowa MA, Petrossians P, Heliövaara E, Jaffrain-Rea ML, Barlier A, et al. Clinical characteristics and therapeutic responses in patients with germ-line AIP mutations and pituitary adenomas: an international collaborative study. *J Clin Endocrinol Metab.* 2010;95(11):E373-83, <http://dx.doi.org/10.1210/jc.2009-2556>.
 38. Toledo RA, Lourenco DM Jr., Toledo SP. Familial isolated pituitary adenoma: evidence for genetic heterogeneity. *Front Horm Res.* 2010;38:77-86, <http://dx.doi.org/10.1159/000318497>.
 39. Naves LA, Daly AF, Vanbellinghen JF, Casulari LA, Spilioti C, Magalhaes AV, et al. Variable pathological and clinical features of a large Brazilian family harboring a mutation in the aryl hydrocarbon receptor-interacting protein gene. *Eur J Endocrinol.* 2007;157(4):383-91, <http://dx.doi.org/10.1530/EJE-07-0533>.
 40. Tichomirowa MA, Barlier A, Daly AF, Jaffrain-Rea M-L, Ronchi CL, Yaneva M, et al. High prevalence of AIP gene mutations following focused screening in young patients with sporadic pituitary macroadenomas. *Eur J Endocrinol.* 2011;165(4):509-15, <http://dx.doi.org/10.1530/EJE-11-0304>.