

Review

Familial Isolated Pituitary Adenomas

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REZUMAT

Adenoame hipofizare familiale izolate

Adenoamele hipofizare sunt tumori benigne frecvente care prezintă însă o morbiditate crescută datorată complicațiilor lor locale. Majoritatea cazurilor apar sporadic, dar 5% sunt familiale, asociate cu alte tumori (cum e cazul pentru MEN1 și MEN4, Complexul Carney, Sindromul McCune-Albright) sau fără alte patologii asociate cum este în FIPA (Adenoame Hipofizare Familiale Izolate). AIP (proteina de interacțiune cu receptorul aril-hidrocarbon), o genă supresor tumoral, prezintă mutații germinale la aproximativ 30% din pacienții FIPA și, într-un procent mult mai mic, la adenoamele hipofizare sporadice. Pacienții prezentând o mutație AIP au anumite caracteristici fenotipice: sunt mai tineri și prezintă adenoame hipofizare mai mari, de obicei secretând hormon de creștere sau prolactina, și sunt mult mai rezistente la terapiile disponibile comparativ cu pacienții care nu prezintă mutație AIP. Recent a fost identificată o nouă modificare genetică la pacienții FIPA cu gigantism debutat devreme în copilărie - microduplicații la nivelul cromozomului Xq26.3 iar acest sindrom a fost denumit X-LAG (acrogigantism X-linkat). Cu toate acestea în mai mult de jumătate din cazurile de FIPA fundalul genetic al bolii nu este cunoscut așa încât studiile suplimentare sunt necesare în această direcție.

Cuvinte cheie: adenom hipofizar, acromegalie, genetica, AIP, FIPA

ABSTRACT

Pituitary adenomas are frequent benign tumors that cause a high morbidity due to their complications. Most cases are sporadic but 5% arise in a familial setting, associated with other tumors (as is for MEN1 and MEN4, Carney Complex, McCune-Albright Syndrome) or without other associated disease as is for FIPA (Familial Isolated Pituitary Adenomas) families. AIP (Aryl-hydrocarbon Receptor Interacting Protein), a tumor suppressor gene, is mutated in approximately 30% of FIPA patients and in a much lesser percent in sporadic pituitary adenomas. Patients harboring an AIP mutation have certain characteristics: are younger and with larger pituitary adenomas, usually secreting growth hormone or prolactin and more resistant to current therapies as compared to AIP negative patients. Recently a new genotype was identified in FIPA patients with early onset gigantism - microduplications on chromosome Xq26.3 and the syndrome was called X-LAG (X-linked acrogigantism). In more than a half of FIPA patients the genetic background of the disease is still unknown and more work is needed in this direction.

Key words: pituitary adenoma, acromegaly, genetics, AIP, FIPA

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Pituitary adenomas (PAs) are the most frequent cause of cranial tumors [1,2], benign by histology but with high morbidity caused by their complications – hypersecretion of pituitary hormones but also compression of surrounding structures thus affecting the visual field or causing pituitary deficiency. Their etiology, although intensely studied in the last 30 years, is still largely unknown.

The natural evolution and the response to current treatment options of PAs (surgery, medication and radiotherapy) are very variable, influenced by various factors, some identified and some still to be found. Early diagnose and treatment is associated with better prognosis thus identifications of patients at risk for developing a PA and targeted follow-up would result in a better management of the disease.

5% of PAs are familial, associated or not with other tumor types. Half of these arise within MEN1 syndrome (Multiple Endocrine Neoplasia type 1 - MIM# 13110) the rest being part of Carney Complex, McCune Albright syndrome, MEN4 and FIPA (Familial Isolated Pituitary Adenomas) – see **Table 1**. 40% of MEN1 patients present PAs associated with parathyroid adenomas (hyperparathyroidism being frequently the first manifestation of the disease), or with gastrinomas, insulinomas or other neuroendocrine tumors of the digestive tract, adrenal adenomas, lipomas, collagenomas or angiofibromas [3]. It is a disease with an autosomal – dominant pattern of inheritance, 80% of the patients carrying a mutation in menin, a tumor suppressor gene. Carney Complex (MIM# 160980) associates pigmented skin lesions, mixomas and endocrine hyperactivity with acromegaly (growth hormone -GH secreting PA) being the most frequent type of PA. Acromegaly due to a PA is not very frequent but the majority of the patients with Carney Complex have alteration in the rhythm of GH secretion with a mild

increase in GH levels and seldom in prolactin (PRL) levels [4]. In MEN4 (MIM# 610755), first described in rats in 2002, PAs can associate with organomegaly, pheochromocytomas, parathyroid adenomas, medullary thyroid carcinoma and neuroendocrine tumors without menin or RET germline mutations, but harboring a germline mutation in CDKN1B (Cyclin-Dependent Kinase Inhibitor 1B) a tumor suppressor gene coding a protein with important role in cell cycle progression from G0 to G1 [5]. In McCune-Albright syndrome (MIM# 174800) the classic triad of polyostotic fibrous dysplasia, cafe-au-lait skin spots and precocious puberty can be associated with hyperthyroidism, Cushing syndrome or gigantism caused by a GH secreting PA [6]. In 2012 Xekouki et al described a kindred harboring a germline mutation in the D subunit of SDH (succinate dehydrogenase) that associated familial paragangliomas and an aggressive GH secreting PA that presented loss of heterozygosity (LOH) at the SDHD locus. SDH is an enzyme with an essential role in Krebs cycle but also in the respiratory chain. SDH mutations associate with familial paragangliomas or pheochromocytomas, Carney-Stratakis syndrome, Cowden disease, renal or thyroid cancer [7].

FIPA (MIM# 102200) was first described 20 years ago and is characterized by the presence, in the same family, of at list two PAs (identical from the point of view of the secretory type – homogenous FIPA or different – heterogeneous FIPA) without other syndromic features. 2% of PAs arise within FIPA and 75% of cases occur in first degree relatives from a family. FIPA patients are diagnosed at an younger age when compared to sporadic cases (4 years earlier) whereas in the same FIPA family patients from the second generation affected are diagnosed earlier as compared to their parents/grandparents,

Table 1 - Familial pituitary adenomas – type of disease, phenotype and genotype

Syndrome	Genetics	Secretory type of PA	Associated phenotype
MEN1	Menin - tumor suppressor	All types but mainly PRL and GH secreting	Hypeparathyroidism, gastrinoma, insulinoma, lipomas, mixomas, adrenal tumors.
FIPA	AIP - tumor suppressor gene Microduplications in Xq26.3	All types but mainly GH and PRL secreting GH secreating – young onset gigantism	No other syndromic features
Carney Complex	PRKAR1A – tumor supressor Unknown putative gene at 2p16, probably oncogene	Acromegaly	Pigmented skin lesions, mixomas and endocrine hyperactivity - Primary Pigmented Nodular Adrenocortical Disease, thyroid nodules, testicular tumors and ovarian cysts.
McCune-Albright	GNAS – mosaic activating mutations	Acromegaly	Polyostotic fibrous displasia, skin spots, hyperthyroidism, Cushing syndrome
MEN4	CDKN1B – tumor suppressor gene	All types of Pas	Organomegaly, medullary thyroid carcinoma, pheochromocitomas, parathyroid adenoma, neuroendocrine tumors
PA associated with familial paragangliomas	SDHB, SDHC, SDHD - tumor suppressor genes	Acromegaly	Familial paragangliomas / pheochromocitomas

probably due to improvement in diagnostic techniques and not to genetic anticipation [8]. The most frequent types of PA in FIPA are those secreting PRL (37.5%), GH (35%) or both (GH and PRL - 6.5%), NFPAs (nonfunctioning pituitary adenomas - 14,5%), the less frequent being Cushing disease or gonadotropinomas each representing less than 3% of FIPA [8,9]. Penetrance of PAs in FIPA families is around 30% but varies in different families, thus suggesting that other environmental or genetic factors might have a protective or predisposing role in tumorigenesis [10]. FIPA is has an autosomal-dominant pattern of inheritance and the first gene identified as having a pathogenic role in PA development in these families was AIP (aryl-hydrocarbon receptor protein) [12].

Prolactinomas are the most frequent tumor type in FIPA, being larger and more invasive in heterogeneous FIPA families than in homogenous FIPA. Still the proportion of FIPA patients with prolactinomas is lower than in sporadic patients (66% of sporadic PA are secreting PRL). One third of PAs in FIPA are GH secreting, IFS patients (Isolated Familial Somatotropinomas - homogenous FIPA with PAs that secrete GH) being younger (10yrs) with larger tumors at diagnosis when compared to sporadic acromegalic patients. Nonfunctioning PAs arise in heterogeneous FIPA, occur at a younger age and are larger when compared to sporadic cases [8].

PAP (Pituitary Adenoma Predisposition) characterizes families predisposed to PAs but with low penetrance of the disease and generally defines those FIPA families in which an AIP germline mutation was identified. The exact prevalence of AIP mutations in FIPA/IFS patients or in sporadic patients is difficult to appreciate, mostly because the studies published to date are based on different study populations, and partially to the methodology - some works use only direct sequencing of the coding region of the AIP gene, other use also MLPA to detect large gene deletions/ insertions. In 2010 Chahal et al reported that overall 22% of FIPA patients harbored an AIP mutation whereas only 2% of sporadic PAs were positive. In IFS families 40% of patients had an AIP mutation [13]. Subsequent studies on selected populations revealed an AIP germline mutation in about 8% of sporadic acromegalic patients resistant to the treatment with somatostatin analogues (SSAs), 17% of large sporadic PAs diagnosed before the age of 30 and 20.5% of pediatric PA patients [14].

Clinical characterizations of AIP positive PA patients

Although to date there are no genotype-phenotype correlations for the patients harboring an AIP mutation they have certain particularities. AIP positive FIPA patients have larger tumors, more likely to invade the surrounding tissues [15, 16] and more resistant to available therapies. AIP positive acromegalic patients need more surgeries compared to AIP negative patients,

are less responsive to SSAs treatment both in the reduction of Gh/IGF1 levels and of the tumor diameter [17]. It seems that abnormal AIP (whose up-regulation is needed for the antiproliferative effects of SSAs) determines the reduction in the ZAC1 (zinc finger transcription factor 1) expression, a tumor suppressor that is down-regulated in PAs. AIP positive patients with prolactinomas frequently need surgery and radiotherapy for tumor control due to the fact that they are often resistant to dopamine agonists [14, 17]. Patients with truncating mutations are significantly younger at the onset of the disease and at diagnosis (gigantism being more frequent in truncating mutations) [18].

AIP positive FIPA patients are in majority GH secreting; the higher frequency of this secretory type of PA may be explained by AIP-cAMP interactions and the role of cAMP in the proliferation of GH secreting cells [19]. AIP positive FIPA patients are younger at diagnosis compared to AIP negative FIPA subject or to sporadic PAs [16]. Some studies (but not all) identified a predominance of male subjects between PA patients with an AIP mutation [20]. FIPA families in which an AIP mutation was identified have a larger number of individuals affected when compared to AIP negative families [21].

Due to the relative newly discovery of the AIP mutations little data about the penetrance of the disease are available. The real penetrance is rather low, approximately 30% of the patients carrying an AIP mutation being diagnosed with a PA, but prospective follow-up of apparently unaffected carriers allows clinical diagnosis of a PA in 11.3% of those originally considered as not having a PA. When biochemical and imaging techniques were used the percentage of AIP mutation carriers diagnosed with a PA varies from 18.6 to 28.1% [18]. This data suggest that detection of AIP mutation carriers and screening them regularly for PA allows, in approximately a quarter of subjects, earlier diagnosis of the disease and possibly an earlier treatment and a better outcome.

Mechanisms of AIP involvement in the tumorigenesis of PA

In normal pituitary AIP is expressed in somatotroph and lactotroph cells, associated to secretory vesicles but its exact function in the pituitary cell is not known. It interacts with many other proteins so that AIP mutations can lead to alteration in multiple cellular signaling paths. In sporadic PAs AIP is expressed in all tumor types, in secretory vesicles in GH secreting PA and in cytoplasm in other sporadic PA types. AIP is a 37kDa ubiquitous protein located at the cytoplasmic level, structurally composed of an immunophilin-like region, 3 TPR (tetra-tricopeptide repeats) each comprising 34 amino-acids forming 2 α -helixes and a final C-terminal α -7 helix. AIP structure is highly conserved between species, as is the genome region where it is located [22]. The TPR region

has both hydrophilic and lipophilic characteristics with essential roles in protein-protein interactions. One of the most important interactions of AIP is within AIP-AhR-hsp90 complex. AhR (Aryl-hydrocarbon Receptor also known as the dioxin receptor) is a cytoplasmic transcription factor involved in the expression of the enzymes that metabolize xenobiotics as a response to environmental pollutants. Dioxin-like substances have high affinity for AhR which mediates most of their toxic effects (carcinogenic, teratogenic and immunosuppressor) and AIP modulates the cellular localization of AhR blocking its transport between nucleus and cytoplasm thus preventing AhR degradation. In this way loss of AIP expression correlates with reduction in AhR expression [23]. AIP forms a complex with AhR and hsp90 (heat shock proteins 90 that, after binding AhR, favors its folding) through the TPR domains and the α -7 helix, especially the last 5 amino-acids. Some studies found that the N-terminus part of AIP has also a role in AIP-AhR interactions, conferring stability to the complex.

In fact AIP has a co-chaperone role, interacting also with cytoskeletal proteins (aktin) and nuclear receptors. AIP interacts with survivin, which inhibits apoptosis and has a role in cell division and the response to stress. Kang et al have shown that AIP stabilizes survivin in cytoplasm and favors its access to the mitochondria and, thus, its actions in controlling cell death [24]. AIP also binds to and limits the activity of PDE4A5, the main enzyme involved in cAMP degradation. At pituitary level cAMP favors the proliferation of somatotroph cells.

Animal studies conducted by Raitila et al showed that heterozygous AIP mice are prone to develop pituitary adenomas (especially somatotropinomas) with complete penetrance by the age of 15 month thus confirming the importance of AIP in pituitary tumorigenesis [25].

AIP mutations in PAs

LOH at 11q13 was previously noticed in a part of sporadic PAs samples. Ten years ago linkage studies in FIPA/IFS families identified sequence changes at 11q13 loci, in the region of the *menin* gene but different from it [11]. The identification of AIP (gene coding aryl-hydrocarbon interacting protein) as being the putative gene was made by Vierimaa et al in 2006 after studying 3 FIPA families (heterogeneous) from northern Finland (two of them having a common ancestor and the third being of different ancestry). Using direct sequencing of genomic DNA from affected individuals the first AIP mutation was identified in both families (c.40C>T, p.Q14X), which was also identified in apparently sporadic acromegalic Finnish patients and was absent in the control group, thus allowing to define it as a founder mutation [12]. After this first report screening different ethnic populations for AIP mutations allowed the identification of all types of AIP sequence changes (both pathogenic or simple SNPs) and the confirmation of loss of the wild-type allele in the

tumor tissue, thus establishing a tumor suppressor role of AIP. All mutations identified were heterozygous probably due to the fact that homozygous mutations in mice cause cardiovascular defects on the embryos that are not compatible to life so all embryos die at different gestational age [26]. AIP comprises 6 exons and 330 codons. Most of AIP mutations identified are nonsense, insertions or deletions that cause a change in C-terminal amino-acids sequence, the region of the protein with important roles in protein-protein interactions as described above. Other mutations are located at the intron/exon junctions affecting splicing or RNA stability but also there was identified a family in which AIP mutation resulted in a promoter sequence change [21]. No somatic AIP mutations were identified to date, even though LOH at 11q13 is found in pituitary tumor tissue from AIP mutated FIPA patients but also in sporadic PA patients and FIPA patients without AIP germline mutations [16].

Mutant AIP loses the ability to interact with other proteins and to reduce cell proliferation thus promoting tumor development. To date there is no certain explanation for the fact that AIP mutations promote only pituitary adenomas and no other tumor types are associated with this genotype.

The most frequent AIP mutations identified to date both in FIPA and sporadic PA cases are located at the codon 304, in the sixth exon (p.R304X, c.910C>T and p.R304Q, c.911G>A) these mutations being identified also in two FIPA families from Romania [16]. Other possible mutational hotspots are c.241C>T, p.R81X and c.811C>T, p.R271W [4].

One of the most controversial sequence change in AIP is p.R16H, c.47G>A first described in 2007 by Daly in a IFS family and then repeatedly identified both in FIPA families (but with only partial segregation with the presence of a PA) and in 13 sporadic PAs but also in 4 apparently healthy controls. This sequence change was also identified in one Romanian patient diagnosed with a sporadic NFPA with an aggressive phenotype [27]. It is located at the level of a highly conserved amino-acid located in the N-terminal part of the AIP with a less important role in the protein-protein interactions of the AIP.

But approximately 70% of FIPA patients do not harbor an AIP mutation and recent studies by Trivellin et al reported several families with gigantism caused by a GH secreting PA diagnosed in early childhood and associated with microduplications on chromosome Xq26.3, in a region with four genes from which GPR101 (that encodes an orphan G-protein-coupled receptor) seemed to be the one involved in the pathogenesis of the disease. The term used for this syndrome is X-LAG (X-linked acrogigantism) [28]. Microduplications at Xq26.3 were identified not only in FIPA families but also in sporadic cases having early onset of gigantism with (onset of growth occurs significantly earlier in X-LAG

then compared to wild-type cases and, as in AIP positive patients, disease control is difficult to obtain [29]. To date only a few cases with this genotype have been identified so supplementary work is needed in order to understand the exact mechanism of tumorigenesis and to fully characterize these FIPA families.

To date there is no guideline regarding AIP screening and the management of FIPA, as it exists for MEN1 patients. AIP screening in unselected cases is not recommended due to the rather rare frequency of AIP mutations in these cases. It is suggested that AIP screening should be performed in all FIPA patients and in sporadic PA diagnosed in childhood or below the age of 30 (especially GH or PRL secreting) [30]. Identifying an asymptomatic AIP mutation carrier should prompt to a closer follow-up that would favor the diagnosis at a non-invasive stage and a better outcome using adequate therapies.

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REFERENCES

- Asa SL, Ezzat S. The pathogenesis of pituitary tumours. *Nat Rev Cancer* 2002; 2(11):836-849.
- Daly AF, Burlacu MC, Livadariu E, Beckers A. The epidemiology and management of pituitary incidentalomas. *Horm Res* 2007; 68 Suppl 5:195-198.
- Scheithauer BW, Laws ER, Jr., Kovacs K, Horvath E, Randall RV, Carney JA. Pituitary adenomas of the multiple endocrine neoplasia type I syndrome. *Semin Diagn Pathol* 1987; 4(3):205-211.
- Vasilev V, Daly AF, Petrossians P, Zacharieva S, Beckers A. Familial pituitary tumor syndromes. *Endocr Pract* 2011; 17 Suppl 3:41-46.
- Fritz A, Walch A, Piotrowska K, Rosemann M, Schaffer E, Weber K, Timper A, Wildner G, Graw J, Hofler H, Atkinson MJ. Recessive transmission of a multiple endocrine neoplasia syndrome in the rat. *Cancer Res* 2002; 62(11):3048-3050.
- Lumbroso, S., Paris, F., Sultan, C. Activating Gs-alpha mutations: analysis of 113 patients with signs of McCune-Albright syndrome - a European collaborative study. *J. Clin. Endocr. Metab.* 2004; 89: 2107-2113.
- Xekouki P, Pacak K, Almeida M, Wassif CA, Rustin P, Nesterova M, de la Luz Sierra M, Matro J, Ball E, Azevedo M et al. Succinate dehydrogenase (SDH) D subunit (SDHD) inactivation in a growth-hormone-producing pituitary tumor: a new association for SDH? *Journal of Clinical Endocrinology and Metabolism* 2012;97: E357-E366.
- Daly AF, Jaffrain-Rea ML, Ciccarelli A, Valdes-Socin H, Rohmer V, Tamburrano G, Borson-Chazot C, Estour B, Ciccarelli E, Brue T, Ferolla P, Emy P, Colao A, De Menis E, Lecomte P, Penfornis F, Delemer B, Bertherat J, Wémeau JL, De Herder W, Archambeaud F, Stevenaert A, Calender A, Murat A, Cavagnini F, Beckers A. Clinical characterization of familial isolated pituitary adenomas. *J Clin Endocrinol Metab* 2006; 91:3316-3323.
- Beckers A, Daly AF. The clinical, pathological, and genetic features of familial isolated pituitary adenomas. *Eur J Endocrinol* 2007; 157:371-382.
- Khoo SK, Pendek R, Nickolov R, Luccio-Camelo DC, Newton TL, Massie A, Petillo D, Menon J, Cameron D, Teh BT, Chan SP. Genome-wide scan identifies novel modifier loci of acromegalic phenotypes for isolated familial somatotropinoma. *Endocr Relat Cancer* 2009; 16(3):1057-1063.
- De ME, Prezant TR. Isolated familial somatotropinomas: clinical features and analysis of the MEN1 gene. *Pituitary* 2002; 5(1):11-15.
- Vierimaa O, Georgitsi M, Lehtonen R, Vahteristo P, Kokko A, Raitila A, Tuppurainen K, Ebeling TM, Salmela PI, Paschke R, Gundogdu S, De ME, Makinen MJ, Launonen V, Karhu A, Aaltonen LA. Pituitary adenoma predisposition caused by germline mutations in the AIP gene. *Science* 2006; 312(5777):1228-1230.
- 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):419-427.
- Tichomirowa MA, Barlier A, Daly AF, Jaffrain-Rea ML, Ronchi C, Yaneva M, Urban JD, Petrossians P, Elenkova A, Tabarin A, Desailoud R, Maiter D, Schurmeyer T, Cozzi R, Theodoropoulou M, Sievers C, Bernabeu I, Naves LA, Chabre O, Montanana CF, Hana V, Halaby G, Delemer B, Aizpun JI, Sonnet E, Longas AF, Hagelstein MT, Caron P, Stalla GK, Bours V, Zacharieva S, Spada A, Brue T, Beckers A. High prevalence of AIP gene mutations following focused screening in young patients with sporadic pituitary macroadenomas. *Eur J Endocrinol* 2011; 165(4):509-515.
- Beckers A, Daly AF. The clinical, pathological, and genetic features of familial isolated pituitary adenomas. *Eur J Endocrinol* 2007; 157(4):371-382.
- Leontiou CA, Gueorguiev M, van der Spuy J, Quinton R, Lolli F, Hassan S, Chahal HS, Igreja SC, Jordan S, Rowe J, Stolbrink M, Christian HC, Wray J, Bishop-Bailey D, Berney DM, Wass JA, Popovic V, Ribeiro-Oliveira A, Jr., Gadelha MR, Monson JP, Akker SA, Davis JR, Clayton RN, Yoshimoto K, Iwata T, Matsuno A, Eguchi K, Musat M, Flanagan D, Peters G, Bolger GB, Chapple JP, Frohman LA, Grossman AB, Korbonits M. The role of the aryl hydrocarbon receptor-interacting protein gene in familial and sporadic pituitary adenomas. *J Clin Endocrinol Metab* 2008; 93(6):2390-2401.
- Daly AF, Tichomirowa MA, Petrossians P, Heliövaara E, Jaffrain-Rea ML, Barlier A, Naves LA, Ebeling T, Karhu A, Raappana A, Cazabat L, De ME, Montanana CF, Raverot G, Weil RJ, Sane T, Maiter D, Neggess S, Yaneva M, Tabarin A, Verrua E, Eloranta E, Murat A, Vierimaa O, Salmela PI, Emy P, Toledo RA, Sabate MI, Villa C, Popelier M, Salvatori R, Jennings J, Longas AF, Labarta Aizpun JI, Georgitsi M, Paschke R, Ronchi C, Valimaki M, Saloranta C, De HW, Cozzi R, Guitelman M, Magri F, Lagonigro MS, Halaby G, Corman V, Hagelstein MT, Vanbellinghen JF, Barra GB, Gimenez-Roqueplo AP, Cameron FJ, Borson-Chazot F, Holdaway I, Toledo SP, Stalla GK, Spada A, Zacharieva S, Bertherat J, Brue T, Bours V, Chanson P, Aaltonen LA, Beckers A. 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-E383.
- Hernandez-Ramirez LC, Gabrovská P, Denes J, Stals K, Trivellini G, Tilley D, Ferrau F, Evanson J, Ellard S, Grossman AB. Landscape of Familial Isolated and Young-Onset Pituitary Adenomas: Prospective Diagnosis in AIP Mutation Carriers. *J Clin Endocrinol Metab* 2015 Sep;100(9):E1242-54.
- Cazabat L, Guillaud-Bataille M, Bertherat J, Raffin-Sanson ML. Mutations of the gene for the aryl hydrocarbon receptor-interacting protein in pituitary adenomas. *Horm Res* 2009; 71(3):132-141.
- Cain J. Role of the aryl hydrocarbon receptor-interacting protein in familial isolated pituitary adenoma. *Expert Rev Endocrinology Metab* 2011;5:681-695.

21. Igreja S, Chahal HS, King P, Bolger GB, Srirangalingam U, Guasti L, Chapple JP, Trivellin G, Gueorguiev M, Guegan K, Stals K, Khoo B, Kumar AV, Ellard S, Grossman AB, Korbonits M. Characterization of aryl hydrocarbon receptor interacting protein (AIP) mutations in familial isolated pituitary adenoma families. *Hum Mutat.* 2010 Aug, 31(8):950-60.
22. Trivellin G, Korbonits M. AIP and its interacting partners. *J Endocrinol* 2011; 210(2):137-155.
23. Jaffrain-Rea ML, Angelini M, Gargano D, Tichomirowa MA, Daly AF, Vanbellinghen JF, D'Innocenzo E, Barlier A, Giangaspero F, Esposito V, Ventura L, Arcella A, Theodoropoulou M, Naves LA, Fajardo C, Zacharieva S, Rohmer V, Brue T, Gulino A, Cantore G, Alesse E, Beckers A. Expression of aryl hydrocarbon receptor (AHR) and AHR-interacting protein in pituitary adenomas: pathological and clinical implications. *Endocr Relat Cancer* 2009; 16(3):1029-1043.
24. Kang BH, Xia F, Pop R, Dohi T, Socolovsky M, Altieri DC. Developmental control of apoptosis by the immunophilin aryl hydrocarbon receptor-interacting protein (AIP) involves mitochondrial import of the survivin protein. *J Biol Chem* 2011; 286(19): 16758-16767.
25. Raitila A, Lehtonen HJ, Arola J, Heliövaara E, Ahlsten M, Georgitsi M, Jalanko A, Paetau A, Aaltonen LA, Karhu A. Mice with inactivation of aryl hydrocarbon receptor-interacting protein (Aip) display complete penetrance of pituitary adenomas with aberrant ARNT expression. *Am J Pathol* 2010; 177:1969-1976.
26. Lin BC, Sullivan R, Lee Y, Moran S, 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.
27. Baciu I, Radian S, Capatina C, Botusan I, Aflorei D, Stancu C, Dumitrascu A, Ciubotaru V, Coculescu M. The p.R16H (c.47G>A) AIP gene variant - report of an invasive non-functioning pituitary macroadenoma case and screening of a control cohort. *Acta Endocrinologica - Buc* 2013;9 [1], 97-108.
28. Trivellin G, Daly AF, Fauz FR, et al. Gigantism and Acromegaly Due to Xq26 Microduplications and GPR101 Mutation. *N Engl J Med.* 2014;371(25): 2363-2374.
29. Lodish MB, Trivellin G, Stratakis CA. Pituitary gigantism: update on molecular biology and management. *Curr Opin Endocrinol Diabetes Obes.* 2015 Nov 14.
30. Korbonits M, Storr H, Kumar AV. Familial pituitary adenomas - who should be tested for AIP mutations? *Clin Endocrinol (Oxf)* 2012; 77(3):351-356.