THEMATIC REVIEW

HEREDITARY ENDOCRINE TUMOURS: CURRENT STATE-OF-THE-ART
AND RESEARCH OPPORTUNITIES**The roles of *AIP* and *GPR101* in familial isolated
pituitary adenomas (FIPA)****Vladimir Vasilev^{1,2}, Adrian F Daly¹, Giampaolo Trivellin³, Constantine A Stratakis³, Sabina Zacharieva² and
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Abstract

Familial isolated pituitary adenoma (FIPA) is one of the most frequent conditions associated with an inherited presentation of pituitary tumors. FIPA can present with pituitary adenomas of any secretory/non-secretory type. Mutations in the gene for the aryl-hydrocarbon receptor interacting protein (*AIP*) have been identified in approximately 20% of FIPA families and are the most frequent cause (29%) of pituitary gigantism. Pituitary tumors in FIPA are larger, occur at a younger age and display more aggressive characteristics and evolution than sporadic adenomas. This aggressiveness is especially marked in FIPA kindreds with *AIP* mutations. Special attention should be paid to young patients with pituitary gigantism and/or macroadenomas, as *AIP* mutations are prevalent in these groups. Duplications on chromosome Xq26.3 involving the gene *GPR101* lead to X-linked acro-gigantism (X-LAG), a syndrome of pituitary gigantism beginning in early childhood; three kindreds with X-LAG have presented in the setting of FIPA. Management of pituitary adenomas in the setting of FIPA, *AIP* mutations and *GPR101* duplications is often more complex than in sporadic disease due to early onset disease, aggressive tumor growth and resistance to medical therapy.

Key Words

- ▶ familial isolated pituitary adenomas
- ▶ FIPA
- ▶ *AIP*
- ▶ pituitary adenoma
- ▶ *GPR101*
- ▶ X-linked acro-gigantism

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Introduction

Pituitary adenomas are intracranial tumors that occur in 10–15% of individuals in autopsy series and in 20–38% of those undergoing CT/MRI (Ezzat *et al.* 2004, Molitch 2009, Freda *et al.* 2011). The vast majority of these adenomas, however, are incidentally discovered, very small, non-functioning pituitary microadenomas with no clinical impact. The medical significance of pituitary adenomas lies in the group of tumors that are sufficiently large and/or hormonally active to cause signs and symptoms. The prevalence of these clinically relevant pituitary adenomas is of the order of 1 case per 1000 of the general population (Daly *et al.* 2006b). The management of clinically relevant pituitary adenomas is often challenging and involves a multidisciplinary team of endocrinologists, neurosurgeons, and radiologists. Despite their benign nature, some pituitary adenomas exhibit aggressive behavior and produce morbidity.

To date, the molecular mechanisms behind the development of the majority of pituitary adenomas are not well understood. Usually, these tumors are sporadic, but approximately 5% have a known genetic or familial background (Daly *et al.* 2009). Pituitary pathology has been described in several syndromes of multiple endocrine neoplasia (MEN). Among them, MEN1 is the most common and accounts for about 3% of all pituitary adenomas (Scheithauer *et al.* 1987). MEN1 is caused by germline inactivating mutations in *MEN1* gene on chromosome 11q13 (Chandrasekharappa *et al.* 1997). Carney complex (CNC) is another inherited syndrome that can include familial pituitary adenomas (usually acromegaly) and is predominantly caused by inactivating mutations in the gene encoding the type 1A regulatory subunit of protein kinase A (*PRKARIA*) (Carney *et al.* 1985, Casey *et al.* 1998). Inherited pituitary adenoma risk is also associated with the recently characterized syndromes of multiple endocrine neoplasia type 4 (MEN4) caused by inactivating mutations of *CDKN1B* gene (Pellegata *et al.* 2006), or in the setting of the pheochromocytoma-paraganglioma with pituitary adenoma association (3PA) that is due to mutations in succinate dehydrogenase (*SDH*) or *MAX* genes (Xekouki *et al.* 2015, Daly *et al.* 2018).

The emergence of FIPA

Individual cases of familial acromegaly and gigantism arising in a non-syndromic setting have been reported in the literature ever since the first description of the disease by

Pierre Marie (de Herder 2009, Beckers *et al.* 2018). Although these first records concerned only acromegaly, by the 1990s several kindreds with familial corticotropinomas, prolactinomas and non-functioning pituitary adenomas (NFPA) had also been reported (Salti & Mufarrij 1981, Yuasa *et al.* 1990, Berezin & Karasik 1995). The concept of familial isolated pituitary adenomas (FIPA) emerged in the late 1990s with the publication of an initial cohort of 27 families with pituitary adenomas, including acromegaly as well as other secretory phenotypes, in the absence of signs and symptoms of MEN1 and CNC (Verloes *et al.* 1999, Valdes Socin *et al.* 2000, Beckers 2004). Currently, FIPA is defined as the presence of pituitary adenomas of any type in at least two related members of the same family in the absence of clinical and genetic evidence of other known syndromic diseases (Daly *et al.* 2006a; Table 1). It is considered to account for approximately 2% of all clinically relevant pituitary adenomas and up to 3.8% when considering only hormonally active tumors (Daly *et al.* 2006a, Marques *et al.* 2017). Genealogical data indicate that FIPA is inherited in an autosomal-dominant manner with variable penetrance that can reach 33% in some kindreds (Daly *et al.* 2006a, 2007, Naves *et al.* 2007). Depending on the functional type of the adenoma, FIPA can be divided into homogeneous, when pituitary tumors of the same type are present in all affected family members, and heterogeneous, with different pituitary adenomas within the kindred. Compared to sporadic pituitary adenomas, FIPA patients are diagnosed significantly earlier (on an average of 4 years). In multigenerational families, descendants are diagnosed at considerably younger age than their parents or grandparents, especially in homogeneous FIPA (Daly *et al.* 2006a). In the overall cohort of FIPA, prolactinomas are the most frequent secretory subtype (37.5%) (Beckers *et al.* 2013). When prolactinomas occur in heterogeneous FIPA, they present with more aggressive characteristics, like higher rates of suprasellar expansion and invasion of the cavernous sinus. Somatotropinomas are the second most common pituitary tumors in FIPA, accounting for 35% of FIPA, and somatoprolactinomas are observed in another 6.4% of cases. They are almost equally divided between homogeneous and heterogeneous families but, unlike FIPA prolactinomas, GH-secreting adenomas are more aggressive when occurring in a homogeneous setting. In homogeneous FIPA, acromegaly can be diagnosed up to 10 years earlier with tumors more frequently displaying extrasellar growth as compared to heterogeneous kindreds and sporadic populations (Beckers *et al.* 2013). Non-secreting adenomas

Table 1 Summary of clinical features in patients with FIPA, *AIP* mutations and *GPR101* duplications.**Familial isolated pituitary adenomas (FIPA)**

- Occurs when at least two related members of the same kindred have isolated pituitary adenomas (i.e. syndromic conditions affecting other endocrine organs like *MEN1* are not present)
- Can present homogeneously (all affected members of the same kindred have the same pituitary adenoma subtype) or heterogeneously (different pituitary adenoma subtypes across the kindred)
- Generally FIPA cases have an earlier onset and have a larger tumor size than sporadic non-FIPA pituitary adenoma cases
- Genetic causes are present in about 20% of kindreds
 - *AIP* mutations
 - *GPR101* duplications (rare presentation)

***AIP* mutations**

- Autosomal dominant disease with incomplete penetrance
- About 20% of *AIP* mutation carriers will develop a pituitary adenoma
- All secretory and non-secretory pituitary adenoma subtypes can occur
 - Predominantly (>90%) somatotropinomas, mixed GH and prolactin secreting tumors and prolactinomas
 - Prolactin co-secretion is common in *AIP*-mutated somatotropinomas
 - Cushing's disease is very rarely associated with *AIP* mutations
- Early onset tumors affecting children, adolescents and young adults (median age at diagnosis 21 years)
- Aggressive growth potential leads to large and expansive macroadenomas
- Pituitary apoplexy is a feature of sporadic and familial *AIP* mutation-related pituitary adenomas
- Rare cases of whole or partial *AIP* gene deletions can be missed on genetic sequencing and require multiplex ligand specific probe amplification (MLPA) to identify
- Disease control in *AIP* mutation-related acromegaly requires greater cumulative use of treatment than non-mutated acromegaly
 - Patients with acromegaly and *AIP* mutation have a decreased responsiveness to first-generation somatostatin analogs
 - There are significantly decreased GH and IGF-1 responses in *AIP*-mutated acromegaly
 - Tumor shrinkage is significantly lower in *AIP*-mutated acromegaly
 - Decreased somatostatin receptor subtype 2 (SST2) can occur in *AIP*-mutated somatotropinomas
 - Octreotide/lanreotide resistant *AIP*-mutated acromegaly can be controlled hormonally and undergo marked tumor shrinkage with pasireotide treatment

***GPR101* duplications**

- X-linked dominant inheritance (100% penetrance)
- Familial early childhood onset pituitary acrogigantism due to chromosome Xq26.3 duplications can present as FIPA in rare cases ($n = 3$ kindreds)
- Inherited duplications involving *GPR101* can be transmitted from affected mother to affected son
- Early-onset (12–36 months of age) pituitary GH and prolactin positive macroadenomas with or without hyperplasia
- GHRH levels can be elevated (suggests a hypothalamic-pituitary pathological axis may exist)
- Hyperprolactinemia is usually present (responsive to dopamine agonists)
- Patients often require radical neurosurgery as part of a multimodal management scheme
- Somatostatin analogs are typically ineffective in controlling GH/IGF-1 secretion and overgrowth
- GH receptor antagonist (pegvisomant) can lower IGF-1 to normal range and control growth

occur predominantly in heterogeneous families and account for 14.5% of FIPA patients. They are diagnosed earlier and are more frequently invasive than their sporadic counterparts. Corticotropinomas, gonadotropinomas and thyrotropinomas are rare in FIPA (2.9%, 2.0% and 0.5%, respectively). They are usually associated with other adenoma types in heterogeneous kindreds (Beckers *et al.* 2013).

Molecular genetics of FIPA

Original linkage studies in familial somatotropinomas detected loss of heterozygosity on chromosome 11q13 in a region different to the *MEN1* locus (Yamada *et al.* 1997, Gadelha *et al.* 1999). Genetic analyses in this genomic region in large Finnish kindreds with heterogeneous

FIPA identified inactivating mutations in the gene for aryl hydrocarbon receptor interacting protein (*AIP*) on chromosome 11q (Vierimaa *et al.* 2006). Its causative role in FIPA was later confirmed in other affected families and by now over 100 different mutations of *AIP* have been described (Daly *et al.* 2010, Beckers *et al.* 2013, Hernandez-Ramirez *et al.* 2015, Pepe *et al.* 2019).

AIP is a tumor suppressor gene, but the exact molecular mechanisms leading to pituitary tumorigenesis have not been completely elucidated. It is widely expressed in various tissues and in normal pituitary, and associated with secretory granules in somatotrope and lactotrope cells (Leontiou *et al.* 2008). Homozygous *AIP*^{-/-} knockout mice develop lethal cardiovascular defects early in the embryonic period, suggesting that *AIP* plays a role in cardiovascular development (Lin *et al.* 2007). Heterozygous *AIP*^{+/-} animals, however, develop a

phenotype that is very similar to human pituitary disease with majority of the mice presenting with aggressive somatotropinomas (Raitila *et al.* 2010), although some variability exists in relation to older age at onset in mice vs humans (Lecoq *et al.* 2016).

The *AIP* gene consists of six exons and encodes a 37-kDa cytoplasmic protein of 330 amino acid residues with a highly conserved sequence among different species (Trivellin & Korbonits 2011). Its N-terminal end displays significant homology with immunophilins but appears not to possess such functional activity. The carboxy-terminal half of the protein contains three tetratricopeptide repeats (TPR) and a terminal α 7-helix which mediate numerous protein-protein interactions (Morgan *et al.* 2012). AIP was initially described as negative regulator of X antigen of the hepatitis B virus (Kuzhandaivelu *et al.* 1996). Furthermore, it was shown to interact also with Epstein-Barr virus-encoded nuclear antigen 3 (EBNA-3) suggesting that AIP may play a role in virus-induced pathology (Kashuba *et al.* 2006). One of the most thoroughly characterized interactive partners of AIP is the aryl hydrocarbon receptor (AhR). It belongs to the family of ligand-activated transcription factors and modulates cellular responses to various xenobiotic toxins, such as dioxins, as well as some endogenous compounds, such as cAMP (Trivellin & Korbonits 2011). In the absence of ligands, AhR binds to two molecules of the 90-kDa heat shock protein (HSP90) and the co-chaperones AIP and p23 to form a multiprotein complex in the cytoplasm. The activation of the complex by its xenobiotic ligand leads to dissociation of the HSP90 dimer and conformational change of AhR that exposes its nuclear localization sequence. In the subsequent nuclear translocation, the complex AhR-AIP binds to the aryl hydrocarbon receptor nuclear translocator (ARNT), also known as HIF1 β , and promotes the transcription of specific genes coding for various drug-metabolizing enzymes (Ramadoss & Perdeu 2005). Ligand-activated AhR may also modulate the activity of other transcription factors such as estrogen and androgen receptors (Trivellin & Korbonits 2011, Beckers *et al.* 2013). AIP has been shown to maintain the stability of the complex by protecting AhR from ubiquitin-dependant degradation (Morales & Perdeu 2007). AhR itself is constitutively active, and it was recently shown that AhR may act as tumor suppressor in the pituitary even in the absence of exogenous ligands (Formosa *et al.* 2017). Reduced AIP expression in pituitary adenomas that are positive for *AIP* mutations is associated with decreased AhR activity, suggesting an inhibitory function of AhR in pituitary tumorigenesis (Jaffrain-Rea *et al.* 2009). Furthermore, AIP

overexpression in cell cultures – including pituitary cell lines – slows down cell proliferation rates (Leontiou *et al.* 2008). Apart from stabilizing the AhR complex, AIP may also be involved in several other nuclear receptor pathways by being able to bind to the peroxisome proliferator-activated receptor α , the glucocorticoid receptor and β -thyroid hormone receptor 1 (Beckers *et al.* 2013). AIP can also interact with the transcript of the RET protooncogene – a tyrosine kinase receptor that is involved in cell growth and regulation of apoptosis. The domain responsible for the pro-apoptotic activity is the same as that responsible for the AIP interaction (Vargiolu *et al.* 2009). This RET-AIP binding presumably prevents the formation of a complex between AIP and survivin – an inhibitor of apoptosis and cell cycle regulator. In the absence of AIP, survivin is subject to proteosomal degradation with consequent increase in apoptosis (Kang & Altieri 2006). However, this interplay of AIP, RET and survivin probably does not have a role in pituitary tumorigenesis. AIP has been shown to participate in the transfer of mitochondrial preproteins from the cytosol by interacting with the translocator of outer mitochondrial membrane 20 (TOMM20) (Yano *et al.* 2003). The list of interacting partners of AIP has recently been updated with some cytoskeletal proteins, especially TUBB and TUBB2A, and it may be suggested that loss of AIP impairs the organisation of the cytoskeleton and contributes to the more invasive nature of *AIP*-mutant pituitary adenomas (Hernandez-Ramirez *et al.* 2018a).

One of the most attractive links between *AIP* mutations and pituitary tumorigenesis is the interaction with the cAMP-dependent signaling pathway. Responsiveness to hypothalamic, peripheral and paracrine ligands is mediated through either stimulatory or inhibitory G-protein coupled receptors which use cAMP as second intracellular messenger. In the pituitary, the activation of the cAMP pathway stimulates cell proliferation and hormonal secretion (Hernandez-Ramirez *et al.* 2018b). In pituitary cell lines in which *AIP* is knocked down, there is an increase in stimulated cAMP levels (Formosa *et al.* 2013). Loss of AIP has been shown to affect inhibitory G-protein function, as *AIP*-mutant pituitary tumors are associated with reduced expression of $G\alpha_{i-2}$ (Tuominen *et al.* 2015). In the anterior pituitary, $G\alpha_i$ proteins mediate somatostatin-related inhibition of GH and prolactin secretion through somatostatin receptors. Thus, a defect $G\alpha_{i-2}$ function could explain the resistance to somatostatin analogues that is usually observed in *AIP*-mutant somatotropinomas (Daly *et al.* 2010). It has recently been demonstrated that AIP physically interacts with both the catalytic (PRKACA) and the regulatory (PRKAR1A) subunits of PKA and likely

regulates its downstream effects (Scherthaner-Reiter *et al.* 2018). Another cAMP pathway interaction of AIP occurs at the level of phosphodiesterases – the enzymes that inactivate cAMP. It has recently been shown that AIP-mutant somatotropinomas exhibit reduced expression of PDE4A4 and PDE4A8 possibly resulting in enhanced cAMP signaling (Bizzi *et al.* 2018).

Despite the large and increasing number of molecular interactions of AIP with different regulatory and functional cascades, none has been proven critical for pituitary tumor development to date. Although AIP is ubiquitously expressed in the body, no other tumor types except pituitary adenomas have been consistently associated with AIP mutations, suggesting the presence of heavily pituitary-specific tumorigenic pathways. Also, somatic AIP mutations are not a major cause of pituitary tumorigenesis (Beckers *et al.* 2013). Almost 70% of mutations affect the C-terminal end of the protein. Nonsense and frameshift mutations lead to premature stop codons with a resulting truncated protein. A genotype-phenotype correlation has been recently suggested, as patients with truncating mutations may develop pituitary disease at younger age than patients with non-truncating mutations (Hernandez-Ramirez *et al.* 2015). Pathogenic missense mutations alter protein stability and lead to rapid proteosomal degradation with a significantly reduced half-life of the mutated protein. Moreover, a direct correlation between half-life of mutant AIP and age at diagnosis has been documented in patients (Hernandez-Ramirez *et al.* 2016). N-terminal mutations have also been proven pathogenic, probably by reducing the ability to inhibit cAMP signaling (Formosa & Vassallo 2017). Apart from point mutations and small insertions and deletions, in a minority of cases, larger genomic alterations like exon or whole gene deletions may be present. Such genomic rearrangements cannot be detected by direct sequencing and require the use of multiple ligation-dependant probe amplification (MLPA) (Georgitsi *et al.* 2008, Beckers *et al.* 2013).

Clinical implications of AIP mutations

AIP mutations explain the pathology of about 20% of FIPA families (Beckers *et al.* 2013), and they are associated with some specific clinical characteristics that differentiate them from patients with wild type AIP (Table 1). Somatotropinomas are the most frequent secretory phenotype representing more than 70% of all tumors in AIP-mutated FIPA kindreds and half of them

exhibit co-secretion of prolactin. In total, acromegaly and prolactinoma families make up almost 90% of all cases, the rest are mainly NFPA. Single cases of thyrotropinomas and Cushing's disease have also been described in association with AIP mutations (Beckers *et al.* 2013). AIP-mutation related somatotropinomas develop at significantly younger age and experience a more aggressive evolution than their non-mutated counterparts. Mutated tumors are also significantly larger and are often already macroadenomas with invasive characteristics and frequent extrasellar expansion at presentation (Daly *et al.* 2010). Due to the young onset of disease, 29–30% of AIP positive GH-secreting adenomas manifest clinically with gigantism (Daly *et al.* 2010, Rostomyan *et al.* 2015). Control of GH excess and tumor growth is also difficult to achieve and maintain in AIP mutation carriers because of poorer responsiveness to first generation somatostatin analogues in these patients. In the long term, AIP-mutated tumors often require multiple surgeries and radiotherapy (Daly *et al.* 2010). A recent report, however, indicates that pasireotide, a second-generation somatostatin analogue, may be effective in providing hormonal control and tumor shrinkage in AIP-positive acromegaly patients (Daly *et al.* 2019b). AIP-mutated prolactinomas also present with large tumor size and invasive features. Resistance to dopamine agonists may be observed in 50% of them, resulting in the need for surgery and/or radiotherapy (Daly *et al.* 2010). Due to rapid growth, AIP mutation-related pituitary adenomas can undergo apoplexy (Fig. 1), so there should be particular vigilance for AIP mutations among young pituitary apoplexy patients or in those with a familial history of pituitary apoplexy (Villa *et al.* 2011, Xekouki *et al.* 2013).

Screening for AIP mutations

The identification of AIP mutations may be beneficial for patients and their relatives by potentially providing early diagnosis and a higher likelihood of successful treatment, although no formal outcome studies of screening have been performed. Currently, genetic screening in unselected pituitary adenoma patients is not justified, because the prevalence of AIP mutations in such population is very low – 0–4% (Barlier *et al.* 2007, Cazabat *et al.* 2012). However, focused screening may be recommended in some specific high-risk groups (Fig. 2). The highest probability of AIP mutation is in patients with pituitary gigantism where such genetic alterations are found in 29% (Rostomyan *et al.* 2015). AIP mutations are present in

Figure 1

Contrast enhanced MRI images showing pituitary macroadenomas in two sisters from an *AIP* mutation positive FIPA family. Both patients presented at a young age (12 and 17 years) with symptoms related to tumor size (headache and visual loss), and on imaging and on surgery, there was evidence of incipient pituitary apoplexy. Reproduced, with permission, from [Villa *et al.* \(2011\)](#).

almost 12% of patients younger than 30 years with early onset large macroadenomas ([Tichomirowa *et al.* 2011](#)) and up to 20% in pediatric patients with macroadenomas (generally GH-secreting) ([Stratakis *et al.* 2010](#)), making these populations good candidates for genetic screening. FIPA patients represent another readily identifiable group in which testing for *AIP* mutations is warranted, as they are present in about 20% of kindreds. Development of risk stratification models to inform genetic testing guidelines remains a work in progress, and the most informative criteria continue to be those identified (i.e. gigantism, young onset, FIPA kindreds and large macroadenomas). A recent study suggests that somatostatin analog resistance is not a helpful additional criterion to identify potential *AIP* mutation-related acromegaly cases ([Daly *et al.* 2019a](#)).

There are no guidelines for the management of *AIP* mutation positive and familial pituitary adenomas, and their treatment largely follows the current guidelines for their sporadic counterparts in terms of indications and therapeutic approaches. Detailed physical examination for extra-pituitary involvement and a comprehensive family history should be initially undertaken, and any suspicion of syndromic conditions such as MEN1 and Carney complex should be investigated when considering patients

and their families for genetic testing. *AIP* mutation carriers should be offered complete clinical, biochemical and MRI evaluation at baseline and regular endocrinological surveillance thereafter. More challenging is the situation in FIPA families without identifiable *AIP* mutations. In such cases, it may be appropriate to inform unaffected subjects about signs and symptoms of pituitary disease and encourage them to seek endocrinological consultation if such symptomatology occurs. The common presence of pituitary gigantism in patients with *AIP* mutations means that particular attention needs to be paid to pediatric mutation carriers. Early diagnosis and a decreased delay before effective treatment have been shown to lower final height in patients with pituitary gigantism ([Rostomyan *et al.* 2015](#)), and efficient management of *AIP* mutation carriers with incipient somatotropinomas could help to limit long term overgrowth.

GPR101 and FIPA

We recently described a novel syndrome of early childhood onset pituitary gigantism, due to chromosome Xq26.3 duplications, called X-linked acrogigantism

Figure 2

Potential at-risk groups for pituitary adenomas related to *AIP* germline mutations. The highest prevalence of *AIP* mutations (green boxes) occurs in pituitary gigantism (29%) and FIPA (20% of kindreds). An intermediate risk (yellow boxes) occurs among pediatric pituitary adenoma patients (particularly GH-secreting adenomas) and in patients with aggressive, large or invasive macroadenomas with disease/symptom onset during adolescence and early adulthood. *AIP* mutation patients with aggressively growing pituitary adenomas can develop apoplexy, so a history of symptoms or radiologic findings suggestive of apoplexy should be considered. Groups of pituitary adenoma patients that are unselected for age at onset, tumor characteristics or family history have a low level of *AIP* mutations in international studies (red box). Similarly, the presence of SSA resistance in acromegaly or DA resistance in prolactinomas alone (without other aggressive/early onset tumor features) does not help in identifying patients with *AIP* mutations (red box). DA: dopamine agonist; SSA: somatostatin analog.

(X-LAG) (Trivellin *et al.* 2014, Beckers *et al.* 2015). Patients with X-LAG are typically born at normal size following unremarkable pregnancies, but over the first 12–36 months of life develop rapid increases in length and weight due to GH/IGF-1 hypersecretion from pituitary somatotrope-somatomammotrope macroadenomas and/or hyperplasia (Trivellin *et al.* 2014, Beckers *et al.* 2015). Growth hormone releasing hormone (GHRH) excess in some cases studied indicates that X-LAG may be a multi-level disease involving both the hypothalamus and anterior pituitary (Daly *et al.* 2016a). Treatment of the pituitary tumor in X-LAG is complex due to the young age of affected children and relatively large tumor size. In addition, first-line medical therapy with somatostatin analogs like octreotide and lanreotide is usually ineffective to control GH/IGF-1 excess and height gain. The GH receptor antagonist, pegvisomant, has proven effective in IGF-1 and growth control in X-LAG cases. The chromosome Xq26.3 duplication includes the gene *GPR101* that encodes an orphan G-protein coupled receptor whose expression is highly elevated in tumors of X-LAG patients (Trivellin *et al.* 2014). This duplication usually occurs spontaneously either as a constitutive duplication or in a somatic mosaic state, the latter occurring in sporadic males with X-LAG (Daly *et al.* 2016b). The chromosome Xq26.3 duplication involving *GPR101* can also be inherited in an X-linked dominant manner, and all carriers of the duplication are affected by pituitary gigantism.

To date, three FIPA kindreds have been described in which the underlying cause of isolated somatotropinomas was proven to be X-LAG. These all involved transmission of the Xq26.3 duplication from affected mother to affected son (two sons in one kindred and one son each in the other two kindreds). In two of the mothers, pregnancy occurred following assisted reproduction techniques that were necessary due to extensive pituitary tumor surgery and secondary gonadotropin deficiency. In one familial case, the Xq26.3 duplication was diagnosed prenatally on chorionic villus sampling and led to a perinatal diagnosis of a pituitary adenoma secreting high levels of GH and prolactin within the first month of life (Gordon *et al.* 2016, Wise-Oringer *et al.* 2019). Further details about *GPR101* and X-LAG are discussed by Trivellin *et al.* in this issue of *Endocrine-Related Cancer* (Trivellin *et al.* 2020).

Conclusions

The definition of FIPA almost 20 years ago and the discovery of *AIP* as a causative gene represent important advances in our expanding knowledge about the genetic background of pituitary adenoma development. The more recent description of X-LAG due to *GPR101* duplications provides a novel mechanism by which families with pituitary gigantism can rarely present in the FIPA setting. However, much remains to be explored in FIPA, as in

almost 80% of FIPA kindreds the genetic causes remain unknown. Besides the wide spectrum of functions that have been ascribed to *AIP*, the precise molecular pathways that lead to pituitary tumorigenesis are yet to be fully explained. Consensus guidelines for genetic testing, management and follow-up of FIPA patients are still to emerge and require long-term monitoring studies to arrive at the most clinically relevant recommendations.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of this review.

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