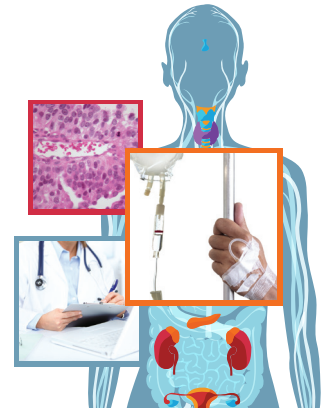
REVIEW



International Journal of Endocrine Oncology

Advances in diagnosis and management of familial pituitary adenomas

Haroun Jedidi[1], Liliya Rostomyan[2], Iulia Potorac[2], Frédérique Depierreux-Lahaye[1], Patrick Petrossians[2] & Albert Beckers*[,2]

Practice points

- Pituitary adenomas are relatively frequent benign intracranial tumors (prevalence of 1/1000).
- Approximately 5–8% of pituitary adenomas occur in a familial setting.
- About 2–3% of all pituitary adenomas fit into the familial isolated pituitary adenoma (FIPA) syndrome, and 15–20% of FIPA cases have mutations in the *AIP* gene and distinct clinical characteristics.
- *AIP* mutations are associated with early-onset and aggressive tumors.
- The genetics of approximately 80% of FIPA families remains unknown.
- X-linked acrogigantism accounts for more than 80% of the cases of early-onset pediatric gigantism and about 10% of pituitary gigantism cases.
- In FIPA families without *AIP* mutation, Xq26.3 microduplications can be regarded as a new cause and by extension X-linked acrogigantism turns out to be a part of the FIPA entity.
- Pituitary adenomas with a genetic predisposition are often aggressive and resistant to conventional treatment options and require specific management.
- Early diagnosis is critical and systematic screening is recommended for patients at risk.
- Apart from the familial cases, genetic testing is recommended in young patients, in case of large and/or aggressive tumors or resistance to medical therapy.
- The main interest of a genome-based classification of familial pituitary adenomas consists in the ability to predict the natural history of pituitary adenomas and to offer appropriate genetic counseling.
- Clearly, clinical, molecular and genetic aspects of familial pituitary adenomas should be studied further in the future and may lead to the development of new forms of therapy.

Familial pituitary adenomas account for approximately 5–8% of all pituitary adenomas. Besides the adenomas occurring as part of syndromic entities that group several endocrine or nonendocrine disorders (multiple endocrine neoplasia type 1 or 4, Carney complex and McCune–Albright syndrome), 2–3% of familial pituitary adenomas fit into the familial isolated pituitary adenomas (FIPA) syndrome, an autosomal dominant condition with incomplete penetrance. About 20% of FIPA cases are due to mutations in the AIP gene and have distinct clinical characteristics. Recent findings have isolated a new non-AIP FIPA syndrome called X-linked acrogigantism, resulting from a microduplication that always includes the GPR101 gene. These new advances in the field of pituitary disease are opening up a new challenging domain to both clinicians and researchers. This review will focus on these recent findings and their contribution to the diagnosis and the management of familial pituitary adenomas.

[1]Neurology Department, CHU of Liège, 1 Avenue de l'hopital, 4000 Liège, Belgium
[2]Endocrinology Department, CHU of Liège, 1 Avenue de l'hopital, 4000 Liège, Belgium
*Author for correspondence: Tel.: +324 366 7083; albert.beckers@chu.ulg.ac.be

Future Medicine part of fsg

First draft submitted: 23 April 2016; Accepted for publication: 12 July 2016;
Published online: 4 November 2016

KEYWORDS
• Aryl hydrocarbon receptor interacting protein
• Carney complex • familial isolated pituitary adenoma
• GPR101 • multiple endocrine neoplasia
• pituitary adenoma
• X-linked acrogigantism

Pituitary adenomas are highly frequent benign intracranial tumors which represent 15–20% of cerebral tumors [1]. Previously considered rare tumors occurring at a rate of approximately 1/3000–5000 individuals [2], clinically apparent pituitary adenomas, were shown in a study conducted by our team to be far more common, with an overall rate of one case in approximately 1000 individuals [3]. These results were later confirmed by other similar research [4]. Autopsy and radiological series have argued total pituitary tumor prevalence, including both asymptomatic lesions and incidentalomas, of 14% and 10–22%, respectively, among the general population [5,6]. In terms of incidence, recent studies have found average values ranging from 2.9 pituitary tumors per 100,000 population in the USA [7] to 4.0 pituitary adenomas per 100,000 in northern Finland [8].

Despite their benign nature, the occurrence of aggressive forms of pituitary adenomas, characterized by a giant size, a recurring pattern, resistance to standard therapy and tendency to invade adjacent structures is not unusual. It is worth noting that, to date, despite the introduction of recent useful molecular markers, there is no clear biomarker capable of facilitating the early identification of aggressive pituitary adenomas and predicting the natural history of a given adenoma.

Considering that clinically similar features could be associated with morphologically heterogeneous tumors, an accurate molecular/genetic/epigenetic classification is needed to predict at an early stage the clinical behavior of the lesion and to allow adequate therapeutic strategies [9,10].

A large number of studies have already been carried out to unravel pituitary adenomas' pathophysiology through molecular genetics of tumorigenesis. Mutations in several genes have been described. The most closely involved of these are somatic mutations of the *gsp* gene, encoding the α-subunit of a heterotrimeric G-protein (Gs). Activating mutations of *gsp* leads to an activation of the stimulatory α-subunit of protein G (Gsα) and, through hyperactivation of adenylyl cyclase, increased production of cAMP [11,12].

It is interesting to note that if a substantial number of genetic mutations or alterations were identified in pituitary adenomas including the recent discovery of mutations in the deubiquitinase gene *USP8* in corticotropinomas [13,14], only a few are involved in inherited or familial conditions. The hereditary forms of pituitary hyperplasia or adenomas are detailed in **Table 1**.

Long regarded as sporadic neoplasms, approximately 5–8% of pituitary adenomas are however part of familial syndromic associations [15,16]. The most frequent and best known of these are

Table 1. Hereditary forms of pituitary hyperplasia or adenomas.

Condition	Gene	Physiopathology	Phenotype
MEN1	*MEN1* (Ch11q13)	Decrease of menin function	All pituitary tumor types
MEN4	*CDKN1B* (Chr 12p13)	Lack of tumor suppression	Only acromegaly and Cushing's disease to date
Carney complex	*PPKR1A* (Ch17q22-24)	1A regulatory subunit of PKA expression/function alteration	GH and GH/prolactin secreting adenomas
McCune–Albright	*GNAS1* (Ch 20q13.3)	Activation of the stimulatory α-subunit of protein G	Pituitary hyperplasia and adenomas, acrogigantism or Cushing's syndrome
3Pas	*SDHA*, *SDHB*, *MEN1* and *SDHC*	Decreased activity of SDH	Often aggressive macroadenomas secreting prolactin or GH
Pituitary blastoma	*DICER1* (Ch14q32.13)	Alteration of DICER1 activity	May be associated with hypersecretion of ACTH and precocious Cushing's disease
FIPA	*AIP* (Ch11q13.32) in 15%–20% of cases	Undetermined	All pituitary adenoma subtypes involved AIP mutation cases include somatotropinomas, prolactinomas, mixed GH/prolactin tumors, nonsecreting adenomas
X-LAG	*GPR101* (ChXq26.3 microduplications)	Increased expression of GPR101 and GH	Early onset acrogigantism, somatotropinomas/somatotroph hyperplasia with prolactin secretion

FIPA: Familial isolated pituitary adenoma; GH: Growth hormone; MEN1: Multiple endocrine neoplasia type 1; MEN4: Multiple endocrine neoplasia type 4; SDH: Succinate dehydrogenase; X-LAG: X-linked acrogigantism; 3Pas: Pituitary adenoma with paraganglioma/pheochromocytoma.

the multiple endocrine neoplasia type 1 (MEN1) syndrome and the Carney complex (CNC). Furthermore, 2–3% of all pituitary adenomas occur in the familial isolated pituitary adenoma (FIPA) context, an autosomal dominant condition with incomplete penetrance. About 15–20% of FIPA cases were found to carry mutations in the *AIP* gene and to exhibit distinct clinical characteristics [3,17]. Finally, recent findings have isolated a new syndrome called X-linked acrogigantism (X-LAG), resulting from a microduplication in the *GPR101* gene, causing early onset gigantism. The same genetic anomaly can explain some cases of non-*AIP* FIPA.

These less frequent entities could be regarded as relevant models to understand the genetic and biochemical pathways of tumorigenesis of pituitary adenomas. This review will focus on these recent findings and their contribution to the diagnosis and management of familial pituitary adenomas.

Familial pituitary adenomas

• MEN1

MEN1 syndrome is an autosomal dominant condition characterized by the association of endocrine and nonendocrine tumors. The most frequently encountered anomalies are primary hyperparathyroidism mostly due to parathyroid hyperplasia, pancreatic and gastrointestinal neuroendocrine tumors and pituitary adenomas. Other possible manifestations are bronchopulmonary and thymic neuroendocrine tumors, adrenocortical tumors, meningiomas and soft tissue tumors such as lipomas and collagenomas [18].

The syndrome is caused by inactivating mutations of the tumor suppressor gene *MEN1*, located on chromosome 11q13 and coding for the protein menin. Menin has a role in controlling the cell cycle and the oxidative stress regulation [19,20]. Both familial and sporadic forms can be observed. More than 700 mutations in *MEN1* have been described [21]. In sporadic pituitary adenomas, loss of heterozygosity of the *MEN1* gene [22] as well as reduced expression of menin [23] has been found in tumor tissue.

Pituitary adenomas occur in approximately 40% of MEN1 patients, with prolactinomas as the most frequent type, followed by nonfunctional, growth hormone (GH)-secreting and ACTH-secreting lesions [24]. Clinically speaking, pituitary disease is more frequent in familial than in sporadic cases of MEN1, especially prolactinomas which are bigger and have a poorer dopamine agonist response than sporadic ones [24,25]. Pituitary adenomas in MEN1 are more likely to be macroadenomas (85%) and local compression symptoms are more frequent than in sporadic pituitary tumors. MEN1 female patients seem to develop pituitary adenomas more frequently than male patients [24]. The possibility of a genetic diagnosis in MEN1 patients has optimized the treatment options and radiological follow-up of these often aggressive tumors [20].

• MEN4

Surprisingly, more than 20% of patients with a MEN1 clinical pattern have no demonstrable genetic anomaly of the *MEN1* gene. This observation led to the hypothesis that there had to be other genetic factors involved. Derived from work performed on murine models, a new clinical syndrome belonging to the MEN spectrum has been described [26].

MEN4 is caused by heterozygous mutations of the tumor suppressor gene *CDKN1B*, located on chromosome 12, and which codes for a 196 amino acid cyclin-dependent kinase inhibitor $p27^{Kip1}$ [27]. Several different mutations were described leading to an inactivation of $p27^{Kip1}$. However, anomalies in the genes coding for other cyclin-dependent kinase inhibitors (p15, p18 and p21) were also found, although rarely, in cases of MEN1 or related states for which *MEN1* mutations were absent [28]. Although the expression of $p27^{Kip1}$ was shown to be decreased in pituitary tumors compared with normal pituitary tissue, mutations of the *CDKN1B* gene have not been described so far in sporadic pituitary tumors [29].

The clinical presentation is similar to that of MEN1 and generally includes parathyroid and pituitary anomalies, but also, although more rarely, pancreatic and gastrointestinal neuroendocrine tumors, adrenal, thyroid tumors and other nonendocrine lesions [27,30–31]. However, *CDKN1B* mutations appear to explain only a minority of MEN1-like syndromes without *MEN1* gene mutations [27,32]. It should also be noted that although MEN4 is an approved genetic cause of pituitary disease, it appears to be very rare and only a few cases have been described so far [31].

• CNC

CNC is a rare autosomal dominant condition defined by the association of endocrine (primary

pigmented nodular adrenocortical disease leading to Cushing's syndrome, pituitary adenomas, thyroid, testicular and ovarian tumors) and nonendocrine manifestations (lentiginosis, blue nevi, *café-au-lait* skin spots, cardiac, skin and mammary myxomas and schwannomas) [33,34]. Hypersecretion of prolactin and GH is frequent (around 75% of patients), but pituitary adenomas are less common (10%). Acromegaly is usually diagnosed at a mean age of 35 years and it has a slow progression [35,36]. Multifocal hyperplasia of somatomammotropic cells of the anterior pituitary is often observed in CNC and may further give rise to adenomas [37].

The syndrome is caused in 60–70% of cases by mutations of the *PRKAR1A* gene which codes for the 1A regulatory subunit of PKA [38,39]. Approximately 70% of CNC patients have an affected parent and 30% have a *de novo* mutation [40]. Interestingly, some genotype–phenotype correlations can be established for *PRKAR1A* mutations. For example, exon-located mutations are more common in relation to cardiac myxomas, lentigines, schwannomas and acromegaly [36]. Paradoxically, haploinsufficient mice for *PRKAR1A* do not develop significant pituitary disease [38,41]. In sporadic pituitary adenomas, mutations of the *PRKAR1A* have not yet been described [29].

Finally, a CNC phenotype consisting of acromegaly, pigmented spots and myxomas was recently described in a female patient with a 1p31.1 triplication, which results in gain of function of *PRKACB,* coding for a catalytic subunit of the PKA [42].

• McCune–Albright syndrome

McCune–Albright syndrome (MAS) is classically defined by the triad *café-au-lait* skin spots, precocious puberty and polyostotic fibrous dysplasia. However, it can also cause pituitary, thyroid, adrenal and parathyroid anomalies, generally manifesting as hyperactivity of these glands [43]. Hypersecretion of GH is described in 20–30% of cases, most often related to pituitary hyperplasia, but also to pituitary adenomas (30% of acromegaly patients with MAS) [39,44]. The prevalence is between 1/100,000 and 1/1,000,000 [44].

The syndrome is caused by postzygotic missense mutation of *GNAS1* gene located on chromosome 20q13.3, leading to a *GNAS1* mosaicism and to constitutive activation of the Gsα, which increases cAMP and, consecutively, cellular activity and growth [45]. Although in transgenic mice, with constitutive expression of Gsα, the mutation is transmitted to offspring [46], in humans, cases of genetic transmission in MAS have not been reported so far.

• Pituitary adenoma with paraganglioma/pheochromocytoma

Pituitary adenoma with paraganglioma/pheochromocytoma is a newly defined rare syndrome characterized by the association of pituitary adenomas with pheochromocytomas or paragangliomas [47,48]. Both familial and isolated cases have been described [47]. Pituitary adenoma with paraganglioma/pheochromocytoma occurs not only in patients harboring germline mutations in SDH subunit genes *SDHA* [49], *SDHB* [48,50], *SDHD* [51] and *SDHC* [52], but also in *MEN1* [50]. However, only 0.3% of all pituitary tumors are estimated to be associated to an *SDH* mutation [53]. Such adenomas are most often prolactinomas, nonfunctioning adenomas or somatotropinomas, and seem to be more aggressive [48,50].

• Pituitary blastoma

Pituitary blastoma is a very rare and recently described embryonal tumor usually occurring in young children that may be associated with hypersecretion of ACTH and precocious Cushing's disease [54,55]. Histologically, the lesion is composed of several cell types featuring those observed in pituitary development, including Rathke's epithelium cells in addition to other secretory cells [54]. This rare condition seems to be caused by germline mutations of the *DICER1* gene in addition to a second somatic *DICER1* mutation, especially in the RNase IIIb domain [56,57]. Pituitary blastoma could be mistaken for a pituitary adenoma [55]. The few cases reported so far have offered new information regarding the pathogenesis and genetics of blastomas and familial tumor syndromes [55].

The FIPA syndrome

• Origins & clinical presentation

The FIPA syndrome was described in Liège at the end of the 1990s, deriving from the previous concept of isolated familial somatotropinomas (IFS), a condition defined by the occurrence of more than two cases of gigantism or acromegaly in a family apart from MEN1 or CNC syndromes [58,59]. When compared with sporadic cases of acromegaly or gigantism, there is a male

predominance, a younger age of onset and the systematic development of macroadenomas in IFS [60].

FIPA syndrome itself (which encompasses a larger range of pituitary adenoma phenotypes than the particular homogeneous cases formerly identified as IFS) could be defined by the occurrence of pituitary tumors of all types, in multiple members of a single family, in the absence of MEN1, CNC or other associative syndrome [17]. FIPA families account for approximately 2% of the overall incidence of pituitary tumors. The first multicenter international study among tertiary referral centers in Europe and the USA led to the identification and the clinical characterization of over 140 FIPA patients from 64 kindreds [60,61]. There are currently several hundred FIPA families identified [17,62].

FIPA may have either a homogeneous (the same type of tumors in all affected family members) or heterogeneous (different types of tumors among family members but almost invariably at least one prolactinoma or GH-secreting adenoma) presentation [60]. Families with two to five affected members have been described [17]. Prolactinomas and somatotropinomas (pure or mixed somatolactotropinomas) are far more frequent in FIPA than other tumor phenotypes, and comprise, respectively, 26.7–37.5% and 41.4–46.6% of cases in large international FIPA cohorts [17,62], followed by nonsecreting tumors (16.5–18.5%), corticotropinomas (2.9–4.8%) and thyrotropinomas (<0.5%). The spectrum of FIPA cohort by tumor phenotype is illustrated in **Figure 1**.

On average, FIPA patients present tumors 4 years earlier than sporadic patients, and first-degree relationship between affected members occurs in 75% of cases [59]. Patients with a homogeneous FIPA presentation are younger at diagnosis than those with a heterogeneous presentation. In multigenerational families, the children/grandchildren have a significantly younger mean age at diagnosis (20 years). It is unclear whether this effect is related to some form of anticipation mechanism at a genetic level, or due to increased awareness on the part of the family [12,17].

Pituitary adenomas in FIPA families usually occur at a younger age and are more aggressive than in sporadic cases. Prolactinomas in FIPA are usually microadenomas occurring in women, while macroadenomas are generally diagnosed in male patients [12]. In the heterogeneous FIPA setting, prolactinomas are more aggressive and macroadenomas are more frequent. The nonsecreting adenomas in this group have a higher rate of invasion than sporadic ones. Somatotropinomas in homogeneous families occur at a younger age and have a more frequent extension that those in heterogeneous FIPA cases. Cushing's disease, TSH-secreting adenomas and secreting gonadotropinomas can also presented in the context of both homogeneous and heterogeneous FIPA, although these tumors are much rarer [12,59].

• *AIP* gene

The genetic mechanisms of FIPA are not yet fully understood. Obviously, FIPA patients have no mutation in *MEN1*, *PRKAR1A*, *GNAS1* or other above-cited genes. The first studies demonstrated genetic linkage to a chromosome 11q13 region [63], then between microsatellite markers (D11S956 and D11S527) on chromosome 11q13.1-q13.3 [64], paving the way for the later identification of AIP gene as a culprit. In 2006, the *AIP* was found to be associated with a pituitary adenoma predisposition in kindreds from Finland with GH-secreting and/or prolactin-secreting tumors [65]. A multi-center study in 2007 identified *AIP* mutations in 15% of FIPA cases [66], especially in homogeneous

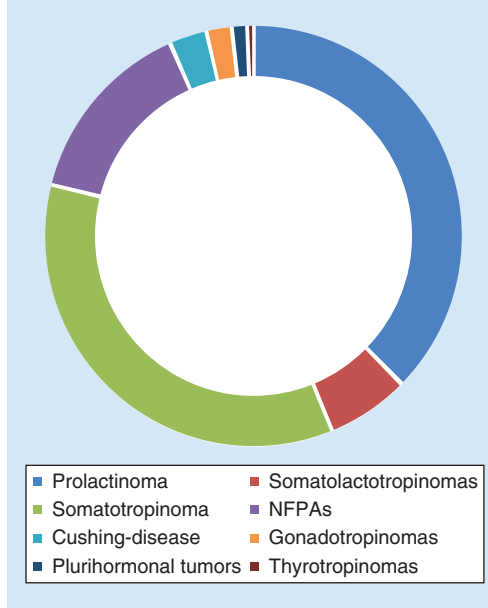


Figure 1. Frequency of the different pituitary adenoma phenotypes in familial isolated pituitary adenoma families.
NFPA: Nonfunctioning pituitary adenoma

somatotropinoma families (42.8%). Patients with *AIP* mutation were younger (12 years) at the diagnosis than other FIPA patients and have larger maximum tumor diameter. Subsequently, these data were confirmed in other FIPA cohorts [17,67]. The majority of patients with *AIP* mutations develop somatotropinomas or both GH/prolactin-secreting adenomas (76.5%) [17]. Somatotropinoma patients with *AIP* mutations are predominantly male and have larger and more aggressive tumors that developed at a younger age (more than 20 years earlier) than those without *AIP* mutations. Consequently, the proportion of acromegaly patients with gigantism appears to be higher among those with germline mutations compared with *AIP* negative GH-secreting adenomas (32% vs 6.5%) [68].

The evidence from a series of studies performed to evaluate *AIP* mutation prevalence pointed to specific subgroups of patients in which *AIP* mutation carriers were discovered more frequently (e.g., children and young adults, pituitary gigantism or FIPA families) [12,59,68–70], whereas in an unselected sporadic pituitary adenoma population, *AIP* mutations are extremely rare [71–73]. In particular, patients with sporadic macroadenomas aged at diagnosis less than 30 years harbor *AIP* mutations in 10% and even in 20% of cases in pediatric patients with macroadenomas [69]. Pituitary adenoma predisposition (including *AIP* status) was also assessed recently in a large international cohort of patients with pituitary gigantism that represents a special population of interest for genetic screening [70]. In this study, 46% of tested cases had genetic alterations. Among these, the most frequent were *AIP* mutations (29%). Additionally, some rarer cases of genetic syndromes discussed above were identified in this group, such as MAS (5%), CNC (1%) and MEN1 (1%).

The clinical management of FIPA regardless of *AIP* status is quite similar to that of sporadic pituitary adenomas in terms of therapeutic options. However, patients with *AIP* mutations frequently have more aggressive tumors with poorer disease control. In particular, *AIP* positive somatotropinomas are frequently resistant to treatment with somatostatin analogs, and require, in many cases, use of multiple treatment modalities (neurosurgery, medical therapy and radiotherapy) [68]. *AIP* mutation should be tested in at least one affected member as these mutations are correlated with more aggressive and earlier onset tumors, making hormonal testing and MRI monitoring recommended in this subgroup. In mutation carriers with no pituitary adenoma visible on MRI, an annual monitoring with hormonal testing (prolactin and IGF-I) and clinical examination is recommended [12,17,59].

The tumors and the secreting pattern appear to be quite heterogeneous in *AIP* mutation positive patients. The same *AIP* mutation may be related to different tumor phenotypes in different families [12,74]. Since its revelation, numerous *AIP* mutations have been described [17,62,65]. However, the exact role of *AIP* mutations in the tumorigenesis of pituitary adenomas remains to be determined. *AIP* represents a new tumor suppressor gene (all mutations in this gene are inactivating with loss of heterozygosity in the pituitary tumors in those patients with germline mutations) [17,65]. It consists of six exons encoding a 330 amino-acid protein from the family of immunophilins. Many of the described *AIP* mutations would involve functional loss of a tetratricopeptide repeat and the carboxy terminal domains that are important for interactions with other proteins including the aryl hydrocarbon receptor and the heat shock protein 90 [75–77]. All germline *AIP* mutations described to date are heterozygous, suggesting that homozygous mutations are lethal *in utero* [78]. The penetrance of pituitary disease in patients with *AIP* mutations, albeit controversial, seems not to be low, around 33% [79]. At the cellular level, *AIP* impaired activity may lead to modulation of phosphodiesterase PDE4A5 and phosphodiesterase PDE2A activities [80]. It must be borne in mind that so far only 20% of FIPA families harbor *AIP* mutations [17], which means that the genetics of FIPA remains widely unknown. Likewise, FIPA families with several affected members can be negative for *AIP* mutations, suggesting that other genes may be involved in the pathophysiology of FIPA.

• X-LAG

X-LAG is a recently described pediatric disorder characterized by early onset gigantism resulting from excess of GH [81]. The syndrome, identified following the collaboration between the University of Liège and the NIH, is caused by germline Xq26.3 microduplications encompassing the *GPR101* gene, but somatic mosaicism can also occur [82,83]. Microduplications of Xq26.3 account for more than 80% of the cases of early-onset pediatric gigantism [81,84] and about 10% of the total pituitary gigantism cases of a recent large international cohort [70]. X-LAG can present as a sporadic form or in the context of FIPA, where penetrance seems to be

complete [81,84]. To date, only transmission from affected mother to affected son was reported, and there are no cases of transmission from affected men described. It leads to the hypothesis that Xq26.3 microduplications have a negative effect on the viability of hemizygous male embryos [82,85]. In FIPA families without *AIP* mutations, Xq26.3 microduplications can be regarded as a new pathophysiologic explanation and by extension X-LAG turns out to be a part of the FIPA entity [81].

The *GPR101* gene was initially studied along with three other genes (*RBMX*, *CD40LG* and *ARHGEF6*) spread over two smallest regions of overlap (SRO1 and 2). Only *GPR101* among those four genes was upregulated in pituitary lesions surgically resected from X-LAG patients compared with sporadic somatotropinomas and normal pituitary tissue. This suggested that *GPR101* might be responsible for the phenotype, as was recently confirmed by a case of X-LAG with duplication of only the *GPR101* gene [86]. The gene encodes a G stimulatory protein-coupled orphan receptor of unknown function (potent activator of adenylyl cyclase) which is highly expressed not only in X-LAG patient tumors, but also in the hypothalamus of both human and rodent [87,88].

The molecular mechanisms of tumorigenesis remain debated. Overexpression of mutated *GPR101* led to increased cAMP signaling as well as both cell proliferation and GH secretion in rat GH3 cells [81].

It was suggested that hypothalamic GHRH dysregulation may also play a pathophysiologic role [84,89]. It should be noted that a p.E308D mutation (other than a microduplication) was identified (mainly in tumor tissue) in sporadic somatotropinoma patients [81,90]. Finally, germline *GPR101* mutations are very rare in patients with sporadic pituitary adenomas of various secretion types [91].

X-LAG syndrome is more frequent in women. X-LAG patients usually present quite aggressive pituitary macroadenomas with or without pituitary hyperplasia and have increased levels of prolactin and especially GH and IGF-I [81,90]. These patients can exhibit overgrowth as young as 2–3 months of age and abnormal growth always occurs before 5 years of age, mostly during the first year. Interestingly, some of X-LAG patients present abnormally increased appetite and signs of insulin resistance [84].

Early diagnosis of X-LAG allows a better management of the disease. X-LAG patients are resistant to medical therapy alone. Response to somatostatin analogs is poor. Neurosurgery and/or GH receptor antagonist pegvisomant treatment and/or radiotherapy may be needed, despite the secondary risk of hypopituitarism [70,84,90].

Conclusion

Familial pituitary adenomas occur more frequently than previously considered and represent an important area of research. They can fit into several syndromic associations or on the contrary occur in an isolated manner. Clearly, clinical, molecular and genetic aspects of familial pituitary adenomas should further be studied in the future.

Regarding treatment options, there are basically similarities in the management of familial and sporadic pituitary adenomas. However, familial pituitary adenomas also have some specific characteristics that are capable of predicting their clinical behavior and their response to treatment.

Thus, as previously seen, familial pituitary adenomas are often aggressive and resistant to conventional treatment options and require specific management such as neurosurgery at the outset and/or radiotherapy or alternative medical treatment programs. Early diagnosis appears to be critical in these familial and hereditary forms as it allows the introduction of an early and appropriate management of the disease and is associated with a better prognosis.

Genetic testing should also be recommended in young patients, in case of large and/or aggressive tumors or resistance to medical therapy and, particularly, for those with a family history of pituitary adenomas. An algorithm for genetic screening is proposed in **Figure 2**. Accordingly, regular sellar region MRI monitoring, clinical examination and hormonal testing should be recommended for people with a genetic predisposition and especially in *AIP* mutation carriers. Nevertheless, this should be balanced against local available economic and logistic resources.

To date, in the absence of a better understanding of tumorigenesis mechanisms and the lack of more specific therapeutic targets, the main interest of an accurate genome-based classification of familial pituitary adenomas consists in the ability to predict the natural history of a given pituitary adenoma or the risk of developing such a disease in an individual carrier of a genetic

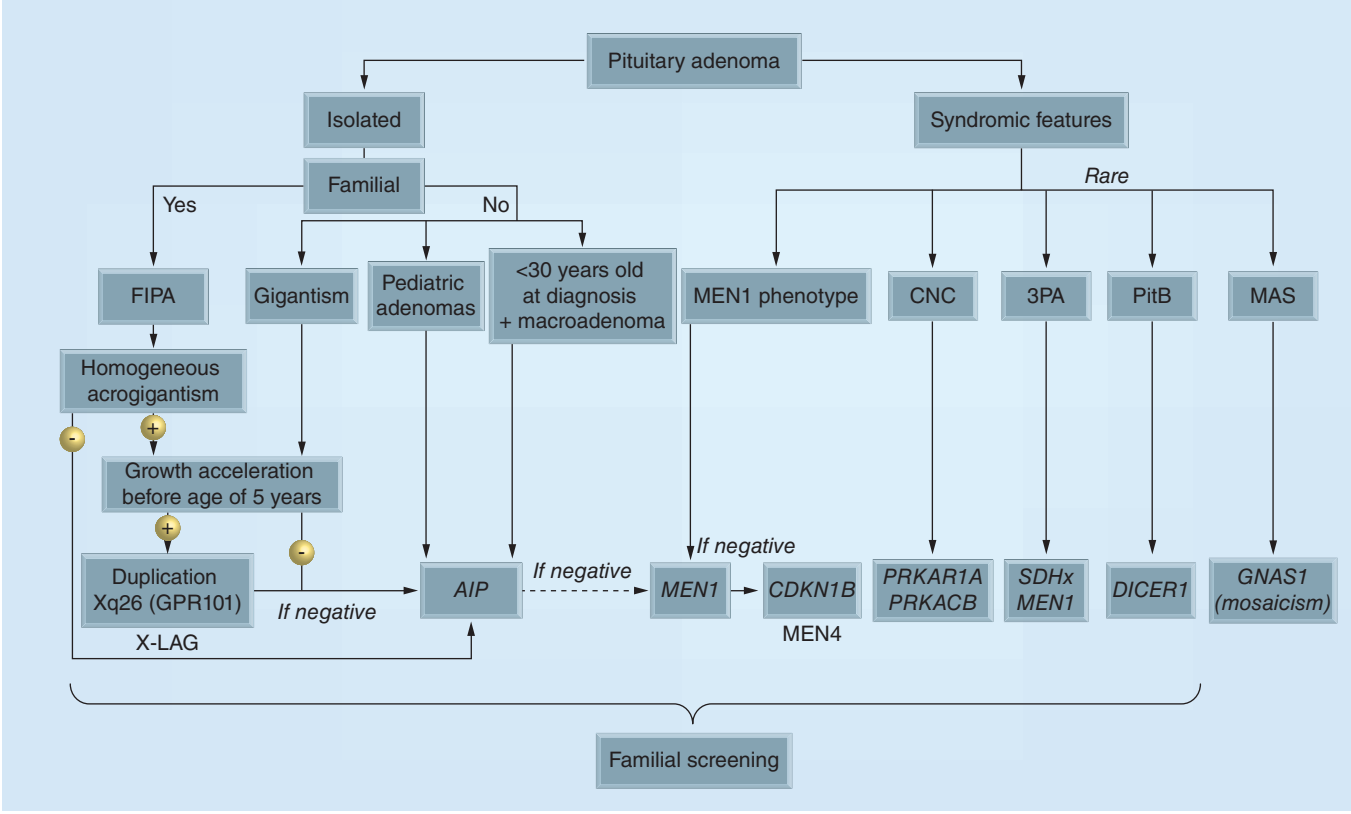


Figure 2. Genetic screening algorithm.
CNC: Carney complex; FIPA: Familial isolated pituitary adenoma; MAS: McCune–Albright syndrome PitB: Pituitary blastoma.

mutation and therefore to offer an appropriate genetic counseling.

Ultimately, the recent discovery of new familial forms of pituitary adenomas must encourage both clinicians and researchers to re-examine the more-established medical and pathophysiological certainties in the light of these findings and the new research models and techniques.

Future perspective

The advances of the last few years in the field of inherited pituitary adenomas (particularly the discovery of *AIP* gene and description of X-LAG syndrome) have highlighted the important role of genetic factors in pituitary adenoma patients.

Since the genetic origin of approximately 80% of the FIPA cases remains unknown, it is predictable that future years will see the description of new loci or causative genes related to new clinical subtypes, contributing to a better understanding of the pathophysiology of both familial and sporadic pituitary adenomas.

The underlying biochemical pathways of tumor growth (e.g., role of *AIP* of *GPR101*) will be better understood, including through the development of new mouse models and the natural disease history will become clearer for each genetic subtype.

The potential mechanisms triggered by other genetic anomalies in the tumorigenesis of pituitary adenomas should also be considered in further studies.

Finally, it is likely that these advances will offer the opportunity to translate genetic discoveries into a more personalized and efficient approach to the management of pituitary adenomas (including genetic counseling) and may also lead to the development of new forms of therapy.

Financial & competing interests

This work was supported by Fonds d'Investissement pour la Recherche Scientifique (FIRS) du Centre Hospitalier Universitaire de Liège. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

No writing assistance was utilized in the production of this manuscript.

References

1 Melmed S. Pathogenesis of pituitary tumors. *Nat. Rev. Endocrinol.* 7, 257–266 (2011).

2 Davis JR, Farrell WE, Clayton RN. Pituitary tumours. *Reproduction* 121, 363–371 (2001).

3 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.* 91, 4769–4775 (2006).

4 Fernandez A, Karavitaki N, Wass JA. Prevalence of pituitary adenomas: a community-based, cross-sectional study in Banbury (Oxfordshire, UK). *Clin. Endocrinol. (Oxf.)* 72, 377–382 (2010).

5 Ezzat S, Asa SL, Couldwell WT *et al.* The prevalence of pituitary adenomas: a systematic review. *Cancer* 101, 613–619 (2004).

6 Hall WA, Luciano MG, Doppman JL, Patronas NJ, Oldfield EH. Pituitary magnetic resonance imaging in normal human volunteers: occult adenomas in the general population. *Ann. Intern. Med.* 120, 817–820 (1994).

7 Gittleman H, Ostrom QT, Farah PD *et al.* Descriptive epidemiology of pituitary tumors in the United States, 2004–2009. *J. Neurosurg.* 121, 527–535 (2014).

8 Raappana A, Koivukangas J, Ebeling T, Pirila T. Incidence of pituitary adenomas in northern Finland in 1992–2007. *J. Clin. Endocrinol. Metab.* 95, 4268–4275 (2010).

9 Syro LV, Rotondo F, Ramirez A *et al.* Progress in the diagnosis and classification of pituitary adenomas. *Front. Endocrinol.* 6, 97 (2015).

10 Melmed S. Pituitary medicine from discovery to patient-focused outcomes. *J. Clin. Endocrinol. Metab.* 101, 769–777 (2016).

11 Asa SL, Ezzat S. Genetics and proteomics of pituitary tumors. *Endocrine* 28, 43–47 (2005).

12 Beckers A, Daly AF. The clinical, pathological, and genetic features of familial isolated pituitary adenomas. *Eur. J. Endocrinol.* 157, 371–382 (2007).

13 Reincke M, Sbiera S, Hayakawa A *et al.* Mutations in the deubiquitinase gene *USP8* cause Cushing's disease. *Nat. Genet.* 47, 31–38 (2015).

14 Ma ZY, Song ZJ, Chen JH *et al.* Recurrent gain-of-function USP8 mutations in Cushing's disease. *Cell Res.* 25, 306–317 (2015).

15 Scheithauer BW, Laws ER Jr, Kovacs K *et al.* Pituitary adenomas of the multiple endocrine neoplasia type I syndrome. *Semin. Diagn. Pathol.* 4, 205–211 (1987).

16 Vasilev V, Daly AF, Petrossians P, Zacharieva S, Beckers A. Familial pituitary tumor syndromes. *Endocr. Pract.* 17(Suppl. 3), 41–46 (2011).

17 Beckers A, Aaltonen LA, Daly AF, Karhu A. Familial isolated pituitary adenomas (FIPA) and the pituitary adenoma predisposition due to mutations in the aryl hydrocarbon receptor interacting protein (AIP) gene. *Endocr. Rev.* 34, 239–277 (2013).

18 Thakker RV, Newey PJ, Walls GV *et al.* Clinical practice guidelines for multiple endocrine neoplasia type 1 (MEN1). *J. Clin. Endocrinol. Metab.* 97, 2990–3011 (2012).

19 Agarwal SK, Lee Burns A, Sukhodolets KE *et al.* Molecular pathology of the *MEN1* gene. *Ann. NY Acad. Sci.* 1014, 189–198 (2004).

20 Thakker RV. Multiple endocrine neoplasia type 1 (MEN1) and type 4 (MEN4). *Mol. Cell. Endocrinol.* 386, 2–15 (2014).

21 Thakker RV. Multiple endocrine neoplasia type 1 (MEN1). *Clin. Endocrinol. Metab.* 24, 355–370 (2010).

22 Zhuang Z, Ezzat SZ, Vortmeyer AO *et al.* Mutations of the *MEN1* tumor suppressor gene in pituitary tumors. *Cancer Res.* 57, 5446–5451 (1997).

23 Asa SL, Somers K, Ezzat S. The *MEN-1* gene is rarely down-regulated in pituitary adenomas. *J. Clin. Endocrinol. Metab.* 83, 3210–3212 (1998).

24 Verges B, Boureille F, Goudet P *et al.* Pituitary disease in MEN type 1 (MEN1): data from the France–Belgium MEN1 multicenter study. *J. Clin. Endocrinol. Metab.* 87, 457–465 (2002).

25 Wautot V, Vercherat C, Lespinasse J *et al.* Germline mutation profile of *MEN1* in multiple endocrine neoplasia type 1: search for correlation between phenotype and the functional domains of the MEN1 protein. *Hum. Mutat.* 20, 35–47 (2002).

26 Piotrowska K, Pellegata NS, Rosemann M *et al.* Mapping of a novel MEN-like syndrome locus to rat chromosome 4. *Mamm. Genome* 15, 135–141 (2004).

27 Pellegata NS, Quintanilla-Martinez L, Siggelkow H *et al.* Germ-line mutations in p27Kip1 cause a multiple endocrine neoplasia syndrome in rats and humans. *Proc. Natl Acad. Sci. USA* 103, 15558–15563 (2006).

28 Agarwal SK, Mateo CM, Marx SJ. Rare germline mutations in cyclin-dependent kinase inhibitor genes in multiple endocrine neoplasia type 1 and related states. *J. Clin. Endocrinol. Metab.* 94, 1826–1834 (2009).

29 Zhou Y, Zhang X, Klibanski A. Genetic and epigenetic mutations of tumor suppressive genes in sporadic pituitary adenoma. *Mol. Cell. Endocrinol.* 386, 16–33 (2014).

30 Pardi E, Mariotti S, Pellegata NS *et al.* Functional characterization of a CDKN1B mutation in a Sardinian kindred with multiple endocrine neoplasia type 4 (MEN4). *Endocr. Connect.* pii: EC-14-0116 (2014) (Epub ahead of print).

31 Lee M, Pellegata NS. Multiple endocrine neoplasia type 4. *Front. Horm. Res.* 41, 63–78 (2013).

32 Georgitsi M, Raitila A, Karhu A *et al.* Germline CDKN1B/p27Kip1 mutation in multiple endocrine neoplasia. *J. Clin. Endocrinol. Metab.* 92, 3321–3325 (2007).

33 Carney JA, Hruska LS, Beauchamp GD, Gordon H. Dominant inheritance of the complex of myxomas, spotty pigmentation, and endocrine overactivity. *Mayo Clin. Proc.* 61, 165–172 (1986).

34 Stratakis CA, Kirschner LS, Carney JA. Clinical and molecular features of the Carney complex: diagnostic criteria and recommendations for patient evaluation. *J. Clin. Endocrinol. Metab.* 86, 4041–4046 (2001).

35 Boikos SA, Stratakis CA. Pituitary pathology in patients with Carney Complex: growth-hormone producing hyperplasia or tumors and their association with other abnormalities. *Pituitary* 9, 203–209 (2006).

36 Bertherat J, Horvath A, Groussin L *et al.* Mutations in regulatory subunit type 1A of cyclic adenosine 5'-monophosphate-dependent protein kinase (PRKAR1A): phenotype analysis in 353 patients and 80 different genotypes. *J. Clin. Endocrinol. Metab.* 94, 2085–2091 (2009).

37 Pack SD, Kirschner LS, Pak E *et al.* Genetic and histologic studies of somatomammotropic pituitary tumors in patients with the 'complex of spotty skin pigmentation, myxomas, endocrine overactivity and schwannomas' (Carney complex). *J. Clin. Endocrinol. Metab.* 85, 3860–3865 (2000).

38 Veugelers M, Wilkes D, Burton K *et al.* Comparative PRKAR1A genotype–phenotype analyses in humans with Carney complex and prkar1a haploinsufficient mice. *Proc. Natl Acad. Sci. USA* 101, 14222–14227 (2004).

39 Rostomyan L, Daly AF, Beckers A. Pituitary gigantism: causes and clinical characteristics. *Ann. Endocrinol. (Paris)* 76, 643–649 (2015).

40 Stratakis CA, Salpea P, Raygada M. Carney complex. In: *GeneReviews®*. Pagon RA, Adam MP, Ardinger HH et al. (Eds). University of Washington, WA, USA (2015).

41 Kirschner LS, Kusewitt DF, Matyakhina L *et al.* A mouse model for the Carney complex tumor syndrome develops neoplasia in cyclic AMP-responsive tissues. *Cancer Res.* 65, 4506–4514 (2005).

42 Forlino A, Vetro A, Garavelli L *et al.* PRKACB and Carney complex. *New Eng. J. Med.* 370, 1065–1067 (2014).

43 Collins MT, Singer FR, Eugster E. McCune–Albright syndrome and the extraskeletal manifestations of fibrous dysplasia. *Orphanet J. Rare Dis.* 7(Suppl. 1), S4 (2012).

44 Dumitrescu CE, Collins MT. McCune–Albright syndrome. *Orphanet J. Rare Dis.* 3, 12 (2008).

45 Vasilev V, Daly AF, Thiry A *et al.* McCune–Albright syndrome: a detailed pathological and genetic analysis of disease effects in an adult patient. *J. Clin. Endocrinol. Metab.* 99, e2029–e2038 (2014).

46 Saggio I, Remoli C, Spica E *et al.* Constitutive expression of Gsalpha(R201C) in mice produces a heritable, direct replica of human fibrous dysplasia bone pathology and demonstrates its natural history. *J. Bone Miner. Res.* 29, 2357–2368 (2014).

47 O'Toole SM, Denes J, Robledo M, Stratakis CA, Korbonits M. 15 years of paraganglioma: the association of pituitary adenomas and phaeochromocytomas or paragangliomas. *Endocr. Relat. Cancer* 22, T105–T122 (2015).

48 Xekouki P, Szarek E, Bullova P *et al.* Pituitary adenoma with paraganglioma/pheochromocytoma (3PAs) and succinate dehydrogenase defects in humans and mice. *J. Clin. Endocrinol. Metab.* 100, e710–e719 (2015).

49 Dwight T, Mann K, Benn DE *et al.* Familial *SDHA* mutation associated with pituitary adenoma and pheochromocytoma/paraganglioma. *J. Clin. Endocrinol. Metab.* 98, e1103–e1108 (2013).

50 Denes J, Swords F, Rattenberry E *et al.* Heterogeneous genetic background of the association of pheochromocytoma/paraganglioma and pituitary adenoma: results from a large patient cohort. *J. Clin. Endocrinol. Metab.* 100, e531–e541 (2015).

51 Xekouki P, Pacak K, Almeida M *et al.* Succinate dehydrogenase (SDH) D subunit (SDHD) inactivation in a growth-hormone-producing pituitary tumor: a new association for SDH? *J. Clin. Endocrinol. Metab.* 97, e357–e366 (2012).

52 Lopez-Jimenez E, de Campos JM *et al. SDHC* mutation in an elderly patient without familial antecedents. *Clin. Endocrinol. (Oxf.)* 69, 906–910 (2008).

53 Gill AJ, Toon CW, Clarkson A *et al.* Succinate dehydrogenase deficiency is rare in pituitary adenomas. *Am. J. Surg. Pathol.* 38, 560–566 (2014).

54 Scheithauer BW, Kovacs K, Horvath E *et al.* Pituitary blastoma. *Acta Neuropathol. (Berl.)* 116, 657–666 (2008).

55 Scheithauer BW, Horvath E, Abel TW *et al.* Pituitary blastoma: a unique embryonal tumor. *Pituitary* 15, 365–373 (2012).

56 de Kock L, Sabbaghian N, Plourde F *et al.* Pituitary blastoma: a pathognomonic feature of germ-line DICER1 mutations. *Acta Neuropathol. (Berl.)* 128, 111–122 (2014).

57 Sahakitrungruang T, Srichomthong C, Pornkunwilai S *et al.* Germline and somatic DICER1 mutations in a pituitary blastoma causing infantile-onset Cushing's disease. *J. Clin. Endocrinol. Metab.* 99, e1487–e1492 (2014).

58 Verloes A, Stevenaert A, Teh BT, Petrossians P, Beckers A. Familial acromegaly: case report and review of the literature. *Pituitary* 1, 273–277 (1999).

59 Tichomirowa MA, Daly AF, Beckers A. Familial pituitary adenomas. *J. Intern. Med.* 266, 5–18 (2009).

60 Daly AF, Jaffrain-Rea ML, Ciccarelli A *et al.* Clinical characterization of familial isolated pituitary adenomas. *J. Clin. Endocrinol. Metab.* 91, 3316–3323 (2006).

61 Valdes Socin HG, Jaffrain-Rea M, Tamburrano G *et al.* Familial isolated pituitary tumors: clinical and molecular studies in 80 patients. Presented at: *The Endocrine Society's 84th Annual Meeting.* CA USA, 19–22 June 2002 647.

62 Hernandez-Ramirez LC, Gabrovska P, Dénes J *et al.* Landscape of familial isolated and young-onset pituitary adenomas: prospective diagnosis in AIP mutation carriers. *J. Clin. Endocrinol. Metab.* 100, e1242–e1254 (2015).

63 Poncin J, Abs R, Velkeniers B *et al.* Mutation analysis of the *MEN1* gene in Belgian patients with multiple endocrine neoplasia type 1 and related diseases. *Hum. Mutat.* 13, 54–60 (1999).

64 Luccio-Camelo DC, Une KN, Ferreira RE *et al.* A meiotic recombination in a new isolated familial somatotropinoma kindred. *Eur. J. Endocrinol.* 150, 643–648 (2004).

65 Vierimaa O, Georgitsi M, Lehtonen R *et al.* Pituitary adenoma predisposition caused by germline mutations in the AIP gene. *Science* 312, 1228–1230 (2006).

66 Daly AF, Vanbellinghen JF, Khoo SK *et al.* Aryl hydrocarbon receptor-interacting protein gene mutations in familial isolated pituitary adenomas: analysis in 73 families. *J. Clin. Endocrinol. Metab.* 92, 1891–1896 (2007).

67 Leontiou CA, Gueorguiev M, van der Spuy J *et al.* The role of the aryl hydrocarbon receptor-interacting protein gene in familial and sporadic pituitary adenomas. *J. Clin. Endocrinol. Metab.* 93, 2390–2401 (2008).

68 Daly AF, Tichomirowa MA, Petrossians P *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.* 95, e373–e383 (2010).

69 Tichomirowa MA, Barlier A, Daly AF *et al.* High prevalence of AIP gene mutations following focused screening in young patients with sporadic pituitary macroadenomas. *Eur. J. Endocrinol.* 165, 509–515 (2011).

70 Rostomyan L, Daly AF, Petrossians P *et al.* Clinical and genetic characterization of pituitary gigantism: an international collaborative study in 208 patients. *Endocr. Relat. Cancer* 22, 745–757 (2015).

71 Iwata T, Yamada S, Mizusawa N *et al.* The aryl hydrocarbon receptor-interacting protein gene is rarely mutated in sporadic GH-secreting adenomas. *Clin. Endocrinol. (Oxf.)* 66, 499–502 (2007).

72 Barlier A, Vanbellinghen JF, Daly AF *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.* 92, 1952–1955 (2007).

73 DiGiovanni R, Serra S, Ezzat S, Asa SL. *AIP* mutations are not identified in patients with sporadic pituitary adenomas. *End. Pathol.* 18, 76–78 (2007).

74 Georgitsi M, Raitila A, Karhu A *et al.* Molecular diagnosis of pituitary adenoma predisposition caused by aryl hydrocarbon receptor-interacting protein gene mutations. *Proc. Natl Acad. Sci. USA* 104, 4101–4105 (2007).

75 Meyer BK, Perdew GH. Characterization of the AhR-hsp90-XAP2 core complex and the role of the immunophilin-related protein XAP2 in AhR stabilization. *Biochemistry* 38, 8907–8917 (1999).

76 Bell DR, Poland A. Binding of aryl hydrocarbon receptor (AhR) to AhR-interacting protein. The role of hsp90. *J. Biol. Chem.* 275, 36407–36414 (2000).

77 Petrulis JR, Perdew GH. The role of chaperone proteins in the aryl hydrocarbon receptor core complex. *Chem. Biol. Interact.* 141, 25–40 (2002).

78 Lin BC, Sullivan R, Lee Y *et al.* Deletion of the aryl hydrocarbon receptor-associated protein 9 leads to cardiac malformation and embryonic lethality. *J. Biol. Chem.* 282, 35924–35932 (2007).

79 Naves LA, Daly AF, Vanbellinghen JF *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.* 157, 383–391 (2007).

80 de Oliveira SK, Hoffmeister M, Gambaryan S *et al.* Phosphodiesterase 2A forms a complex with the co-chaperone XAP2 and regulates nuclear translocation of the aryl hydrocarbon receptor. *J. Biol. Chem.* 282, 13656–13663 (2007).

81 Trivellin G, Daly AF, Faucz FR *et al.* Gigantism and acromegaly due to Xq26 microduplications and GPR101 mutation. *New Eng. J. Med.* 371, 2363–2374 (2014).

82 Daly AF, Yuan B, Fina F *et al.* Somatic mosaicism underlies X-linked acrogigantism syndrome in sporadic male subjects. *Endocr. Relat. Cancer* 23, 221–233 (2016).

83 Rodd C, Millette M, Iacovazzo D *et al.* Somatic GPR101 duplication causing X-linked acrogigantism (XLAG)-diagnosis and management. *J. Clin. Endocrinol. Metab.* 101, 1927–1930 (2016).

84 Beckers A, Lodish M, Giampaolo T *et al.* X-linked acrogigantism (X-LAG) syndrome: clinical profile and therapeutic responses. *Endocr. Relat. Cancer* 22(3), 353–367 (2015).

85 Lodish MB, Trivellin G, Stratakis CA. Pituitary gigantism: update on molecular biology and management. *Curr. Opin. Endocrinol. Diabetes Obes.* 23, 72–80 (2016).

86 Iacovazzo D, Caswell R, Bunce B *et al.* Germline or somatic *GPR101* duplication leads to X-linked acrogigantism: a clinico-pathological and genetic study. *Acta Neuropathol. Commun.* 4, 56 (2016).

87 Bates B, Zhang L, Nawoschik S *et al.* Characterization of Gpr101 expression and G-protein coupling selectivity. *Brain Res.* 1087, 1–14 (2006).

88 Castinetti F, Daly AF, Stratakis CA *et al.* *GPR101* mutations are not a frequent cause of congenital isolated growth hormone deficiency. *Horm. Metab. Res.* 48, 389–393 (2016).

89 Daly AF, Lysy PA, Desfilles C *et al.* GHRH excess and blockade in X-LAG syndrome. *Endocr. Relat. Cancer* 2, 161–170 (2016).

90 Naves LA, Daly AF, Dias LA *et al.* Aggressive tumor growth and clinical evolution in a patient with X-linked acro-gigantism syndrome. *Endocrine* 51, 236–244 (2016).

91 Lecoq AL, Bouligand J, Hage M *et al.* Very low frequency of germline GPR101 genetic variation and no biallelic defects with AIP in a large cohort of patients with sporadic pituitary adenomas. *Eur. J. Endocrinol.* 174, 523–530 (2016).