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Anterior pituitary adenomas: inherited syndromes, novel genes and molecular pathways

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Abstract

Pituitary adenomas are common tumors. Although rarely malignant, pituitary adenomas cause significant morbidity due to mass effects and/or hormonal hypo- and/or hyper-secretion. Molecular understanding of pituitary adenoma formation is essential for the development of medical therapies and the treatment of post-operative recurrences. In general, mutations in genes involved in genetic syndromes associated with pituitary tumors are not a common finding in sporadic lesions. By contrast, multiple endocrine neoplasia type 1 (*MEN-1*) and aryl hydrocarbon receptor-interacting protein (*AIP*) mutations may be more frequent among specific subgroups of patients, such as children and young adults, with growth hormone-producing adenomas. In this article, we present the most recent data on the molecular pathogenesis of pituitary adenomas and discuss some of the most recent findings from our laboratory. Guidelines for genetic screening and clinical counseling of patients with pituitary tumors are provided.

Keywords

Carney complex; clinical picture; epigenetics; familial syndromes; molecular pathways; multiple endocrine neoplasia; pituitary adenomas

Anterior pituitary adenomas occur frequently in the general population but most are small and are recognized only incidentally [1]. Clinically significant pituitary adenomas occur in as many as one in 1064 individuals of the general population, which is three–five times higher than what was previously thought [2–4]. While they are almost invariably benign, anterior pituitary adenomas cause significant morbidity due to hormone excess or deficiency, tumor growth, and the need for neurosurgical, radiological and chronic medical therapy for disease control.

The pathological processes that cause most anterior pituitary adenomas remain unclear despite the recent identification of a number of potential molecular genetic abnormalities [5]. While up to 40% of sporadic growth hormone (GH)-secreting pituitary adenomas demonstrate somatic mutations in *GNAS* or other genes [6], relatively few hereditary conditions have been associated with a predisposition to pituitary adenoma [7]. For example,

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less than 5% of these tumors are associated with germline mutations of the multiple endocrine neoplasia type 1 (*MEN-1*) and *PRKARIA* genes, in the context of MEN-1 and Carney complex (CNC), respectively [8,9]. *MEN-1* and *PRKARIA* mutations almost never cause sporadic (i.e., nonsyndromic/nonfamilial) pituitary adenomas, at least in adult patients [10–13].

Mutations in additional genes that may confer predisposition to pituitary adenoma development have been identified more recently [14,15]. The aryl hydrocarbon receptor-interacting protein (*AIP*) gene accounts for approximately 15% of familial isolated pituitary adenoma (FIPA) cases [16], approximately 5% of cases of sporadic acromegaly, and an as yet unknown proportion of sporadic prolactinomas and Cushing's disease [17,18]. Defects in cyclin-dependent kinase inhibitor (*CDKI*) genes have been found in a small number of kindreds with familial pituitary tumors: *CDKN1B/p27Kip1* gene mutations have been reported in kindred with MEN-4 (MENX) with Cushing's disease and hyperparathyroidism, and a limited number of other patients [14,19]. More recently, germline mutations in the *CDKN1B* (*p27Kip1*), *CDKN2C* (*p18INK4c*) and other *CDKI* genes were identified in patients with MEN-1-like features [20].

The majority of pituitary tumors caused by *MEN-1*, *AIP* and *CDKI* mutations secrete GH and/or prolactin (PRL) [14–16,21]. Cushing's disease (due to adrenocorticotrophic hormone [ACTH]-producing pituitary tumors) is very rarely seen in the context of *MEN-1*, *AIP* or *CDKN1B/p27Kip1* mutations [18,22,23]. Somatic mutations of the glucocorticoid receptor (*GR*) gene, dysfunction of genes related to GR function and *TP53*-inactivating defects occur in individual cases of large, aggressive or recurrent Cushing's disease-causing tumors [24–26], but germline mutations of these genes have not been described in this setting. Additionally, some intriguing reports have described patients with pituitary adenomas that are strongly suggestive of a more general tumor-predisposing condition [27,28]. These syndromic patients have a variety of manifestations in addition to pituitary tumors and lack defined genetic abnormalities.

In the following sections, we present the various pathways involved in pituitary tumorigenesis. We then summarize these findings and provide some general recommendations regarding molecular screening.

Cell signaling pathways in pituitary tumorigenesis

The process of signal transduction often involves the activation of a number of different pathways, such as those involving the protein serine–threonine kinases, tyrosine kinases and others that ultimately affect the function of a variety of transcription factors and cell cycle genes (Figure 1). Errors in these processes have been implicated in the development of familial as well as sporadic pituitary tumors [29,30].

Gsa/protein kinase A/cAMP pathway

G-proteins are a family of heterotrimeric proteins that regulate the activity of effector molecules such as adenylyl cyclase (AC) and ion channels, resulting in biological responses. A G-protein molecule is composed of three different subunits: $G\alpha$, $G\beta$ and $G\gamma$. The identity of a G-protein is defined by the nature of its α -subunit. The major G-proteins involved in hormone action are G_s (stimulates AC), G_i (which inhibits AC, regulates Ca^{2+} and K^+ channels) and $G_q/11$ (which acts through stimulation of phospholipase $C\beta$).

Activation of a G-protein-coupled receptor by a ligand (i.e., hormone) causes a conformational change in the G-protein, resulting in dissociation of the GDP molecule, which is bound to the α -subunit in the basal inactive state, and promotes the binding of a

GTP. This leads to dissociation of the other β - and γ -subunits. The activated G-protein subunits detach from the receptor and initiate signaling from many downstream effector proteins, including phosphodiesterases, ACs, phospholipases and ion channels that permit the release of second messenger molecules such as cAMP, cyclic-GMP, inositol triphosphate, diacylglycerol and Ca^{2+} . The increased levels of intracellular cAMP bind to the inhibitory regulatory subunit of inactive protein kinase A (PKA), which lead to the release of the catalytic subunits, thereby permitting their serine-threonine kinase activity [31]. The catalytic subunits phosphorylate a variety of cellular substrates and the cAMP response element-binding protein (CREB), which mediates many of the known transcriptional responses to cAMP in the nuclear compartment, as well as the inducible cAMP early repressor [31]. In response to elevation of cAMP, the cAMP-specific phosphodiesterases (PDEs) and PKA, hydrolyze cAMP and thus eventually terminate cAMP signaling [32].

McCune Albright syndrome (MAS) is a genetic syndrome caused by a postzygotic mutational event in the *GNAS* gene (which occurs in a mosaic fashion) early in embryonic life. The *GNAS* locus maps on human chromosome 20q13 encoding for the $\text{Gs}\alpha$ subunit of the Gprotein. *GNAS* is imprinted in a tissue-specific manner. In endocrine tissues, such as the ovaries, thyroid or pituitary, $\text{Gs}\alpha$ -encoding transcripts are monoallelically expressed predominantly from the maternal allele [33].

The primary defect responsible for MAS is an activating somatic mutation of the *GNAS* gene, which results in constitutive hyperfunction of the cell that bears the mutated gene and expresses its product [34]. MAS is defined by the triad of gonadotropin-independent sexual precocity, café au lait skin lesions and fibrous dysplasia of the bone (either monostotic or polyostotic). However, individuals may also develop tumors or nodular hyperplasia of a number of endocrine glands, leading to hypersecretory syndromes such as acromegaly, hyperthyroidism, hyperprolactinemia, Cushing's syndrome and hyperparathyroidism [34]. Interestingly, patients with this condition may also develop hypophosphatemic rickets, caused by increased secretion of FGF-23 that is produced by the dysplastic bone lesions [35]. They may also have nonendocrine organ involvement such as hepatic, cardiac and gastrointestinal dysfunction [35].

Growth hormone excess is found in up to 20% of patients, but pituitary tumors detectable by MRI are identified in only a few patients [36]. The pituitary gland in patients with MAS may show GH- or PRL-producing cell hyperplasia [37]. GH hypersecretion in MAS differs from the classical acromegaly: patients are generally young at the onset of the disease (<20 years) and diagnosis is usually based on growth acceleration rather than dysmorphic features, which are difficult to assess owing to fibrous dysplasia [34,36]. The increased GH levels may cause worsening of polyostotic fibrous dysplasia [38]. Surgical removal of a pituitary adenoma can be extremely difficult in patients with MAS because of the concurrent skull fibrous dysplasia, which may not allow access to the sellar region by the transsphenoidal approach [35]. Drug treatment with cabergoline and octreotide has shown partial response, whereas long-acting somatostatin analog treatment normalized IGF-1 levels in 50% of the nonresponder patients to cabergoline [35]. Pegvisomant, a GH receptor antagonist, has been successfully used in MAS patients with GH hypersecretion [39]. Radiotherapy may be an option for the treatment of acromegaly in patients with MAS when surgery is impossible and somatostatin-analog therapy is ineffective. However, there have been a few reports of bone sarcomatous transformation within the radiation field. Rare cases of spontaneous sarcomas within fibrous dysplasia, without prior radiotherapy, have also been described [35].

Activating mutations in the *GNAS* oncogene have been found in 30–40% of the sporadic GH-secreting pituitary adenomas [40–42]. As cAMP normally mediates growth hormone

releasing hormone (GHRH) signaling, the mutated somatotroph G-protein activation bypasses the requirement of GHRH-mediated activation, and persistent high levels of cAMP activate PKA, leading to phosphorylation of the CREB, which results in constitutive GH hypersecretion and proliferation of somatotroph cells [43]. Compared with *GNAS* mutation-negative tumors, the former are smaller, are believed to be growing slowly, have increased intra-tumoral cAMP, do not respond vigorously to GHRH and show better sensitivity to somatostatin analogs [44,45]. However, no difference was found in age, sex, duration of the disease or cure rate between patients with and without the mutation [44]. The *GNAS*-activating mutations are rarely detected in nonfunctioning adenomas (<10%) or in ACTH-secreting adenomas (6%) and they are absent from prolactinomas and thyroid-stimulating hormone-secreting adenomas [30,46].

A sevenfold increase in PDE activity has been demonstrated in tumors harboring *GNAS* mutations [47]. The mRNA levels of the transcription factors CREB and ICER are both increased in these tumors, and PDE blockade induces an increase in P-CREB (the phosphorylated activated form of CREB), suggesting that, in these tumors, an increase in PDE activity most probably counteracts the activation of the cAMP pathway [30].

Inactivating mutations in the gene encoding for the regulatory subunit 1- α (R1a) of PKA (*PRKARIA*) have been found to be responsible for more than 60% of patients with CNC, a rare autosomal dominant condition that has been described in approximately 500 individuals to date [48,49]. *PRKARIA* has been found to act as a tumor-suppressor gene as it has been observed with linkage analysis and use of loss-of-heterozygosity (by microsatellite markers), and allelic loss, by FISH, of the 17q22–24 *PRKARIA* locus in CNC tumors [49].

Carney complex is associated with spotty skin pigmentation, myxomas, endocrine tumors and schwannomas. The endocrine organs involved most commonly are the adrenal glands, where a specific adrenal pathology-termed primary pigmented nodular adrenocortical disease, a form of ACTH-independent Cushing's syndrome, is detected in 33–50% of patients with this disease [48]. Other endocrine glands affected in CNC include the thyroid (thyroid nodules are a common finding whereas thyroid cancer is observed in only 3% of patients) and the gonads (ovarian cystadenomas in women and large-cell calcifying Sertoli cell tumors in men).

The pituitary is another endocrine gland affected by CNC, and it includes hypersomatotropinemia and hyperprolactinemia, which often begin in adolescence [50]. Nevertheless, clinically evident acromegaly due to a GH-producing tumor is a relatively infrequent manifestation of CNC. The incidence of GH-producing pituitary tumors in CNC has been estimated to be less than 10%, whereas GH 'paradoxical' responses to various stimuli (such as to thyrotropin-releasing hormone) or IGF-I elevation may be present in up to 80% of affected patients who have no detectable tumors [51]. As in the case of MAS, somatomammotrophic hyperplasia, a precursor of GH-producing adenoma, may precede clinically evident acromegaly in CNC patients [51]. This was confirmed with histopathologic analysis, where adenohypophyseal hyperplasia has been seen in most pituitary gland tissues excised from CNC patients [52]. A zone of probable transition from hyperplasia to adenoma, characterized by the gradual disappearance of the reticulin pattern and increasing cellularity, was also documented in these cases [52]. Additionally, pathology examination of pituitaries from patients who had clinically evident acromegaly showed multiple macroscopic and microscopic tumors. In these patients, extratumoral pituitary parenchyma showed evidence of GH- and PRL-producing cell hyperplasia. All CNC-related GH-producing tumors stained positive for PRL, and occasionally for other hormones [52]. Thus, acromegaly in this condition shows a slow, progressive course, and may not become apparent until the patient is operated on for Cushing's syndrome, which could be explained

by the dynamic interactions between cortisol and GH [53]. Prolactinomas have been reported in a small number of patients [52].

Most patients with CNC have some abnormality of GH secretion due to the underlying hyperplasia, but display negative pituitary imaging studies. In these cases, somatostatin analogs are recommended for normalization of IGF-1 levels [54]. For the subgroup of patients with normal IGF-1 levels but abnormal responses to the oral glucose-tolerance test and normal pituitary imaging, annual evaluation should be performed for the detection of any changes that might require treatment [54].

PRKARIA is normally expressed and not mutated in all sporadic somatotroph tumors that have been checked to date [11,55]. Lania *et al.* have shown that, in a cohort of 30 pituitary adenomas, although the mRNA of the three subunits was detected in all of the pituitary tumors, at the protein level, the R1A subunit was underexpressed, or even absent [56]. On the contrary, R2A and R2B were expressed at high levels almost in all of the tumors included in the study. The effect of the low ratio of R1A:R2 was tested in cultured cells from human GH-secreting adenomas and a dramatic increase in cyclin D1 expression and proliferation of the cells was detected, indicating that a cAMP-dependent pathway may activate proliferative signals in somatotrophs [56]. By contrast, low-ratio R1A:R2 failed to generate proliferative signals in nonfunctioning pituitary tumors [57].

MAPK & PI3K/Akt pathways

Six distinct groups of MAPKs have been characterized in mammals [58]. Extracellular signal-regulated kinases (ERK1 and ERK2), also known as the classical MAPK signaling pathway, are preferentially activated in response to growth factors and regulate cell proliferation and cell differentiation [59]. Signal transduction is often initiated by receptor tyrosine kinases, such as those of the Ret family, IGF-1 receptor, EGF, VEGF and FGF receptor families [60]. Ligand binding results in engagement and activation of the MAPK cascade comprised of the Ras/Raf (the product of the *BRAF* gene), MEK and ERK kinases [60,61]. Sustained ERK signaling promotes the accumulation of genes required for the cell cycle, such as cyclin D1, and represses the expression of genes that inhibit proliferation [62].

It is now established that the cAMP and MAPK pathways interact with each other. In particular, the Gs-mediated cAMP/PKA pathway can stimulate or inhibit the ERK1/2 pathway, depending on the cell type [63]. Phosphoinositide 3-kinases (PI3Ks) are a family of enzymes involved in cellular functions such as cell growth, proliferation, differentiation, motility, survival and intracellular trafficking, which in turn are involved in cancer. PI3K is activated by several hormones including insulin and growth factors, and by several forms of cellular stress such as oxidative stress or cell swelling, and by activation of Ras [64]. A key downstream effector of PI3K is the serine–threonine kinase Akt, which, in response to PI3K activation, phosphorylates and regulates the activity of a number of targets including other kinases, transcription factors and other regulatory molecules [64]. It seems that the PI3K pathway affects Ras/ERK at multiple levels, although the exact mechanism of this crosstalk has not yet been elucidated [65]. PI3K dependent Akt activation can be regulated through the tumor-suppressor gene *PTEN* (phosphatase and tensin homolog), which works essentially in the opposite way to PI3K mentioned previously.

Of the members of the Ras–MAPK signaling pathway, Ras and Raf have been identified as proto-oncogenes. Gain-of-function mutations (activating mutations) of these genes drive a cell towards cancer [66]. Common cancers with oncogenic Ras activation include pancreatic (90%), thyroid (60%) and colorectal (45%) cancers. Furthermore, 35% of cancers show increased MAPK activity [66,67]. Experimental studies in animals have shown that in cultures of rat pituitary lactotrophs, IGF-1- induced proliferation, and this was abolished by

the presence of a MAPK pathway inhibitor, whereas it inhibited apoptosis through activation of the PI3K/Akt [68,69]. In GH4C1 somatotroph cell lines overexpressing wild-type Gs α protein and *GSP* oncogene it was shown that cAMP levels were tenfold lower in wild type Gs α -overexpressing cell lines compared with mutant cells. It is worth noting that sustained MAPK and ERK1/2 activation was observed in both cell lines through a PKA-dependent pathway. Additionally, forskolin – an agent that increases intracellular levels of cAMP, induced a large increase in ERK1/2 activity in *GSP*-negative tumors, suggesting that the ERK1/2 activity could be attributed to the cAMP/PKA pathway – an indication supporting the role of the ERK1/2 pathway in pituitary tumorigenesis [70]. Nevertheless, in another study of nonfunctioning pituitary adenomas, the increase of cAMP caused a reduction in ERK1/2 pathways [12], indicating that cAMP, through activation of PKA, may induce cell growth or arrest depending on the cell type.

In a recent study, mutations of the *PIK3CA* gene encoding for the p110 subunit of the PI3K were assessed in 353 pituitary tumors. A total of 9% of invasive tumors harbored somatic mutations of the *PIK3CA* gene, but none of the noninvasive tumors did so [71]. In a study in which *BRAF* mutations, mRNA expression and protein synthesis in pituitary adenomas were evaluated, no *BRAF* mutations were found. However, *BRAF* mRNA overexpression was detected only in nonfunctioning pituitary adenomas, whereas Raf protein expression was found to be often elevated [72]. Musat *et al.* analyzed the mRNA and protein expression of Akt, PTEN and p27^{Kip1} in pituitary adenomas and normal controls. In adenomas, mRNA expression of Akt and protein expression of phosphor-Akt were found to be increased compared with controls. No difference was found in PTEN transcripts between adenomas and normal pituitaries. However, immunohistochemical analysis showed that the protein expression of PTEN and p27^{Kip1} were lower in adenomas [73].

Tumor-suppressor genes, oncogenes, growth factors & cell cycle regulators involved in pituitary tumorigenesis

Menin gene—*MEN-1* is a tumor-suppressor gene localized to chromosome 11q13; inactivating mutations in this gene have been implicated in the development of MEN-1, an autosomal dominant disorder characterized by predisposition to pituitary adenomas, parathyroid hyperplasia, pancreatic and other gastrointestinal endocrine tumors, adrenal adenomas, subcutaneous lipomas, skin collagenomas and multiple facial angiofibromas (particularly in the upper lip) [74]. Menin is predominantly a nuclear protein that has been demonstrated to interact with proteins involved in transcriptional regulation, genome stability, cell division and proliferation [75]. Menin interacts with transcription factor JUND, a member of the AP-1 transcription factor family, to inhibit JUN-activated transcription, as well as with other proteins such as nuclear factor- κ B (NF- κ B), the Smad family (the canonical signaling pathway that TGF- β family members signal through), DNA and the mixed lineage leukemia proteins [76]. Menin controls the expression of the CDKIs p27^{Kip1} and p18Ink4c. Loss of function of menin (e.g., through those mutations associated with MEN-1) results in downregulation of p27^{Kip1} and p18Ink4c and abnormal cell growth [76]. The majority of the mutations (>70%) lead to truncated forms of menin [77].

Pituitary adenomas occur in approximately 40% of patients with *MEN-1* mutation [5]. The majority secrete PRL, followed by those secreting GH alone, nonfunctioning adenomas and those secreting ACTH [5]. Pituitary tumors in MEN are rarely malignant, but they tend to be larger and more aggressive than the sporadic ones, with macroadenomas being present in 85% of the MEN-1 cases compared with only 42% of the sporadic cases [5]. The response of MEN-1-related prolactinomas to dopamine agonists is poor, with only 44% of patients being controlled [78]. Comparison of the clinical features in patients and their families with the same mutations reveals an absence of phenotype–genotype correlation [5,78].

MEN-1 mutations are extremely rare in non-MEN-1 sporadic pituitary adenomas (<2%) [5]. Theodoropoulou *et al.* found that menin was detectable (and not lost) in 67 out of 68 sporadic non-MEN-1 pituitary tumors. Nevertheless, in sporadic pituitary adenomas, there was a significant decrease in menin immunoreactivity when compared with the normal pituitary [79].

CDKN1B gene—Approximately 20% of clinically suspected MEN-1 patients do not exhibit *MEN-1* mutations, indicating that other genes may be responsible for this phenotype. A germline nonsense mutation in the human *CDKN1B* gene, known also as *p27* and *KIP1*, was identified in a family with a MEN-1-like condition [14]. This condition is characterized by acromegaly due to GH-producing adenoma and primary hyperparathyroidism due to parathyroid adenoma. A germline heterozygous TGG >TAG nonsense mutation at codon 76 was identified, which resulted in premature truncation of the p27 protein at codon 76. Subsequent pedigree analysis revealed that the mutation segregated with another affected member of the family who presented with renal angiomyolipoma, another feature of MEN-1 syndrome. The finding that a germline heterozygous truncating *CDKN1B* mutation predisposed to a MEN-1-like phenotype led the authors to conclude that in endocrine cells, *p27* plays an important role as a tumor suppressor, and its inactivation leads to multitissue tumor formation in humans [14]. Although no loss of heterozygosity was detected in the tumors, immunohistochemical staining showed no p27 protein staining [14]. Germline mutation in *CDKN1B* was then also identified in a Dutch MEN-like patient who presented with small-cell neuroendocrine cervical carcinoma, Cushing's disease and hyperparathyroidism [19]. No other cases have been reported so far in other large series of patients [80]. The syndrome, now designated as MEN-4 (previously known as MENX), was based on a naturally occurring rat strain with features overlapping with both human MEN-1 and -2 [81].

Nuclear CDKN1B protein negatively regulates cell cycle progression by inhibiting cyclin/cyclin-dependent complexes and thus, the progression of G1 to S phase in the cell cycle. No mutations in the *p27* gene have been found in sporadic pituitary tumors [82]. Nevertheless, underexpression of p27 protein has been found in most human pituitary tumors [83]. Protein stability is critical in maintaining p27 protein expression, suggesting epigenetic mechanisms of p27 alteration. Upregulation and activation of Akt have been implicated in the phosphorylation of p27, an essential step for its degradation [84], further supporting the role of the PI3K/Akt pathway in pituitary tumorigenesis, as previously discussed.

Aryl hydrocarbon receptor-interacting protein gene—Pituitary tumors of all types can occur in members of a single kindred in the absence of mutations in genes related to MEN-1 or CNC. A condition termed FIPA was recognized in 1999 [85], and since then, more than 130 FIPA families have been reported [86]. Affected family members can present the same type of pituitary tumor (homogenous presentation) or can have different types of tumors (heterogeneous presentation) [87]. Prolactinomas are the most frequent adenomas detected in FIPA (41%), with somatotropinomas being the second most frequent (30%) and nonsecreting adenomas the third most frequent (13%). Somatolactotropinomas, gonadotropinomas, corticotropinomas and thyrotropinomas all occur less frequently [87]. There is a female predominance (62%), with prolactinomas being the most frequent phenotype encountered [88]. Pituitary tumors in patients with FIPA tend to present 4 years earlier than the sporadic ones, are significantly larger, and tend to have a higher rate of invasion in the cavernous sinus, particularly those from heterogeneous families [88]. Second- and third-generation affected individuals tend to be diagnosed significantly earlier (almost 20 years) [88]. In 2006, the *AIP* locus on chromosome 11q13.3 was identified as being associated with the pituitary tumors in the FIPA settings [15]. Loss of heterozygosity in tumor samples indicated that *AIP* acts most likely as a tumor-suppressor gene [15]. In a

multicenter study in which 73 FIPA families from nine countries were tested for *AIP* mutations, 15% were found to be positive for a germline mutation [16]. Patients who tested positive for *AIP* mutations had a younger age at diagnosis and larger tumors compared with those who tested negative. Mutations were more frequent among young acromegalic patients (50% of patients with isolated familial somatotropinoma). Interestingly, strong positive family history was a weak indicator for the presence of *AIP* mutations, which implies that other genes may also be involved [16]. *AIP* mutations are less frequent in sporadic pituitary tumors and are mainly involved in somatotropinomas; a germ-line mutation of *AIP* could be expected in 1–7% of all apparently sporadic acromegalic patients [89]. Clinical data analysis from a study in a large cohort of sporadic acromegaly showed that mutated patients were younger, and several had gigantism [17]. These observations suggest that young patients with aggressive pituitary tumors are more likely to have an *AIP* mutation. Therefore, testing for genomic alterations in this gene, even in apparently sporadic cases, in this subpopulation of patients is strongly suggested.

The mechanism by which *AIP* mutations are involved in pituitary tumorigenesis is still obscure. The AIP protein has tetratri-copeptide repeat motifs that are important for the protein–protein interaction, and many *AIP* mutations described involve the loss of one of the repeat motifs [88]. The possible effect of these mutations at the cellular level was tested in human fibroblast and pituitary (GH3) cell lines. Overexpression of wild-type AIP in GH3 pituitary cell lines dramatically reduced cell proliferation, while mutant AIP lost this ability [86]. Interestingly, all the mutations led to a disruption of the protein–protein interaction between AIP and phosphodiesterase-4A5, a member of the PDE4 cAMP-specific phosphodiesterases that hydrolyze cAMP and thereby contribute to the regulation of its levels in cells [86]. These findings support a possible role of the PDE4A5 and, therefore, cAMP, in these pituitary tumors.

Pituitary tumor-transforming gene—Pituitary tumor-transforming gene (*PTTG*), also known as ‘securin’ initially isolated from pituitary tumor cells, facilitates sister chromatid separation during metaphase [90]. *PTTG* exhibits oncogene properties. PTTG protein is expressed at higher than normal levels in several tumors, including those of the pituitary, thyroid, colon, ovary, testis and breast, as well as in hematopoietic neoplasms. In some tumors, including those of the thyroid, pituitary, esophagus and colorectum, high levels of expression of PTTG correlate with tumor invasiveness, recurrence and poor prognosis [91]. *PTTG* has been implicated in the initiation and development of pituitary adenoma, since targeted expression of PTTG was conducted using the mouse α GSU promoter results in focal PTTG expression in luteinising hormone-, thyroid stimulating hormone- and GH-producing cells, ranging from hyperplasia to frank adenoma development [92]. PTTG has been found to act through the FGF family. One of them, FGF2 (also known as basic or bFGF) is important in pituitary regulation with mitogenic, angiogenic and hormone regulatory functions. Abnormal expression of FGF2 and its receptor isoforms have been reported previously in pituitary adenomas [93].

Interestingly, PTTG deficiency and overexpression were both found to trigger intranuclear p21 expression in GH3 rat pituitary cells [94]. As a transcriptional target of p53, p21 acts to constrain the cell cycle in unstable or aneuploid cells [95,96]. Induction of p21 triggers senescence, which leads to retinoblastoma (Rb) hypophosphorylation and tumor growth arrest [97]. The finding that PTTG overexpression induces p21 protein expression is inconsistent with the finding that the deletion of *PTTG* restrains pituitary tumor formation through p21 activation. Nevertheless, it has been found that both loss and overexpression of *PTTG* result in aneuploidy and genetic instability [98], and that high PTTG levels initially lead to excessive cell proliferation and subsequently to defective DNA replication and aneuploidy [99].

Cloning of PTTG in pituitary tumors has shown that approximately 90% of pituitary adenomas overexpress this gene compared with normal pituitary tissue, which expresses very little PTTG [94]. The premature senescence observed in pituitary cells overexpressing PTTG maybe constitute one of the reasons that pituitary cells in general tend to escape aggressive growth and malignant transformation.

Growth factors & their receptors—It has been demonstrated that some growth factors are critical for normal pituitary development [100]. Alterations in their expression or action may have important roles in the growth of tumors.

TGF- α has been implicated as the mediator of estrogen-induced lactotroph proliferation. Overexpression of TGF- α , under the control of the prolactin promoter, results in lactotroph adenomas in transgenic mice, indicating a role for this growth factor in pituitary tumorigenesis [101]. Expression of EGF receptor, the TGF- α receptor, has been found to correlate with pituitary tumor aggressiveness, especially among GH-producing tumors [102]. Elevated circulating FGF levels have been implicated in pituitary adenoma development. FGF2 is overexpressed by pituitary tumor cells in more aggressive tumors [103]. A N-terminally truncated form of FGF receptor-4 (pituitary tumor-derived FGFR4) has been isolated from human pituitary tumors [104]. FGFR4 expression has been found in approximately 60% of cases, including GH-, ACTH-, FSH/luteinising hormone-expressing and nonfunctioning adenomas, and very rarely in prolactinomas. Expression of pituitary tumor-derived-FGFR4 is more abundant in macroadenomas, and is associated with more invasive tumors in patients with GH-secreting pituitary adenomas [105].

Bone morphogenetic proteins (BMPs) belong to the TGF- β family of multifunctional secretory peptides that regulate diverse cellular responses, such as cell differentiation, migration, adhesion, proliferation and cell death [106]. More than 20 BMP-related proteins have been identified, and can be subdivided into several groups based on their structure and function, with BMP-2 and BMP-4 being the best-studied members in the BMP family [107]. BMPs interact with specific receptors on the cell surface, referred to as BMP receptors [108]. Signal transduction through BMP receptors results in mobilization of members of the SMAD family of proteins [107,109].

It has been shown that BMP-4 plays a crucial role in pituitary development [110]. Giacomini *et al.* showed that most BMP-4 immunopositivity in normal pituitary is confined to somatotroph and corticotroph, but not lactotroph, cell populations [111]. Its overexpression occurs in prolactinoma models such as the dopamine receptor type 2 knockout mice (D2R^{-/-}), estrogen-induced prolactinomas in female rats and human prolactinoma, while expression of its antagonist, noggin, is decreased [112]. The authors showed that BMP-4 signal transduction interacts with estrogen, and that this interaction is mediated by the estrogen receptors (ERs) and Smad4. This finding could explain the increased incidence of prolactinomas in women. The finding that anti-estrogens partially inhibit the BMP-4 effects in prolactinoma cells indicates a possible new role for specific anti-estrogenic drugs [112].

Bone morphogenetic protein 4 has a contrasting role in different types of pituitary tumors – it was demonstrated to inhibit corticotropinoma development [113]. An interesting finding was that retinoic acid, an agent used in different types of cancer [114], which inhibits corticotropinoma cells growth [115], may act through BMP-4 expression in corticotroph cells. Therefore, BMP-4 induction by retinoic acid may present an interesting therapeutic option for the treatment of Cushing's disease.

Cell cycle & epigenetic gene silencing in pituitary tumorigenesis—

Retinoblastoma 1 is a tumor-suppressor gene located on chromosome 13q and encodes a

nucleoprotein (pRb) that plays a key role in the cell cycle regulation complexes that govern the G1–S transition of cells [116]. *Rb1*-deficient mice developed pituitary intermediate-lobe tumors [117]; nevertheless, somatic mutations of the *Rb1* gene do not seem to play a significant role in pituitary tumorigenesis [118]. Interestingly, methylation of CpG islands in the *Rb1* promoter and of other cell cycle regulatory genes of the Rb1 pathway (*p16^{INK4a}* and *p15^{INK4b}*) resulting in gene silencing, is a frequent finding in sporadic pituitary tumors [119,120].

The HMGA2 protein belongs to the high mobility group A (HMGA) family. These are small, nonhistone, chromatin-associated proteins that bind DNA in AT-rich regions. The HMGA protein family members have no intrinsic transcriptional activity, but they can regulate transcription by altering the architecture of chromatin and facilitating the assembly of multiprotein complexes of transcriptional factors [121]. HMGA overexpression represents a common feature of malignant neoplasias and a poor prognostic index since it often correlates with the presence of metastases and with reduced survival [122].

Rearrangements of the *HMGA2* gene have been frequently detected in human benign tumours of mesenchymal origin, for example, lipomas, pulmonary hamartomas, uterine leiomyomas and fibroadenomas of the breast [123,124], whereas transgenic mice overexpressing HMGA2 develop mixed GH/PRL cell pituitary adenomas [125]. It has been shown that HMGA2 induces the development of mouse pituitary adenomas by binding to the pRb and inducing E2F1 activity (a transcription factor activating a number of genes required for the S phase of the cell cycle) by displacing HDAC1 from the pRb/E2F1 complex, a process that results in E2F1 acetylation and activation [126].

Other genes with a suggested role in pituitary tumorigenesis on the basis of their promoter methylation are the pituitary tumor apoptosis gene (*PTAG*), the maternally expressed protein 3 A (*MEG3A*) and the *ZAC* gene, all of which are highly expressed in the normal pituitary but are not detected in pituitary adenomas [127,128].

MEG3A in particular, an imprinted gene expressed from the maternal allele, suggested to function as a noncoding RNA, seems to have a central role in preventing pituitary tumor formation since loss of *MEG3A* expression has been demonstrated to lead to gonadotroph-derived nonfunctioning pituitary tumors [129]. *MEG3A* is strongly expressed in all cell types of the normal pituitary gland as well as in tumor cells of all functioning pituitary adenomas, but no expression was found in clinically nonfunctioning pituitary tumors [130]. Interestingly, *MEG3A* tumor-suppressive properties were found to be p53 and Rb mediated, involved in two important tumor-suppressor pathways [131].

Finally, Ikaros (Ik) is an interesting transcription factor that has been investigated as a possible candidate in tumor formation. In the endocrine pituitary gland, Ik is abundantly expressed during development in hormone-producing corticotroph cells, where it binds to the pro-opiomelanocortin promoter to activate the endogenous gene [132]. Altered expression of Ik isoforms are implicated in human pituitary tumorigenesis through their actions on *FGFR4* transcription [133]. The dominant negative isoform of this protein, Ik6, has been found to be expressed in nearly half of all primary pituitary tumors, enhancing cell survival with antiapoptotic features. In these tumors, Ik is not expressed and its loss is associated with CpG island methylation and concomitant histone modification [134].

Conclusion

In a recent study from our laboratory [135], we reported that eight out of 88 (9.1%) children and young adults with hormone-secreting pituitary adenomas were found to have a germline genetic defect in a known gene. This is a much higher proportion than would be expected

from the current literature, and indicates that pediatric patients are a particularly appropriate target for genetic analyses. Looking at the group in greater detail, *AIP* or *MEN-1* mutations explained five out of 11 (45.5%) pediatric patients with GH- or PRL-secreting pituitary adenomas. In only one of these cases, a family history had been investigated that identified other features of MEN-1. An additional element of clinical relevance is that tumors with germline mutations were less frequently controlled by neurosurgery and often needed irradiation; this echoes the findings of other genetic defects found in other case series of patients with pituitary tumors. Thus, it appears that more general screening for both *AIP* and *MEN-1* mutations among pediatric patients, irrespective of family history, may be of clinical value and needs to be considered [136]. Equally important in our study was the high proportion of pediatric patients without germline genetic abnormalities. One out of 73 patients with pediatric Cushing's disease had an *AIP* gene defect (1.4%) – only the second such patient described in the literature [18]. Given the size of the pediatric cohort in the current study, along with the fact that *AIP* mutations appear to occur in younger patients, this indicates that a Cushing's disease phenotype probably plays a minor role in *AIP* mutation-related disease. Interestingly, none of the patients with a GH- or PRL-secreting tumor that occurred in the setting of other syndromic features had mutations in *MEN-1*, *AIP*, *PRKARIA*, *CDKN1B* or *CDKN2C*, which strongly indicates that other genetic factors remain to be identified within the MEN spectrum. The lack of mutations in *PRKARIA* among all 18 patients with GH- or PRL-secreting pituitary adenomas requires separate comment. This suggests that very rarely, if ever, will patients with a germline *PRKARIA* mutation present with acromegaly or a prolactinoma in the absence of other cardinal signs and symptoms of CNC. These major signs are frequently a cardiac myxoma or other tumors, including adrenal (primary pigmented nodular adrenocortical disease) or testicular lesions and schwannomas. This point cannot be generalized to *MEN-1* mutation-positive individuals, who may present in the pediatric age with a pituitary tumor without any other signs of MEN-1. These data lead to the recommendations provided in Figure 2.

In conclusion, the significant progress that has been made in the field of molecular biology and genetics has led to better understanding of the processes that contribute to pituitary tumor formation. More is expected in the future, and it is hoped that this information will soon lead to better therapies.

Expert commentary & five-year view

Pituitary tumorigenesis follows the multistep process that has been described in the neoplastic transformation of other tissues, involving loss of expression of tumor suppressors, the overexpression of pituitary-specific oncogenes, the subsequent abnormalities in cell cycle regulation and lack of control of cell proliferation. Although somatic mutations in genes implicated in familial syndromes have also been found in sporadic pituitary adenomas, for most of them, the initiating genetic event(s) remain(s) unknown (Table 1). It is expected that in the next 5 years, many more defects will be identified; hopefully, these discoveries will also lead to new (and exciting) pharmacological intervention strategies.

Key issues

- Familial pituitary tumors account for up to 4–5% of all pituitary adenomas in children and young adults, and a much smaller percentage in older adults. Involved familial predisposition syndromes include multiple endocrine neoplasia (MEN)-1, McCune Albright syndrome, familial isolated pituitary adenomas, Carney complex and MEN-4.
- The *GNAS* oncogene has been found in 30–40% of the sporadic growth hormone-secreting pituitary adenomas. Mutations in other genes involved in

genetic syndromes associated with pituitary tumors are not a common finding in sporadic tumors.

- There are preclinical data and human pituitary studies that implicate the involvement of the Ras/ERK and PI3K/Akt pathways, growth factors and other cell cycle regulators in sporadic pituitary tumors; inappropriate promoter hypermethylation of *p15*, *p16*, *RBI*, *PTAG*, *MEG3A* and *Ikaros* genes has been reported in sporadic pituitary tumors.

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- of interest
- of considerable interest

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Figure 1. A diagram of the main molecular pathways involved in the genesis of the pituitary tumors

AC: Adenylyl cyclase; AIP: Aryl hydrocarbon receptor-interacting protein; AHR: Aryl hydrocarbon receptor; ARNT: Aryl hydrocarbon nuclear translocator; CDK1: Cyclin-dependent kinase 1; ERK: Extracellular signal-regulated kinase; PDE: Phosphodiesterases; PKA: Protein kinase A; PTTG: Pituitary tumor-transforming gene; RTK: Receptor tyrosine kinase.

Figure 2. Recommended algorithm for genetic testing in pituitary adenomas

ACTH: Adrenocorticotrophic hormone; *AIP*: Aryl hydrocarbon receptor-interacting protein; FIPA: Familial isolated pituitary adenoma; GH: Growth hormone; MEN-1: Multiple endocrine neoplasia type 1; PRL: Prolactin.

Table 1

Genes implicated in pituitary adenoma development.

Gene	Function	Familial disease	Pituitary disease in familial settings	Mutation prevalence in sporadic pituitary adenomas	Other mechanism
<i>GNAS</i>	Oncogene	McCune Albright	Hyperplasia (mostly GH/PRL) Rarely adenomas	Somatic mutations in: 30–40% of GH-secreting, <10% of NFA and in 6% of ACTH-secreting adenomas	
<i>PRKARIA</i>	Tumor suppressor	Carney complex (60% of cases)	80% hyperplasia (mostly GH/PRL) <10% GH-secreting adenomas	Not mutated	
<i>MEN-1</i>	Tumor suppressor	MEN-1 (80% of cases)	40% (PRL- > GH- > NFA- > ACTH-secreting adenomas) Mostly macroadenomas	<2%	
<i>CDKN1B</i>	Tumor suppressor	MEN-4	GH-/ACTH-secreting adenomas	Not mutated	
<i>AIP</i>	Tumor suppressor	FIPA (15% of cases)	PRL- > GH- > NFA-secreting adenomas	1–7%	
<i>PTTG</i>	Securin			90% of pituitary adenomas overexpress PTTG	Premature senescence
<i>RBI</i>	Tumor suppressor			Not mutated	Epigenetic silencing
<i>MEG3</i>	Proliferation inhibitor				Epigenetic silencing

ACTH: Adrenocorticotrophic hormone; FIPA: Familial isolated pituitary adenoma; GH: Growth hormone; MEN: Multiple endocrine neoplasia; NFA: Nonfunctioning adenoma; PRL: Prolactin.