**Genetics of pituitary adenomas**

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**Abstract:**
Clinically relevant pituitary tumors presenting with altered hormonal secretion or mass effect represent a significant proportion of patients in endocrinology clinics. However, in recent years, these patients are also referred to clinical genetic services due to possible germline mutations causing syndromic or isolated pituitary adenomas. While somatic mutations have been identified in GNAS, USB8, PIK3CA, GPR101 and rarely in RAS, germline mutations have been identified in MEN1, cyclin dependent kinase inhibitor genes, AIP, DICER1, PRKAR1A, PRKACA, SDH genes and GPR101. In this review, we present a short overview of pituitary adenoma classifications, pituitary development and somatic and germline genetic changes identified in these adenomas.

**Key Words:** Pituitary, AIP, acromegaly, MEN1, GPR101, FIPA

**Key Messages:**
Genetic alterations are increasing recognised in pituitary adenomas. Syndromic disease, positive family history and childhood-onset adenomas represent the highest risk factors for a germline mutation predisposing to pituitary adenomas. Identification of mutations can help to provide best care for the patient and permits an early diagnosis in carrier family members.

**What are pituitary adenomas?**

Pituitary adenomas are benign tumors of the pituitary gland, the pea-sized endocrine structure that sits in the sella turcica of the sphenoid bone called the pituitary fossa [Figure 1]. The pituitary gland is composed of two main lobes – the anterior and posterior. The anterior lobe originates embryologically from Rathke’s pouch, which is an invagination of the oral ectoderm. It is composed of three distinct parts; the pars tuberalis (wraps around the infundibular stalk of the posterior pituitary), pars distalis (where the hormone secreting cells lie), and the pars intermedia (a structure that is usually diminished to a single cell layer in humans). On the other hand, the posterior lobe is embryologically derived from neuroectoderm and is therefore considered an extension of the hypothalamus. The main body is known as the pars nervosa (where the hormones are released) and is connected to the hypothalamus by the infundibular stalk.\(^1\)

The anterior lobe has 7 main cell types – somatotrophs, secreting growth hormone (GH), mammotrophs, making prolactin; the rare somatomammotrophs, secreting a combination of the two, thyrotrophs secreting thyroid stimulating hormone (TSH); corticotrophs, secreting adrenocorticotropic hormone (ACTH); gonadotrophs, secreting luteinizing hormone (LH) and follicle stimulating hormone (FSH); and the supporting folliculostellate cells. The posterior lobe contains axons from the hypothalamus releasing arginine vasopressin (AVP) /antidiuretic hormone (ADH) and oxytocin [Tables 1 and 2].

Table 1 shows the different cell types of the anterior pituitary, the hormones they produce, and their effects on their target organs.\(^3\) Table 2 shows the different hormones produced and their effects on their target organs.\(^3\)

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The development of the pituitary gland

The development of anterior pituitary gland is guided by a succession of activation and then inhibition of several transcription factors. The process begins early in embryological development around embryonic age day 6 (E.6). A transcription factor known as Hesx 1 is expressed which initiates the formation of Rathke’s pouch. The levels of another transcription factor known as SOX3 increases to a set level. This transcription formation of Rathke’s pouch. The levels of another transcription factor known as SOX3 increases to a set level. This transcription process is triggered by two key signalling molecules BMP4 and NeuroD1, and LIF, all of which interact with one another to activate the POMC promoter which leads to the formation of corticotroph cells [Figure 2].

Finally the most dorsal cells, which experience higher levels of FGFR signalling, have higher expression of PITX1, TPT1, NeuroD1, and LIF, all of which interact with one another to activate the POMC promoter which leads to the formation of corticotroph cells [Figure 2].

There are numerous types of lesions which can be identified in the pituitary fossa including the ones listed in Table 3 (data in Table 3 is simplified from reference[6,10] and [25]). Pituitary adenomas are far the most common, but craniopharyngiomas, metastases from other tumors and meningiomas also occur regularly.
Epidemiology

Pituitary adenoma is the third most common CNS tumor, accounting for 10% of all CNS tumors. The estimated worldwide prevalence of pituitary adenomas is approximately 17%.[11] However, the prevalence for clinically relevant tumors is approximately 1:1000 in the general population[12] or approximately 81 per 100,000[13] with an incidence of 0.4 to 8.2 new cases per 100,000 per year.[14] The prevalence of pituitary adenomas increases with age, with the peak age of diagnosis being between 30 and 60 years. They tend to occur in women earlier but this maybe because prolactinoma occurs more frequently in young women than in young men.[15] Looking at the epidemiological differences between genders, it was found that the prevalence for pituitary adenomas in males was far less than that of females (46/100,000 and 105/100,000, respectively).[16] Incidence is approximately 2 per 100,000 for males and approximately 6.0 per 100,000 for females.[17]

It should be noted that autopsy studies have indicated that the true prevalence of pituitary adenomas may be closer to 30% due to incidental findings as most of these tumors are small and nonfunctional.[15] According to one article, incidental pituitary adenomas can be found in approximately 20% of computed tomography (CT) scans and 10% of magnetic resonance imaging (MRI) scans incidentally.[18]

The mean age of diagnosis of patients varies with the type of pituitary adenoma. For example, for prolactinomas, the mean age of diagnosis was 32; for somatotroph adenomas, the age was 47; for corticotroph adenomas, the mean age was 57, and finally for NFPAs, the mean age was 52 years.[19] The prevalence of pituitary adenomas also appears to vary with the type of adenoma. For example, one study found that prolactinomas had the highest prevalence of 54/100,000 followed by NFPAs (41/100,000), somatotroph adenomas (14/100,000), and corticotroph adenomas (6/100,000).[20]

Classification

Pituitary adenomas can be classified in different ways: By their size (Hardy classification) [Table 4], by their extension (Knosp Classification) [Figure 3], and by their function. The...
There is a revision of the WHO classification, which will be published in 2017. Preliminary presentations suggest that the term atypical adenoma will not be used anymore and subclassification with pituitary transcription factors will be employed.

Furthermore, there is a novel classification system which combines neuroradiological and histopathological data based on the work of Trouillas et al. The grade of tumor is based on (1) invasion, determined by imaging and surgical findings; and, on (2) proliferation markers, based on Ki-67 and p53. The combination of these categories allowed the tumor to be classified into 5 different grades. A Grade 1a tumor is not invasive and not proliferative, a Grade 1b tumor is noninvasive but proliferative, a Grade 2a tumor is an invasive tumor whereas a Grade 2b tumor is one that is invasive and proliferative. Finally, a Grade 3 tumor is a tumor that has already metastasized into the cerebrospinal area or systemically. The suggested advantage of this classification system is that it allows the clinician to establish the likelihood of the patient’s disease not recurring/progressing after surgery, i.e., their prognosis. Patients with Grade 2b tumor (invasive and proliferative) are 12 times more likely to have progression or recurrence of disease postoperatively compared to patients who have a Grade 1a tumor.

**Genetic Background of Pituitary Adenomas**

**Sporadic**

Many factors influence pituitary tumorigenesis either due to altered RNA and/or protein expression or due to genetic mutations. Here, we will concentrate on genetic changes. Genetic alterations may occur somatically only in the tumor cells or in the organism at an early developmental stage (mosaic); or, the change could be in the germline either as de novo or inherited from the parents.

The vast majority (95%) of pituitary adenomas occur in a sporadic setting where somatic mutations, mosaic mutations, and sometimes familial low penetrance mutations occur in the background. Familial cases are rare but more increasingly recognized.

Most of the hormones produced by the pituitary gland are regulated predominantly by G protein coupled receptors (GPCRs). For example, growth hormone releasing hormone of a pituitary adenoma refers to its ability to produce hormones. Pituitary adenomas less than 1 cm are defined as microadenomas and pituitary adenomas >1 cm are classified as macroadenomas.

This Knosp classification system is based on the extent of invasion of the tumor through the cavernous sinus.

Over 65% of all pituitary adenomas are functional, i.e., secretory, and 35% are nonfunctional. The nonfunctioning tumors, most of the time, are of gonadotroph origin; however, silent ACTH, GH, and rarely prolactin adenomas have also been described. The latter three types often have a more aggressive behavior. The most common is a prolactinoma which occurs 48% of the time. The second most common is a GH producing adenoma (10%) followed by an ACTH producing adrenocorticotropic adenoma (6%) and a TSH producing thyrotrop adenoma (1%).

In 2004, the World Health Organisation (WHO) devised a classification system based on the histological characteristics of pituitary tumours [Table 5]. It was formulated to reflect the advances in immunohistochemical techniques to help identify pituitary carcinomas, which in 75% cases are missed by clinicians due to their silent nature. As a consequence of classifying pituitary adenomas histologically, the WHO identified a new clinical subtype of pituitary adenoma; the atypical adenoma. This is an adenoma which has a higher proliferative index (Ki-67), increased mitosis, and increased p53 staining (the three parameters measured by the WHO classification system). This is similar to pituitary carcinoma but does not exhibit metastases [Table 5]. Criticism of this classification was directed at the fact that there were no quantified values for p53 staining and mitoses. In addition, it did not take into consideration the invasiveness of the tumors.

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hormone (GHRH) binds its receptor, and GDP bound to the alpha subunit of G protein is converted to GTP. The alpha subunit then dissociates from the beta and gamma subunits and this allows it to interact with its effector molecules [Figure 4]. In this example, it would be cAMP leading to rising levels, which in turn leads to increased levels of protein kinase A. PKA then activates CREB in the nucleus, which then activates the PIT1 (POUIF1) transcription factor, which stimulates GH synthesis. 

**GNAS**

Somatic mutation in this gene accounts for up to 40% of somatotrophinomas.[30] The GNAS gene encodes the alpha subunit of the Gs protein, and the mutated form is traditionally referred to as the gsp oncogene. Mutations in this gene destroy the GTP-ase activity of the alpha subunit, rendering it constitutively activated leading to increased adenylate cyclase activity. This enzyme is required for the formation of cAMP, and hence, the mutation leads to increased production of cAMP. This leads to increased activation of the cAMP-dependent PKA molecule, which leads to increase in the binding of CREB to the PIT1 promoter regions. This subsequently leads to increased GH synthesis and cell proliferation. The most common point mutation within the GNAS gene is at codon 201 C>T, resulting in an amino acid substitution of arginine to cysteine (TGT), and at codon 227 A>T, resulting in an amino acid substitution of glutamine (CGT) to leucine (CTG). One of the studies identified 40 somatotroph tumors; 22 (55%) of these were gsp oncogene positive. Of these, 21 (95%) had a codon 201 point mutation whereas only 1 tumor (5%) had a point mutation at codon 227,[29] suggesting, in agreement with other papers, that the overwhelming majority of GNAS mutations occur at codon 201. Another study found 9 gsp oncogene positive somatotrophinomas with codon 201 mutation in 8 (89%) of the tumors whereas codon 227 mutation occurred in one tumor (11%). This same study also investigated the frequency of GNAS mutations in NFPAs and suggested that the prevalence is approximately 7%.[31] In addition, another study identified at least one case of corticotrophinoma with a GNAS mutation.[31]

**Protein kinase C**

Protein kinase C (PKC) is a protein that phosphorylates and activates CREB.[32-33] Mutations increase CREB dimerization which leads to increased transcription of POUIF1 and GH. A mutation can also occur specifically in the alpha subunit of PKC (PKCa). The somatic point mutation at Asp294Gly (aspartic acid to glycine at codon 294) affects the calcium-binding site of this protein leading to increased activation of the calcium channels and therefore increased secretion of GH.[32] While this PKC mutation was found in 4 invasive adenomas in this study,[33] it was not identified in another.[36]

**PI3K**

PIK3CA gene encodes for the α-subunit of PI3K (phosphoinositide-3-kinase), which is involved in the PI3K/AKT signalling pathway.[34,35] Somatic mutations in exons 9 and 20 of this gene lead to stimulation of the pathway, which promotes increased cell proliferation and cell survival. PI3K also has a role in cell motility, hence, pituitary adenomas with this mutation are more invasive.[34] This study showed that, of the 33 pituitary adenomas of various subtypes (6 ACTH microadenomas, 5 GH macroadenomas, 7 PRL macroadenomas, and 15 nonfunctioning macroadenomas), only 4 had a PIK3CA mutation (12%). Three of these were NFPAs and one was a corticotroph adenoma. Interestingly, all the mutations were found on exon 20. In a previous Chinese study of 353 pituitary adenomas, the authors found that only 8 tumors harbored the PIK3CA mutation (2%); however, interestingly they were all invasive tumors (prevalence of 9% among all 91 invasive tumors). In fact of all 262 of the other noninvasive tumors, none had this mutation.[34] This study thus suggests that although the PIK3CA mutation is relatively rare in pituitary adenomas as a whole, if you do find one, then this tumor is more likely to be invasive in nature. This idea is further supported by another paper. In this particular study, 353 pituitary adenomas were sequenced; i.e., 91 invasive tumors and 262 noninvasive tumors. They found that 8/91 invasive pituitary tumors (9%) contained the PIK3CA mutation but no mutations were found in the noninvasive tumors. Of the 8 invasive tumors, 1 was a corticotroph adenoma, 2 were prolactinomas, 2 were plurihormonal, and 4 were NFPAs. Interestingly, this study also assessed PIK3CA amplification. They found that the PIK3CA was amplified in 20–40% of invasive and noninvasive tumors. Only 1/33 invasive pituitary tumors that showed amplification had a PIK3CA mutation. This suggests that the two genetic alterations are almost mutually exclusive oncogenic factors. It seems that PIK3CA amplification is common, while the rare mutations may occur in more invasive adenomas.[34]

**RAS**

The RAS protein is a component of the Raf/MEK/ERK pathway. It has many important roles including propagation of messages from growth factor receptors. There are three RAS genes (K, N, and H RAS genes); however, it appears that only the H-RAS is implicated in pituitary adenomas.[37] A mutation in this particular gene leads to the activation of genes related to cell proliferation, leading to the highly invasive prolactinomas. While no mutations were found in a study of 18 adenomas,[37] in another study, a mutation at codon 12 of the H-RAS gene was identified in a recurrent prolactinoma. This prolactinoma was highly invasive and ultimately fatal to the patient. This suggests that this gene mutation appears...
to be very rare; however, this could be a marker of the invasiveness of tumors. In fact, out of 91 invasive tumors, RAS mutation was found in 6 (7%).[48] Interestingly, another paper studied this relationship previously and discovered that activation of the RAS protein also leads to activation of the PI3K pathway.[49] This may suggest that these genes work synergistically to transform a tumor into an invasive one. Furthermore, H-RA5 mutations were identified in 3 cases of pituitary adenoma metastases, but in the corresponding pituitary sample.[40]

**USP8**

The USP8 (ubiquitin specific peptidase 8) gene codes for the enzyme ubiquitin carboxyl-terminal hydrolase 8. This enzyme's function is to remove the protein ubiquitin from other proteins such as receptors and prevent their degradation known as deubiquitination. Exome sequencing on 10 corticotroph adenomas identified a USP8 mutation in 4 of the tumors.[43] Mutations in this gene lead to increased hydrolase activity, and therefore, increased deubiquitination particularly of the epithelial growth factor (EGF) receptor.[44] This leads to increased EGF receptor signalling and increased cell growth.[45] The mutations in USP8 always affect the 12-3-3 protein binding region and have been found most commonly in corticotroph adenomas causing Cushing’s disease. Mutation is most likely to affect females (3–5 times more likely compared to males) of 20–60 years of age.[42] These data were confirmed in a larger population of samples on 134 functioning and 11 silent corticotroph adenoma. USP8 mutation occurred in 48 (36%) of the functioning tumors, while the mutation was not present in any of the silent corticotrophinomas. Patients with the mutation were more likely to be adults as opposed to paediatric cases.[43] Another study identified, from 108 ACTH-producing pituitary adenomas, 67 which contained the USP8 mutation. This suggests that the prevalence may now be closer to approximately 62% and the number of unique mutations increased to 17. These changes could be the basis of a new targeted treatment for Cushing’s disease. Currently, the best direct treatment for these pituitary adenomas is surgery. However, due to the small size and highly invasive nature, surgery is difficult even for the most experienced neurosurgeon. Consequently, remission rates are low and recurrence occurs. Knockdown of USP8 or the anti-EGFR drug gefitinib were both effective in reducing ACTH secretion.[44] In mice studies, gefitinib has also been shown to decrease tumor size and reverse the effects of hypercortisolemia such as hyperglycemia and truncal obesity.[45] It has also been found that tumors with USP8 mutations are more responsive to the somatostatin analog pasireotide, suggesting that these tumors have a high expression of the receptor SSTR (somatostatin receptor type 5) for which pasireotide has high affinity. In addition, the same paper found that the USP8 mutated tumors had higher expressions of POMC, SSTR5, and MGMT.[46]

**Familial**

Familial genetic disorders of the pituitary account for up to 5% of all pituitary adenomas and are characterized by genetic mutations present in either one or both parents that are passed on to every generation. The most common disorders are described below.

**Syndromic**

**Multiple endocrine neoplasia (MEN) type 1**

This is an autosomal dominant disease due to a mutation in the MEN1 gene characterized typically by hyperparathyroidism (in 90% cases), pancreatic endocrine tumors (PETs; in 30–80% of cases), and pituitary adenomas (in 20–50% cases). Some other manifestations such as skin fibromas (up to 80% of cases) may also be present (present in 1 in 30,000 individuals with no preference for sex, race, or ethnicity). The pituitary adenomas tend to be very rare; however, this could be a marker of the invasiveness of tumors. In fact, out of 91 invasive tumors, RAS mutation was found in 6 (7%).[48] Interestingly, another paper studied this relationship previously and discovered that activation of the RAS protein also leads to activation of the PI3K pathway.[49] This may suggest that these genes work synergistically to transform a tumor into an invasive one. Furthermore, H-RA5 mutations were identified in 3 cases of pituitary adenoma metastases, but in the corresponding pituitary sample.[40]

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MEN1 (parathyroid and pituitary tumors). The identification of CDKN1B originated from studies of MENX, a MEN1-like syndrome in rats.[53] However, it should be noted that around 2–7% of MEN1-like syndrome patients do not have either a MEN1 mutation or a CDKN1B mutation.[54] This implies that other genes are involved. In a few MEN1-like syndrome cases, mutations in other cell cycle inhibitors, such as p15 (CDKN2B), p18 (CDKN2C), and p21 (CDKN1A) have been described.[55] While all MEN4 patients have parathyroid adenomas, approximately one-third of MEN4 syndrome patients have pituitary adenomas, mostly somatotroph adenomas, but corticotroph, lactotroph, and nonfunctioning adenomas have also been described. Other MEN4 pituitary manifestations include adrenal tumors, renal angiomyolipomas, uterine fibroids, gastrinomas, neuroendocrine cervical carcinomas, bronchial carcinoids, papillary thyroid carcinomas, and gastric carcinomas.[56]

Carney’s complex

This is an autosomal dominant disease most often caused by mutations in the PRKARIA gene on chromosome 17q22-24. The gene codes for the “A” regulatory subunit of PKA. The PKA heterotrimeric protein is composed of two regulatory and two catalytic subunits, where the regulatory subunits inhibit the binding of cAMP and activation of the kinase activity of the catalytic subunit. Mutations in PRKARIA account for over 70% of all Carney’s complex (CNC) cases. Another mutation at locus at 2p16 accounts for the rest of the cases; however, the exact nature of this gene has not been identified yet. A single case has also been described with duplication of one of the catalytic subunit genes.[57] PRKARIA mutations destroy the inhibitory function of this regulatory subunit on the catalytic subunit leading to excessive phosphorylation of the cAMP-response element protein CREB. Clinically, CNC manifests as cardiac myxomas, skin hyperpigmentation, and various endocrine over-activities. Biochemical alterations in GH and prolactin levels are found in approximately 75% of the patients due to somatomammatroph hyperplasia or tumorigenesis leading to 10% of the cases manifesting as acromegaly.[60] Classical pigmented micronodular hyperplasia of the adrenal cortex results in Cushing’s syndrome often in young children. Other manifestations include testicular tumors such as large-cell calcifying Sertoli cell tumor (LCCSCT), thyroid adenoma/carcinoma, ovarian cysts, psammomatosus melanotic schwannoma (PMS), breast ductal adenoma, and osteochondromyxoma (a rare type of bone cancer).[61] A large review of 338 cases identified that 57% of the patients were female and 70% of the patients had familial disease.[62]

Succinate dehydrogenase related pituitary adenomas

Succinate dehydrogenase (SDH) is a large enzyme complex composed of multiple subunits – SDHA, SDHB, SDHC, and SDHD. It is mainly involved in the electron transfer chain of the mitochondria but is also member of the Kreb’s cycle and plays a role in oxygen sensation and tumor suppression. The current hypothesis is that mutations in any of the genes for the subunits can lead to impairment of the electron transfer chain, which leads to an accumulation of metabolites, leading to the eventual accumulation of hypoxia-inducible factor (HIF). HIF is then responsible for causing resistance to apoptotic signals and enhances glycolysis for the tumor.[63] Clinically, patients are found to have paragangliomas/pheochromocytomas. Pituitary neoplasms were described in a few cases but the coexistence of pituitary adenomas and paragangliomas/pheochromocytomas within the same patient is a rare phenomenon.[64–66] These pituitary adenomas tend to be larger and grow aggressively, with one described case of metastasis.[67] Screening a large (n = 309) cohort of unselected pituitary adenoma samples with staining for SDHA and SDHB, only one showed reduced staining suggesting that lack of the SDH complex is rare in sporadic pituitary adenomas.[68]

Pituitary blastoma

Pituitary blastoma is a pituitary tumor developing in infancy (all cases have been identified under the age of 24 months) caused by mutations in the DICER1 gene. It is a rare component of the DICER1 syndrome. Its called a “blastoma” as the pituitary glands of these individuals appear like embryonic tissue. DICER1 itself is a RNA cleavage enzyme that cleaves precursor microRNA into mature miRNA. miRNAs are regulatory proteins that control the expression and/or degradation of specific RNA molecules. The main clinical presentations of neonates are pressure symptoms due to the large tumor and signs and symptoms of Cushing’s disease, which is highly unusual in this age group. The differential diagnosis of very young onset Cushing’s syndrome is CNC. In 2014, there were only 13 known cases around the world, hence it is a very rare tumor with <1% penetrance in DICER1 mutation carriers.[69] An interesting feature in DICER1 patients is that the second hit almost always occurs at a specific site at exon 24 and 25 of the gene, which encode for the RNase III subunit, a metal ion binding domain.[70]

Nonsyndromic-familial isolated pituitary adenomas

In nonsyndromic-familial isolated pituitary adenomas (FIPA), there are no known manifestations of the disease apart from pituitary adenomas. Currently, only two causative genes have been identified, AIP mutations and GPR101 duplications; however, the majority (70–75%) of the patients have AIP- and GPR101-mutation negative disease.[68]

Aryl hydrocarbon receptor-interacting protein (AIP) mutations

Heterozygous mutations in AIP, located on chromosome 11q13.2, cause a low penetrance autosomal dominant disorder, representing approximately 20% of all FIPA cases.[71] AIP codes for the 330 amino acid long co-chaperone. AIP mutations predispose to growth hormone or prolactin-producing pituitary adenomas with no other associated disorders. FIPA patients with AIP mutations are generally young at diagnosis and present with larger adenomas than FIPA patients without AIP mutations. The most common manifestation is a sparsely granulated somatotrophinoma with invasive behavior and poor response to somatostatin analogues. The majority of AIP mutations are truncating mutations (stop codon, splice mutations, frameshifts). A few hotspot mutations have been described, such as the R304Stop mutation, which has been shown to be a founder mutation in Ireland[72,73] and Italy,[74] but has also been identified in India, UK, and Mexico.[75,76] or the R81Stop or the R271W, which has been identified in several independent cases. It is important to remember that only ~20% of AIP mutation carriers actually develop the disease, which usually occurs in teenage years, and patients over the age of
30 years with normal MRI and biochemistry results are unlikely to develop the disease later. On the other hand, younger family members benefit from screening as several cases have been identified and operated early, avoiding major long-term complications.[77] Interestingly, somatrophinomas without AIP mutations but with low levels of AIP protein tend to be more invasive[78] and respond poorly to somatostatin analog therapy.[79]

X-linked acrogigantism (XLAG)
In a characteristic subgroup of very young-onset GH-excess patients, duplications have been identified in the GPR101 gene located on the X chromosome (Xq26.3).[80] The protein GPR101 encoded is an orphan G-protein coupled receptor, which has been found to be highly upregulated in pituitary adenomas. It leads to hypersecretion of GH and IGF-1 from a very early age (all cases have been identified with rapid growth before the age of 5 years), which are often accompanied by signs of acromegaly (coarse facial features, sweating, headache) with the addition of increased appetite/food seeking behavior.[81] The disease usually manifests in the first year of life (median of 36 months) with a predisposition for the female gender. Two large studies studying patients with gigantism identified altogether 31 cases with XLAG, either due to a pituitary adenoma or pituitary hyperplasia.[82,83] Disease control can be challenging often needing complete pituitary removal, complex medical therapy with dopamine agonist, somatostatin analogue and GH receptor antagonist, or radiotherapy.[84][85][86]

Mosaic McCune Albright syndrome
Embryonic age mutations in GNAS result in the mosaic disease McCune - Albright syndrome (MAS) with skin pigmentation, bone abnormalities and early puberty, in addition to other endocrine manifestations. Most commonly, the onset of MAS is in early childhood (mean age is 4 years) and tends to occur twice as much in females than in males.[86] GH excess, hyperthyroidism, Cushing’s syndrome, and thyroid abnormalities can also develop. In addition, 21% of MAS patients develop growth hormone excess (due to an adenoma or hyperplasia) with hyperprolactinemia also being present in 92% of these patients.[87,88]

X-LAG
It seems that XLAG patients can also have the disease in a mosaic form in males.[83][89][90]

Summary
Pituitary adenomas are benign tumors of the pituitary gland. They mainly occur in isolation in sporadic cases but they can also be inherited and passed down the generations in familial cases. Familial cases can be further subdivided into syndromic diseases, where pituitary adenomas are just but one component of a cluster of diseases that frequently arise together; or, nonsyndromic diseases, where pituitary adenomas are the only manifestation. Enhancing our knowledge of the genetics of pituitary adenomas allows better understanding of the nature and clinical behavior of the adenomas and their impact on the patients’ quality of life. In addition, knowing the genetic etiology may enable clinicians to predict the other possible manifestations of the condition. Furthermore, we can then screen the patients’ family members to identify asymptomatic individuals predisposed to developing the illness, thus allowing an earlier diagnosis and treatment. This will also provide these patients the opportunity to be educated, prepared, and counselled regarding the consequences of the disorder to their future. Finally, knowledge of the genetics of pituitary adenomas provides opportunities to develop possible targeted therapies for these patients in the future.

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References


