COMMENTARY

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Genetics of pituitary adenomas

Mario Shaid, Márta Korbonits

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]

Figure 1 shows the anatomy of the pituitary gland as its sits in the pituitary fossa (sella turcica of the sphenoid bone) and its relation with the hypothalamus anteriorly.[2]

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]

Department of Endocrinology, St. Bartholomew's Hospital, William Harvey Research Institute, Barts and the London School of Medicine, Queen Mary University of London, Charterhouse Square, London EC1M 6BQ, United Kingdom

Address for correspondence:
Prof. Márta Korbonits, Department of Endocrinology, St. William Harvey Research Institute, Barts and the London School of Medicine, Queen Mary University of London, Charterhouse Square, London EC1M 6BQ, United Kingdom.
E-mail: m.korbonits@qmul.ac.uk

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Table 1: Cells of the anterior pituitary

Cell type	Hormone produced	Target organ	Function
Corticotrophs	ACTH	Adrenal Glands	Cortisol production from the adrenal glands
Thyrotrophs	TSH	Thyroid Gland	Thyroxine (T4) and triiodothyronine (T3) release from the thyroid gland
Somatotrophs	GH	Liver	IGF-1 production from the liver
Lactotrophs	PRL	Breast	Milk production in the mammary glands of the breast
Gonadotrophs	FSH and LH	Testes (males)	LH stimulates ovulation in women and testosterone production in men
		Ovaries (females)	FSH stimulates growth of ovarian follicles and their production of estrogen and stimulates spermatogenesis and spermatocyte maturation in men

Table 2: Posterior pituitary hormones

Posterior pituitary hormone	Target organ	Function
Antidiuretic hormone (ADH)	Kidneys	Water reabsorption in the kidneys
Oxytocin	Breast, uterus, spermatic cord	Lactation from the mammary glands and uterine contractions in women; and, stimulates ejaculation in men

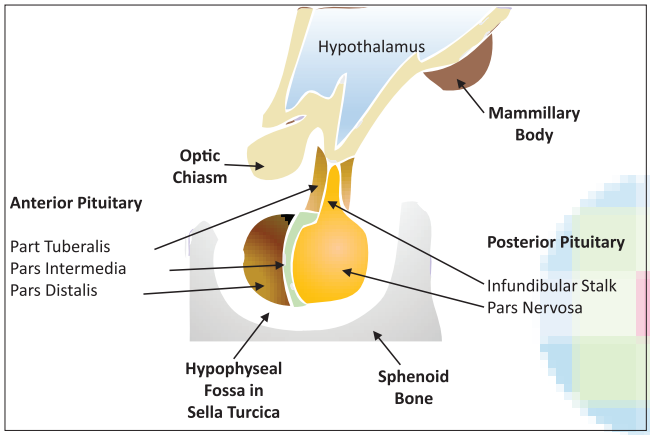

Figure 1: Gross anatomy of the pituitary gland

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 factor assists Hesx 1 in the formation of Rathke's pouch. Studies in mice show that, as pituitary cells progressively become more differentiated, the levels of these transcription factors slowly decline until they are undetectable. Deficiencies in the expression of these transcription factors lead to central nervous system (CNS) malformations. In humans, one of the identified phenotype is septo-optic dysplasia (SOD). This is characterized by any combination of two or more of the following: optic nerve hypoplasia, pituitary gland hypoplasia, and midline abnormalities of the brain such as absence of the corpus callosum and septum pellucidum. It is said to occur every 1 in 10000 live births.[4]

The next step is the invagination of Rathke's pouch. This process is triggered by two key signalling molecules BMP4 and NKX2 which, once activated, cause Rathke's pouch to fold in on itself and form the basic structure of the pituitary gland. Simultaneously, pituitary precursor cells migrate into the pouch. Next, Lhx 3 and Lhx 4 transcription factors are activated. Lhx 3 is predominantly involved in pituitary cell differentiation, and Lxh4 is required for pituitary cell proliferation. These transcription factors work synergistically with Pitx 1 and 2 to enable the establishment of ventral-dorsal gradient of BMP2 and FGF8. This step is essential as it is this gradient that determines what cell type specific transcription factors are activated, which in turn determines what the precursor cells differentiate into. For example, ventral precursor cells are more exposed to BMP2, which implies that the transcription factor Gata2 is activated within them. This ensures that the precursor cells differentiate into gonadotrophic cells. Sometimes, a combination of transcription factors is required. For example, for a thyrotroph cell to develop, it needs activation of both Gata2 and *POU1F1* (previously known as Pit1). For the development of lacto- and somatotrophs, which originate from the same precursor cell, *POU1F1* activation is required. However, it is the activation of certain secondary transcription factors that determine the outcome of the cell. For example, somatotroph differentiation is encouraged by the presence of a small zinc finger protein Zn15. *POU1F1* is a transcription factor involved in the differentiation of thyro-, lacto-, and somatotrophs. Mutations in this transcription factor leads to pituitary deficiencies of these hormones which manifests itself clinically as dwarfism and hypothyroidism.[6] In addition, there is a transcription factor known as Prop1, which is expressed slightly earlier than *POU1F1*. Mutations in the transcription factor lead to a condition known as combined pituitary hormone deficiency (CPHD). Clinically, patients are deficient in TSH, growth hormone (GH), and prolactin (similar to *POU1F1* mutated patients) but also have additional deficiencies in FSH and LH leading to delayed/incomplete secondary sexual characteristics and infertility.[7]

Finally the most dorsal cells, which experience higher levels of FGF8 signalling, have higher expression of PITX1, TPIT, 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].[8]

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 [9-10] 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]

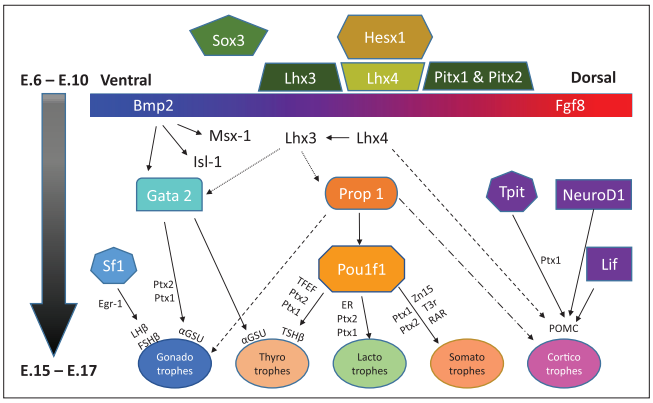

Figure 2: Illustration of the development of the specific cell types of the anterior pituitary. In response to the BMP2–FGF8 ventral–dorsal gradient, pituitary cell types are determined by certain transcription factors. Solid arrows indicate the activation of expression, dotted arrows indicate an unknown role in the activation of expression, dashed arrows indicate an undefined role, and dash–dot arrows indicate an action of an important factor in the maintenance of long-term cell function. E.6, E.10, E115 and E.17 mark embryonic days in mouse development. Figure is adapted from de Moraes *et al*.[8]

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

Table 3: Pituitary fossa lesions

Tumors	Hyperplastic lesions	Infective/inflammatory lesions	Cysts
Pituitary adenoma and carcinoma	Hyperplasia of ACTH cells	Granulation tissue	Rathke's cyst
Craniopharyngioma, adamantinous	Hyperplasia of prolactin cells	Lymphocytic hypophysitis	Colloid cyst
Craniopharyngioma, papillary	Hyperplasia of GH cells	Granulomatous hypophysitis	Arachnoidal cyst
Meningioma	Hyperplasia of FSH/LH cells	Tuberculous hypophysitis	Epidermoid cyst
Chordoma		Abscess	Mucocele
Squamous carcinoma		Necrosis	
Gangliocytoma (with adenoma)			
Chondrosarcoma			
Granular cell tumor			
Neurinoma			
Astrocytoma			
Pituicytoma			
Ganglioglioma			
Neurocytoma			
Suprasellar germinoma			
Gliomatous tumor			
Histiocytosis of Langerhans			
Malignant lymphoma			
Fibroma			
Haemangioma			
Hamartoma			
Fibrous dysplasia			
Plasma cell granuloma			

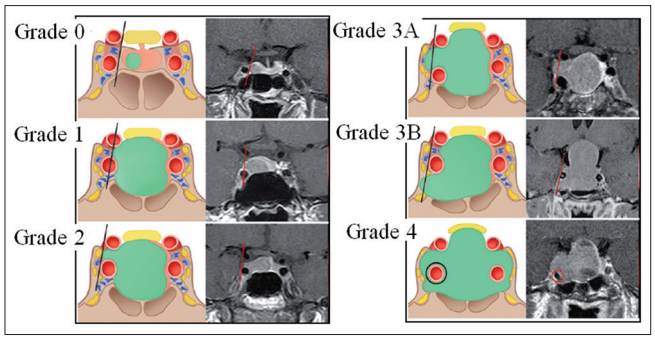

Figure 3: Knosp classification of pituitary adenomas according to their invasion, Adapted from Micko *et al*.[24] Grade 0 = tumor not within the cavernous sinus space, Grade 1 = the tumor extends to a hypothetical line through the middle of the intracavernous and supracavernous internal carotid arteries (ICAs), Grade 2 = the tumor extends to the lateral aspects of the ICAs, Grade 3a = the tumor extends beyond the lateral aspects of the ICAs and into the superior cavernous sinus compartment, Grade 3b = the tumor extends beyond the lateral aspects of the ICAs and into the inferior cavernous sinus compartment, Grade 4 = the tumor invades the entire cavernous sinus.[24]

function 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.[21]

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.[22] The most common is a prolactinoma which occurs 48% of the time. The second most common is a GH producing somatotroph adenoma (10%) followed by an ACTH producing adrenocorticotroph adenoma (6%) and a TSH producing thyrotroph adenoma (1%).[23]

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[25] 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.

There is a revision of the WHO classification, which will be published in 2017. Preliminary presentations suggest that

Table 4: Hardy's classification of pituitary adenomas

Grade	Definition
Grade I	<10 mm
Grade II	>10 mm, within the sella
Grade III	>10 mm, focal sellar erosions, outside the sella
Grade IV	Infiltrate sphenoid and cavernous sinuses, compress optic nerve, cranial nerves, and/or invade adjacent brain

Table 5: World Health Organisation (WHO) classification of pituitary adenomas 2004

	Ki-67 (%)	Mitoses	p53 Staining	Metastases
Typical	<3	-	-	-
Atypical	>3	Increased	Extensive	-
Carcinoma	>3	Increased	Extensive	Present

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*.[26] 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.[26]

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 (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 (POU1F1) transcription factor, which stimulates GH synthesis.

GNAS

Somatic mutation in this gene accounts for up to 40% of somatotrophinomas.[28] 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 (CGT) to cysteine (TGT), and at codon 227 A>T, resulting in an amino acid substitution of glutamine (CAG) 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 NFPA and suggested that the prevalence is approximately 7%.[30] 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 *POU1F1* and *GH*. A mutation can also occur specifically in the alpha subunit of PKC (PKCα). 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.[32]

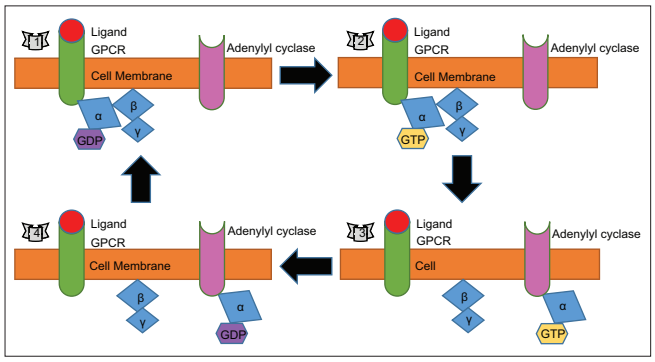

Figure 4: The G protein coupled receptor signalling pathway. When a substrate (red circle) interacts with the GPCR (green object) causing phosphorylation and separation of the alpha subunit (blue diamond) which then binds to an effector molecule (steps 1–3). Step 4 depicts the hydrolysation of GTP and resolution of the process. Adapted from Jähnichen.[27]

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 NFPA 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 tumours). In fact of all 262 of the other noninvasive tumors, none had this mutation.[36] 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.[36]

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%).[36] Interestingly, another paper studied this relationship previously and discovered that activation of the RAS protein also leads to activation of the PI3K pathway.[38] This may suggest that these genes work synergistically to transform a tumor into an invasive one. Furthermore, *H-RAS* mutations were identified in 3 cases of pituitary adenoma metastases, but in the corresponding pituitary sample.[39]

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 deubiqutination. Exome sequencing on 10 corticotroph adenomas identified a *USP8* mutation in 4 of the tumors.[40] Mutations in this gene lead to increased hydrolase activity, and therefore, increased deubiqutination particularly of the epithelial growth factor (EGF) receptor.[40] This leads to increased EGF receptor signalling and increased cell growth.[41] The mutations in USP8 always affect the 12-3-3 protein biding 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 tumours 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 30000 individuals with no preference for sex, race, or ethnicity). The pituitary adenomas tend to be prolactinomas (60% of clinically diagnosed *MEN1* pituitary adenomas), and can present in childhood showing an aggressive behavior. Systematic screening also identified small nonfunctioning adenomas in *MEN1* mutation carriers, which often do not precipitate clinical problems. *MEN1* is a tumor suppressor gene (TSG) found at locus 11q13 and is composed of 10 exons. It codes for the 610 amino acid protein MENIN. MENIN's main function appears to regulate the promoter activity of genes responsible for endocrine cell cycle and proliferation pathways by interacting with histone methyltransferase (HMT) complex. This complex consists of a series of enzymes which are responsible for histone modifications by catalyzing the transfer of methyl groups to lysine and arginine residues of histone proteins, leading to epigenetic modification, which regulates the transcription of genes.[47] As of 2008, over 1300 *MEN1* mutations have been reported occurring mostly in exons but some have been found in introns as well. In over 70% of cases, alterations result in a premature stop codon. In 90% of MEN1 cases, tumorigenesis follows the Knudson's two-hit hypothesis.[48] The first hit is usually inherited from one of the parents or represents a *de novo* mutation in the proband. The second hit is usually a somatic mutation, often resulting in loss of heterozygosity (LOH) of the *MEN1* locus or upregulation of a microRNA influencing *MEN1* expression. This second hit can be a large deletion (45% of cases); however, 25% of cases are due to nonsense mutations, 15% are insertions, 10% are missense mutations, and less than 5% are splice-site mutations.[49] MEN1 syndrome has a high penetrance. Approximately 50% of patients develop symptoms by the age of 20 years, and 95% of patients have symptoms by 40 years of age.[50] The likelihood of a MEN1 patient presenting with a pituitary adenoma as their first sign/symptom is approximately 25%, usually at a young age. When compared to non-MEN1 pituitary adenomas, MEN1-related pituitary adenomas tend to be larger, more invasive, more symptomatic, and more resistant to treatment of the consequent pituitary hormone hypersecretion;[51,52] although systematic screening has resulted in the identification of a subgroup of patients with relatively mild diseases.[53]

Multiple endocrine neoplasia (MEN) type 4

A few cases of MEN1-like syndrome patients without a mutation in *MEN1* have been described with a mutation in *CDKN1B* coding for cyclin kinase inhibitor p27. This disease has been named MEN4, inherited in an autosomal dominant manner. *CDKN1B* is found at chromosome 12p13 and codes for the 196 amino acid p27 protein. p27 inhibits the binding of cyclins to cyclin dependent kinase, such as the cyclin D-CDK4 interaction, resulting in reduced phosphorylation of the retinoblastoma protein and maintained/induced cell cycle arrest.[54] Loss of this functionality leads to tumorigenesis which manifests clinically very similarly to

MEN1 (parathyroid and pituitary tumors). The identification of *CDKN1B* originated from studies of MENX, a MEN1-like syndrome in rats.[55] 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.[56] 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.[57] 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.[58]

Carney's complex

This is an autosomal dominant disease most often caused by mutations in the *PRKAR1A* gene on chromosome 17q22-24. The gene codes for the "A" regulatory subunit of PKA. The PKA heterotetramer 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 *PRKAR1A* 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.[59] *PRKAR1A* 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 somatomammotroph 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, psammomatous 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.[58]

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, somatotrophinomas 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.[81,84,85]

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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Conflicts of interest

There are no conflicts of interest.

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