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**Review**

# Clinical Biology of the Pituitary Adenoma

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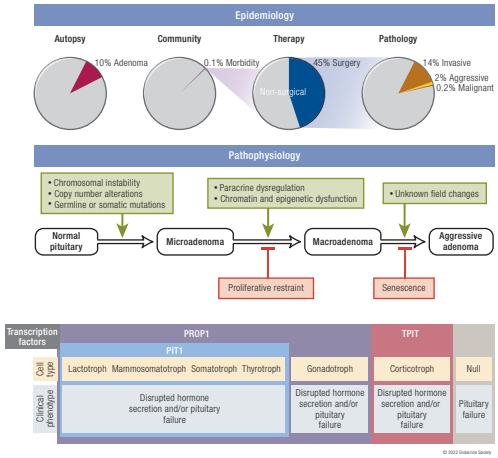
## Abstract

All endocrine glands are susceptible to neoplastic growth, yet the health consequences of these neoplasms differ between endocrine tissues. Pituitary neoplasms are highly prevalent and overwhelmingly benign, exhibiting a spectrum of diverse behaviors and impact on health. To understand the clinical biology of these common yet often innocuous neoplasms, we review pituitary physiology and adenoma epidemiology, pathophysiology, behavior, and clinical consequences. The anterior pituitary develops in response to a range of complex brain signals integrating with intrinsic ectodermal cell transcriptional events that together determine gland growth, cell type differentiation, and hormonal production, in turn maintaining optimal endocrine health. Pituitary adenomas occur in 10% of the population; however, the overwhelming majority remain harmless during life. Triggered by somatic or germline mutations, disease-causing adenomas manifest pathogenic mechanisms that disrupt intrapituitary signaling to promote benign cell proliferation associated with chromosomal instability. Cellular senescence acts as a mechanistic buffer protecting against malignant transformation, an extremely rare event. It is estimated that fewer than one-thousandth of all pituitary adenomas cause clinically significant disease. Adenomas variably and adversely affect morbidity and mortality depending on cell type, hormone secretory activity, and growth behavior. For most clinically apparent adenomas, multimodal therapy controlling hormone secretion and adenoma growth lead to improved quality of life and normalized mortality. The clinical biology of pituitary adenomas, and particularly their benign nature, stands in marked contrast to other tumors of the endocrine system, such as thyroid and neuroendocrine tumors.

## Graphical Abstract

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**Key Words:** pituitary adenoma, acromegaly, prolactinoma, Cushing's disease, aggressive pituitary tumor, hypothalamus

**Abbreviations:** αSU, alpha-subunit of glycoprotein hormones; ACTH, adrenocorticotropic hormone; cAMP, cyclic adenosine monophosphate; CNA, copy number alteration; CRH, corticotrophin-releasing hormone; CT, computed tomography; ERα, estrogen receptor α; FIPA, familial isolated pituitary adenoma; FSH, follicle-stimulating hormone; GH, growth hormone; GHRH, growth hormone–releasing hormone; GIPR, gastric inhibitory peptide receptor; GnRH, gonadotrophin-releasing hormone; GPCR, G protein coupled receptor; GR, glucocorticoid receptor; IGF-1, insulin-like growth factor 1; IHC, immunohistochemistry; LH, luteinizing hormone; MRI, magnetic resonance imaging; NPY, neuropeptide Y; PET, positron emission tomography; PRL, prolactin; POMC, proopiomelanocortin; SCNA, somatic copy number alteration; SF1, steroidogenic factor 1; SRL, somatostatin receptor ligand; SST, somatostatin; TIDA, tubero-infundibular dopamine; TPIT, T-box family member TBX19; TRH, thyrotrophin-releasing hormone; TSH, thyrotrophin (thyroid-stimulating hormone); WHO, World Health Organization; X-LAG, X-linked acrogigantism.

The anterior pituitary gland is composed of highly differentiated oral ectoderm-derived cells that express unique hormonal products largely determined by cell-specific transcription factor(s). Thus, lactotrophs express prolactin (PRL); somatotrophs express growth hormone (GH); corticotrophs express proopiomelanocortin (POMC), the precursor to adrenocorticotropic hormone (ACTH); gonadotrophs express follicle-stimulating hormone (FSH) and luteinizing hormone (LH); and thyrotrophs express thyrotrophin (thyroid-stimulating hormone; TSH). Pituitary adenomas, which are overwhelmingly benign, arise from one (or more) of these cell lineages, or from null cells expressing no discernible gene product (1-3).

Pituitary adenoma biology has long been a subject of fascination and intrigue because of the highly variable spectrum and diversity of behavior exhibited by these neoplasms, ranging from innocuity to malignancy, along with their widely varied impact on health. The rarity of significant endocrine disease arising from pituitary adenomas, despite their very high prevalence, has impeded a better understanding of their natural history. Furthermore, pituitary adenomas are not classified uniformly by pathologists, surgeons, endocrinologists, and radiologists, restraining improved understanding of their treatment and prognosis. Thus, considerable investigation has focused on mechanisms for pituitary adenoma formation, progression, behavior, and clinical consequences.

This comprehensive critical review elucidates the evidence underlying pituitary adenoma biology and natural history, focusing on cell biology, genetics, physiology, classification, and epidemiology, as well as the morbidity and mortality associated with clinical endocrine syndromes in patients harboring pituitary adenomas.

**ESSENTIAL POINTS**

- The anterior pituitary gland is organized during embryonic development into distinct structural and functional networks comprising cell-type specific lineages
- Pituitary adenomas are commonly encountered, with most benign and remaining clinically inapparent
- Disease-causing adenomas develop from somatic and germline mutations causing unregulated hormone secretion and growth characterized by chromosomal instability and cell senescence
- Aggressive behavior is uncommon and malignant transformation a rare exception
- Secretory adenomas cause clinical phenotypes (including acromegaly/gigantism, Cushing's disease, and prolactinomas) determined by the type of excessive hormones secreted
- Co-morbidities including mass effects are managed effectively by multimodal therapies

## Human Anterior Pituitary Gland

The pituitary comprises anatomically and functionally distinct anterior and posterior lobes. Hypothalamic neuropeptides traverse pituitary stalk portal vessels and signal to cognate pituitary cell surface receptors to induce or suppress systemic release of pituitary hormones, which elicit peripheral tissue endocrine and trophic effects.

### Development

Several lines of evidence are consistent with the existence of pituitary stem cells, including identification of non-hormone-secreting, self-renewing primitive cells expressing SOX2 that exhibit differentiating capacity into hormone-secreting cell lineages (4-6) with subsequent persistent but slow postnatal proliferation (7, 8). Thus, mature hormone-secreting cells respond to physiological demands (9), enabling healthy developmental function.

#### Cell-specific terminal differentiation

Embryonic cells of ectodermal origin derived from Rathke's pouch follow temporally regulated and lineage-specific pathways to form distinctive terminally differentiated hormone-producing cells. Lineage differentiation is determined by expression of cell type-specific factors, and cell specification and proliferation are enabled by a finely balanced cascade of transcription and soluble factors (10-12) as reflected by PROP1 induction (13).

In turn, PROP1 induces expression of another transcription factor, PIT1 (also termed POU1F1), which determines lineage development of somatotrophs, lactotrophs, and thyrotrophs (14). Estrogen receptors abundantly expressed in PIT1-expressing cells favor PRL whereas thyrotroph embryonic factor (TEF) and GATA1 induce TSH expression. Gonadotroph development is driven by cell-specific expression of steroidogenic factor (SF1) and dosage-sensitive sex reversal, adrenal hypoplasia critical region (DAX1). Corticotrophs, expressing the ACTH precursor POMC, require T-box family member TBX19 (TPIT). Inactivating mutations of these factors may cause pituitary hormone deficit(s). Pioneer transcription factors that directly bind condensed chromatin also specify differentiation and may reflect cooperation between nuclear and nonnuclear determinants of pituitary cell hormone specificity (15).

### Pituitary Cell Proliferation

Several lines of evidence point to a niche of adenoma progenitor cells as observed in the postnatal murine pituitary, where early stem cell–like progenitor cells may differentiate into hormone-synthesizing pituitary cells (16, 17). The role of progenitor cells in adenoma cytogenesis is exemplified by lineage-tracing of murine PAX7, a downstream nestin marker, also expressed in human corticotroph adenomas (18).

Although turnover of the mature pituitary cell is slow, the gland exhibits a plastic response to extrinsic stimuli (19). The pituitary gland enlarges during puberty, pregnancy, and in the setting of peripheral target gland failure. For example, longstanding thyroid failure results in thyrotroph hyperplasia (20), as low thyroxine levels drive thyrotrophin-releasing hormone (TRH) to enable thyrotroph proliferation. By contrast, lactotroph cell hyperplasia during pregnancy occurs mostly due to elevated estrogen levels, which directly stimulates the lactotrophs (21, 22).

Pituitary adenomas arise from hormone-secreting cell types with resultant clinical phenotypes determined by the cell of origin and specific overproduced hormone. Thus, lactotroph adenomas cause infertility and lactation, somatotroph adenomas lead to acromegaly/gigantism, corticotroph adenomas to hypercortisolism with Cushing's disease, and thyrotroph adenomas to hyperthyroidism and goiter. Adenomas arising from gonadotroph cells are usually nonsecreting, and commonly present with hypogonadism (23, 24) (Fig. 1). Null cell adenomas may arise from a primitive precursor or from loss of lineage-specific tumorigenic factors.

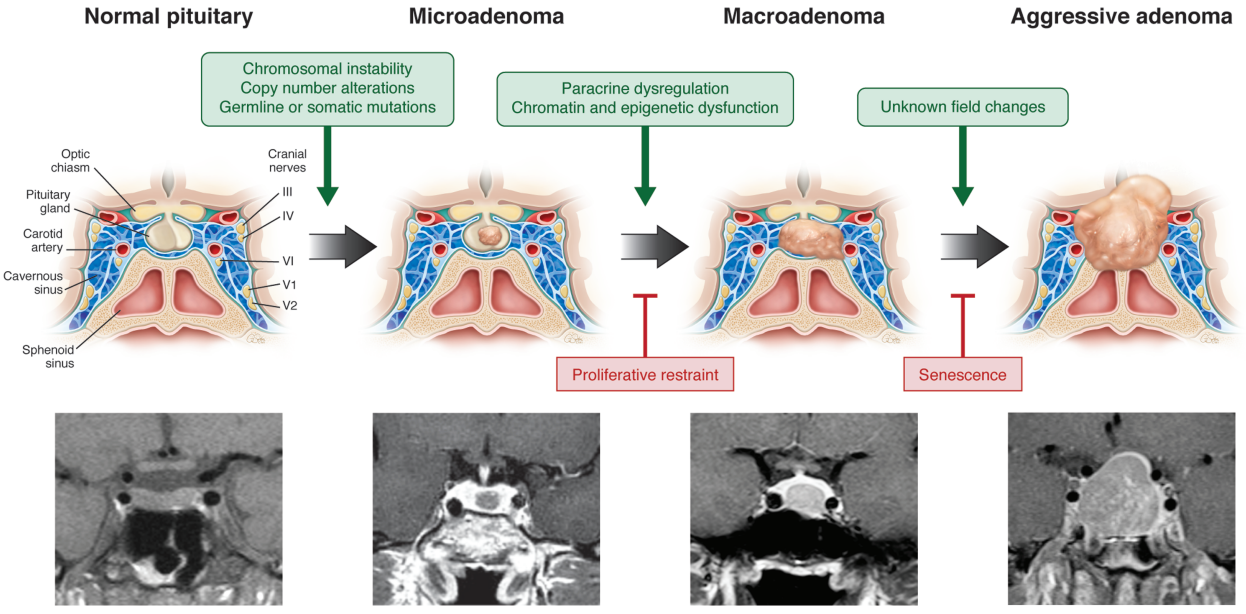
## Physiology of the Hypothalamic-Pituitary Axis

The pituitary gland responds to hypothalamic neuropeptides as well as hormonal signals from target organs. Hypothalamic control is mediated by adenohypophysiotrophic hormones secreted into the hypothalamic portal system and binding to anterior pituitary cell surface receptors (Fig. 2). These G protein coupled cell surface membrane receptors (GPCRs) expressed on pituitary cells are highly selective and specific for each of the hypothalamic hormones and elicit positive or negative signals to mediate specific pituitary hormone production. Hypothalamic neuropeptides expand committed progenitors during normal development and sustain proliferation of mature hormone-secreting cells.

Prader-Willi syndrome serves as a model of hypothalamic dysfunction and highlights the critical role of the hypothalamus in regulating pituitary function. It is a rare genetic neurodevelopmental disorder resulting from the loss of expression of maternally imprinted genes located in the paternal chromosomal region 15q11-13, characterized by cognitive disabilities, behavioral disorders, and hypothalamic dysfunction (25). Impaired pituitary development and function is increasingly recognized as the consequence of much of the phenotype of Prader-Willi syndrome. Pituitary hypoplasia occurs in 63% to 74% of patients, and GH deficiency, hypogonadism, hypothyroidism, ACTH deficiency, and premature adrenarche and/or precocious puberty are all observed.

### Lactotroph Regulation

PRL is synthesized in randomly distributed acidophilic lactotrophs, which comprise about 20% of pituitary cells. PRL




| | PROP1 | | | | | TPIT | |
|---|---|---|---|---|---|---|---|
| | PIT1 | | | | | | |
| **Cell type** | Lactotroph | Mammosomatotroph | Somatotroph | Thyrotroph | Gonadotroph | Corticotroph | Null |
| **Hormone secreted** | PRL | PRL/GH | GH | TSH | FSH/LH | ACTH | None |
| **Clinical phenotype** | High PRL<br>Pituitary failure | High PRL, high GH, and/or high IGF1<br>Pituitary failure | High GH, high IGF1<br>Pituitary failure | High/low TSH, high/low T4<br>Pituitary failure | High/low FSH, high/low LH<br>Pituitary failure | High ACTH, high cortisol<br>Pituitary failure | Pituitary failure |

**Figure 1.** Pathogenesis of pituitary tumors. Pituitary adenomas arise from a differentiated hormone-expressing cell or from a null cell. Clinical phenotype is determined by the cell of origin and the presence or absence of autonomous, specific hormone hypersecretion.

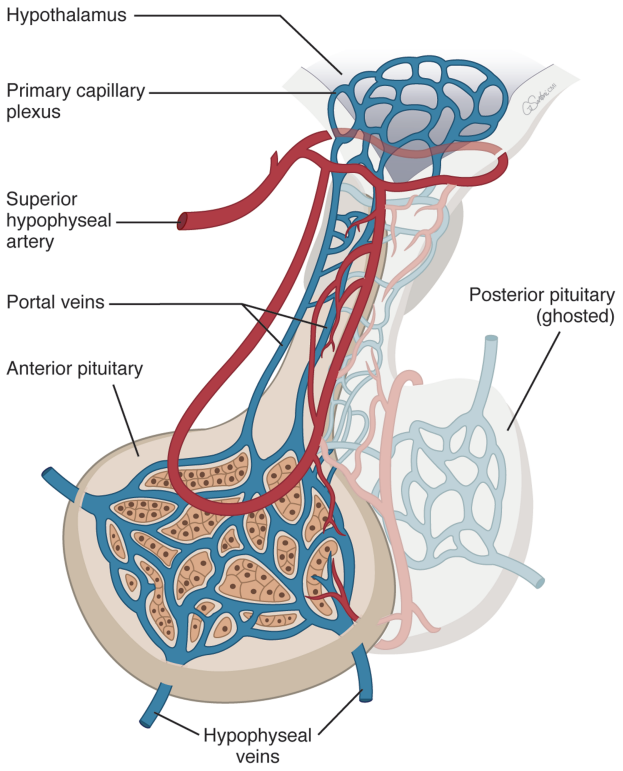



**Figure 2.** Hypothalamic-pituitary vascular and functional relationships.

is weakly homologous to GH and is under tonic hypothalamic dopaminergic inhibition. Lactotrophs and somatotrophs are derived from a common progenitor (26) that may give rise to a tumor that secretes both PRL and GH. On histology, cytoplasmic PRL secretory granules may be densely packed or appear as clusters. Estrogen causes lactotroph cell hyperplasia, which occurs transiently during pregnancy. It is yet unclear whether estrogen pharmacotherapy causes prolactinoma formation or induces growth of preexisting adenomas. Prolactinomas are the most common type of pituitary adenoma, and incidence rates are considerably higher in women (discussed below). However, neither oral contraceptives, estrogen replacement, nor multiple pregnancies are linked to prolactinoma formation (27). Although prolactinomas have been reported after long-term high-dose estrogen therapy in transgender women, no increased risk has been reported in retrospective cohort studies (28, 29).

PRL secretion is under tonic inhibitory control by dopamine, produced by tubero-infundibular dopamine (TIDA) neurons in the dorsomedial arcuate nucleus of the hypothalamus. Dopamine reaches the lactotrophs via the hypothalamic-pituitary portal circulation and binds to lactotroph type 2 dopamine (D2) receptors to inhibit PRL secretion. PRL, in turn, participates in negative feedback to control its own release by increasing tyrosine hydroxylase activity, and thereby dopamine synthesis, in TIDA neurons. In PRL-deficient mice, dopamine is decreased in the median eminence, while mice lacking the D2 receptor develop hyperprolactinemia and lactotroph proliferation (30, 31). Dopamine D2 receptors signal through Gαi, and resultant inhibitory effects on adenylyl cyclase-mediated cellular transduction pathways suppress PRL secretion and lactotroph proliferation. These actions have been leveraged for development of dopamine receptor agonists such as bromocriptine and cabergoline for treatment of lactotroph tumors (32). While loss of *Prlr* leads to large pituitary tumors in mice, homozygous loss-of-function *PRLR* mutations in a human patient with hyperprolactinemia and inability to lactate was not associated with a pituitary tumor (33). Rather, physiologic, pharmacologic, or pathologic alterations in dopamine availability or action disrupt PRL regulation. Thus, PRL hypersecretion occurs with use of dopamine antagonists, as well as when the hypophyseal-portal system is disrupted by compression or stalk damage, regardless of mass etiology (34). As discussed below, PRL levels are elevated (~10-fold) during pregnancy, and PRL induces and maintains lactation, even while suppressing reproductive function.

## Somatotroph Regulation

GH is the most abundant anterior pituitary hormone. Acidophilic somatotrophs constitute ~50% of pituitary cells, localized mainly in the lateral wings and containing prominent cytoplasmic secretory GH granules (23, 35). The pituitary GH gene (*hGH-N*) encodes a 22-kDa GH and a less abundant 20-kDa GH (36). Hypothalamic growth hormone–releasing hormone (GHRH) stimulates synthesis and secretion of GH (37) while somatostatin inhibits GH secretion (38). GH secretion is also stimulated by ghrelin, which is synthesized predominantly in the gastrointestinal tract. Somatostatin (SST) binds SST2 and SST5 receptor subtypes to preferentially signal to suppress GH (and TSH). Insulin-like growth factor 1 (IGF-1), the peripheral target hormone induced by GH, mediates many growth-promoting effects of GH and also feeds back negatively to suppress GH (39). Integrated effects of these complex neurogenic influences determine the final secretory pattern of GH production.

GHRH released by the hypothalamus interacts with its receptor, GHRHR, on the somatotroph cell membrane to increase activation of adenylyl cyclase through Gαs, leading to increased cyclic adenosine monophosphate (cAMP) production and activation of *GH* expression and cell proliferation. Overexpression of *Ghrh* in mice results in pituitary adenomas secreting excessive amounts of GH, and these effects are also seen with ectopic GHRH-secreting tumors in humans (40, 41). Induced cAMP pathway occurs with activating somatic mutations of Gαs-encoding *GNAS*, seen in up to 40% of somatotroph adenomas as well as in the McCune-Albright syndrome, and in the presence of increased protein kinase A activity, due either to loss of the inhibitory action of the regulatory subunit PRKAR1A or to increased PRKACB catalytic subunit activity as seen in Carney complex (42). GPR101, an orphan GPCR that couples to $G_s$ and $G_{q/11}$, leads to increased cAMP and stimulation of GH secretion. Accordingly, germline or somatic *GPR101* microduplication on chromosome Xq26.3 results in X-linked acrogigantism (X-LAG), a rare condition associated with somatotroph adenoma development and early-onset gigantism (43). These and other familial and inherited disorders are discussed below.

Ghrelin is a 28-amino acid peptide that binds the GH secretagogue receptor (44) to stimulate pituitary GH release, an action potentiated with GHRH, which acts as an allosteric co-agonist for the ghrelin receptor. Hypothalamic ghrelin exerts a range of central actions on appetite and metabolism (45-47), but a role in pituitary tumorigenesis has not been defined.

Somatostatin acts on pituitary SST2 and SST5 receptors to signal predominantly via inhibitory Gαi pathways, leading to inhibition of adenylyl cyclase as well as effects on potassium

and calcium ion channels, culminating in reduced GH secretion and decreased somatotroph proliferation. These properties have been applied for therapeutic intervention with development of somatostatin receptor ligands (SRLs) (48).

## Corticotroph Regulation

Basophilic ACTH-secreting corticotroph cells constitute ~20% of pituitary cells. They are located mainly in the central median wedge and contain abundant cytoplasmic neurosecretory granules, often with perinuclear vacuoles. They express POMC, which gives rise to ACTH as well as other products, including β-lipotrophin, endorphins, and enkephalins. Pituitary *POMC* gene transcription is primarily under positive regulation by corticotrophin-releasing hormone (CRH) and negative regulation by glucocorticoids. Vasopressin, cytokines, catecholamines, and vasoactive intestinal polypeptide activate pituitary corticotroph *POMC* gene expression while somatostatin and atrial natriuretic peptide inhibit its expression (49, 50). *POMC* gene expression is regulated differently in extrapituitary tissues than in the pituitary (51).

The CRH type 1 receptor is predominantly expressed on the corticotroph, and receptor activation increases cAMP, protein kinase A, and CREB induction to the promoter, leading to POMC transcription. Vasopressin is co-secreted with CRH and potentiates CRH action, as do β-adrenergic catecholamines, to enhance POMC transcription and ACTH production. Normal pituitary corticotrophs also express somatostatin SST2 and SST5 receptors, and somatostatin inhibits ACTH secretion, albeit in a glucocorticoid-sensitive manner (52). Dopamine receptors have not been characterized in normal human corticotrophs, although they are highly expressed in a subset of human corticotroph adenomas (53).

The hypothalamic-corticotroph-adrenal axis maintains overall cell homeostasis and transduces neuroendocrine stress responses by integrating peripheral and central signals, resulting in appropriate adrenal steroidogenesis. Responses to stressors, including pain, infection, inflammation, hemorrhage, hypovolemia, trauma, psychological stress, hypoglycemia, and critical illness, are mediated mostly by CRH, but also involve vasovagal, catecholamine, and cytokine activation (50, 54).

## Gonadotroph Regulation

Basophilic gonadotrophs, comprising up to 10% of pituitary cells, are mainly located centrally and laterally and express FSH and/or LH-β-subunits within the cell. The secreted glycoprotein hormones FSH and LH comprise a common α-subunit as well as a unique β-subunit that confers hormone specificity (55). Hypothalamic gonadotrophin-releasing hormone (GnRH) regulates both pulsatile LH and FSH secretion, and determines reproductive cycles. Kisspeptin and activins also induce LH/FSH, while inhibins suppress their secretion (56), and FSH and LH regulate germ cell development and maturation and sex steroid synthesis. Primary gonadal failure is associated with gonadotroph hyperplasia, reflecting loss of feedback suppression by sex steroids.

Hypothalamic GnRH neurons are pivotal integrators of central and peripheral signals in regulating the pituitary-gonadal axis. Neurotransmitters that directly or indirectly modulate GnRH secretion include norepinephrine, dopamine, serotonin, γ-aminobutyric acid (GABA), glutamate, opiates, neuropeptide Y (NPY), and galanin. Glutamate and norepinephrine generally provide stimulatory drive, whereas GABA and opioid peptides are inhibitory. Kisspeptins, encoded by the *KISS1* gene, and their cognate receptor, KISS1R, are key GnRH secretagogues (57-59). Neurokinin B, a member of the substance P–related tachykinin family, is co-expressed with kisspeptin in the hypothalamus and appears to act through control of kisspeptin secretion to modulate GnRH release. Indeed, hyperprolactinemia suppression of gonadotrophins is mediated at the level of kisspeptin neurons (60, 61). Substance P also modulates GnRH secretion. Leptin, a product of peripheral adipose tissue, is a positive regulator of the hypothalamic-pituitary-gonadal axis. This adipokine enables a pivotal link between body fat and reproduction, signaling energy availability centrally. Hypothalamic GnRH secretion is pulsatile, resulting in episodic gonadotroph stimulation. Thus, in patients with GnRH deficiency, restoration of gonadotrophin secretion can be achieved after exogenous pulsatile GnRH treatment, whereas continuous GnRH exposure suppresses gonadotrophin secretion. Although GnRH is trophic to gonadotrophins, there is no clear evidence for a role of GnRH in the pathogenesis of gonadotroph adenomas.

## Thyrotroph Regulation

Basophilic thyrotrophs constitute approximately 5% of the pituitary cell population, located mainly in the antero-medial portion of the gland. Hypothalamic TRH induces TSH production, visible as granular deposits. TRH also induces PRL secretion, likely explaining the hyperprolactinemia typically observed with hypothyroidism. Thyroid hormones, dopamine, somatostatin, and glucocorticoids suppress TSH by overriding central TRH induction, while thyrotroph proliferation and TSH secretion are both unrestrained when negative feedback suppression by low thyroid hormone is removed (62).

Transcription of genes encoding the α and β TSH subunits is induced by TRH and suppressed by dopamine. Hypothalamic TRH neurons centrally regulate the hypothalamic-pituitary-thyroid axis setpoint by regulating pituitary TSH release. Hypothalamic TRH synthesis is, in turn, regulated primarily by thyroid hormones. Neuronal groups mediating other physiologic stimuli include adrenergic medullary input, which mediates stimulatory effects of cold exposure on the TRH neuron. TRH neurons also receive projections from 2 leptin-responsive neuronal populations that regulate energy homeostasis. POMC neurons, which promote weight loss, activate TRH neurons, while NPY/agouti-related protein (AGRP) neurons, which promote weight gain, inhibit TRH neurons. Fasting reduces TRH expression, which is mediated by suppression of POMC and stimulation of NPY/AGRP (63). Postnatal thyrotroph expansion is blocked in mice with disrupted *Trh*, illustrating the trophic effects of TRH on thyrotrophs.

## Nonhormonal Cells

The pituitary contains a mixed population of nonhormonal supporting cells scattered throughout the gland as well as cells involved in autoimmune mechanisms (64, 65). These include folliculostellate cells (66), primitive undifferentiated null cells (67), and immune lymphocytes and macrophages (68), all of which may express intrapituitary cytokines that regulate pituitary function and contribute to tumorigenesis (50, 69).

## Regulation of Pituitary Hormone Secretion

Central signals transduced by the pituitary to effect peripheral endocrine chemical messaging reflect a net consolidation

of qualitative, temporal, and quantitative pathways. Pituitary hormone production requires integrated central control of hypothalamic neuropeptides, intrapituitary paracrine and autocrine signals, and target gland hormone feedback to generate uniquely timed and sized secretory hormone pulses to optimize peripheral hormone actions. In turn, target gland functions require timed pulses at each level, generating secretory profiles unique to each pituitary axis to effect peripheral tissue function in an axis-specific manner.

The chronobiology is unique for each axis. GH secretion is characterized by orderly secretory pulses that follow a distinct circadian pattern of predominant nocturnal release triggered by sleep onset, while ACTH exhibits a circadian profile of orderly episodic secretion peaking in the early morning followed by a fall to a later evening nadir. However, pituitary adenomas behave autonomously and do not respond appropriately to central or peripheral feedback signals. This disrupts the homeostatic transduction axis, leading to either endocrine hyperfunction or failure (19).

## Pituitary Tumor Classification

Pituitary adenomas are classified by histology, genomics, surgical anatomy, and phenotypic behavior, each reflecting the multidisciplinary impact of their respective clinical biology.

### Pathologic Classification

#### Cell lineage

Historically, histological classification of pituitary adenomas was based on pituitary hormone content as assessed by immunohistochemistry, as well as on the ultrastructural features of the cells. A change made in the fourth edition of the *WHO Classification of Tumors of the Pituitary Gland* in 2017 was the adaptation of a pituitary adenohypophyseal cell lineage as the main principle for classification (70-72). The 5th edition will include changes in classification of both neuroendocrine and non-neuroendocrine tumors (73), including a discussion of transitional terminology for pituitary neuroendocrine tumors (PitNET) (74, 75), with a goal of aligning disease coding across all neuroendocrine tumors (73, 75). The matter of whether pituitary neoplasms should be termed adenomas or neuroendocrine tumors has been the subject of an international workshop (76). For consistency and conceptual clarity, this review uses the term adenoma to designate neoplasms of pituitary cell origin unless otherwise stated.

Transcription factors are not only essential for cellular differentiation (77, 78) but also are meaningful for clinicopathological practice due to their dependable expression in human pituitary tissues. PIT1 leads to differentiation of mammosomatotrophs, somatotrophs, lactotrophs, and thyrotrophs; TPIT drives the POMC lineage with differentiation of corticotrophs; and SF1 regulates gonadotroph cell differentiation (77-79). Accordingly, tumors are categorized into 4 large groups:

1. *PIT1 lineage tumors* encompass somatotroph, lactotroph, and thyrotroph adenomas and their several histological variants, as well as adenomas that may secrete/express 2 or more hormones, including mammosomatotroph and mixed somatotroph-lactotroph adenomas that secrete/express GH and PRL and rare plurihormonal adenomas that secrete/express GH, PRL, and TSH-β.
2. *TPIT lineage tumors* encompass corticotroph adenomas and its variants, including the common densely granulated corticotroph adenoma, the rare sparsely granulated corticotroph adenoma, and the Crooke's cell adenoma, considered a high-risk tumor (discussed below).
3. *SF1 lineage tumors* encompass gonadotroph adenomas that may express the glycoprotein hormones FSH-β, LH-β, and α subunit in variable combinations, or may express only the SF1 transcription factor with minimal or no hormonal expression.
4. Adenomas without a distinct cell lineage differentiation include null cell adenomas and rare unclassified plurihormonal tumors with variable lineage combinations.

Details of the cell lineage family of tumors and variants are shown in Table 1. Adenomas in each of these categories may present clinically with evidence of hormone excess, that is, as hormone-secreting tumors, or as nonsecreting tumors. Immunohistochemistry directed toward GH, PRL, TSH-β, ACTH, FSH-β, LH-β, and, if possible, alpha-subunit of glycoproteins (αSU) is required for pathologic characterization. The application of the transcription factors PIT1, TPIT, and SF1 immunostaining complements characterization, particularly if a tumor is not classifiable by pituitary hormones alone. Immunohistochemical assessment of pituitary transcription factors is, however, critical in specific situations, including:

1. When an adenoma is not classifiable by hormone immunostains alone due to either focal/weak hormonal staining or staining for multiple hormones from different cell lineages;
2. When establishing the diagnosis of a null cell adenoma, now classified as a tumor immunonegative for pituitary hormones and transcription factors; and
3. When the presence of a pituitary transcription factor is inherent to a tumor definition, for example, plurihormonal PIT1-lineage adenomas.

Immunohistochemistry stains for other cofactors (estrogen receptor α [ERα], GATA3) and cellular components (cytokeratin) are helpful for subclassification of variants and subtypes (Table 1). With the combination of morphology and immunohistochemical markers, there is minimal necessity for ultrastructural analysis for adenoma classification (Fig. 3).

The cell lineage classification is geared to align biological and clinical adenoma classifications more uniformly. For example, application of this classification has resulted in a shift in the reported prevalence of the so-called null cell adenomas due to their previous unclear pathologic classification. Once representing about 20% of all pituitary adenomas in large tumor registries (80) and almost a third of the hormone-negative nonfunctioning tumors (80, 81), null cell adenomas currently represent only 1% to 2% of all pituitary tumors (81-84). This raises the question whether these adenomas really exist or whether they reflect limitations of our diagnostic methodologies for further characterization of cell lineage (83, 85). Null cell adenomas classified by their lack of cell lineage differentiation by both pituitary hormone and transcription factor immunoexpression may have a more aggressive clinical behavior than other nonsecreting adenomas (86, 87).

**Table 1.** Pathologic classification of pituitary adenomas

| Lineage | Type | Morphological variants | Hormone and cytokeratin staining | Transcription factors |
|---|---|---|---|---|
| **PIT1** | Lactotroph | Sparsely granulated | PRL | PIT1, ERα |
| | | Densely granulated | PRL | PIT1, ERα |
| | | Acidophilic stem cell | PRL, GH (focal and variable) | PIT1, ERα |
| | Somatotroph | Densely granulated | GH ± αSU<br>CK perinuclear staining | PIT1 |
| | | Sparsely granulated | GH<br>CK highlights fibrous bodies | PIT1 |
| | Dual hormonal | Mammosomatotroph | GH + PRL (in same cells) ± αSU | PIT1, ERα |
| | | Mixed somatotroph-lactotroph | GH + PRL (in different cells) ± αSU | PIT1, ERα |
| | Thyrotroph | | TSH-β, αSU | PIT1 |
| | Plurihormonal | Immature PIT1 lineage | GH, PRL, TSH-β ± αSU (all focal) | PIT1 |
| | | Mature PIT1 lineage | GH (predominant), PRL, TSH-β ± αSU | |
| **TPIT** | Corticotroph | Densely granulated | ACTH | TPIT |
| | | Sparsely granulated | ACTH | TPIT |
| | | Crooke's cell | ACTH<br>CK forming ring-like appearance | TPIT |
| **SF1** | Gonadotroph | | FSH-β, LH-β, αSU (various combinations) | SF1, GATA3, ERα |
| **No distinct lineage** | Null cell | | None or focal αSU | None |
| | Plurihormonal | Adenomas with unusual immunohistochemical combinations | Various combinations: ACTH/GH, ACTH/PRL | Unknown |

Abbreviations: αSU, alpha-subunit of glycoprotein hormones; ACTH, adrenocorticotropic hormone; CK, cytokeratin; ERα, estrogen receptor α; FSH, follicle-stimulating hormone; GH, growth hormone; LH, luteinizing hormone; PIT1, POU1F1a transcription factor; macroadenoma; PRL, prolactin; SF1, steroidogenic factor 1; TPIT, T-box family member TBX19; TSH, thyrotrophin (thyroid-stimulating hormone).

### Grading

The vast majority of pituitary adenomas are benign and slow growing, with a very low relapse rate over many years after surgical resection (88, 89). The fourth World Health Organization (WHO) classification grading scheme defined "pituitary adenoma" and "pituitary carcinoma," with the latter comprising tumors with cerebrospinal and/or systemic metastasis (72). Importantly, it abandoned the "atypical adenoma" terminology, which had been introduced in the third edition, due to the lack of prognostic clinical value for this pathologic diagnosis, even while recognizing that these adenomas may be locally invasive, precluding clinical cure and demonstrating more aggressive clinical behavior (90-92). Morphologic features distinguishing indolent tumors from locally aggressive ones are still unidentified and, currently, no single prognostic parameter can determine the risk of growth or malignant progression (93-95). Evaluation of tumor proliferation (by mitotic count and/or Ki-67 labeling index) and of tumor invasion may be meaningful on an individual basis as both features correlate with more aggressive tumor behavior (96, 97). At this point, there is no significant evidence correlating genetic abnormalities driving invasive and/or metastatic pituitary tumors (98, 99).

Some histologic adenoma variants are recognized as having a more aggressive clinical behavior. These so-called *high-risk* lesions show proclivity for higher recurrence rates and resistance to standard therapies, and include sparsely granulated somatotroph adenomas, silent corticotroph adenomas, and Crooke's cell adenomas, defined as corticotroph adenomas harboring larger percentage of cells with Crooke hyaline change characterized by cytoplasmic ring-like cytokeratin expression, as well as immature PIT1-lineage adenomas (100-105). In the upcoming fifth WHO classification, no new tumor grading system is introduced, although a terminology change of *pituitary carcinoma* to *metastatic pituitary neuroendocrine tumor* is recommended, in addition to the specific lineage characterization (eg, metastatic lactotroph pituitary neuroendocrine tumor) for tumors with discontinuous spread and distant metastasis (75).

### Summary

Pathologic classification of pituitary adenomas is based on histological determination of cell lineage and associated transcription factors. Molecular analyses are not currently integrated into routine diagnosis as clinical correlates of genetic mechanisms underlying the pathogenesis of pituitary adenomas are as yet unclear (see below). Identification of potentially aggressive adenomas should be made on an individual basis by considering the adenoma subtype, proliferative potential, and tumor invasion assessment. Attention should be given to recognize "high-risk" tumor variants that have intrinsic substantial risk for recurrence and more adverse clinical behavior.

## Genomic Classification

Pangenomic, high-throughput, large-scale omics analyses have been applied to study the transcriptome, miRNome, methylome, chromosomal, and sequence alterations in pituitary adenomas (106-108). Recent studies of large sample sets (ie, > 100) have enabled robust assessment of pituitary adenoma pangenomic profiles, improving understanding of the

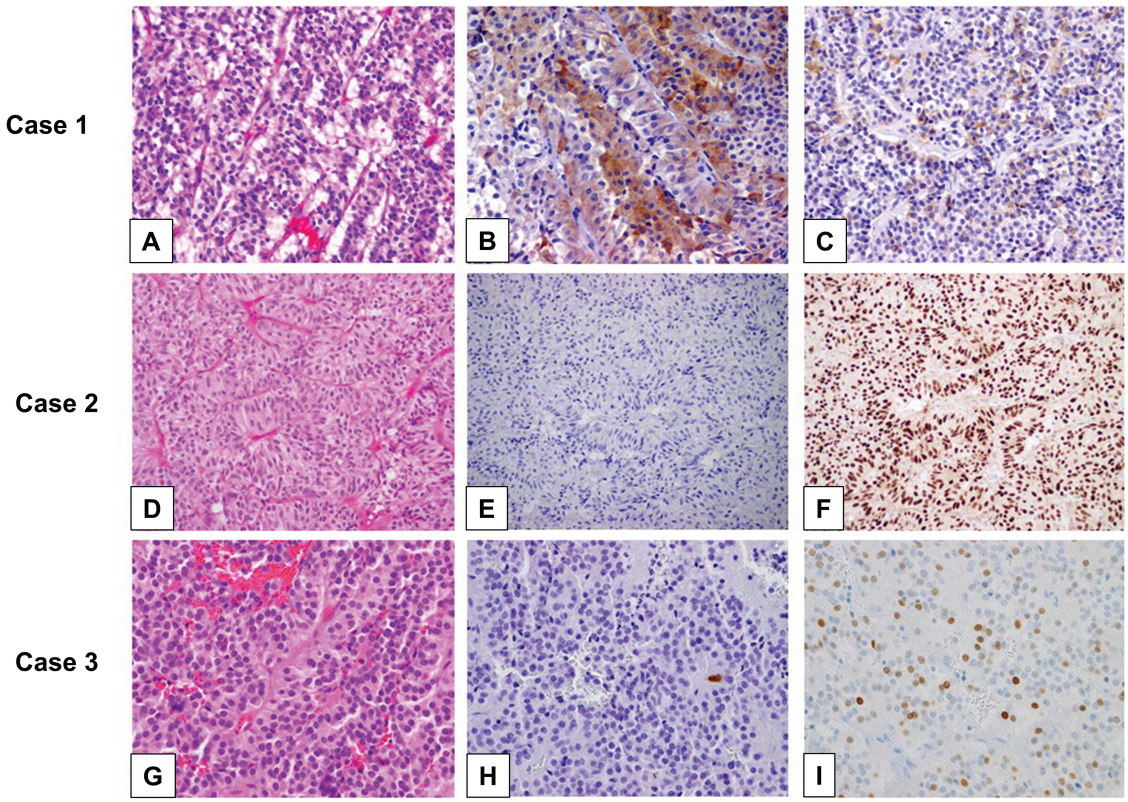



**Figure 3.** Representative pituitary adenomas classified by immunohistochemistry for pituitary hormones and transcription factors. (A-C, Case 1) (A) A gonadotroph adenoma showing typical chromophobic cells arranged in nests, with trabecular and sinusoidal arrangements. The majority of the gonadotroph adenomas express the gonadotrophins (B) FSH-β and (C) LH-β despite being clinically silent. (A: H&E; B: FSH-β immunohistochemistry [IHC]; C: LH-β IHC; A-C: 40× original magnification). (D-F, Case 2) (D) A gonadotroph adenoma showing typical histological appearance, but (E) completely devoid of gonadotrophin (FSH-β) expression and (F) expressing the gonadotroph-lineage transcription factor SF1. (D: H&E; E: FSH-β IHC; F: SF1 IHC; D-F: 40× original magnification). (G-I, Case 3) (G) A clinically nonsecreting adenoma with chromophobic appearance on H&E, showing (H) rare ACTH-positive cells and (I) multifocal positivity for TPIT, diagnosed as corticotroph adenoma (clinically silent). (G: H&E; H: ACTH IHC; I: TPIT IHC; G-I: 40× original magnification). Note that Case 2 and Case 3 most likely would be diagnosed as null cell adenomas if transcription factors were not considered.

landscape of genetic and epigenetic alterations and forming the basis for a molecular classification of pituitary adenomas.

Large-scale transcriptome analysis has identified distinct pituitary adenoma groups based on gene expression profiles (99, 109). These groups generally correlate with the fourth WHO classification, but also offer specific insights relevant to clinical practice. For example, 2 corticotroph adenoma subtypes linked to hormonal secretory status have been identified, distinguishing between overt Cushing's disease and silent corticotroph adenomas that exhibit a gene expression signature closer to that of gonadotroph adenomas. Transcriptome analysis also revealed that mixed lactotroph-somatotroph tumors share a gene expression profile with GH-secreting tumors rather than with pure lactotroph tumors. Gene expression signatures driving this molecular classification have been identified (99) and include increased expression of cell cycle genes in secretory corticotroph tumors vs overexpression of genes associated with oxidative phosphorylation in gonadotroph tumors and overexpression of MYC targets in lactotroph tumors. Furthermore, meta-analysis of microarray data from several studies showed overall dysregulation of differentially expressed genes related to metabolism in pituitary adenomas (109). Differences in gene expression profile between invasive and noninvasive pituitary adenomas have been suggested (110-112).

Pangenomic analysis of epigenetic changes also reveals specific molecular signatures for each group of pituitary adenomas, with the methylation pattern revealing a molecular classification (113-115). Methylation profiles differentiate somatotroph adenomas from gonadotroph and secretory corticotroph adenomas (99). Global hypomethylation is observed in somatotroph adenomas, mainly due to the CpG sites located in low CpG density regions (ie, the "open sea"). Of note, methylation level negatively correlates with cis-expression of key genes. For example, hypomethylation of the *GH1* and *SST5* gene promoter is associated with their overexpression in somatotroph adenomas; similarly, the *POMC* gene is hypomethylated in corticotroph adenomas (114).

The miRNome is a determinant of pituitary adenoma molecular classification, with at least 4 different molecular profiles of pituitary adenomas identifiable by miRNome analysis (99). Interestingly a specific cluster of 85 miRNA, known as MEG3, located on chromosome 14q32.2 and associated with somatotroph adenomas (116), is associated with GH secretion and a higher expression of PIT1 and DLK1. A main driving effect of this miRNA cluster in pituitary adenoma differentiation is supported by functional studies (116).

Integration of pangenomic genetic and epigenetic alterations in pituitary adenomas now provides a basis for an informed molecular classification to enable clinical investigation and histological analysis. This classification identifies

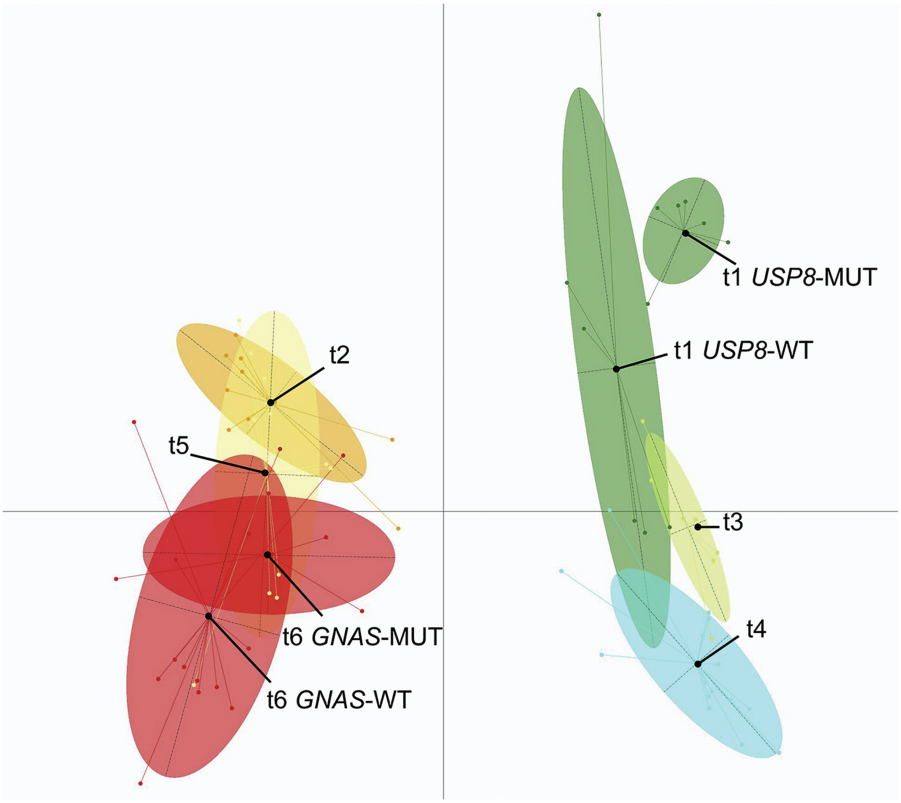



**Figure 4.** Pangenomic classification of pituitary adenomas. Multiple factor analysis of the transcriptome, miRNome, methylome, mutations, and chromosomal alterations in a series of 134 adenomas. t1: corticotroph adenomas with or without *USP8* somatic mutation, t2: lactotroph adenomas, t3: silent corticotroph adenomas, t4: gonadotroph adenomas, t5: thyrotroph and plurihormonal adenomas, t6: somatotroph adenomas with or without *GNAS* somatic mutation. Reprinted with permission from Neou et al. (2020) (99).

PIT1 differentiation as the main driver (Fig. 4), while analysis of somatic mutations of *GNAS* and *USP8* combined with transcriptome analysis identifies subgroups that correlate with specific genetic and epigenetic features and clinical/histological characteristics. Pangenomic classification also suggests that gonadotroph adenomas share genomic profiles with silent corticotroph and null cell adenomas (99).

## Surgical Classification

### Anatomic considerations

The pattern of pituitary adenoma growth is characterized either by expansion into or infiltration of surrounding parasellar tissues. Slow and expanding growth results in a mass with a well-circumscribed border that exerts increasing pressure on healthy nontumorous tissue and on the bony sella, displacing and compressing normal functional pituitary tissue and surrounding structures. By contrast, infiltrative growth results in penetration, incorporation, and destruction of adjacent tissues, resulting in a mass with poorly defined tumor margins. Initially, individual cells, tumor cell clusters, or tongues of adenoma tissue may infiltrate the dura, affecting bone, sphenoid sinus mucosa, cavernous sinuses, or other structures depending on growth direction. Up to 35% of adenoma types exhibit gross invasion, with macroadenomas showing higher rates (117, 118).

The direction of growth may be superior, inferior, anterior, posterior, or lateral to the sellar fossa, or a combination of patterns. Superior growth is the most common, as the diaphragm sella and its opening are a weak barrier to expansion. Tumors may compress and damage the optic nerves and chiasm; with a postfixed chiasm, the tumor may grow forward to the subfrontal area, whereas with a prefixed chiasm, growth is backward to the third ventricle and hypothalamus. Inferior growth produces sellar remodeling, enlargement, and bone resorption, leaving a free path for sphenoid sinus spread. Infiltrative tumors may directly penetrate the sphenoid bone and clivus, and, with further growth, may extend into the nasopharynx or nasal cavity. Anterior growth encroaches the planum sphenoidale, inferior surfaces of the frontal lobes, and ethmoid sinuses. Posterior growth produces expansion to the interpeduncular cistern and brainstem. Lateral growth may be either by expansion into or infiltration of the cavernous sinuses.

The behavior of pituitary adenomas is evaluated from changes in morphology and the degree of encroachment on regional anatomical structures such as the cavernous sinus. Although the pituitary gland appears to lack a capsule, there are reports the gland may be covered by a thin capsule, or that an adenoma capsule (or pseudocapsule) is simply compressed normal pituitary tissue (119-121). The medial wall of the cavernous sinus bordering the sella varies in structural thickness or defects. Thus, the tumor may invade, invaginate (122, 123), or extend to the cavernous sinus (124, 125).

### Surgical classification and outcomes

The simplest way to characterize a pituitary adenoma is according to its size, using a 10-mm cutoff to define micro- vs macroadenoma. Tumors measuring > 40 mm are generally considered giant adenomas (126). No histological differences distinguish micro- from macroadenomas, nor are there

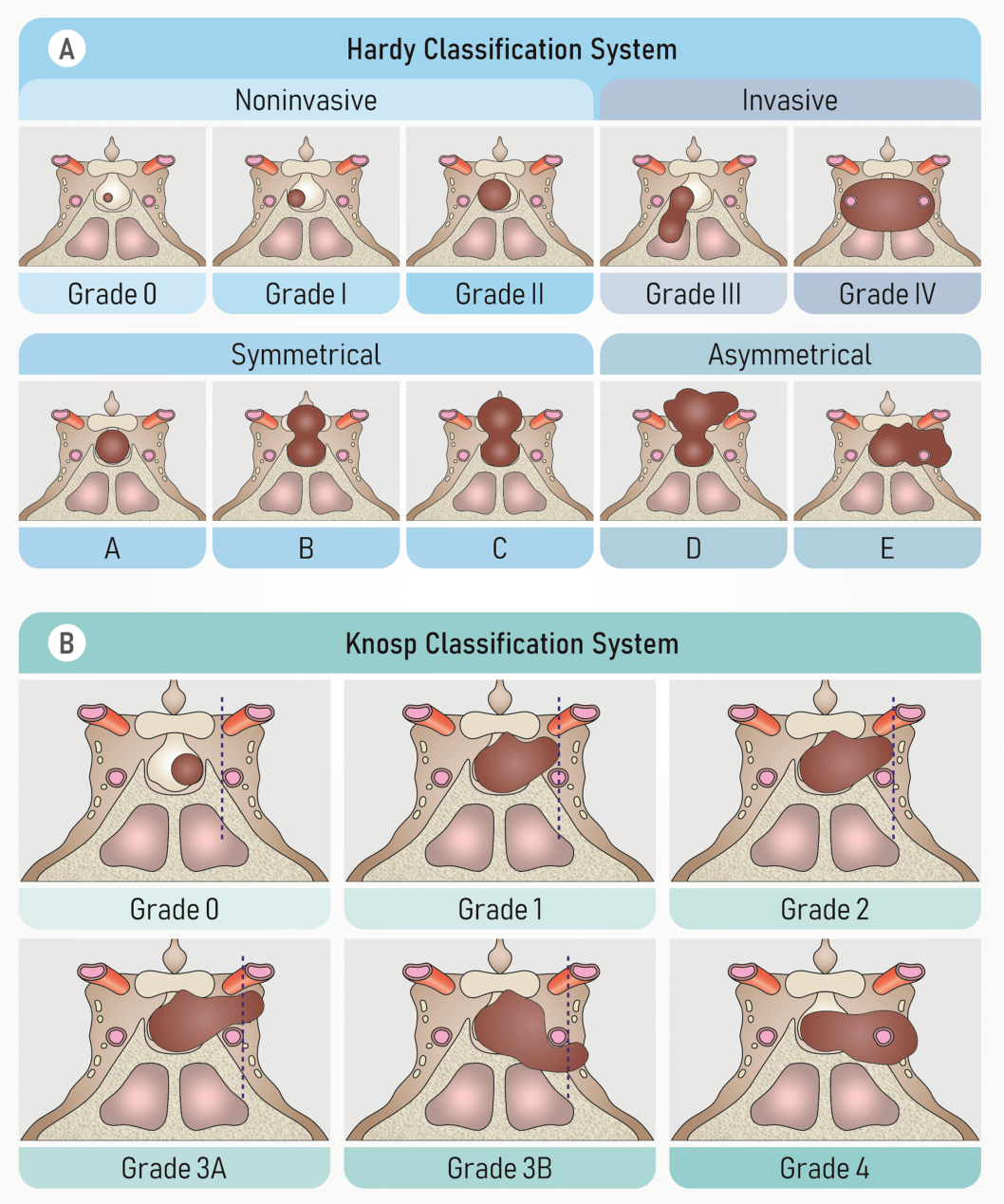



**Figure 5.** Classification systems used to characterize pituitary adenomas. (A) Hardy classification system. Sella turcica tumors can be noninvasive (grade 0, grade I, grade II), or invasive (grade III, grade IV). Suprasellar tumors can be symmetrical (grade A, grade B, grade C), or asymmetrical (grade D, grade E). (B) Knosp classification system. Grade 0, no cavernous sinus involvement; grades 1 and 2, the tumor invades the medial wall of the cavernous sinus, but does not go beyond a hypothetical line extending between the centers of the 2 segments of the internal carotid artery (grade 1) or it goes beyond such a line, but without passing a line tangent to the lateral margins of the artery itself (grade 2); grade 3A, the tumor extends laterally to the internal carotid artery into the superior cavernous sinus compartment; grade 3B, the tumor extends laterally to the internal carotid artery into the inferior cavernous sinus compartment; grade 4, total encasement of the intracavernous carotid artery. From Di Ieva A et al. (2014) (127).

morphological features that predict growth. By contrast, as tumor size is a predictor of more favorable surgical outcome, size-based classifications are clinically useful (127).

According to the Hardy classification (128), small, intrasellar, symmetrical pituitary tumors are noninvasive, whereas those causing bone destruction are invasive (Fig. 5A). As cavernous sinus involvement considerably limits surgical resection, and preoperative imaging aids in assessing its feasibility, Knosp (129, 130) classified adenomas based on the degree of cavernous sinus involvement, identifying the parasellar internal carotid artery on coronal magnetic resonance imaging (MRI) as a critical imaging landmark to gauge the presence of cavernous sinus invasion (Fig. 5B). This is a widely used classification due to its clarity and simplicity. The Knosp classification of adenomas correlates with surgical outcomes and biochemical remission. Indeed, resection of adenomas that invade the cavernous sinus has a low success rate (130).

With advanced understanding of pituitary adenoma pathogenesis and availability of novel medical therapies, anatomic classifications may diminish in practical value. New classifications will consider personalized biomarkers, response to therapy, and patient-centric determinants (105, 131).

## Classification Based on Phenotypic Behavior

Although most pituitary adenomas are benign, an aggressive subgroup invade the sphenoid or cavernous sinus, present with multiple recurrences despite surgical or medical treatment, or, very rarely, develop distant metastases.

### Invasive pituitary adenomas

Pituitary adenomas invading the sphenoid or cavernous sinus occur in up to 40% of surgical resections (96, 97, 132, 133). As noted above, complete surgical resection is not likely to be achieved when there is tumor invasion of the cavernous sinus, and the presence of residual tumor increases the likelihood of regrowth or of recurrence assessed by MRI from 10%–20% to 25%–50% in a 5-year study of nonsecreting adenomas (134). Nevertheless, despite its negative prognostic impact, invasion was not included in the fourth WHO classification, as intraoperative or histopathological evidence of tissue invasion was considered an imprecise and controversial biomarker (135). Rather, invasion, whether radiological or histological, is included with a cluster of other markers describing clinically aggressive adenomas (136).

### Aggressive pituitary adenomas

The term *aggressive pituitary tumor* has been used variably to describe invasive tumors, giant tumors, and refractory behavior, as there is currently a lack of an agreed definition for these adenomas. In light of these uncertainties, it is not possible to draw conclusions on their epidemiology or to identify predictive markers.

*Definition.* The European Society of Endocrinology guidelines define an aggressive pituitary adenoma as a radiologically invasive tumor with an unusually rapid growth rate, or as a tumor presenting with clinically relevant growth despite optimal use of standard medical, surgical, and radiotherapeutic therapies (89). This is largely a clinical definition.

Although aggressive pituitary adenomas are usually macroadenomas at diagnosis, tumor size does not necessarily correlate with aggressive behavior, as exemplified by giant lactotroph tumors that can be quite responsive to medical treatment (137). Moreover, surgical success is not solely determined by tumor size (96, 130, 138).

The prevalence of aggressive pituitary adenomas has been estimated from surgical series. Based on reported percentages of invasive tumors and postoperative recurrences, approximately 2% of pituitary macroadenomas are aggressive (139), with the proportion influenced by tumor type, and higher for secretory tumors.

There is no consensus as to the definition of unusually rapid tumor growth, the hallmark of an aggressive tumor (140). As employed for other solid tumors, the longest diameter according to the RECIST 1.1 criteria may be adopted for objective evaluation pituitary neoplasms enabling rigorous assessment of tumor response to therapy (141), as this measure correlates with tumor volume (142). Thus, based on these criteria, significant tumor growth can be considered a 20% increase in diameter, and growth considered as unusually rapid when assessed over a standardized duration (143).

*Predictive markers.* The major limitation in defining a pituitary adenoma as aggressive is the absence of predictive cell markers.

The fourth WHO classification recommends evaluation of tumor proliferation (ie, mitotic count and Ki-67 index) and tumor invasion as features of aggressive clinical behavior. However, cutoff values for these parameters are not specified (72). Although "high-risk" adenoma subtypes with poor prognosis have been identified, this histological classification does not grade clinical behavior (135). As an adjunct to the WHO classification, a 5-tiered grading system for clinical prognostication has been proposed, which combines indices of invasion and proliferation, specifically mitotic index > 2, Ki-67 ≥ 3%, and p53 immunopositivity (97). This grading system has been evaluated in at least 4 independent cohorts comprising 1992 patients (96, 144-146). Grade 2b (invasive and proliferative) tumors, which represented 5.4% to 8.8% of the surgical series, were associated with an increased likelihood of "aggressive" behavior, characterized by a high risk of recurrence or progression despite medical therapy (136).

Many studies have sought to identify molecular markers associated with tumor behavior. However, the confusion between invasiveness and aggressiveness, the low number of tumors analyzed, and the absence of prospective validation studies have largely precluded identification of biomarkers that distinguish aggressive or invasive pituitary adenomas from the very rare carcinomas. PTTG1 (147), which maintains chromosomal stability, appears to be a reliable marker of invasiveness. PTTG1 abundance is associated with tumorigenesis and invasion (22) and is highly expressed in tumors that recur (148, 149). Markers of cell cycle regulation, including cyclin D1, phosphorylated RB, CDKN1B, p21, and p16, are associated with recurrence or progression in some subtypes and in a few studies (149-152). A recent multiomics study (99), however, did not identify a specific signature or pathway associated with prognosis. Chromosomal instability appears not to be associated with prognosis but rather with the functional properties of the tumor. Indeed, secreting tumors are more prone to exhibit copy number alterations (CNA) in comparison to nonsecreting null cell or gonadotroph tumors (99, 114, 153-156).

These reports suggest that additional mechanisms underlie tumor recurrence or resistance to medical treatment, including the contribution of soluble factors and the pituitary tumor microenvironment to aggressive behavior. For example, an association between high expression in the extracellular matrix of metalloproteinase 9 (MMP-9) and tumor invasion, angiogenesis, and proliferation has been demonstrated (157, 158). Cytokines and chemokines, tumor-associated fibroblasts, angiogenesis, and immune cells likely contribute to pituitary tumor pathogenesis and behavior, opening up new perspectives for identifying novel treatment targets for these tumors (64, 158-160).

### Pituitary carcinomas

*Definition.* In the absence of a specific pathological marker, the occurrence of cranio-spinal or systemic metastasis is required to classify a pituitary tumor as a carcinoma (72, 89). Despite this clear definition, differential diagnosis can be difficult in the presence of a well-differentiated neuroendocrine tumor of visceral origin with pituitary metastasis (161).

True pituitary carcinomas are exceedingly rare. Their prevalence, estimated from large pathology collections, ranges from 0.13% to 0.4% of all resected tumors (80, 97, 162). Interestingly, published cases describing pituitary carcinomas has increased dramatically following the first descriptions of successful treatment of these tumors with the oral alkylating agent temozolomide, leading to publication of case series or large cohort studies describing therapeutic results (163-165).

*Natural history*. The majority of pituitary carcinomas originate from invasive macroadenomas, are resistant to medical treatment, and require multiple surgeries and radiation therapy to achieve tumor control (166, 167). From a review of the literature (168) and a survey of European Society of Endocrinology members (169), 112 cases of pituitary carcinomas were identified (65 men and 47 women), with a median age at diagnosis of 45 years (range, 9-75 years). Corticotroph and lactotroph tumors were the most frequent subtypes. The switch from a nonfunctioning to functioning tumor should alert the physician to the potential for an aggressive pituitary tumor and the risk of distant metastasis, especially with a switch from a silent corticotroph adenoma to overt Cushing's disease.

De novo metastasis at the time of diagnosis is extremely rare. The median time from initial diagnosis to identification of metastases was 7 years, and the reported latency period was up to 31 years. Most metastases were intracranial and spinal, although metastases to liver, bone, lymph nodes, and lung were detected. Screening for metastasis is indicated when there is discordance between imaging results and biochemical findings, in the presence of nonpituitary site-specific symptoms in a patient with a known pituitary adenoma, or as pretherapeutic staging in the presence of an aggressive pituitary tumor. In these cases, in addition to whole-body computed tomography (CT) scan and brain and spinal MRI, functional imaging should be considered where available. Positron emission tomography (PET) using 68-Gallium DOTATOC may be helpful in identifying tumors/metastases, as well as for identifying candidates for peptide receptor radionuclide therapy (143).

*Predictive markers*. The rarity of pituitary carcinomas is a major limitation for discovery of predictive markers. Most studies combine invasive and aggressive adenomas with pituitary carcinomas, enabling identification of markers associated with tumor progression but not specific to malignant tumors. As discussed above, upregulated cyclin D1, vascular endothelial growth factor, MMP-9, and p21Cip1 seem to be associated with disrupted tumor cell cycle progression, vasculogenesis, metastasis, and invasion, and may contribute to malignant transformation of pituitary adenomas to carcinomas (170).

*ATRX* and *TP53* mutations may be more specifically associated with corticotroph carcinomas. In a study of 39 aggressive pituitary tumors and 9 carcinomas, investigators found that 5 corticotroph carcinomas and 1 GH-PRL carcinoma, as well as 3 aggressive corticotroph or lactotroph tumors, harbored somatic mutations in the *ATRX* gene, which is involved in heterochromatin remodeling and telomere maintenance (171). Loss of ATRX immunoexpression was confirmed in all tumors, suggesting that ATRX immunostaining may allow early identification of patients at risk of developing pituitary carcinomas. Interestingly, additional inactivating somatic mutations in tumor suppressor genes, specifically *TP53, PTEN, RB1,* and *NF2*, as well as *CDKN2A/B* deletion were identified in 8 of 9 ATRX-immunonegative tumors. Although *TP53* is rarely mutated in pituitary adenomas, a higher-than-expected prevalence of *TP53* mutations was observed in aggressive corticotroph tumors, and these were associated with chromosome instability (155).

The very limited number of patients with these tumors at any one center constrains identification and development of predictive markers, highlighting the need for multicenter international collaborations to inform risk stratification and optimization of therapeutic strategies.

## Molecular Pathogenesis

More than 95% of all pituitary adenomas are sporadic (172). Whole genome sequencing studies have enabled major advances in elucidating their pathophysiology (173), yet the genetic background of a large proportion of pituitary tumors still remains unknown, largely because of technical challenges in studying surgically resected adenoma samples (174). The tissue pieces are often quite small, can contain intermingled normal pituitary tissue, vasculature, or mesenchymal cells, yield low-abundance mutations, and are genetically heterogeneous, all factors increasing background heterogeneity.

Pituitary tumors are monoclonal in composition (175, 176), with somatic, mosaic, and familial low penetrance variations being the potential causes of tumorigenesis (177). A recent genome-wide association study in a Han Chinese population of 771 pituitary adenomas and 2788 control subjects discovered 3 chromosomal susceptibility loci at 10p12.31, 10q21.1, and 13q12.13 with genome-wide significance ($P < 5 \times 10^{-8}$), suggesting that sporadic pituitary tumor formation also includes inherited genetic variations, although no specific gene mutations were found (178).

The mutational spectrum observed in pituitary tumors using whole genome or whole exome sequencing demonstrates lineage-dependent genetic diversity. The average number of somatic mutations in the coding region is low, with fewer than 10 per tumor sample (114, 154, 156, 179-181). Overall, commonly encountered oncogene mutations are not observed, and recurrent mutations are reported mostly in *GNAS* (for somatotroph adenomas) and *USP8* (for corticotroph adenomas) and very rarely in *NR3C1*. Thus, molecular mechanisms include activating mutations in key pathways causing hormone hypersecretion and receptor mutations impairing hormone feedback mechanisms or activating intracellular pathways. Additional reported proproliferative and pro-secretory factors include chromosomal instability and DNA damage, senescence mechanisms, and molecular changes favoring both benign adenoma growth and hormonal secretory activity. Furthermore, nongenomic mechanisms may also contribute to adenoma pathogenesis and hormone hypersecretion, including soluble intrapituitary factors such as STAT3 activation (182) and Klotho (183, 184).

### Activating Mutations

Targeted sequencing of candidate oncogenes and tumor suppressor genes has not yielded a high rate of oncogenic mutations. Thus, *RAS* mutations were reported in 3 rarely encountered metastatic pituitary carcinomas but not in the respective primary lesions (185); using droplet digital polymerase chain reaction (PCR), a mutant *K-RAS* was detected in a gonadotroph macroadenoma (186).

Recurrent *GNAS* mutations were identified in GH-secreting tumors (42) with a prevalence of around 40% (187). The mutations result in a substitution of highly conserved Arg201, or less frequently Gln227, with subsequent constitutive activation of the mutated Gsα subunit (187). Mechanistically, these

mutations inhibit GTPase activity of the G protein alpha chain, increasing cAMP levels and turning Gsα into a constitutive active oncogene, termed *Gsp*. Its relevance was confirmed more recently in 2 whole genome and exome sequencing studies reporting a *GNAS* mutation rate of 25% and 31%, respectively (188, 189). Patients with somatotroph *Gsp* mutations are older at diagnosis and have smaller, less invasive tumors. Histopathologically, the tumors are densely granulated in comparison with nonmutated somatotrophinomas. Constitutive cAMP activation in somatotroph adenomas appears to mimic effects of excess GHRH signaling to induce both somatotroph proliferation with DNA damage, as well as GH secretion. Furthermore, somatotroph adenomas exhibit higher levels of *PDE4D*, further sustaining cAMP levels (156). Some studies reported a favorable response to SRLs, an observation disputed by others (187).

The pathogenesis of corticotroph adenomas was elucidated in 2015, when recurrent somatic heterozygous activating driver mutations were identified in the ubiquitin-specific protease *USP8* gene (179, 190). The mutations appear to be specific to corticotroph tumors, with a prevalence ranging from 12% to 60% depending on study methodology and patient ethnicity (mean prevalence, 35.5%) (191, 192). *USP8* mutations are primarily present in patients who are mostly female and of younger age, and who harbor microadenomas. Whole exome sequencing studies of *USP* wild-type tumors identified mutations in the deubiquitinase *USP48*, the glucocorticoid receptor *NR3C1*, the *BRAF* oncogene, and *TP53* (193, 194). Moreover, *USP8* mutant and *USP8* wild-type corticotroph tumors cluster into 2 distinct groups with distinct transcriptomic profiles, thus offering a more robust molecular classification of these adenomas (99).

*USP8* mutations affect the 14-3-3 protein binding site, a highly conserved area that protects USP8 from cleavage. Cleaved USP8 deubiquitinates EGFR, protecting it from lysosomal degradation. Recycled EGFR, in turn, leads to increased expression of POMC and ACTH release (195). *USP8* mutations appear to have negligible effect on proliferation. Activating *USP48* mutations were detected in 10% to 20% of wild-type *USP8* tumors (193, 194). USP48 is also a deubiquitinase, and mutations occurred predominantly in female patients with smaller tumors. These mutations changed the structural conformation of USP48 and increased its catalytic activity toward the physiological substrates histone 2A and zinc finger protein Gli1, thereby enhancing POMC and ACTH secretion.

Activating somatic mutations in the p110-α catalytic subunit of PIK3CA have been identified in PRL- and ACTH-secreting and nonsecreting adenomas (196, 197). The mutations lead to constitutive activation of the AKT pathway and increased invasiveness (198).

## Receptor Signaling Defects

Receptor signaling defects, a hallmark of endocrine disease pathophysiology, are present in patients with familial isolated pituitary adenomas (FIPA) harboring germline *AIP* mutations or in patients with X-LAG syndrome (discussed below). In sporadic pituitary tumors, whole genome sequencing identified a recurrent hotspot somatic mutation in splicing factor 3 subunit B1, SF3B1$^{R625H}$, in about 20% of 227 prolactinomas. Mutant prolactinomas displayed higher PRL concentrations and shorter progression-free survival compared with wild-type tumors. The SF3B1$^{R625H}$ mutation caused aberrant splicing of estrogen-related receptor gamma and enhanced binding of PIT1, increasing PRL secretion and lactotroph proliferation (199). This mutation was not identified recently in another whole genome sequencing study of 16 lactotroph tumors (99).

Receptor signaling defects in the glucocorticoid receptor (GR) gene *NR3C1* in corticotroph tumors may disrupt physiologic glucocorticoid feedback on tumor cells. A somatic frameshift mutation in *NR3C1* with premature termination of the coding sequence was identified in tumor tissue of a patient with corticotroph tumor progression following bilateral adrenalectomy (Nelson's syndrome) (200). Mutations in the coding region of *NR3C1* are rare in Cushing's disease: they were identified in 1 of 12 tumors studied by whole exome sequencing (190), but in none of 18 corticotroph tumors using Sanger sequencing (201), nor in 18 *USP8* mutation-negative tumors using exome sequencing (194). Very recently, next-generation sequencing identified 3 *NR3C1* mutations in 49 corticotroph adenomas (202). Clinical phenotypes were similar in patients harboring *NR3C1* mutations and those with wild-type tumors. In vitro studies showed that the p.R469X mutant generated a truncated GR protein, and the p.D590G and p.Y693D GR mutants resulted in lower GR expression. The mutations reduced nuclear translocation of the GR following dexamethasone treatment in AtT-20 cells, increased cell proliferation, and attenuated suppression of POMC transcription.

Ectopic production of gastric inhibitory peptide receptor (GIPR) has been identified in subgroups of patients with acromegaly, with 184 of 496 (37%) patients with GH-secreting adenomas showing a paradoxical GH response to oral glucose tolerance testing. At diagnosis, these patients were older, had smaller tumors, higher basal GH normalized for tumor volume, and a lower rate of hyperprolactinemia, and they had a more favorable response to SRLs (203). In another study, GIPR expression was detected in 32% of samples, including all resected tissues from patients with paradoxical GH responses. GIPR-expressing somatotrophinomas did not show *GNAS* mutations (204, 205). GIPR expression was associated with a general hypermethylation phenotype, including in the *GIPR* gene, potentially driving ectopic expression (173, 204). It is interesting to speculate whether this represents a similar mechanism as described for GIPR expression in cortisol-producing primary bilateral macronodular adrenal hyperplasia (206).

## Chromosomal Instability and DNA Damage

Studies on chromosomal alterations using CGC and exome and/or genome sequencing have reported either chromosomal losses or gains occurring most often on chromosomes 1, 2, 7, 8, 11, 18, 19, and 22 (154, 172, 207, 208). The alterations vary among adenoma types and range from extended chromosomal losses or gains to almost no change in adenomas with a "quiet" genome (99). Early studies demonstrated that adenoma *PTTG* overexpression leads to chromosomal instability and aneuploidy due to unfaithful centromere separation (22, 151, 209). The molecular basis of these earlier aneuploidy observations has been extended based on comparative genomic hybridization (CGH) analysis (205, 210, 211) and are shown to be more frequent in invasive adenomas (211).

In a study of 42 pituitary macroadenomas, whole exome sequencing identified chromosome arm–level copy number alterations (CNA) across large fractions of the genome in 29% of samples. Chromosomal alterations are more frequent in secreting adenomas, especially in GH-secreting adenomas (154, 156, 180, 188, 212-214), and in atypical null cell adenomas (180). By contrast, alterations are less frequent and extensive in nonsecreting and gonadotroph adenomas (99, 154). In a prospective study of 159 resected adenomas, somatic CNA (SCNA) were overwhelmingly detected in secreting adenomas, with far fewer chromosomal abnormalities observed in nonsecreting adenomas. Using single-gene SCNA pathway analysis, cAMP pathways were identified in somatotroph adenomas, and both GH production and DNA damage were induced by a GHRH analogue of cAMP activation, thereby linking GH hypersecretion to SCNA and genome instability (156). The central role of constitutively elevated cAMP in eliciting DNA replicative stress, cell proliferation, and hormone hypersecretion may direct pituitary cells toward senescence rather than apoptosis (215) (see below). Taken together, an accumulating body of evidence suggests that sporadic pituitary adenomas have distinct copy number profiles that associate with hormonal and histologic subtypes and influence gene expression.

DNA methylation profiles show GH-secreting adenomas being dominated by hypomethylated sites (114, 181). Increased expression of *GH* and *SST5* genes in GH-secreting adenomas and *POMC* gene in ACTH-secreting adenomas was associated with hypomethylation of the respective promoter regions (114). These findings were extended by CGH array analysis of 195 fresh-frozen pituitary adenomas showing CNA highest in lactotroph (median 38% of probes) compared to corticotroph (11%), somatotroph (5%), gonadotroph (0%), and immunonegative tumors (0%) (153).

### Senescence Mechanisms

Cellular senescence characterized by largely irreversible cell cycle arrest constitutes an antiproliferative response, triggered by DNA damage, chromosomal instability and aneuploidy, loss of tumor suppressive signaling, or oncogene activation (216). Mechanisms underlying the invariably indolent growth pattern of pituitary adenomas has, thus, been explained by activation of cellular senescence (151). GH-secreting pituitary adenomas exhibit PTTG-provoked aneuploidy and DNA damage and abundantly express p21 as well as beta-galactosidase, a hallmark of senescence (151, 217). p21 induces both proliferative cell cycle arrest and senescence in somatotroph adenomas (151); in turn, induction of senescence stimulates GH expression and triggers the p53/p21 senescence pathway. p53 binds specific GH promoter motifs and enhances GH production in senescent pituitary adenoma cells, which further protects pituitary tumor cells from apoptosis (218).

Another pathway implicated in pituitary senescence is mediated by paracrine IL-6 signaling, leading to premature cell cycle arrest and evidence for pituitary tumor cell senescence (219). This cytokine also selectively induces PRL and ACTH production (220).

### Summary

Overall, the available body of evidence suggests that recurrent cell-specific oncogenic mutations are uncommon. Unique activating mutations have been detected for *USP8* in corticotrophinomas and *GNAS* in somatotrophinomas (179). Overall, the biology of pituitary adenomas is underpinned by somatic signaling driver pathways that induce chromosomal instability and senescence, accounting for both benign proliferative phenotypes as well as hormone hypersecretion (181).

## Clinical Spectrum

### Epidemiology

Epidemiological studies have provided valuable information on the clinical biology and clinical significance of pituitary adenomas (1, 221).

#### Overall prevalence

In 1924, Costello first reported that small adenomas were frequently present in pituitary glands of subjects deceased from causes unrelated to pituitary disease (222). Among 1000 unselected pituitary glands, 225 harbored adenomas and a few glands contained multiple distinct adenomas. In subjects aged from 2 years to 91 years, he observed equal gender distribution and peak frequency in the sixth decade (Fig. 6A). Studies from unselected autopsies have since confirmed a high prevalence of asymptomatic adenomas in the general population. In a comprehensive review of 16 studies encompassing more than 21 000 unselected autopsies, an average prevalence of 10% was reported, with immunological staining for PRL seen in up to 40% of these subclinical adenomas (224). Most lesions are < 3 mm in size; clinically inapparent macroadenomas are rare.

The subclinical prevalence of pituitary adenomas has also been estimated from imaging surveys. Studies employing CT scanning reported discrete pituitary lesions in about 10% of normal volunteers (225-227), while those using MRI observed pituitary abnormalities in 10% to 40% (228, 229) of subjects. The observed abnormalities were small, with none > 10 mm in diameter. However, this higher rate may also include nonpituitary pathological lesions that have a similar appearance.

Unlike prevalence derived from autopsies of people who died from causes unrelated to pituitary adenomas, the clinical significance of pituitary adenomas is derived from epidemiological studies of patients harboring known pituitary adenomas within a defined community (149, 223, 230-234). Based on registry studies and record reviews, the overall prevalence of pituitary adenomas is estimated to range from 680 to 1430 cases per million persons (Table 2). Thus, on a population level, the prevalence is nearly 1 case per 1000 persons, or approximately one-thousandth the number of subclinical adenomas reported from unselected autopsies (Table 3). The estimated incidence of clinically significant pituitary adenomas is 40 per million persons per year (149, 233, 234).

The overall prevalence of invasive adenomas in 6 studies evaluating 1705 patients was 14.2%, representing 6% of clinically significant pituitary adenomas (235). The prevalence of aggressive adenomas is estimated at 2% of surgically resected tumors (139) based on a consolidated definition that embraces invasion, histological markers of proliferation, and a clinical course of recurrence despite multimodal treatments. Malignant transformation is very rare. Studies of surgical specimens from the United States, Germany, France, and Canada totaling more

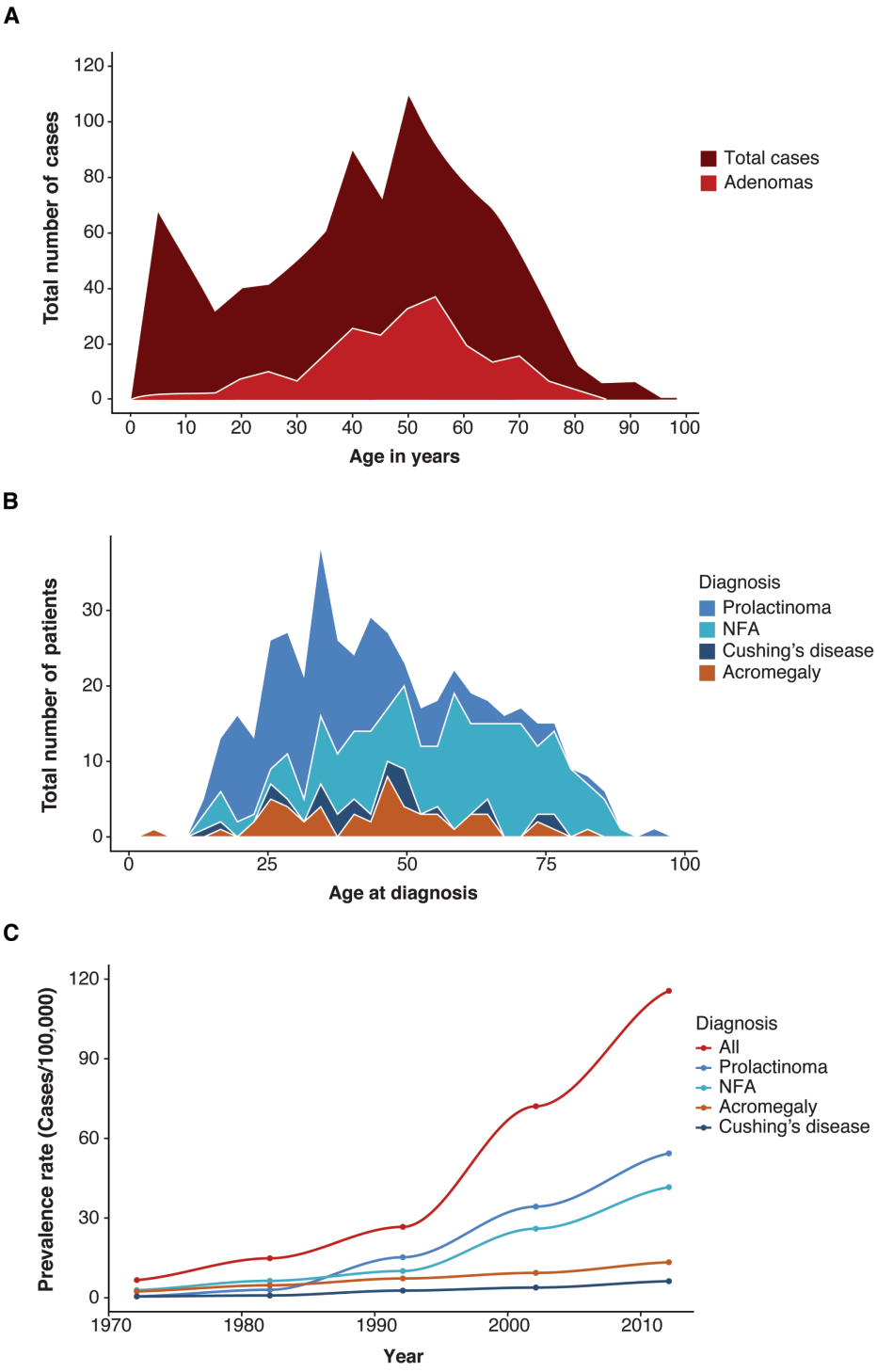



**Figure 6.** Epidemiology of pituitary adenomas. (A) Number of pituitary adenomas and cases plotted at age of death in 1000 unselected autopsies reported in 1936 (222). (B) Number of patients with a prolactinoma, acromegaly, Cushing's disease, or a nonfunctioning pituitary adenoma at age of diagnosis from a nationwide study in Iceland from 1955-2012 (223). NFA, nonfunctioning adenoma. (C) Increasing prevalence of clinically significant pituitary tumors during 1972–2012 showing a clear rise since around 1990, mainly explained by the increased prevalence of prolactinomas and nonfunctioning adenomas (223). NFA, nonfunctioning adenoma.

than 12 000 tumors have identified a total of 30 carcinomas. This collectively yields an average prevalence of 0.25% among surgically resected adenomas (80, 97, 162, 236).

Prevalence rates for subclinical, clinically significant, and malignant pituitary adenomas is summarized in Table 3. Available data indicate that pituitary adenomas are common, exhibit a mostly benign natural history, and cause disease of variable severity in less than 0.1%, with a 1 in 100 000 risk of malignancy.

### Morbidity and mortality

The burden of pituitary tumor-related morbidity can be gleaned from the distribution of adenoma types, the proportion requiring surgical treatment, and the fraction with

**Table 2.** Prevalence of clinically significant pituitary adenomas

| Author | Year | Country | Population | Adenomas | Prevalence, 1 per N | Prevalence, N per million | Female, % | Macro,% |
|---|---|---|---|---|---|---|---|---|
| Daly (230) | 2006 | Belgium | 71,972 | 68 | 1064 | 940 | 68 | 43 |
| Fontana (231) | 2009 | Switzerland | 55,000 | 44 | 1241 | 800 | NR | 44 |
| Fernandez (232) | 2010 | England | 81,149 | 63 | 1289 | 780 | 67 | 41 |
| Raappana (233) | 2010 | Finland | 242,400 | 164 | 1471 | 680 | 71 | 46 |
| Gruppetta (149) | 2013 | Malta | 400,000 | 316 | 1321 | 790 | 70 | 43 |
| Tjornstrand (234) | 2014 | Sweden | 1,590,640 | 592 | 2686 | 370 | 52 | 66 |
| Agustsson (223) | 2015 | Iceland | 330,000 | 471 | 865 | 1430 | 60 | 55 |
| Average | | | | | 1420 | 830 | 65 | 48 |

Abbreviations: Macro, macroadenoma; NR, not reported.

**Table 3.** Clinical epidemiology of pituitary adenomas

| | Expected N per 1 million |
|---|---|
| Subclinical (autopsies) | 100,000 |
| Clinically significant | 830 |
| Requiring surgery | 380 |
| Invasive | 53 |
| Carcinoma | 1 |

aggressive behavior and malignant transformation, the latter of which add disproportionately to the burden of morbidity.

Clinically significant pituitary adenomas are more common in women than in men. About half of all tumors are macroadenomas and two-thirds are functional, secreting PRL, GH, and ACTH in order of descending frequency (Fig. 7A). A national database study in Iceland over 60 years from 1950 to 2012 observed that the prevalence rate increased after the 1990s, with contributions mainly from prolactinomas and nonsecreting adenomas (223) (Fig. 6B). Age-related prevalence differences in adenoma subtypes were also noted, with prolactinomas presenting at younger ages compared with nonsecreting adenomas (223) (Fig. 6C), while the age-related prevalence for acromegaly and Cushing's disease was similar.

Acromegaly increases mortality about 2-fold, but this is reversed in both sexes by treatments that control GH hypersecretion (237-240). Cushing's disease increases mortality up to 4-fold. Successful treatment reduces excess mortality, but rates are not usually restored to those seen in the general population (241-244).

### Histological subtypes

In community and single-center surveys, about 45% of symptomatic tumors are surgically resected (230, 245, 246); this includes both nonsecreting and secreting adenomas, with the latter comprising a proportion treated primarily medically but remaining inadequately controlled. The distribution of histological types in more than 7000 specimens from the German Pituitary Tumor Registry (80) is shown in Fig. 7B. Classified based on immunohistochemistry staining, null and LH/FSH-staining adenomas together account for > 50% of cases; ACTH-positive adenomas comprise 15%, followed by GH, PRL, and mixed GH/PRL adenomas in descending frequency.

### Clinical subtypes

Epidemiological studies assessing frequency of pituitary adenomas based on clinical diagnosis suggest that rates have increased in more recent years. However, the influence of factors unrelated to clinical biology of pituitary adenomas, including study methodology, improved diagnostic strategies, and physician awareness, remains to be determined (247).

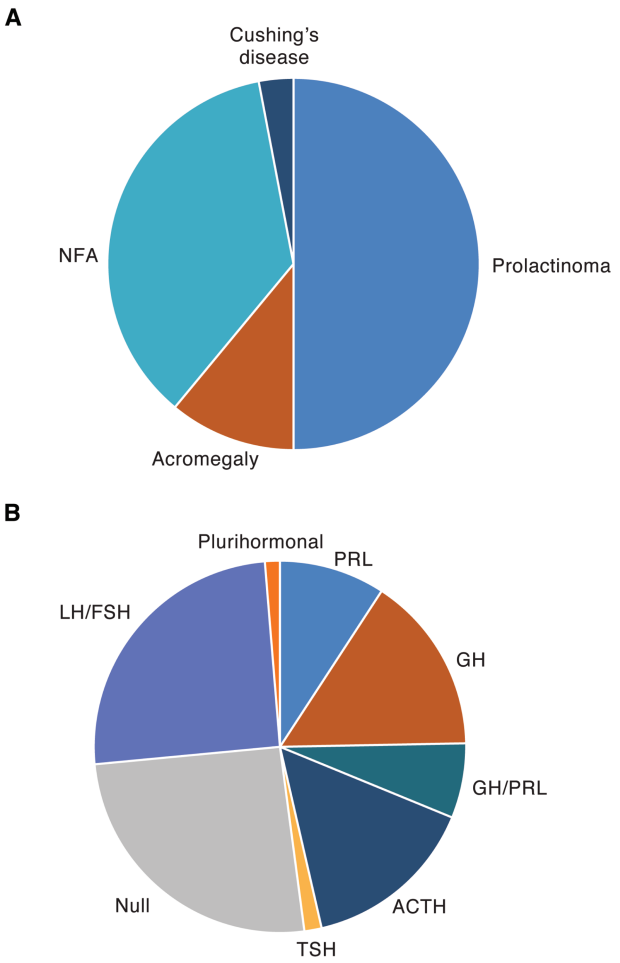



**Figure 7.** Frequency of pituitary adenoma subtypes. (A) Frequency of PRL-, GH-, and ACTH-secreting and nonfunctioning adenomas in patients with clinically significant pituitary adenomas from 7 regions in Europe and the United Kingdom (149, 223, 230-234). NFA, nonfunctioning adenoma. (B) Distribution of surgically resected pituitary adenoma subtypes from the German Pituitary Tumor Registry classified by immunohistochemistry (80).

*Prolactinoma.* The estimated prevalence of prolactinomas is 444 to 540 per million (149, 223, 232), and the annual

incidence is 16 to 26 per million, with much higher rates in women than in men (24-37 vs 7.6-9.0 per million, respectively) (223, 233, 234). The peak incidence in women occurs during the third and fourth decade of age; after menopause, the incidence rate is similar to that of men. A study from Korea based on a nationwide health insurance database reported an annual incidence of 23.5 per million, which is similar to previous studies, but they reported a considerably lower prevalence of 82.5 per million (248). Interestingly, 6% to 12% of prolactinomas were identified from evaluation of incidentally discovered pituitary adenomas (223, 233).

*Acromegaly.* A review of treatment data between 1926 and 1996 estimated the annual incidence of acromegaly in New Zealand at approximately 3.3 per million (249). A nationwide Danish study of national health care registries and verified by patient records reported an annual incidence of 3.8 per million and a prevalence of 85 per million between 1991 and 2001, with a mean age at diagnosis of 48.7 years (250). A Finnish study reported an annual incidence of 3.4 per million and a median age at diagnosis of 40.5 years between 1992 to 2007 (233), and a regional study in Sweden reported a similar incidence of 3.5 per million between 2001 and 2011 (234). A nationwide Icelandic study based on patient registries and patient records estimated a higher annual incidence of 12 per million in 2012, and a prevalence of 136 per million (223), while a study in the United States using administrative claims data from 2008 to 2012 estimated the annual incidence was 11 cases per million and the prevalence was 78 per million (251). Taken together, these results suggest that the annual incidence of acromegaly has increased. However, it remains unclear whether this represents a true increasing incidence or whether it is due to methodological differences.

*Cushing's disease.* There are few studies on the incidence and prevalence of Cushing's disease. In a nationwide study identifying Swedish patients through public health care registries, review of patient records to verify the diagnosis showed that 534 (41%) of 1317 cases of Cushing's syndrome had confirmed Cushing's disease, resulting in an incidence of Cushing's disease of 1.6 cases per million per year. The incidence was somewhat higher between 2005 and 2013 as compared with rates between 1987 and 2004 (252). A higher annual incidence of 2.3 per million was reported from a recent Korean study based on health insurance database, but there was no patient record verification in this study (248). It is therefore likely that these studies relying on healthcare databases may have overestimated the incidence of Cushing's disease. Indeed, 8 previous studies reported an annual incidence of between 1.2 and 2.4 per million, and nationwide studies from Denmark and New Zealand reported lower incidences of 1.2 and 1.3 per million per year, respectively (253, 254). Thus, there is uncertainty as to whether incidence has truly increased with time (233), or whether the apparent increased incidence of Cushing's disease is the result of methodological differences.

*Nonsecreting adenomas.* Based on national registry data, the incidence in Sweden of nonfunctioning pituitary adenomas increased from 6 to 11 per million between 1975 and 1991 (255). The estimated annual incidence was 20.3 per million at a later time period from 2002 to 2011, indicative of a rise in incidence (256). Similarly, in a regional Finnish study, the annual incidence was 10 per million between 1992 and 2007, with occurrences of incidentally discovered masses tripling over this time period (233).

Changes in incidence rates by sex and age are less clear (257). A Swedish regional report based on public health care registries and patient records reported an annual standardized incidence ratio of 18 per million between 2001 and 2011 that did not differ between men and women (234), while an Icelandic study showed the incidence clearly increased with time to 22 per million in women and 26 per million in men in 2012 (223). Overall, the incidence of nonfunctioning pituitary adenomas is low in childhood and peaks at age 60 to 65 years (233, 256). However, mean age at diagnosis is younger in women than in men (40-58 vs 58-62 years) despite approximate equal distribution between the sexes (149, 233, 256).

Of note, nearly all of these studies reported an increasing number of incidentally discovered pituitary adenomas. In the Icelandic and Finnish studies, nonsecreting adenomas were incidentally discovered in 30.5% and 51% of cases, respectively (223, 233). Thus, not surprisingly, the natural history of conservatively managed nonsecreting pituitary adenomas is not well studied (258). Nevertheless, a meta-analysis of incidentally discovered masses and of treated pituitary adenomas suggests that patients with macroadenomas are at higher risk for development of apoplexy, new pituitary hormone deficiencies, and visual field defects compared with patients with microadenomas (259).

**Summary**

Pituitary adenomas are common, with the overwhelming majority undetected and remaining harmless and indolent during the living years. Among the minority that are clinically significant, morbidity arises from hormonal hypersecretion or from growth and local invasion, with malignant transformation a very rare exception. The incidence of clinically relevant pituitary adenomas appears to be rising. However, results of epidemiological studies are affected by era and duration of study, availability of imaging and laboratory technology, and differences in methodological approaches, all of which influence detection and diagnosis.

## Familial and Inherited Syndromes

Although most pituitary adenomas arise sporadically without a family history of pituitary or other tumors, about 5% have a familial form or a genetic tumor syndrome (260), many of which have identifiable molecular drivers. In general, adenomas arising from genetic mutations exhibit greater clinical aggressiveness, with earlier onset, accelerated tumoral growth and invasion, as well as relative treatment refractoriness (Table 4). Thus, although familial adenomas account for a small minority of cases, their management can be complex. Screening and familial genetic risk assessments are required in this population, but are not germane to management of the overwhelming majority of patients harboring sporadic pituitary adenomas (187).

**Multiple endocrine neoplasia type 1**

Multiple endocrine neoplasia type 1 (MEN1) is an autosomal dominant disorder caused by mutations in the tumor suppressor gene *MEN1* (261). Pituitary adenomas occur in association with other endocrine tumors, typically of the parathyroids and pancreas, although other sites may be affected

**Table 4.** Somatic and germline genetic causes of pituitary adenomas

| | Gene | Phenotype | Pituitary features |
|---|---|---|---|
| Germline | *AIP* | ~20% of FIPA | Younger age (<30 years) |
| | | ~13% of young sporadic macroadenomas<br>~23% of pediatric pituitary adenomas<br>~29% of gigantism | Male predominance<br>Large invasive adenomas |
| | *GPR101*(mosaicism in sporadic males) | X-LAG syndrome<br>10% of gigantism | Early onset (<36 months)<br>Acromegaly features<br>Increased appetite<br>Hyperprolactinemia<br>Hyperplasia |
| | *MEN1* | Up to 50% have pituitary adenoma | Mainly prolactinomas<br>Plurihormonal and multiple adenomas<br>Female predominance<br>Larger and more invasive |
| | *CDKN1B* | ~37% of MEN4 have pituitary adenoma | All subtypes |
| | *PRKAR1A* | Pigmentations, myxomas, hormone hypersecretion | Up to 12% have acromegaly |
| | *PRKACB* | | Multiple adenomas with surrounding hyperplasia |
| | *SDHx, SSDHA, SDHB, SDHC, SDHD, SDHAF2* | ~30% have pheochromocytoma and/or paraganglioma and pituitary adenoma | Prolactinomas, somatotrophinomas, nonsecreting adenomas<br>Extensive cytoplasmic vacuolization<br>Mostly aggressive macroadenomas |
| | *MAX* | 3PAs<br>Aggressive pheochromocytoma | Prolactinomas, somatotrophinomas |
| | *NF1* | Neurofibromatosis type 1 | Acromegaly or gigantism |
| | *DICER1* | Pleuropulmonary blastoma | Cushing's disease with high mortality in early infancy |
| | *CABLES1* | Corticotrophinomas | Invasive macroadenomas with high Ki-67 index |
| Somatic | *GNAS* | 30-60% of somatotrophinomas | Smaller, densely granulated, older age |
| | | McCune-Albright syndrome (café-au lait macules, fibrous dysplasia, endocrine hyperactivity) | 10-15% acromegaly and/or gigantism<br>Pituitary hyperplasia |
| | *PIKA3CA* | All types | Mainly large adenomas |
| | *USP8* | 30-60% of corticotrophinomas | Female predominance |
| | *USP48* | ~20% of USP8 WT corticotrophinomas | No difference vs WT |
| | *BRAF* | ~16% of USP8 WT corticotrophinomas | Higher ACTH and cortisol |

Abbreviations: 3PAs, pituitary adenomas, paragangliomas, and pheochromocytomas; FIPA, familial isolated pituitary adenoma; WT, wild-type; X-LAG, X-linked acrogigantism. Adapted with permission from Vandeva et al. (2019) (187).

(262). Approximately 30% to 40% of these patients will have developed a clinically relevant pituitary adenoma during their lifetime (263); in 17% of adult patients and 30% of young patients, it is the first tumor diagnosed (263, 264). In general, MEN1-related pituitary adenomas are more likely to be larger and invasive and to express more than one pituitary hormone (263, 265, 266). In addition, cohort studies involving young patients with large or invasive macroadenomas report the occurrence of *MEN1* mutations, as exemplified by studies of acrogigantism demonstrating that 1% also harbor *MEN1* mutations (267, 268). Genetic testing guidelines recommend biochemical and imaging screening for pituitary adenomas in suspected carriers beginning from the age of 5 (262).

### Multiple endocrine neoplasia type 4

Multiple endocrine neoplasia type 4 (MEN4) is caused by germline mutations of *CDKN1B*. It mimics MEN1 in affected patients with no other distinctive features (269, 270), yet is very rare. Fewer than 20 MEN4-related pituitary adenomas have been reported. Isolated cases of *CDKN1B* mutations in patients with Cushing's disease have also been reported (271).

### Carney complex

Carney complex is usually caused by germline mutations in *PRKAR1A* (272). The most frequent endocrine and nonendocrine features include skin lesions, myxomas, and tumors of the adrenal gland, testis, pituitary, and thyroid (273). Rare cases of *PRKAR1A* mutations in patients with Cushing's disease have also been reported (274). Retrospective analyses suggest that approximately 10% of patients develop acromegaly (sometimes due to somatomammotroph hyperplasia), which occurs 10 to 20 years earlier than sporadic acromegaly (275-277). Up to three-quarters of these patients have abnormal GH/IGF-1 or PRL levels (275). Because *PRKAR1A* mutations do not play a role in sporadic acromegaly, testing for *PRKAR1A* mutations should be sought only from individuals with a family history of Carney complex or with syndromic presentation suggestive of the disorder (278).

### McCune-Albright syndrome

First described in 1937, the McCune-Albright syndrome involves pituitary disease in the setting of multiple endocrine, bone, and cutaneous disorders (279, 280). Mosaicism for

post zygotic activating *GNAS* mutations is the cause of the classical triad of café-au-lait skin macules, polyostotic fibrous dysplasia, and precocious puberty seen in these patients, with pituitary adenomas/hyperplasia a common finding (281). GH excess is an important feature, although adenomas commonly express both GH and PRL. GH excess affects nearly a third of patients (282) and exacerbates craniofacial fibrous dysplastic bony deformity (282-285), which may also cause optic or auditory nerve impingement (286, 287). GH excess may occur in early childhood (283), and this syndrome accounts for about 5% of pituitary gigantism (268). Treatment can be challenging: neurosurgical access to the sellar region is difficult and may be constrained by thick dysplastic skull base bone, and radiotherapy is often avoided due to the concern of inducing sarcomatous changes. Early and effective control of GH excess is a goal to avoid gigantism and other serious effects in these patients (288).

### Familial isolated pituitary adenomas

Familial isolated pituitary adenoma (FIPA) is defined as kindreds with 2 or more pituitary adenomas in related members in the absence of syndromic conditions such as those discussed above. To date, hundreds of FIPA kindreds have been reported (289, 290) and it accounts for up to 2% of pituitary adenomas (291). FIPA can present homogeneously with the same clinical phenotype of pituitary adenoma in all affected members (eg, acromegaly), or heterogeneously with different subtypes in affected family members. Acromegaly is a prominent feature of FIPA, with approximately 35% of FIPA patients harboring somatotrophinomas (292). In general, pituitary adenomas in FIPA, including acromegaly, present 5 to 20 years earlier than in patients with sporadic adenomas, frequently with larger and more invasive neoplasms (291).

Not all genetic causes of FIPA are known. Among those identified are *AIP* mutations and chromosome Xq26.3 microduplications involving the *GPR101* gene causing X-LAG syndrome, both of which are described below (43, 293). Together, these account for about 20% of FIPA cases, but rarely may also present sporadically in patients with no familial history of pituitary adenomas.

### AIP mutations

Inactivating mutations or deletions of *AIP* exhibit autosomal dominant inheritance with incomplete penetrance (289). About 10% to 20% of *AIP* mutation carriers develop a clinically relevant pituitary adenoma (289, 290). While *AIP*-related pituitary adenomas can have any clinical phenotype, somatotrophinomas or mixed GH- and PRL-secreting adenomas comprise more than two-thirds of cases (289, 290, 294). Pituitary adenomas with *AIP* mutations exhibit aggressive features and early onset, with a median age of < 18 years (295). GH-secreting adenomas with *AIP* mutations are the main cause of pituitary gigantism, accounting for nearly 30% of cases (268). Pituitary adenomas due to *AIP* mutations are also typically larger and more invasive at diagnosis as compared to sporadic adenomas (295), and they are resistant to some medical therapies (295).

### X-LAG syndrome

Sporadic and familial early childhood-onset pituitary gigantism may be caused by Xq26.3 microduplications (43, 296). Overexpression of GPR101 in somatotrophs leads to constitutive activation of multiple G proteins, including Gs and Gq/11, and stimulation of GH secretion through protein kinase A and protein kinase C (297). Low-expressing GPR101 ligands have been suggested, including endometrial GnRH1-5 and a leukocyte inflammatory modulator resolvin D5 (298-300). Given strong GPR101 somatotroph constitutive activity, it is unclear whether these putative ligands play a role in modulating pituitary function.

X-LAG syndrome is exceptionally rare, with only 40 patients described (301). Most occur sporadically due to constitutional duplications in females or somatic mosaicism in males. Three FIPA families have been identified, all with transmission from mother to son (260). Disease onset is typically in the first 12 months of life, and almost all patients are diagnosed by the age of 3 with a pituitary macroadenoma secreting high levels of GH and PRL (43, 296). The young age and large tumor size renders neurosurgical treatment difficult. X-LAG causes 10% of pituitary gigantism, but accounts for some of the tallest individuals reported (302, 303). Pituitary tumors in X-LAG grow relentlessly and are resistant to monotherapy (296, 304), often requiring multimodal therapies.

### Other conditions

Pituitary adenomas, paragangliomas, and pheochromocytomas can rarely arise in the same patient due to shared pathogenic mechanisms (known as 3PA). Mutations of *SDHx* and *MAX* have been documented in these individuals (305-307). Different pituitary adenoma subtypes occur in the setting of 3PA, including acromegaly and prolactinomas.

## Pregnancy

Increasing use of assisted reproductive techniques and advances in pituitary clinical and surgical treatments have resulted in more women with pituitary disorders achieving fertility and conceiving (308). Accordingly, pregnancy is now common in women harboring pituitary adenomas. However, during pregnancy, these adenomas may enlarge and pituitary volume increases by up to 136%, mostly due to estrogen-stimulated lactotroph hypertrophy and hyperplasia with a subsequent increased risk of sellar mass effect (309).

Pituitary adenomas, especially when associated with pituitary failure, may impair fertility and preconception, and affect endocrine outcomes throughout pregnancy (308, 310). Prior to pregnancy, hormone replacement therapy should be optimized in women with pituitary adenoma and hypopituitarism.

Evaluation of a newly discovered pituitary adenoma during pregnancy is challenging, as interpretation of biochemical testing can be difficult and imaging may be constrained due to radiation or gadolinium risks. Notably, the differential diagnosis in a pregnant woman with no known prior pituitary adenoma should include that of lymphocytic hypophysitis.

Most pregnant women with a pituitary adenoma should receive standard obstetrical care, with frequent maternal and fetal surveillance (308, 311). Those with macroadenomas and compressive symptoms would likely require cesarean section and should be managed by a multidisciplinary team.

### Pituitary gland changes during pregnancy

Pituitary morphological adaptations result in altered pituitary hormonal secretion ensuring optimal fetal development. PRL secretion increases significantly throughout pregnancy due to hyperplasia, with the number of PRL-secreting lactotrophs usually increasing from up to 30% of cells to 60% to 70% by pregnancy end. Gonadotroph cells notably decrease, concordant with reduced gonadotrophin production. Although

the number of corticotrophs and thyrotrophs remains stable, ACTH secretion increases moderately while TSH decreases slightly. Placental GH production rises continuously during pregnancy, suppressing pituitary GH secretion and somatotroph cell numbers by mid-second trimester (308). Notably, pituitary and placental GH share a 96% sequence homology; commercial assays do not distinguish between these 2 forms of GH during pregnancy. Furthermore, placental GH is not subjected to feedback regulation (308).

### Lactotroph adenomas

Prolactinomas account for up to 75% of all pituitary adenomas in women (1). Dopamine agonist treatment is discontinued once pregnancy is confirmed, except in cases of large macroadenomas. Estrogen may induce prolactinoma cell proliferation, *PTTG* mRNA, and fibroblast and vascular endothelial growth factor expression (312), while rat antiestrogen treatment decreased both PRL levels and prolactinoma size (313).

Risk of overall microadenoma enlargement is ~5%, with 2% to 3% exhibiting significant growth, yet almost half of microadenomas > 5 mm may enlarge during pregnancy (314) (Table 5). Interestingly, pregnancy also may induce remission of some microprolactinomas, typically those overexpressing ERα (317). Likelihood of remission has been associated with smaller initial adenoma size and pituitary MRI normalization after pregnancy. Breastfeeding is unlikely to induce adenoma growth.

**Table 5.** Pituitary adenomas in pregnancy

| | Symptomatic growth during pregnancy | Radiological growth during pregnancy | Peri-pregnancy change in adenoma size |
|---|---|---|---|
| **PRL-secreting** (311)<br>*753 pregnancies*<br>*652 patients*<br>*13 studies* | All adenomas (n = 578): 9.0% (95% CI: 6.8-11.6)<br>Microadenomas (n = 46): 15.2% (95% CI: 15.2; 6.3-28.9)<br>Macroadenomas (n = 118): 30.5% (95% CI: 22.4-39.7) | All adenomas (n = 376): 10.6% (95% CI: 7.7-14.2)<br>Microadenomas (n = 104): 14.4% (95% CI: 8.3-22.7)<br>Macroadenomas (n = 137): 13.9% (95% CI: 8.6-20.8) | *Population*<br>n = 175 in 4 studies with available data before and after pregnancy<br>*No change (1 study)*<br>• 5.0 mm (95% CI: 1.6-14.4) before and 5.0 mm (95% CI: 0-12.0) after pregnancy<br>*Increased size (2 studies)*<br>• Range, 0.0-1.4 cm; mean 0.7 cm in macroadenomas<br>• Median 4 mm (range, 2-8); 3.0 mm in macroadenomas and 0.5 mm in microadenomas<br>*Decreased size (1 study)*<br>• Median 1 mm (range, –19 to + 12); no change (range, –5 to + 6) in microadenomas and 6.5 mm reduction (range, –19 to + 12) in macroadenomas |
| **PRL-secreting** (315) | Macroadenomas with no prior surgery/radiation (n = 238): 21.0%<br>Macroadenomas with prior surgery/radiation (n = 148): 4.7% | N/A | N/A |
| **GH-secreting** (311)<br>*128 pregnancies*<br>*97 patients*<br>*4 studies* | All adenomas (n = 128): 7.0% (95% CI: 3.3-12.9)<br>Microadenomas (n = 10): 30.0% (95% CI: 6.7-65.2)<br>Macroadenomas (n = 97): 4.1% (95% CI: 1.1-10.2) | All adenomas (n = 111): 5.4% (95% CI: 2.0-11.4)<br>Microadenomas (n = 8): 25.0% (95% CI: 3.2-65.1)<br>Macroadenomas (n = 82): 3.7% (95% CI: 0.8-10.3) | N/A |
| **Clinically nonsecreting** (311, 327)<br>Observational study of > 2000 patients<br>71 confirmed pituitary macroadenomas | Macroadenomas (n = 16): 37.5% (95% CI: 15.2-64.6) | Macroadenomas (n = 4): 25% (95% CI: 7.3-52.4) | N/A |
| **TSH-secreting** (316)<br>3 cases | Macroadenomas: 2 of 3 cases | Macroadenomas: 2 of 3 cases | *No change (1 case)*<br>• Treated with continuous octreotide throughout pregnancy<br>*Increased size (2 cases)*<br>• Extensive enlargement during pregnancy despite continuation of bromocriptine<br>• Increased at 6 months of pregnancy and octreotide withdrawal, reduction back toward baseline after octreotide reintroduction |

Patients may have had multiple pregnancies.
Values shown are from cohort studies, case series, and case reports with an overall very low quality of evidence.
Data from Luger et al. (2021) (311), Lambert et al. (2017) (328), Huang et al. (2019) (316), and Molitch (2015) (315).

Prior to conception, a pituitary MRI obtained at baseline serves to guide subsequent management (318). Clinical examination each trimester for microadenomas and visual field exams for macroprolactinoma are warranted (311). Pituitary MRI without contrast should be undertaken in pregnant women with persistent headaches and/or vision changes and for those with macroadenoma. MRI without contrast (T1 and T2) has been suggested at 28 to 32 weeks, as T2-hypointense prolactinomas seem to be more prone to growth during pregnancy than hyperintense adenomas (312). Safety data on women with resistant prolactinomas requiring high cabergoline doses is lacking.

For large/invasive macroadenomas, continuation of dopamine agonist during pregnancy and frequent monitoring should be planned. In contrast to earlier recommendations, only routine endocrine follow-up has recently been recommended in pregnant women with small intrasellar microprolactinomas and normal prepartum pituitary function (311). In most patients with rapidly enlarging adenomas, dopamine agonist reinitiation controls tumor growth and surgery is rarely necessary (319). Induced delivery may be an option if pregnancy is sufficiently mature. Most women with prolactinomas can deliver vaginally, although preplanning for cesarean section should be considered if optic chiasm abutment is a risk. Rarely, postpartum imaging may reveal macroprolactinoma shrinkage or hemorrhage (309).

### Somatotroph adenomas

Preconception assessment of disease activity, comorbidities, and fertility status in women with acromegaly is required. Pregnancy could, in rare cases, trigger growth of a GH-secreting adenoma, especially mixed lactotroph-somatotroph or mammosomatotroph phenotypes; withholding SRLs in patients with known acromegaly can also induce rebound adenoma growth (320).

In newly diagnosed acromegaly patients with mildly elevated IGF-1 levels or in those who underwent surgical tumor resection, IGF-1 levels will usually decrease during pregnancy as high estrogen levels increase GH hepatic resistance. Frequently, symptoms improve considerably during the first half of pregnancy. Symptomatic adenoma growth in pregnant women with acromegaly occurs in ~7% (95% CI, 3.3%-12.9%) (311). However, GH and IGF-1 levels do not correlate with tumor growth. Comorbidities associated with acromegaly should be closely monitored as risk for hypertension and diabetes are increased (321). Indeed, gestational diabetes in women with acromegaly is more common than in those without acromegaly (322).

### Corticotroph adenomas

Corticotroph adenomas may express estrogen receptors, yet direct proliferative effect of estrogens has not been described. Although more than 25% of women of reproductive age with Cushing's disease exhibited hypercortisolism within 1 year of childbirth (323), it is unclear whether this is due to pituitary corticotroph hyperactivity in the peripartum period or rather increased frequency of Cushing's disease in young women (1). A large retrospective study found that both plasma ACTH and pituitary adenoma volume may increase during pregnancy in patients undergoing bilateral adrenalectomy, but pregnancy does not accelerate corticotroph tumor progression per se (324).

Treatment of endogenous Cushing's syndrome during pregnancy has been reported in fewer than 200 cases (325). Maternal morbidity from hypertension, diabetes mellitus, heart failure, pre-eclampsia, and eclampsia is increased (326) as is the rate of preterm births (327). Prophylactic anticoagulation may be warranted in selected patients (311).

### Nonsecreting adenomas

Pregnancy is very rare in patients with nonsecreting adenomas as these patients have impaired gonadotrophin activity and or/hyperprolactinemia (316). A large prospective, observational, population study of more than 2000 pregnant women reported 71 pituitary macroadenomas, of which 16 were nonsecreting; microadenomas were not analyzed in this study (328). Women with pituitary adenomas were 4 years older than the comparator group ($P = 0.001$) and none undergoing pre-pregnancy surgery and/or radiotherapy experienced symptomatic tumor expansion.

Women with nonsecreting adenomas are more likely to present with features consistent with tumor expansion such as visual symptoms (RR 4.59; 95% CI, 1.48-14.3). There is no evidence for adverse pregnancy outcomes in these patients, although cesarean section was more likely among those with nonsecreting adenomas vs control (RR 2.06) (328). By contrast, in the same study, women with a macroprolactinoma were not more likely to undergo cesarean deliveries compared with control (328). Given the almost invariably benign natural history of these adenomas, routine endocrine follow-up during pregnancy has not been recommended for smaller adenomas not impinging on critical structures (311). However, this approach should be individualized based on adenoma size, location, and previous history of tumor growth and/or treatment.

### Pituitary apoplexy during pregnancy

Apoplexy and infarction risk factors during pregnancy include tumor growth with neurological and visual symptoms due to hemorrhage and infundibular and hypophyseal vessel compression. Cystic areas may reflect previous intratumoral hemorrhage and apoplexy predisposition. In a systematic review of 23 patients presenting with pituitary adenomas during pregnancy, including 12 with apoplexy (329), symptoms occurred mainly in the second trimester and included visual changes and headache. Apoplexy may occur rarely with microprolactinomas (330). Clinical suspicion requires urgent imaging, visual, and/endocrine evaluation. Treatment should be individualized; some patients with prolactinoma require observation and most require dopamine agonist reinitiation or surgery.

### Summary

A normal pregnancy course is anticipated for most patients with a pituitary adenoma. Although most adenomas are small, and pregnancy-induced enlargement is negligible, some patients may exhibit symptomatic adenoma enlargement requiring urgent management. Surgical indications include vision loss and uncontrolled hypercortisolism in patients with corticotroph adenomas. Due to the rare but serious risk of maternal and fetal morbidity and mortality, specialized care is required. Vaginal delivery is preferred in women with a microadenoma. However, for a woman with a macroadenoma with visual impairment or severe headache, most would suggest cesarean section.

## Long-term Comorbidities and Mortality Outcomes

Untreated macroadenomas enlarge by about 50% at 4 years (331). Central mass effects caused by pituitary macroadenomas may cause local compression with invasion, leading to cranial nerve defects and impaired pituitary function, particularly among those with nonsecreting adenomas (332, 333). Additional comorbidities may arise from inappropriate hormone replacement in patients with hypopituitarism, especially overtreatment with glucocorticoids (334) or thyroid hormones (335), leading to increased cardiovascular, metabolic, and bone comorbidities (336, 337) as well as mortality (338). Postsurgical regrowth of nonfunctioning adenomas and apoplexy may also occur (339). As most secreting adenomas express cell surface receptors for hypothalamic neuropeptides controlling hormone secretion and adenoma growth, selective ligands have been developed for therapy. Most PRL- and GH-secreting adenomas, and some ACTH- and TSH-secreting adenomas, respond well to medical therapy, which can provide sustained biochemical and tumor growth control (2, 340, 341). For example, although prolactinomas in middle-aged men are often large and highly invasive, they shrink remarkably after dopamine agonist therapy, exemplifying the benign nature of the adenomatous proliferation (Fig. 8).

### Prolactinoma

Prolactinoma is the most frequently encountered adenoma in clinical practice and are most frequently diagnosed in women of reproductive age presenting with menstrual irregularities and no other comorbidities (343). Due to the effectiveness of dopamine agonist therapy, few patients require other treatments to control hyperprolactinemia (319). However, diagnosis may be delayed, particularly in men who, unlike young women, often present with macroadenoma and mass-associated comorbidities rather than features of hyperprolactinemia (343). As higher doses of dopamine agonist therapy may be required for disease control, men may also be more at risk for adverse effects, including impulse disorders, which can impact treatment adherence (344).

#### Cardiometabolic comorbidities

The prevalence of metabolic syndrome is increased in patients with prolactinoma (345). Body mass index, fat mass (males only), and LDL cholesterol are increased, and HDL cholesterol is reduced compared with controls (346). The cause is not clear but may be due to hypogonadism induced by hyperprolactinemia as well as the action of PRL on key enzymes and transporters associated with glucose and lipid metabolism (343). Treatment with dopamine agonists may improve components of the metabolic syndrome in these patients (346).

#### Musculoskeletal comorbidities

Skeletal fragility occurs commonly, usually manifesting as reduced lumbar spine bone mineral density affecting trabecular more than cortical bone (347). There is a high prevalence (> 30%) of morphometric vertebral fractures and a 5-fold increased fracture rate in both women and men with prolactinomas compared with a control population (348, 349). Hypogonadism arising from hyperprolactinemia and PRL excess, per se, both contribute to bone loss. Low bone mineral density attributable to hypogonadism, longer disease duration, and elevated PRL levels is associated with fracture risk (347).

#### Mortality

Few studies have addressed mortality in prolactinomas. In a single study based on a National Health Insurance database from South Korea, there was no reported increase in the standardized mortality ratio of 136 patients followed over 10 years (350).

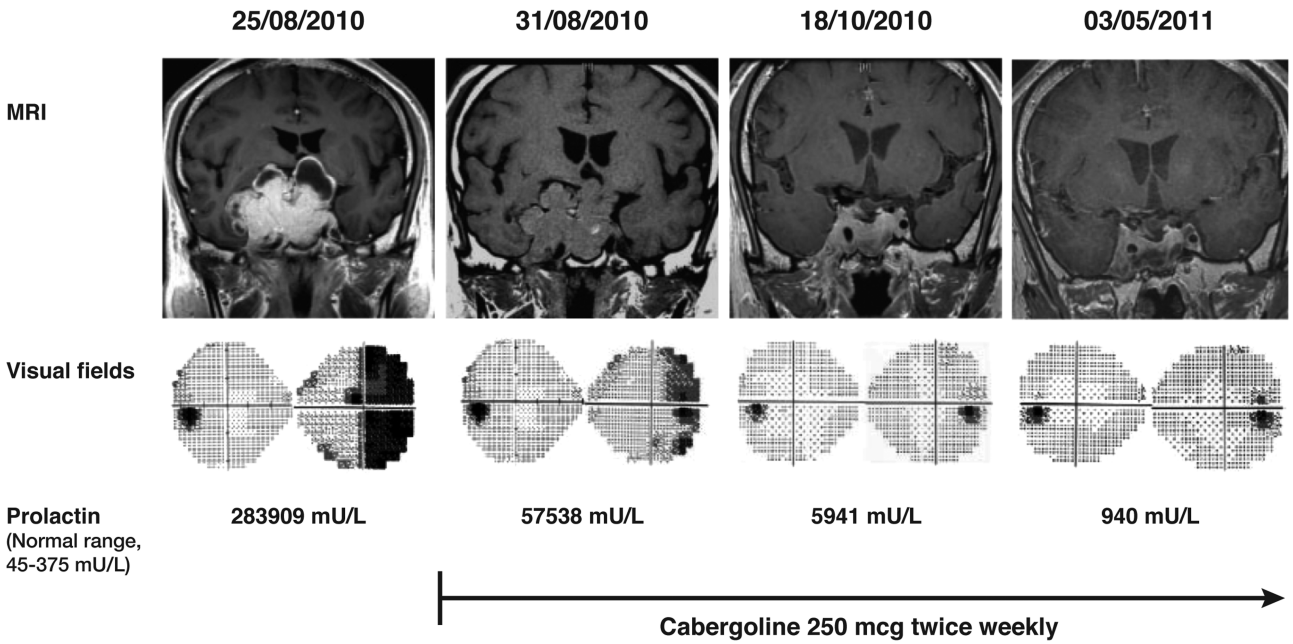



**Figure 8.** Cabergoline-induced shrinkage of a prolactinoma. Sequential MRIs, PRL levels, and visual fields over approximately 6 months of cabergoline treatment in a 27-year-old male with a 5 cm PRL-secreting tumor in the sphenoid with bilateral cavernous sinus extension and posterior extension to the clivus. Reprinted with permission from Dash et al. (2013) (342).

## Acromegaly

Diagnostic delay contributes to long-term comorbidities and increases mortality in patients with acromegaly. This delay leads to increased risk of tumor growth, mass effects, hypopituitarism (351, 352), and poor disease control despite surgery, radiation therapy, and medical therapy (353) (Fig. 9).

### Cardiometabolic and respiratory comorbidities

Cardiovascular morbidity has fallen in recent years because of earlier diagnosis, improved treatment (238), and increased awareness (354). Indeed, cardiovascular disease is no longer the leading cause of death in these patients (238, 239, 355). Hypertension, variably affecting 30% to 60% of patients, is a strong contributor to cardiovascular mortality (356). Increased sodium and water retention and plasma volume (357) may persist despite biochemical control (358, 359), and left ventricular hypertrophy, seen even in normotensive subjects, and more rarely, arrhythmia, often with prolonged QT interval, heart failure, and regurgitative valve disease, are all encountered (360). Ischemic heart disease prevalence is not markedly increased (361).

The cardiorespiratory response to exercise is reduced (362) and obstructive sleep apnea affects more than two-thirds of newly diagnosed patients, mainly due to pharyngeal soft tissue swelling (363). Sleep apnea is an independent cardiovascular risk factor (364) that may persist after acromegaly therapy (365).

Up to half of patients have impaired glucose tolerance and diabetes mellitus (366) due to GH-mediated insulin resistance and long-term decreased pancreatic insulin reserve (367). Diabetes mellitus increases cardiovascular mortality (368) and influences the choice of medical therapy, with pegvisomant generally preferred to the SRL pasireotide due to a greater risk for hyperglycemia with use of pasireotide (369).

### Musculoskeletal comorbidities

Arthropathy in acromegaly results from cartilage hypertrophy and osteophyte growth that narrow joint spaces. Arthropathic pain, a symptom of progressive joint degeneration, is a major determinant of reduced quality of life, often leading to important loss of function over time (370). Patients often experience bilateral carpal tunnel syndrome due to median nerve enlargement (371). Morphometric vertebral fractures affect more than half of patients with active disease, who have a 3- to 8-fold higher prevalence than that of the general population (372). The risk of fracture is reduced with improved biochemical control (373) and is not affected by bone density and gonadal status (374).

### Oncological comorbidities

Due to the pro-proliferative action of GH and IGF-1, there has been intense interest as to whether cancer rates are increased in acromegaly. The incidence of colorectal and renal cancer is increased, with a standardized incidence ratio of 1.5 and 4, respectively, reported in a recent Swedish registry study. However increased screening frequency may be a confounding factor because cancer-specific mortality rates were not increased (375). Excess mortality due to cancer may therefore be more closely linked to increased life expectancy in acromegaly rather than GH/IGF-1 excess per se (376).

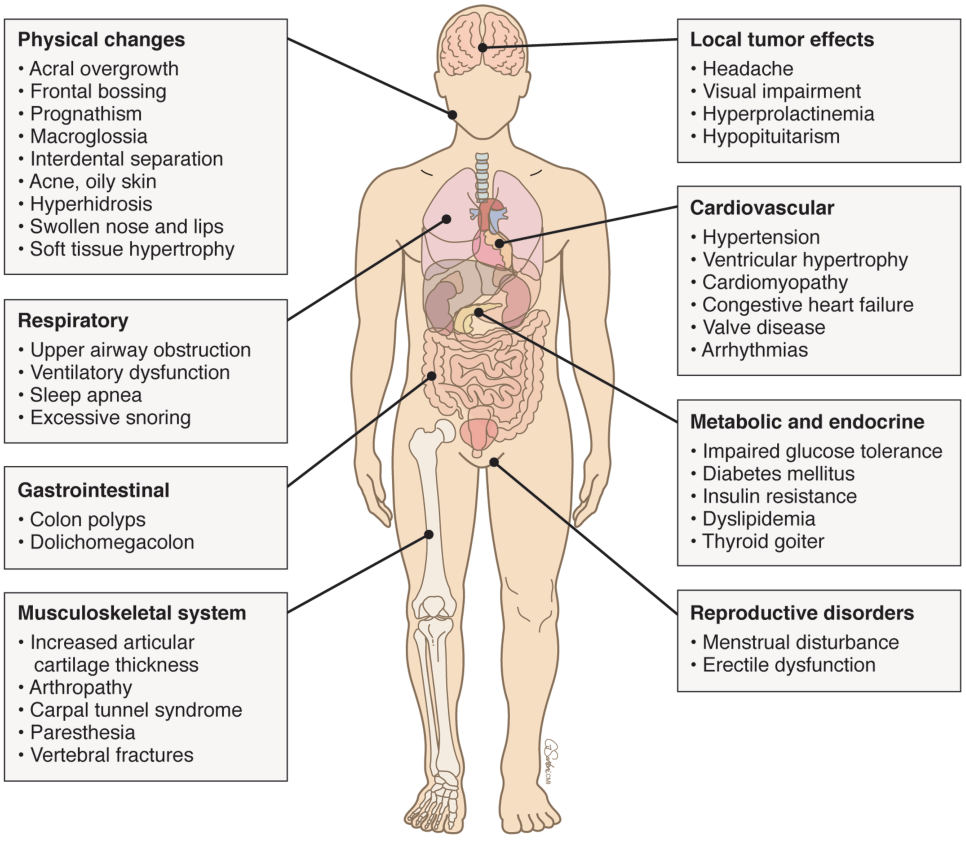



**Figure 9.** Clinical features of acromegaly.

### Mortality

The mortality rate in acromegaly has decreased in comparison to previously reported rates (355). However, there is still an excess mortality compared to the general population, with recent reports of standardized mortality ratio ranging from 1.41 to 1.45 (250, 352, 377). Last recorded GH or IGF-1 level (378), diagnostic delay (352), and disease duration (377) are mortality determinants.

## Cushing's Disease

Patients with Cushing's disease are often diagnosed when the pituitary adenoma is barely visible, and selective surgical removal of the microadenoma may be difficult (379). Furthermore, in patients with persistent disease after unsuccessful surgery, medical treatment is often not effective in achieving long-term biochemical control (380). Therefore, long-term comorbidities may occur, adversely impacting quality of life and survival (381) (Fig. 10).

### Cardiometabolic comorbidities

Because of an inherent hypercoagulable state, patients with Cushing's disease have > 10-fold increased risk of thromboembolic events compared with the general population (382). Activated partial thromboplastin times are shortened, and high circulating levels of fibrinogen and factor VIII, as well as impaired fibrinolysis, all contribute to the increased risk (383).

Cardiovascular risk is also increased as most patients are overweight or obese, exhibiting increased visceral, subcutaneous, and total fat mass and decreased lean mass (384). These changes may also be mediated by glucocorticoid-induced central GH suppression (385). More than one-third of Cushing's disease patients have diabetes mellitus (386) and more than half are dyslipidemic, with elevated triglycerides and LDL cholesterol and reduced HDL cholesterol (387). Patients are often hypertensive and have left ventricular hypertrophy, heart failure, and dilated cardiomyopathy (388).

### Musculoskeletal comorbidities

Up to 50% of patients develop bone fractures, mostly vertebral. Fractures are often detected early in the course of the disease and may be seen at a subclinical stage using vertebral morphometry (389). Skeletal fragility due to long-term suppressed bone formation may be a direct result of cortisol excess or an indirect effect of suppressed GH/IGF-1 and hypothalamic-pituitary-gonadal axes as well as disrupted PTH pulsatility (390). Fractures may occur with normal bone mineral density as the quality of bone is deleteriously affected by cortisol excess (391) The protein catabolism of hypercortisolism causes myopathy, reducing physical capacity and function and quality of life. Myopathy may not recover after successful surgery in patients with low IGF-1 (392, 393).

### Infections

Immune function is suppressed, increasing susceptibility to sepsis and opportunistic infections (394) reported in up to 50% as a result of immunosuppression and altered immune responses (395). Cushing's disease may also be a predisposing factor for SARS-CoV-2 infection and severe COVID-19 (396).

### Psychiatric disturbances

Psychiatric and neurocognitive symptoms, including depression and anxiety, mania, and psychosis, are common

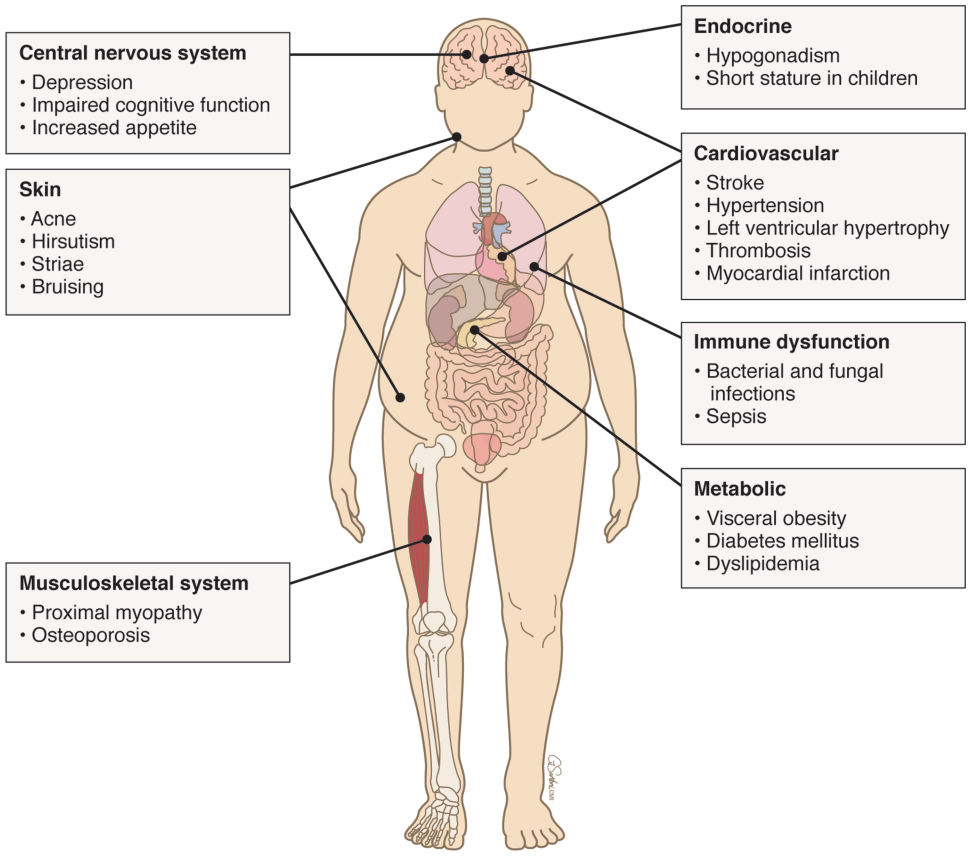



**Figure 10.** Clinical features of Cushing's disease.

complications that reduce quality of life, and memory and attention may also be impaired. Depression and cognitive dysfunction may persist after treatment (397).

#### Mortality

The standardized mortality ratio is increased from 4- to 16-fold in patients with active/persistent Cushing's disease compared with the general population, mainly from myocardial infarction and stroke (398). Recent epidemiological results show that death due to cardiovascular disease was increased > 4-fold and mortality rate was 5-fold higher among those with diabetes mellitus and 7-fold higher with persistent hypercortisolism (399). Risk did not revert to normal with disease remission (400).

### Thyrotrophinoma

TSH-secreting adenomas are very rare, causing secondary hyperthyroidism, which is frequently misdiagnosed. Patients usually present with macroadenomas, and in one-third, co-manifestation of plurihormonal (often GH) secretion is observed (401). Response to medical therapy with SRLs is often favorable and can be used as a diagnostic test (401). However, not infrequently, despite surgery and SRL therapy, disease control remains suboptimal (402). Patients may experience cardiac complications such as atrial fibrillation (403), increasing the risk of stroke (350). In a retrospective case series, more than half of patients showed morphometrical vertebral fractures associated with age and serum free T4, but not with TSH levels (404). Patients with adenomas co-secreting TSH and ACTH have an increased a standardized mortality ratio of 1.9 compared with the general population (350).

## Summation and Conclusion

The anterior pituitary gland develops from a range of complex brain signals integrating with intrinsic transcriptional events that together determine cell type differentiation and hormonal secretion, in turn regulating somatic growth, metabolism, nutrition, reproduction, and physical health. Although pituitary adenomas are common, the overwhelming majority remain indolent throughout life, with malignant transformation an extremely rare exception. Mechanisms underlying pathogenesis of these adenomas likely include disrupted intrapituitary signaling pathways promoting benign cell proliferation associated with chromosomal instability, with cellular senescence acting as a protective buffer against progression to malignancy.

Although representing less than one-thousandth of all pituitary adenomas, clinically relevant tumors variably and adversely affect morbidity and mortality depending on cell type, hormone secretory activity, and growth pattern. In most cases, multimodal therapy controlling hormone secretion and adenoma growth will lead to improved quality of life and a normalization of mortality rates to the same as that of the general population. The clinical biology of pituitary adenomas and particularly their benign nature stands in marked contrast to other tumors of the endocrine system such as thyroid (405) and neuroendocrine tumors (406).

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