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Genomic Alterations in Sporadic Pituitary Tumors

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Abstract

Purpose of Review Pituitary tumors are undergoing a transformation in histopathologic and molecular classification, coincident with the continued refinement of increasingly powerful methods of genomic annotation and discovery. We highlight novel genomic alterations identified in pituitary adenomas and craniopharyngiomas and discuss their clinical implications.

Recent Findings Sporadic pituitary adenomas are associated with relatively few recurrent somatic mutations. Recurrent mutations occur largely in subsets of hormone-producing tumors, including *GNAS* and *GPR101* in somatotroph adenomas and *USP8* in corticotroph adenomas. Additionally, they manifest with a dichotomous signature of copy number alterations, ranging from almost none to widespread genome instability, while microduplication of chromosome Xq26.3, containing the *GNAS* gene, defines X-linked acrogigantism. Papillary craniopharyngiomas are defined by $BRAF^{V600E}$ mutations while β-*catenin* alterations characterize adamantinomatous craniopharyngiomas.

Summary Genomic annotation of pituitary tumors is defining increasing subsets of neuroendocrine adenohypophyseal tumors and craniopharyngiomas, offering rationale-based pharmacologic targets and potential biomarkers for clinical outcome.

Keywords Pituitary adenoma · Craniopharyngioma · Genomics · Precision medicine

Introduction

Tumors of the pituitary region are among the most common of the primary brain tumors. Adenomas of the pituitary, while generally non-cancerous, may still cause significant morbidity, through either elaboration of supraphysiologic levels of hormones, compression and subsequent hypofunction of the pituitary gland, or growth and compression of sensitive adjacent neurologic and vascular anatomy. As common as they are—and for as long as they have been described, which dates to nearly the dawn of modern neurological surgery—the sentinel genetic events which drive their origin have been poorly characterized. In an era where genomic annotation of human tumors is revolutionizing our understanding of biological mechanisms and uncloaking new therapeutic approaches, pituitary tumors are just now becoming defined by their molecular features. This is especially timely as pituitary adenomas are undergoing a reappraisal of their pathologic classification, and additional classifiers and predictors of aggressive behavior are being sought.

We herein review the contemporary understanding of the genomic architecture of pituitary adenomas and craniopharyngiomas, highlighting important clinically relevant alterations where possible.

Pituitary Gland

The pituitary gland serves as a nexus of embryologic tissues and cell types, leading to a variety of tumor lineages. The anterior pituitary gland, or adenohypophysis, derives from Rathke's pouch, which is formed from an upward invagination of oral ectoderm, while the posterior pituitary gland, or neurohypophysis, derives from neuroectodermal floor of the diencephalon. The anterior pituitary contains five primary hormone-secreting cellular lineages that are distinct in structure and function. These corticotroph, lactotroph, somatotroph, thyrotroph, and gonadotroph cells are topologically arranged and secrete adrenocorticotropic hormone (ACTH), prolactin (PRL), growth hormone (GH),

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thyroid-stimulating hormone (TSH) and gonadotropins (follicle-stimulating hormone [FSH], and luteinizing hormone [LH]), respectively. Additional populations of adenohypophyseal cells secrete no hormones or more than one hormone from the same cell. The posterior pituitary stores and secretes two hormones, vasopressin and oxytocin, that are produced by the supraoptic and paraventricular nuclei of the hypothalamus.

Tumors of the Anterior Pituitary

Classification

Tumors of the pituitary gland are undergoing a transformation in classification, as codified by updates in the 2017 World Health Organization (WHO) scheme [1•, 2, 3]. Tumors of the adenohypophysis, which account for the majority of pituitary neoplasms, have been traditionally classified by their immunohistochemical hormone profile, histopathologic features, and ultrastructural features. Additionally, renewed focus on the role of transcription factors (TF) in defining adenohypophyseal cell lineage has been incorporated into the formal classification criteria (Fig. 1).

Specifically, the adenohypophyseal progenitor cell differentiates into three lineages: acidophilic, corticotroph, and gonadotroph. The acidophilic lineage further differentiates into somatotroph, lactotroph, and thyrotroph cells, marked by expression of additional TFs and hormones. The diagnosis of cell lineage-associated adenoma subtypes requires a combination of hormone and transcription factor expression, while a null cell adenoma is defined by absence of adenohypophyseal hormones and transcription factors (Fig. 1).

Within the codified neuroendocrine adenomas, the WHO highlighted five subtypes that have demonstrated increased propensity for clinical aggressiveness in terms of rapid growth, early recurrence, resistance to treatment, and increased proliferative index. These are the sparsely granulated somatotroph adenoma, silent corticotroph adenoma, lactotroph adenoma in men, plurihormonal PIT-1 positive adenoma, and Crooke's cell adenoma (Table 1).

Sparsely granulated somatotroph adenomas express GH and pituitary-specific POU-class homeodomain transcription factor (PIT-1). The tumors are reactive to cytokeratin staining, which distinguishes them from other somatotroph morphological variants, although consistent interpretation of staining patterns can be challenging in practice at times. Both silent corticotroph and Crooke's cell adenoma express ACTH and the T-box family member TBX19 transcription factor (T-PIT).

Fig. 1 Significant transcription factor expression and hormone staining in adenoma classes and subclasses. *ACTH* adrenocorticotropic hormone, *ERα* estrogen receptor α, *GH* growth hormone, *β-LH* luteinizing hormone, *PIT-1* pituitary-specific POU-class homeodomain transcription factor, *PRL* prolactin, *SF-1* steroidogenic factor 1, *TF* transcription factor, *T-PIT* T-box family member TBX19, *β-TSH* thyroid-stimulating hormone

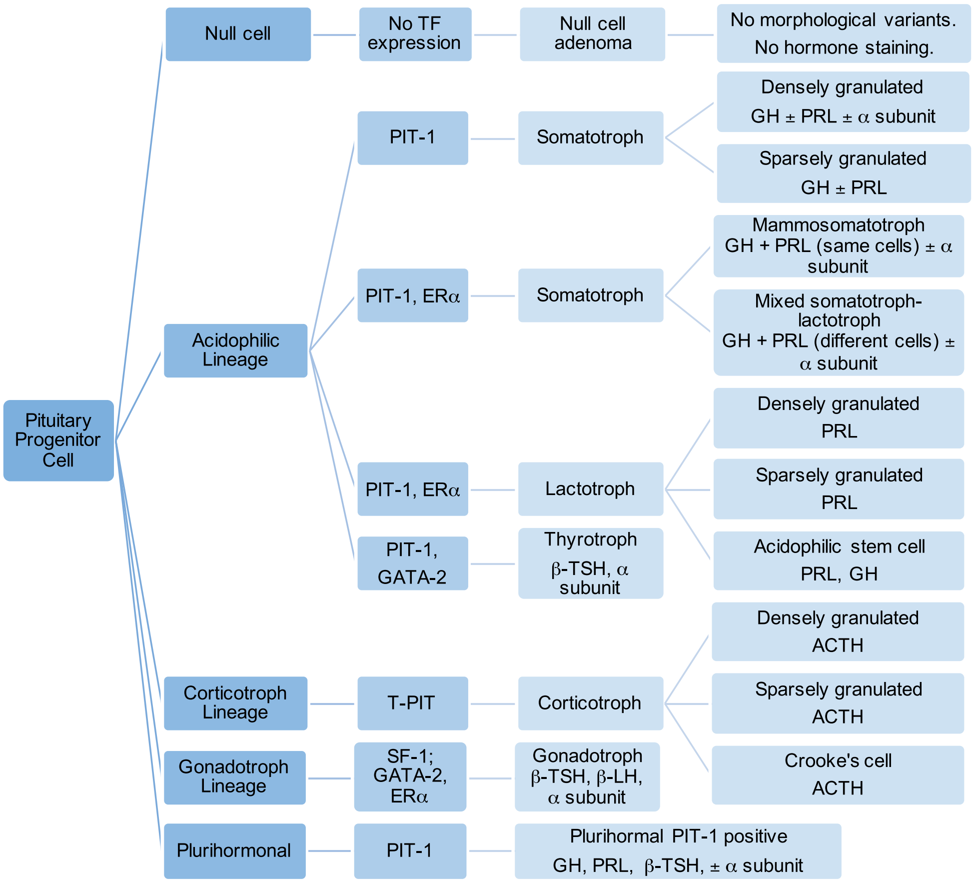

Table 1 Pituitary neuroendocrine tumors with increased risk of clinically aggressive behavior

	TF expression	Hormone expression	Other histopathological features
Sparsely granulated somatotroph	PIT-1	GH ± PRL	CK positive. Other somatotroph subtypes do not express CK
Silent corticotroph	T-PIT	± ACTH	Clinically non-functional. Expression of ACTH can vary. T-PIT is expressed uniformly
Lactotroph in men	PIT-1, ERα	PRL	
Plurihormonal Pit-1 positive	PIT-1	± GH, ± PRL, ± β-TSH, ± α subunit	Varying hormone secretion and functional status
Crooke cell adenoma	T-PIT	ACTH	> 60% of cells have Crooke's hyaline change (cytokeratin deposited in ring-like shape)

ACTH adrenocorticotropic hormone, *CK* cytokeratin, *ERα* estrogen receptor α, *GH* growth hormone, *β-LH* luteinizing hormone, *PIT-1* pituitary-specific POU-class homeodomain transcription factor, *PRL* prolactin, *SF-1* steroidogenic factor 1, *TF* transcription factor, *T-PIT* T-box family member TBX19, *β-TSH* thyroid-stimulating hormone

Silent corticotrophs are considered non-functional, with absence of clinically apparent sequelae from hormone overproduction, and have variable immunohistochemical expression of ACTH. Crooke's cell adenomas contain a preponderance of cells with Crooke's hyaline change, which demonstrates perinuclear reactivity to cytokeratin in a ring-like shape. Plurihormonal PIT-1 positive adenomas express GH, PRL, β-TSH, and PIT-1. These tumors were formally known as silent subtype 3 adenomas but were reclassified because of varying hormone secretion and clinical functional status observed in patients with this tumor.

Additionally, appreciation for variability in the clinical behavior of pituitary tumors has led to a proposal to shift the terminology from adenoma, which implies a benign nature of the lesion, to tumor, and cessation of the "atypical" designation, given its inability to accurately and consistently predict aggressive clinical behavior [1•, 2, 3]. Assessment of tumor proliferation and tumor invasiveness remains recommended for individual cases of clinically aggressiveness tumors. However, more objective markers for tumor behavior and clinical outcome remain to be defined for pituitary adenomas.

Mutations

Given the inconsistent correlation of traditional histopathologic classifications with the natural history of pituitary tumors, increased efforts have centered upon understanding the genetic and cellular origins of pituitary tumors. Hereditary syndromes, including multiple endocrine neoplasia type I (MEN1), MEN4, familial isolated pituitary adenomas (FIPA), McCune-Albright syndrome, and Carney complex, have long suggested a link between discrete genetic causes and pituitary tumors. In addition to germline mutations in *AIP* [4, 5], *MEN1* [6, 7], *CDKN1B* [8, 9], and *PRKAR1A*, which have been associated with these familial syndromes, next-generation sequencing of pituitary adenomas has identified several somatic genomic alterations associated with specific tumor subtypes [10, 11•, 12•, 13•].

Observation of recurrent mutations in the catalytic subunit of protein kinase A in cortisol-producing adenomas of the adrenal cortex prompted application of a similar whole-exome sequencing strategy for Cushing's disease, with identification of mutations in the deubiquitinase *USP8* in a third to two-thirds of pituitary corticotroph adenomas [11•, 12•]. USP8 contributes to lysosomal trafficking of ligand-activated epidermal growth factor receptor (EGFR). Gain-of-function mutations in *USP8* inhibit EGFR endocytosis, leading to increased EGFR stimulation of *Pomc* gene transcription and increased ACTH secretion [12•, 14]. Interestingly, while USP8 is exclusively localized to the nucleus in mutant adenomas, non-mutant tumors can manifest with either cytoplasmic or nuclear expression, suggestive of alternative mechanisms other than mutation leading to subcellular compartmentalization and activation of USP8 [12•]. Furthermore, *USP8* mutations have been associated with increased expression of somatostatin reception 5 (SSTR5) and O^6-methylguanine DNA methyl-transferase (MGMT) [14]. Collectively, these data support a therapeutic role for EGFR inhibition and somatostatin analogues in *USP8*-mutated corticotroph adenomas.

In somatotroph adenomas, recurrent somatic mutations in the gene encoding the stimulatory G-protein α subunit, *GNAS*, are identified in a third of tumors [15–18]. This is concordant with the causative role of *GNAS* mutations in McCune-Albright syndrome, which is associated with acromegaly, and leads to constitutive activation of the cyclic AMP (cAMP) mitogenic pathway. Other mutations in scattered genes involved in cAMP signaling have also been reported, although not at a significantly recurrent incidence [18].

Additionally, a recurrent somatic mutation in the G-protein coupled receptor, $GPR101^{E308D}$, has been reported in approximately 4.4% of acromegaly patients [13•]. Introduction of this mutation into a rat GH-secreting cell line produced increased proliferation and GH secretion in vitro. *GPR101* resides on chromosome Xq26.3, and microduplication of this locus is implicated as the cause of X-linked acrogigantism in children [13•].

On the whole, recurrent mutations are sparse across the majority of sporadic pituitary adenomas, including the most common subtype, null cell adenomas [10]. This suggests alternative biological mechanisms that contribute to pituitary tumorigenesis, including copy number alterations, rearrangements, and epigenetic changes [10, 19•, 20].

Chromosomal Alterations

Beyond somatic and germline mutations associated with pituitary adenomas, genomic profiling points to two distinct classes of pituitary adenomas based on their level of copy number alterations [19•]. One class harbors almost no chromosomal alterations, while the other is marked by widespread genomic disruption (Fig. 2). Compared to most other tumor types, focal gains and losses are rare relative to broad arm-level chromosomal alterations in pituitary adenomas, the significance of which remains to be elucidated [19•].

While the genomically quiet cohort is enriched for null cell adenomas and the genomically disrupted cohort has a relatively higher fraction of hormone-expressing adenomas, this association is not consistent [21]. Silent corticotroph adenoma and prolactinoma express a particularly high frequency of genome disruption in small series [21]. However, the threshold for and incidence of genome disruption in adenomas merit closer inspection in larger cohorts to better define possible associations with high-risk adenoma subtypes and clinical outcome [10, 19•, 21].

Mutation Signatures of Craniopharyngioma

The molecular landscape of the craniopharyngioma, like pituitary adenoma, has also been subjected to genomic profiling—with some of the findings bearing immediate therapeutic relevance. Craniopharyngiomas, arising from the pituitary stalk, are among the most challenging of intracranial tumors to manage because of their pattern of growth, associated morbidities, and high recurrence rate. Radiotherapy and chemotherapy provide adjuvant treatment options, but many cases remain refractory despite aggressive treatment and re-treatment. Of the two histological subtypes, adamantinomatous craniopharyngiomas are the most common overall, with almost exclusive representation among pediatric cases, while papillary craniopharyngiomas are predominantly observed in adults.

Strikingly, the *BRAF*^{V600E} mutations were identified in 81–95% of papillary craniopharyngiomas, illuminating a powerful target for pharmacotherapy [22•, 23]. *BRAF*^{V600E} mutation leads to overactivity of B-Raf signaling and subsequent mitogenic sequelae, an oncogenic strategy usurped by multiple tumors, including melanoma, where BRAF inhibition has led to promising extension of survival [24–26]. This has translated to successful administration of combined BRAF and MEK inhibitors in two patients with multiple recurrent papillary craniopharyngioma [27, 28].

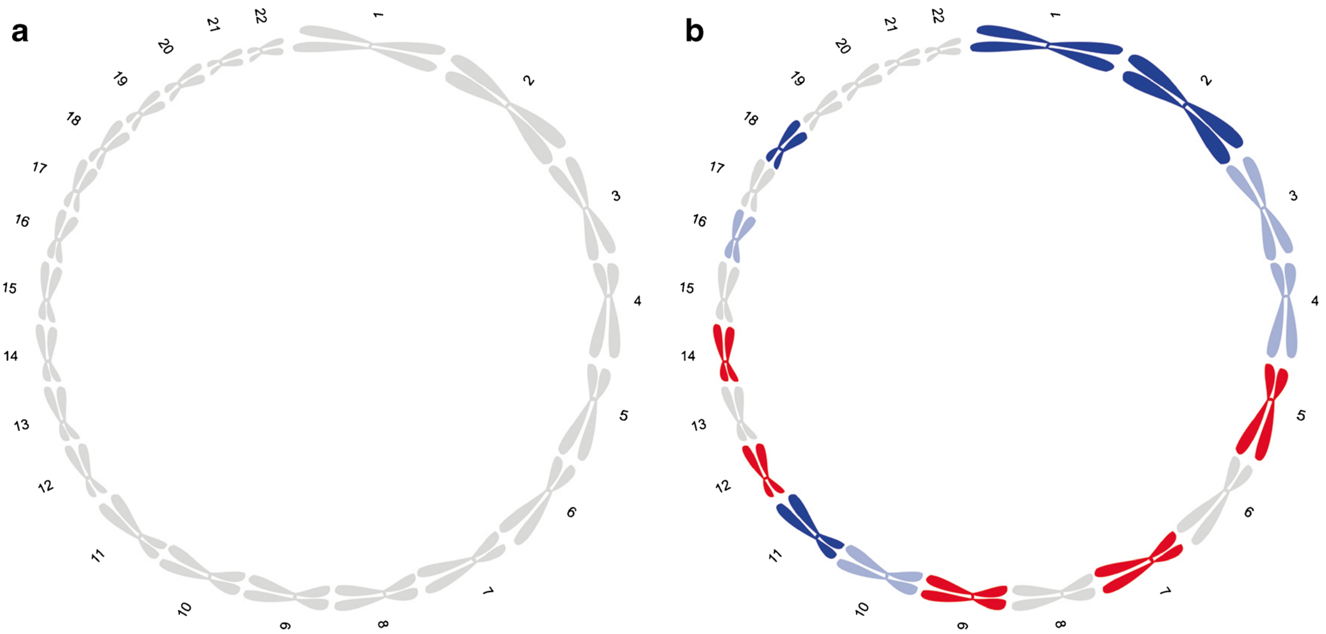

Fig. 2 Schematic of two genomic categories of pituitary adenomas, stratified by the copy number alteration burden. **a** One class harbors almost no chromosomal alterations, while **b** the other is marked by widespread copy number gains and losses in recurrently observed chromosomes. Red indicates amplification, navy blue indicates high frequency of loss, pale blue indicates lower frequency of loss, and gray indicates neutral copy number status

In comparison, the adamantinomatous subtype is characterized by near ubiquitous mutations in the β-catenin gene, *CTNNB1*, and also demonstrates disruptions in multiple growth factor signaling axes, extracellular matrix regulation, and its immune microenvironment [22•, 23]. Interestingly, co-occurrence of the *BRAF*^{V600E} mutation and *CTNNB1* mutation in two cases of adamantinomatous craniopharyngioma has been reported, suggestive of a potential shared phylogeny in the pathogenesis of select craniopharyngiomas [23].

Conclusions and Future Directions

Genomic characterization of tumor of the pituitary region—pituitary adenomas and craniopharyngiomas in particular—has shed new insights into pharmacologic mutational targets as well as unique copy number alterations. As molecular profiling becomes incorporated into routine clinical practice, elucidation of the epidemiologic associations and prognostic consequences of genomic and epigenomic signatures may yield new insights into the ontology of tumors in this area, the relationship of specific genomic profiles to growth and recurrence, and the prospect of tailored management strategies for patients as the scope of therapeutic targets broadens.

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Compliance with Ethical Standards

Conflict of Interest Wenya Linda Bi, Alexandra Giantini Larsen, and Ian F. Dunn declare no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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