Table 24-1 Classification of Pituitary Adenomas

Pituitary Cell Type	Hormone	Adenoma Subtypes	Associated Syndrome*
Lactotroph	Prolactin	Lactotroph adenoma Silent lactotroph adenoma	Galactorrhea and amenorrhea (in females) Sexual dysfunction, infertility
Somatotroph	GH	Densely granulated somatotroph adenoma Sparsely granulated somatotroph adenoma Silent somatotroph adenoma	Gigantism (children) Acromegaly (adults)
Mammosomatotroph	Prolactin, GH	Mammosomatotroph adenomas	Combined features of GH and prolactin excess
Corticotroph	ACTH and other POMC-derived peptides	Densely granulated corticotroph adenoma Sparsely granulated corticotroph adenoma Silent corticotroph adenoma	Cushing syndrome Nelson syndrome
Thyrotroph	TSH	Thyrotroph adenomas Silent thyrotroph adenomas	Hyperthyroidism
Gonadotroph	FSH, LH	Gonadotroph adenomas Silent gonadotroph adenomas ("null cell," oncocytic adenomas)	Hypogonadism, mass effects, and hypopituitarism

ACTH, Adrenocorticotrophic hormone; FSH, follicle-stimulating hormone; GH, growth hormone; LH, luteinizing hormone; POMC, pro-opiomelanocortin; TSH, thyroid-stimulating hormone.
*Note that nonfunctional (silent) adenomas in each category express the corresponding hormone(s) within the neoplastic cells, as determined by special immunohistochemical staining on tissues. However, these adenomas do not produce the associated clinical syndrome, and typically present with *mass effects* accompanied by *hypopituitarism* due to destruction of normal pituitary parenchyma. These features are particularly common with gonadotroph adenomas.
Partially adapted from Asa SL, Essat S: The pathogenesis of pituitary tumors. Annu Rev Pathol Medch Dis 4:97; 2009.

exceed 1 cm in diameter. Non-functional adenomas are likely to come to clinical attention at a later stage than those associated with endocrine abnormalities and are therefore more likely to be macroadenomas. Based on autopsy studies, the prevalence of pituitary adenomas in the population is estimated to be about 14%, but the vast majority of these lesions are clinically silent microadenomas ("pituitary incidentaloma").

With recent advances in molecular techniques, substantial insight has been gained into *the genetic abnormalities associated with pituitary adenomas* (Table 24-2):

- **G-protein mutations are one of the most common alterations in pituitary adenomas**. G proteins are described in Chapter 1; here their function in the context of endocrine neoplasms is reviewed. G proteins play a

Table 24-2 Genetic Alterations in Pituitary Tumors

Gene	Protein Function	Mechanism of Alteration	Most Commonly Associated Pituitary Tumor
Gain of Function			
GNAS	GNAS encodes for alpha subunit of stimulatory G-protein, Gsα. Oncogenic mutation of GNAS constitutively activates Gsα, leading to upregulation of intracellular cyclic AMP (cAMP) activity	Activating mutation	GH adenomas
Protein kinase A, regulatory subunit 1 (PRKAR1A)*	*PRKAR1A* encodes for a negative regulator of protein kinase A (PKA), a downstream mediator of cAMP signaling. Loss of PKA regulation leads to inappropriate cAMP activity	Germline inactivating mutations of *PRKARIA* are present in autosomal dominant Carney complex	GH and prolactin adenomas
Cyclin D1	Cell cycle regulatory protein; promotes G1-S transition	Overexpression	Aggressive adenomas
HRAS	Ras regulates multiple oncogenic pathways including proliferation, cell survival and metabolism	Activating mutation	Pituitary carcinomas
Loss of Function			
MEN1*	MEN1 encodes for menin, a protein with protean roles in tumor suppression, including repression of oncogenic transcription factor JunD, and in histone modification.	Germline inactivating mutations of *MEN1* (multiple endocrine neoplasia, type 1)	GH, prolactin, and ACTH adenomas
CDKN1B (p27/KIP1)*	The p27 protein is a negative regulator of the cell cycle	Germline inactivating mutations of CDKN1B ("MEN-1-like" syndrome)	ACTH adenomas
Aryl hydrocarbon receptor interacting protein (AIP)*	Receptor for aryl hydrocarbons and a ligand-activated transcription factor	Germline mutations of *AIP* cause pituitary adenoma predisposition [PAP] syndrome	GH adenomas (especially in patients younger than 35 years of age)
Retinoblastoma (RB)	Retinoblastoma protein is a negative regulator of the cell cycle (Chapter 7)	Methylation of *RB* gene promoter	Aggressive adenomas

ACTH, Adrenocorticotrophic hormone; GH, growth hormone.
*Genetic alterations associated with *familial* predisposition to pituitary adenomas.
Partially adapted from Boikos SA, Stratakis CA: Molecular genetics of the cAMP-dependent protein kinase pathway and of sporadic pituitary tumorigenesis. Hum Mol Genet 16:R80-R87, 2007.