Genetics of Cushing's Syndrome

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KEYWORDS

• Cushing's syndrome • Glucocorticoids • ACTH • Corticotropinoma
• Pituitary adenoma • Adrenal hyperplasia • cAMP • *USP8*

KEY POINTS

- Cushing's syndrome (CS) of pituitary or adrenal origin usually presents as a sporadic entity and is most commonly due to somatic gene defects.
- Cortisol-producing adenomas are the most common cause of adrenal CS and these lesions are frequently caused by somatic activating mutations in the *PRKACA* gene.
- Somatic gain-of-function mutations in the *USP8* gene constitute the most common genetic defect in corticotropinomas.
- Although infrequent, familial forms of CS may present either isolated or in association with various familial syndromes of multiple endocrine and nonendocrine neoplasia.
- Understanding the genetic defects that drive corticotroph and adrenocortical tumorigenesis should lead to unraveling novel therapeutic targets, which will hopefully be translated into more efficient strategies for the medical treatment of patients with CS.

INTRODUCTION

Characterized by multisystemic manifestations of hypercortisolemia, endogenous Cushing's syndrome (CS) is caused in two-thirds of cases by an adrenocorticotropic hormone (ACTH)-secreting pituitary adenoma (corticotropinoma), and in up to one-quarter of cases by benign adrenal lesions, whereas other causes are more infrequent.[1] CS may have a familial presentation, as part of various syndromes of multiple neoplasia, or present sporadically in the presence of specific germline and/or somatic gene defects (**Table 1**). Vast progress has been achieved in recent years on identifying the molecular and genetic causes of CS of adrenal and pituitary (Cushing's disease [CD]) origin. In this review, we have compiled and summarized the most relevant genetic causes of adrenal and pituitary CS so far described.

Disclosure: The authors have nothing to disclose.

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Endocrinol Metab Clin N Am 47 (2018) 275–297
https://doi.org/10.1016/j.ecl.2018.02.007
0889-8529/18/Published by Elsevier Inc.

Table 1
Causes of endogenous Cushing's syndrome and their genetic bases

Origin	Lesion Type	General Molecular Mechanisms	Clinical Presentation	Known Genetic Causes
Cushing's disease (60%–70% of cases)	Corticotropinoma	Resistance to glucocorticoid negative feedback, cell-cycle dysregulation, overexpression of membrane receptors (arginine-vasopressin receptors, epidermal growth factor receptor)	Sporadic Cushing's disease, no associated manifestations	Somatic *USP8* GOF hotspot mutations Somatic *GNAS* GOF mutations (codon 201 or 227) Somatic *RASD1* LOF mutation
			Carney complex	Germline *PRKAR1A* LOF mutations/deletions, uncharacterized defect in 2p16, *PRKACB* amplification
			Familial isolated pituitary adenoma	Germline *AIP* LOF mutations/deletions, unknown genetic defect in 80% of cases
			Familial Cushing's disease with very low penetrance?	Germline *CABLES1* LOF mutations
			Multiple endocrine neoplasia type 1	Germline *MEN1* LOF mutations/deletions
			Multiple endocrine neoplasia type 2	Germline *RET* GOF mutations
			Pheocromocytoma/paraganglioma and pituitary adenoma	
			Multiple endocrine neoplasia type 4	Germline *CDKN1B* LOF mutations/deletions
			Tuberous sclerosis	Germline *TSC1* or *TSC2* LOF mutations