TABLE 406-7 CAUSES OF PRIMARY ADRENAL INSUFFICIENCY

Diagnosis	Gene	Associated Features
Autoimmune polyglandular syndrome 1 (APS1)	*AIRE*	Hypoparathyroidism, chronic mucocutaneous candidiasis, other autoimmune disorders, rarely lymphomas
Autoimmune polyglandular syndrome 2 (APS2)	Associations with HLA-DR3, CTLA-4	Hypothyroidism, hyperthyroidism, premature ovarian failure, vitiligo, type 1 diabetes mellitus, pernicious anemia
Isolated autoimmune adrenalitis	Associations with HLA-DR3, CTLA-4	
Congenital adrenal hyperplasia (CAH)	*CYP21A2, CYP11B1, CYP17A1, HSD3B2, POR*	See Table 406-10 (see also **Chap. 410**)
Congenital lipoid adrenal hyperplasia (CLAH)	*STAR, CYP11A1*	46,XY DSD, gonadal failure (see also **Chap. 410**)
Adrenal hypoplasia congenita (AHC)	*NR0B1 (DAX-1), NR5A1 (SF-1)*	46,XY DSD, gonadal failure (see also **Chap. 410**)
Adrenoleukodystrophy (ALD), adrenomyeloneuropathy (AMN)	*X-ALD*	Demyelination of central nervous system (ALD) or spinal cord and peripheral nerves (AMN)
Familial glucocorticoid deficiency	*MC2R*	Tall stature
	MRAP	None
	STAR	None
	NNT	None
	MCM4	Growth retardation, natural killer cell deficiency
Triple A syndrome	*AAAS*	Alacrima, achalasia, neurologic impairment
Smith-Lemli-Opitz syndrome	*SLOS*	Cholesterol synthesis disorder associated with mental retardation, craniofacial malformations, growth failure
Kearns-Sayre syndrome	Mitochondrial DNA deletions	Progressive external ophthalmoplegia, pigmentary retinal degeneration, cardiac conduction defects, gonadal failure, hypoparathyroidism, type 1 diabetes,
IMAGe syndrome	*CDKN1C*	Intrauterine growth retardation, metaphyseal dysplasia, genital anomalies
Adrenal infections		Tuberculosis, HIV, CMV, cryptococcosis, histoplasmosis, coccidioidomycosis
Adrenal infiltration		Metastases, lymphomas, sarcoidosis, amyloidosis, hemochromatosis
Adrenal hemorrhage		Meningococcal sepsis (Waterhouse-Friderichsen syndrome), primary antiphospholipid syndrome
Drug-induced		Mitotane, aminoglutethimide, abiraterone, trilostane, etomidate, ketoconazole, suramin, RU486
Bilateral adrenalectomy		E.g., in the management of Cushing's or after bilateral nephrectomy

Abbreviations: AIRE, autoimmune regulator; CMV, cytomegalovirus; DSD, disordered sex development; MC2R, ACTH receptor; MCM4, mini chromosome maintenance-deficient 4 homologue; MRAP, MC2R-accessory protein; NNT, nicotinamide nucleotide transhydrogenase.

(Table 406-7); tuberculous adrenalitis is still a frequent cause of disease in developing countries. Adrenal metastases rarely cause adrenal insufficiency, and this occurs only with bilateral, bulky metastases.

Inborn causes of primary adrenal insufficiency other than congenital adrenal hyperplasia are rare, causing less than 1% of cases. However, their elucidation provides important insights into adrenal gland development and physiology. Mutations causing primary adrenal insufficiency (Table 406-7) include factors regulating adrenal development and steroidogenesis (DAX-1, SF-1), cholesterol synthesis, import and cleavage (DHCR7, StAR, CYP11A1), and elements of the adrenal ACTH response pathway (MC2R, MRAP) (Fig. 406-5), and factors involved in redox regulation (NNT) and DNA repair (MCM4, CDKN1C).

Secondary adrenal insufficiency is the consequence of dysfunction of the hypothalamic-pituitary component of the HPA axis **(Table 406-8)**. Excluding iatrogenic suppression, the overwhelming majority of cases are caused by pituitary or hypothalamic tumors or their treatment by surgery or irradiation **(Chap. 403)**. Rarer causes include pituitary apoplexy, either as a consequence of an infarcted pituitary adenoma or transient reduction in the blood supply of the pituitary during surgery or after rapid blood loss associated with parturition, also termed Sheehan's syndrome. Isolated ACTH deficiency is rarely caused by autoimmune disease or pituitary infiltration (Table 406-8). Mutations in the ACTH precursor POMC or in factors regulating pituitary development are genetic causes of ACTH deficiency (Table 406-8).

Clinical Manifestations In principle, the clinical features of primary adrenal insufficiency (Addison's disease) are characterized by the loss of both glucocorticoid and mineralocorticoid secretion **(Table 406-9)**. In secondary adrenal insufficiency, only glucocorticoid deficiency is present, as the adrenal itself is intact and thus still amenable to regulation by the RAA system. Adrenal androgen secretion is disrupted in both primary and secondary adrenal insufficiency (Table 406-9). Hypothalamic-pituitary disease can lead to additional clinical manifestations due to involvement of other endocrine axes (thyroid, gonads, growth hormone, prolactin) or visual impairment with bitemporal hemianopia caused by chiasmal compression. It is important to recognize that iatrogenic adrenal insufficiency caused by exogenous glucocorticoid suppression of the HPA axis may result in all symptoms associated with glucocorticoid deficiency (Table 406-9), if exogenous glucocorticoids are stopped abruptly. However, patients will appear clinically cushingoid as a result of the preceding overexposure to glucocorticoids.

Chronic adrenal insufficiency manifests with relatively nonspecific signs and symptoms such as fatigue and loss of energy, often resulting in delayed or missed diagnoses (e.g., as depression or anorexia). A distinguishing feature of primary adrenal insufficiency is hyperpigmentation, which is caused by excess ACTH stimulation of melanocytes. Hyperpigmentation is most pronounced in skin areas exposed to increased friction or shear stress and is increased by sunlight **(Fig. 406-15)**. Conversely, in secondary adrenal insufficiency, the skin has an alabaster-like paleness due to lack of ACTH secretion.

Hyponatremia is a characteristic biochemical feature in primary adrenal insufficiency and is found in 80% of patients at presentation. Hyperkalemia is present in 40% of patients at initial diagnosis. Hyponatremia is primarily caused by mineralocorticoid deficiency but can also occur in secondary adrenal insufficiency due to diminished inhibition of antidiuretic hormone (ADH) release by cortisol, resulting in mild syndrome of inappropriate secretion of antidiuretic hormone (SIADH). Glucocorticoid deficiency also results in slightly increased TSH concentrations that normalize within days to weeks after initiation of glucocorticoid replacement.

Acute adrenal insufficiency usually occurs after a prolonged period of nonspecific complaints and is more frequently observed in patients with primary adrenal insufficiency, due to the loss of both glucocorticoid and mineralocorticoid secretion. Postural hypotension may progress to hypovolemic shock. Adrenal insufficiency may mimic features of acute abdomen with abdominal tenderness, nausea, vomiting, and fever. In some cases, the primary presentation may resemble neurologic disease, with decreased responsiveness, progressing to stupor and coma. An adrenal crisis can be triggered by an intercurrent illness, surgical or other stress, or increased glucocorticoid inactivation (e.g., hyperthyroidism).