Genetics and Screening CNC type 1 (CNC1) is due to mutations of the protein kinase A (PKA) regulatory subunit 1 α (R1α) (*PPKAR1A*), a tumor suppressor, whose gene is located on chromosome 17q.24.2 (Table 408-2). The gene causing CNC type 2 (CNC2) is located on chromosome 2p16 and has not yet been identified. It is interesting to note, however, that some tumors do not show LOH of 2p16 but instead show genomic instability, suggesting that this CNC gene may not be a tumor suppressor. Screening and treatment of these endocrine tumors are similar to those described earlier for patients with MEN 1 and MEN 2 (Tables 408-3 and 408-4).

COWDEN'S SYNDROME

Clinical Manifestations Multiple hamartomatous lesions, especially of the skin, mucous membranes (e.g., buccal, intestinal, and colonic), breast, and thyroid are characteristic of Cowden's (CWD) syndrome, which is an autosomal dominant disorder. Thyroid abnormalities occur in two-thirds of patients with CWD syndrome, and these usually consist of multinodular goiters or benign adenomas, although <10% of patients may have a follicular thyroid carcinoma. Breast abnormalities occur in >75% of patients and consist of either fibrocystic disease or adenocarcinomas. The investigation and treatment for CWD tumors are similar to those undertaken for non-CWD patients.

Genetics and Screening CWD syndrome is genetically heterogenous, and six types (CWD1–6) are recognized (Table 408-2). CWD is due to mutations of the phosphate and tensin homologue deleted on chromosome 10 (*PTEN*) gene, located on chromosome 10q23.31. CWD2 is caused by mutations of the succinate dehydrogenase subunit B (*SDHB*) gene, located on chromosome 1p36.13; and CWD3 is caused by mutations of the *SDHD* gene, located on chromosome 11q13.1. *SDHB* and *SDHD* mutations are also associated with pheochromocytoma. CWD4 is caused by hypermethylation of the Killin (*KLLN*) gene, the promoter of which shares the same transcription site as *PTEN* on chromosome 10q23.31. CWD5 is caused by mutations of the phosphatidylinositol 3-kinase catalytic alpha (*PIK3CA*) gene on chromosome 3q26.32, and CWD6 is caused by mutations of the V-Akt murine thymoma viral oncogene homolog 1 (*AKT1*) gene on chromosome 14q32.33. Screening for thyroid abnormalities entails neck ultrasonography and fine-needle aspiration with analysis of cell cytology.

MCCUNE-ALBRIGHT SYNDROME (SEE ALSO CHAP. 426e)

Clinical Manifestations McCune-Albright syndrome (MAS) is characterized by the triad of polyostotic fibrous dysplasia, which may be associated with hypophosphatemic rickets; café au lait skin pigmentation; and peripheral precocious puberty; other endocrine abnormalities include thyrotoxicosis, which may be associated with a multinodular goiter, somatotrope tumors, and Cushing's syndrome (due to adrenal tumors). Investigation and treatment for each endocrinopathy are similar to those used in patients without MAS.

Genetics and Screening MAS is a disorder of mosaicism that results from postzygotic somatic cell mutations of the G protein α stimulating subunit (Gsα), encoded by the *GNAS1* gene, located on chromosome 20q13.32 (Table 408-2). The Gsα mutations, which include Arg201Cys, Arg201His, Glu227Arg, or Glu227His, are activating and are found only in cells of the abnormal tissues. Screening for hyperfunction of relevant endocrine glands and development of hypophosphatemia, which may be associated with elevated serum fibroblast growth factor 23 (FGF23) concentrations, is undertaken in MAS patients.

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409 Autoimmune Polyendocrine Syndromes

Peter A. Gottlieb

Polyglandular deficiency syndromes have been given many different names, reflecting the wide spectrum of disorders that have been associated with these syndromes and the heterogeneity of their clinical presentations. The name used in this chapter for this group of disorders is *autoimmune polyendocrine syndrome* (APS). In general, these disorders are divided into two major categories, APS type 1 (APS-1) and APS type 2 (APS-2). Some groups have further subdivided APS-2 into APS type 3 (APS-3) and APS type 4 (APS-4) depending on the type of autoimmunity involved. For the most part, this additional classification does not clarify our understanding of disease pathogenesis or prevention of complications in individual patients. Importantly, there are many nonendocrine disease associations included in these syndromes, suggesting that although the underlying autoimmune disorder predominantly involves endocrine targets, it does not exclude other tissues. The disease associations found in APS-1 and APS-2 are summarized in Table 409-1. Understanding these syndromes and their disease manifestations can lead to early diagnosis and treatment of additional disorders in patients and their family members.

TABLE 409-1 DISEASE ASSOCIATIONS WITH AUTOIMMUNE POLYENDOCRINE SYNDROMES

Autoimmune Polyendocrine Syndrome Type 1	Autoimmune Polyendocrine Syndrome Type 2	Other Autoimmune Polyendocrine Disorders
Endocrine	**Endocrine**	IPEX (immune dysfunction polyendocrinopathy X-linked)
Addison's disease	Addison's disease	Thymic tumors
Hypoparathyroidism	Type 1 diabetes	Anti-insulin receptor antibodies
Hypogonadism	*Graves' disease or autoimmune thyroiditis*	POEMS syndrome
Graves' disease or autoimmune thyroiditis	*Hypogonadism*	Insulin autoimmune syndrome (Hirata's syndrome)
Type 1 diabetes		Adult combined pituitary hormone deficiency (CPHD) with anti-Pit1 autoantibodies
		Kearns-Sayre syndrome
		DIDMOAD syndrome
Nonendocrine	**Nonendocrine**	Congenital rubella associated with thyroiditis and/or diabetes
Mucocutaneous candidiasis	Celiac disease, dermatitis herpetiformis	
Chronic active hepatitis	Pernicious anemia	
Pernicious anemia	Vitiligo	
Vitiligo	*Alopecia*	
Asplenism	*Myasthenia gravis*	
Ectodermal dysplasia	*IgA deficiency*	
Alopecia	*Parkinson's disease*	
Malabsorption syndromes	*Idiopathic thrombocytopenia*	
IgA deficiency		

Abbreviations: DIDMOAD, *d*iabetes *i*nsipidus, *d*iabetes *m*ellitus, progressive bilateral optic *a*trophy, and sensorineural *d*eafness; POEMS, *p*olyneuropathy, *o*rganomegaly, *e*ndocrinopathy, *M*-protein, and *s*kin changes.

Note: Italics denote less common disorders.