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Rare and Unusual Endocrine Cancer Syndromes with Mutated Genes

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Abstract

The study of a number of rare familial syndromes associated with endocrine tumor development has led to the identification of genes involved in the development of these tumors. Major advances have been made expanding our understanding of the pathophysiology of these rare endocrine tumors, resulting in the elucidation of causative genes in rare familial diseases and a better understanding of the signaling pathways implicated in endocrine cancers. Recognition of the familial syndrome associated with a particular patient's endocrine tumor has important implications in terms of prognosis, screening of family members, and screening for associated conditions.

This article provides a brief overview of a number of uncommon syndromes associated with endocrine tumors. The rare conditions covered in this chapter can be divided into those that are associated with 1) adrenocortical tumors, 2) those that are characterized by the development of hamartomas, 3) those that are associated with gastrointestinal stromal tumors and paragangliomas, and finally 4) those that are associated with the rare gastroenteropancreatic neuroendocrine tumors. Reviewed will be genetic syndromes and endocrine tumors, particularly tumors of the adrenal gland.

I. Rare endocrine syndromes associated with adrenocortical tumors

Although most cases of adrenocortical cancer appear to be sporadic, a number of hereditary cancer syndromes and inherited diseases are associated with adrenocortical tumors (Table 1). These syndromes and diseases include the Carney complex, familial polyposis coli (FPC), Li-Fraumeni, Beckwith-Wiedemann, hereditary leiomatosis and renal cancer (HLRC), and McCune-Albright syndromes, and multiple endocrine neoplasia type I (MEN1). Optimal care of patients with these syndromes requires recognition of the unique characteristics of the endocrine tumors associated with these hereditary diseases.

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Management of patients with hereditary adrenocortical tumors is distinct from that of isolated and sporadic adrenal tumors. This chapter highlights the underlying genetic defects, diagnosis, as well as therapy of the rare heritable tumor syndromes associated with adrenocortical malignancies. Two rare conditions that are associated with benign bilateral adrenocortical tumors include primary pigmented nodular adrenocortical disease (PPNAD), which is found in Carney Complex, and adrenocorticotrophic hormone (ACTH)-independent macronodular adrenal hyperplasia (AIMAH).

Carney Complex/PPNAD

Carney complex is a dominantly inherited multiple endocrine neoplasia syndrome first described in 1985 that is characterized by spotty skin pigmentation (lentiginosis), cardiac and peripheral myxomas, schwannomas, and endocrine overactivity.^{1,2} The endocrine tumors associated with Carney complex include PPNAD, growth hormone secreting pituitary adenomas, large-cell calcifying Sertoli cell tumors, Leydig cell tumors, and thyroid follicular neoplasms.³⁻⁵ PPNAD, a form of “micronodular adrenocortical disease”, as it was previously also known, is a rare cause of corticotropin (ACTH) independent Cushing syndrome. The majority of PPNAD cases are associated with Carney complex. The adrenal glands in PPNAD contain autonomously functioning nodules that secrete cortisol independent of signaling from the pituitary, in the setting of suppressed ACTH levels. Due to the lack of ACTH stimulation, the adrenals in PPNAD may be small-normal in size with multiple black nodules in conjunction with an atrophic adrenal cortex, giving them a characteristic irregular contour on magnetic resonance imaging (MRI) and computer tomography (CT) scans.^{6,7} Patients with PPNAD may have periodic or atypical Cushing syndrome. One diagnostic clue to the presence of PPNAD is a paradoxical increase of urinary free cortisol during the high dose dexamethasone administration of the Liddle’s test.⁸ The molecular cause of the disease in most patients with Carney complex and PPNAD has been identified as mutations within the gene *PRKARIA* on chromosome 17q22-24.⁹ *PRKARIA* encodes the regulatory subunit type 1- α of Protein Kinase A, a key regulator of the cyclic-AMP-dependent signaling pathway that has been implicated in endocrine tumor formation.¹⁰ Inactivating mutations of *PRKARIA* have been reported in 45–80% of families with Carney complex.^{11,12} Identification of adrenocortical tumors within the context of Carney complex is possible based on the characteristic response to the dexamethasone suppression test, imaging of the adrenal glands, and genotype analysis. The treatment of choice for PPNAD is bilateral adrenalectomy. Identification of affected patients and family members is crucial to screen for other features of Carney complex, namely potentially critical cardiac myxomas that require surgical removal.¹³

Other bilateral adrenocortical hyperplasias (BAH)

ACTH-independent adrenocortical hyperplasias are categorized on the basis of the size of the associated nodules, presence or absence of pigment, and hyperplasia or atrophy of the cortex surrounding the nodules.¹⁴ Three distinct types of macronodular hyperplasias (> 1 cm nodules) have been described, including bilateral macroadenomatous hyperplasia (BMAH), childhood BMAH, and adrenocorticotropin-independent macronodular adrenocortical hyperplasia (AIMAH). Micronodular hyperplasia (< 1 cm nodules) consists of PPNAD (which we described above in the context of Carney complex) and isolated micronodular adrenocortical disease (iMAD). All of these adrenocortical causes of Cushing syndrome are linked to increased cyclic AMP signaling. One classic example is the development of BMAH in children with McCune Albright syndrome, who harbor a somatic activating mutation in *GNAS* which encodes the stimulatory G-protein α subunit.¹⁵ Genetic defects of the phosphodiesterase (PDE) 11A and 8B genes (*PDE11A* and *PDE8B*) have also been

associated with the development of BAH.¹⁶ PDE11A and PDE8B catalyze the hydrolysis of cyclic AMP and are both highly expressed in the adrenal cortex.¹⁷

Li-Fraumeni

The Li-Fraumeni syndrome is an autosomal dominant familial syndrome initially described in 1969. Components of Li-Fraumeni syndrome include adrenocortical cancer as well as breast cancer, soft tissue and bone sarcoma, leukemia, and brain tumors.¹⁸ Adrenal cancer develops in approximately 1–3% of patients with Li-Fraumeni syndrome.^{19,20} Of note, children may present with virilization and elevated cortisol levels associated with adrenocortical tumors as the only manifestation of the Li-Fraumeni syndrome.²¹ Li-Fraumeni syndrome is associated with heterozygous germ line inactivating mutations of the *p53* tumor suppressor gene on chromosome 17p.²² Loss of heterozygosity by deletion of the wild-type *p53* allele has been demonstrated in adrenocortical tumors isolated from patients with Li-Fraumeni syndrome.²¹ Because of the strong link between individuals with adrenocortical cancer and germline *p53* mutations, genetic testing of *p53* is recommended for individuals with ACC; screening for the spectrum of cancers associated with Li-Fraumeni syndrome should therefore be performed in these patients.²³

Beckwith-Wiedemann syndrome

Beckwith-Wiedemann syndrome is a congenital overgrowth syndrome that is usually recognized at birth. It is characterized by Wilms' tumor, rhabdomyosarcoma, macroglossia, abdominal wall defects (omphalocele, umbilical hernia, or diastasis recti), neuroblastoma, hemihypertrophy, and hepatoblastoma, in association with other cancers, including adrenal cancer.²⁴ The molecular basis of Beckwith-Wiedemann syndrome is complex, involving deregulation of imprinted genes found within the 11p15 region, including *IGF2*, *H19*, *KCNQ1*, *KCNQ1OT1*, and *CDKN1C*.^{25,26} Individuals with Beckwith-Wiedemann syndrome often have uniparental paternal isodisomy for the *IGF2* locus, leading to overexpression of *IGF2* and subsequent tumor progression; rearrangements at the 11p15 locus and overexpression of *IGF2* are also seen in sporadic adrenocortical tumors.²⁷ In 15% of cases, Beckwith-Wiedemann syndrome is inherited in an autosomal dominant pattern with variable penetrance, however in 85% of cases, it presents in a sporadic form.²⁵ Approximately 3% of patients with Beckwith-Wiedemann syndrome develop adrenocortical tumors, usually with steroid overproduction; thus, screening recommendations for these patients include annual urinary free cortisol collection, annual alpha-fetoprotein levels, as well as annual adrenal ultrasound until age 9.²⁸ Hypoglycemia due to hyperplastic islets of Langerhans is a feature leading to hypoglycemia in 54% of patients with Beckwith-Wiedemann syndrome.²⁵

Familial polyposis coli (FPC)

Familial polyposis coli (FPC) is an autosomal dominant disorder due to mutations in the adenomatous polyposis coli gene (APC) located on chromosome 5q21-22.²⁹ Affected individuals usually develop hundreds to thousands of adenomatous polyps of the colon and rectum, a small proportion of which will progress to carcinoma if not surgically removed. In addition to colorectal polyps, FPC includes a predisposition to thyroid carcinoma, sarcoma, hepatoblastoma, pancreatic carcinoma, and medulloblastoma.³⁰ In addition to thyroid cancer, patients with APC have a 7–13% lifetime prevalence of developing adrenal tumors.^{31–33} While several cases of hormonally active adrenal adenomas and adrenal carcinomas have been reported, the majority of cases are incidental nonhypersecretory adenomas.³⁴

Hereditary leiomyomatosis and renal cell carcinoma (HLRCC)

Hereditary leiomyomatosis and renal cell cancer (HLRCC) is an autosomal dominant disorder caused by mutations in the fumarate hydratase gene (FH) on chromosome 1q42.3-43.35-36 HLRCC is characterized by benign smooth muscle tumors of the skin and the uterus, renal cell carcinoma, and uterine leiomyosarcoma. A case of one patient with HLRCC and atypical Cushing syndrome due to bilateral, ACTH-independent adrenocortical hyperplasia and massive macronodular adrenocortical disease (MMAD) has been described.³⁷ The patient had a germline-inactivating mutation in FH, an enzyme that catalyzes the conversion of fumarate to malate in the tricarboxylic acid cycle. Though only an isolated case, this report demonstrated for the first time the role of the mitochondrial oxidation pathway in the formation of an adrenocortical tumor. A larger population-based study found a 12% frequency of adrenal adenomas among patients with HLRCC.³⁸

II. Endocrine Hamartomas

Endocrine Tumors in Neurofibromatosis type 1, Tuberous Sclerosis Syndromes, Peutz-Jeghers syndrome, and Cowden syndrome

Neurofibromatosis type 1 (NF-1), tuberous sclerosis complex (TSC), Peutz-Jeghers syndrome, and Cowden syndrome are rare familial syndromes all associated with the development of hamartomas (Table 2). NF-1 and TSC are both disorders of unregulated progression through the cell cycle, in which causative genes behave as characteristic tumor suppressor genes. Both syndromes are involved in the regulation of the mammalian target of rapamycin (mTOR) pathway. Peutz-Jeghers syndrome and Cowden syndrome are two related syndromes that also converge on the mTOR pathway. The discovery of mTOR inhibitors has led to a promising potential treatment for patients with endocrine tumors as part of these familial syndromes.

Neurofibromatosis type 1

NF-1 is an autosomal dominant condition characterized by multiple café-au-lait spots and associated cutaneous neurofibromas. NF-1 affects about 1 in 4000 individuals worldwide.³⁹ NF-1 is caused by mutations of the gene encoding neurofibromin, located on chromosome 17q11.2.40-41 Neurofibromin is a tumor suppressor involved in the control of intracellular signaling and cell growth, that serves to negatively regulate the p 21 ras proto-oncogene.⁴² Loss-of function mutations in NF-1 lead to dysregulated growth due to increased signaling via downstream pathways, including the mitogen-activated protein kinase (MAPK) pathway and mTOR pathway.⁴³ The National Institutes of Health Consensus Conference developed diagnostic criteria that require at least two of the following clinical features, as outlined in Table 3, in order to diagnose NF-1.⁴⁴⁻⁴⁶

Patients with NF1 have 5–15 percent lifetime risk of developing a malignancy.^{47,48} NF-1 is associated with a variety of neuroendocrine tumors, including carcinoids, pheochromocytomas, gastrointestinal stromal tumors (GIST), paragangliomas, as well as pancreatic neuroendocrine tumors.⁴⁹ The lifetime risk for the development of pheochromocytoma in patients with NF1 is between 1 and 5%.⁵⁰⁻⁵¹ Pheochromocytomas in NF-1 are characteristically confined to the adrenal glands; surgery is usually curative.⁵⁰ Serum fractionated metanepherines should be measured in hypertensive patients with NF-1.⁵⁰ If biochemical testing is positive, conventional imaging as well as functional imaging with I¹²³ MIBG may be utilized for additional tumor characterization. Tumor cell lines derived from NF1 patients are highly sensitive to the mTOR inhibitor rapamycin, which may serve as a promising therapy for NF1.⁵² Drugs that block mTOR and ras are currently under investigation for treatment of NF-1 associated malignancies.

Tuberous sclerosis syndromes—Tuberous sclerosis (TSC) is an autosomal dominant disorder with an incidence of approximately 1 in 5,000 to 10,000 live births.⁵³ TSC is caused by mutations of two tumor suppressor genes, *TSC1* and *TSC2*. The *TSC1* gene maps to chromosome 9q34 and encodes the hamartin protein.^{54,55} The *TSC2* gene maps to chromosome 16p13.3 and encodes the tuberin protein.^{56,57} Hamartin and tuberin together form a complex that acts to negatively regulate the cell cycle.⁵⁸ TSC is a multisystem disorder with involvement of the eyes, brain, skin, kidneys, lungs and heart with distinctive hamartomatous lesions. The classic TSC triad, known as Vogt's triad, includes mental retardation, seizures, and facial angiofibromas.⁵⁹

The diagnostic criteria for TSC include the presence of 2 major features, or 1 major and 2 minor features, as outlined in Table 4.^{59,60} The relative risk of malignancy in children with TSC is approximately 18-fold higher than the general population.⁶¹ Although neuroendocrine tumors have been reported in patients with TSC, they are not currently considered one of the major features TSC.⁶² A number of case reports have documented endocrine tumors in patients with TSC, including pituitary tumors (adrenocorticotrophic hormone, growth hormone, and prolactin secreting), as well as parathyroid hyperplasia.^{63–69} Rarely, pancreatic endocrine tumors including gastrinoma and insulinomas have also been described in TSC.^{70–78} Additional endocrine tumors associated with TSC include rare cases of pheochromocytoma and carcinoid.^{79–80} Resection of a pancreatic tumor is the first line of treatment; however, the optimal systemic treatment for advanced pancreatic NETs continues to be debated. Somatostatin analogue therapy, systemic chemotherapy, and radionuclide therapy are all treatment modalities for endocrine pancreatic NETs.⁴⁹ As constitutive activation of mTOR contributes to the growth of tuberous sclerosis lesions and endocrine tumors, treatment with mTOR inhibitors may provide promising treatment for this disorder.⁸¹

Cowden Disease

Cowden disease is associated with the formation of hamartomas as well as endocrine tumors. Patients have increased susceptibility to malignancies including breast cancer, follicular thyroid cancer, and endometrial carcinoma.⁸² The diagnosis of Cowden disease requires the presence of at least one major and three minor criteria. Major diagnostic criteria for Cowden disease include macrocephaly, Lhermitte-Duclos disease (hamartomas of the cerebellum with associated ataxia), as well as breast and thyroid cancer; minor diagnostic criteria include lipomas, fibromas, genitourinary tumors, fibrocystic breast disease thyroid disease (adenoma and goiter), gastrointestinal hamartomas, and developmental delay.⁸³ Mutations in the phosphatase and tensin gene (*PTEN*) on chromosome 10q23.31 are found in approximately 80 percent of patients with Cowden disease.⁸⁴ Loss-of-function mutations in this regulator of neuroendocrine development lead to constitutive activation of mTOR.⁸⁵ Nearly 10% of patients with Cowden disease develop follicular thyroid cancer, and up to 75% develop benign thyroid lesions.^{85,86}

Peutz-Jeghers

Peutz-Jeghers syndrome (PJS) is an autosomal dominant disorder associated with the development of endocrine tumors. Features of PJS include hyperpigmented macules involving the mucosa, as well as gastrointestinal polyposis. The endocrine tumors found in PJS include thyroid cancer, benign ovarian sex cord tumors, calcifying Sertoli tumors of the testis, endometrial cancer, breast cancer, gastrointestinal cancer, pancreatic cancer, and cervical cancer.⁸⁷ The Sertoli cell tumors may be associated with increased aromatase expression and subsequent gynecomastia.⁸⁹ In over one half of cases, PJS is due to mutations in the serine-threonine kinase *STK11/LKB1* tumor suppressor gene, located on 19p13.⁸⁸ Mutations in *STK11/LKB1* lead to deregulated mTOR signaling.

III. Paragangliomas and gastrointestinal stromal tumors

Carney Triad

Carney triad is a rare syndrome that consists of GIST, paraganglioma, and pulmonary chondroma. In this novel form of multiple endocrine neoplasia with a female predilection, the causative genetic defect remains unknown (Table 5).⁹⁰ A number of additional lesions have been associated with Carney triad, including pheochromocytomas, esophageal leiomyomas, and adrenocortical adenomas.⁹¹

Carney-Stratakis Syndrome

Another syndrome consisting of multifocal GIST together with paragangliomas has been described in younger individuals and is distinct from the Carney's triad and referred to as Carney-Stratakis syndrome. The Carney-Stratakis syndrome, first described in 2002, affects both males and females and is not associated with pulmonary chondromas and is inherited in an autosomal dominant manner with incomplete penetrance.⁹² Germline loss-of-function mutations of the *SDHB*, *SDHC*, and *SDHD* genes have been found in the majority of patients with the Carney-Stratakis syndrome.^{93,94} SDH is a component of the mitochondrial electron transport chain; mutations cause increased susceptibility to cancer by acting as a tumor suppressor gene, leading to aberrant regulation of tumor growth.

IV. Pancreatic endocrine tumors

GPNETs (Gastroenteropancreatic tumors other than carcinoids that are associated with endocrine conditions)

A number of rare, noncarcinoid gastroenteropancreatic neuroendocrine tumors exist that cause distinct clinical syndromes depending on the hormone secreted (Table 6). The incidence of pancreatic neuroendocrine tumors is approximately 1 per 100,000 people per year, accounting for less than 2% of all pancreatic tumors.⁹⁵⁻⁹⁶ To date, the molecular basis for tumor formation in sporadic GPNETS has not been elucidated, however a number of genetic alterations have been found in PET patients, including loss of heterogeneity at chromosome 11q, 6q, and 3p.⁹⁷ Familial syndromes known to be associated with GPNETS are addressed elsewhere in this text, including multiple endocrine neoplasia type 1 (MEN-1), von Hippel-Lindau disease, and NF-1. Many of these tumors secrete specific biochemical markers that offer important diagnostic clues, and additional markers including pancreastatin, neurokinin A, and chromogranin A are emerging as important investigational and therapeutic tools.⁹⁸

Insulinoma

The insulinoma syndrome is characterized by fasting hypoglycemia and inappropriately elevated insulin and proinsulin. Over 90% of the cases are caused by a single, usually benign, neuroendocrine tumor of the pancreas, although insulinomas can also be malignant in approximately 6% of patients.⁹⁹⁻¹⁰⁰ Patients with MEN1 are more likely to present with multiple islet tumors.¹⁰¹ The clinical finding of inappropriately high serum insulin concentrations during a period of fasting hypoglycemia is pathognomonic for this condition.¹⁰² Tumor localization is accomplished by CT scan, ultrasound, or fluorine-18-L-dihydroxyphenylalanine (18F-DOPA) positron emission tomography.¹⁰³ In patients with suspected insulinoma and negative imaging studies, selective arterial calcium stimulation with hepatic venous sampling can aid in tumor localization.¹⁰⁴ Surgical tumor resection is usually curative; multiple options for the medical management for control of symptomatic hypoglycemia are available, including diazoxide and octreotide.¹⁰⁰⁻¹⁰⁵ Glycemic control in non-resectable cases of insulinoma has been recently reported with the use of mTOR inhibitors.^{106,107}

Gastrinoma

The gastrinoma or Zollinger-Ellison syndrome (ZES) is characterized by hypergastrinemia, peptic ulcer disease, diarrhea, and non-beta cell islet tumors of the pancreas.¹⁰⁸ This syndrome is caused by neuroendocrine tumors that occur both intra and extrapancreatic and are frequently malignant.⁹⁹ ZES may occur sporadically, or as a manifestation of MEN1. Fasting serum gastrin concentration should be measured in patients suspected of having ZES, and in patients with nondiagnostic values, the secretin stimulation test may be employed to help further identify the syndrome.¹⁰⁹ Tumor localization is aided by somatostatin receptor imaging with ¹¹¹Indium-pentetreotide (Octreoscan), single photon emission CT (SPECT), and endoscopic ultrasound; in difficult cases, secretin injection and portal venous sampling is another available technique.¹¹⁰ As patients with both MEN1 and ZES present with multiple sites of disease, medical therapy has emerged as the standard of care for these patients, whereas patients with sporadic ZES are often managed with surgical resection. Medical management includes proton pump inhibitor therapy to limit the complications of peptic ulcer disease.¹¹¹ Unresectable metastatic gastrinoma is difficult to treat; available palliation options include, somatostatin analogues, interferon, and conventional chemotherapy.¹¹² Some NETs may be amenable to embolization or radio-frequency ablation. Peptide receptor targeted radiotherapy may lead to reduction in tumor size but in most circumstances has a tumor-stabilizing effect. New targeted antiangiogenesis and growth factor-targeted agents are emerging as promising therapies for neuroendocrine tumors, however the most agents have not yielded expected results.¹¹³ Results of the phase III trial of sunitinib versus placebo for treatment of advanced pancreatic neuroendocrine tumors show that sunitinib prolonged progression free survival, and increased objective response rate and overall survival in those studied.¹¹⁴

VIPoma

Vasoactive intestinal polypeptide (VIP) is located throughout the nervous system, and modulates the action of an adenylate cyclase-coupled receptor. Excessive secretion of VIP, usually by a pancreatic or duodenal tumor, leads to the WDHA syndrome (severe watery diarrhea, hypokalemia, and achlorhydria), also known as the Verner-Morrison syndrome or pancreatic cholera.¹¹⁵ Elevated levels of plasma VIP, and radiologic findings of a pancreatic tumor, are characteristic of this condition. Patients with a VIP secreting tumor, or VIPoma, should be treated with somatostatin analogue therapy in addition to intravenous fluid and electrolytes, and surgical resection offers the only option for cure.¹¹⁶

Glucagonoma

Glucagon is normally released by the alpha cells in the pancreatic islets of Langerhans, and it serves as a counter-regulatory hormone in the regulation of glucose metabolism.¹¹⁷ Neuroendocrine pancreatic tumors associated with excessive glucagon secretion lead to a characteristic syndrome comprised of steatorrhea, diabetes, gallstones, diarrhea, necrolytic migratory erythema, weight loss, and deep venous thrombosis.¹¹⁸ The diagnosis is confirmed by elevated plasma levels of glucagon, along with findings of a tumor on imaging studies. Management includes nutritional supplementation, somatostatin analogue therapy, prophylactic anticoagulation, as well as tumor resection. Neuroendocrine tumors that secrete excessive amounts of somatostatin are associated with diabetes, cholelithiasis, and steatorrhea, along with local tumor effects, including jaundice, abdominal pain, and gastrointestinal bleeding.¹¹⁸ As many as 50% of patients with duodenal somatostatinomas have NF-1.¹¹⁹ Another rare type of sporadic pancreatic neuroendocrine tumors are PPomas, which predominantly secrete pancreatic polypeptide and have not been associated with a specific clinical syndrome.¹²⁰ Somatostatinoma is a rare tumor of the gastroenteropancreatic neuroendocrine axis; excessive somatostatin secretion leads to a syndrome consisting of diabetes, diarrhea, gallbladder disease, hypochlorhydria and weight loss.¹²¹ ¹²² Additional

types of rare functional neuroendocrine tumors of the gastrointestinal tract include those that secrete excessive amounts of adrenocorticotrophic hormone, corticotropin-releasing hormone, or growth hormone releasing factor.¹¹⁸

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Table 1

Rare endocrine syndromes associated with adrenocortical tumors

Syndrome	Types of endocrine tumors	Gene (chromosomal location)	OMIM
Li-Fraumeni	Adrenal, Breast	<i>P53</i> (17p13)	151623
Beckwith-Wiedemann	Adrenal, pancreas	<i>IGF2</i> , <i>H19</i> , <i>KCNQ1</i> , <i>KCNQ1OT1</i> , and <i>CDKN1C</i> (11p15)	130650
Carney Complex	PPNAD Pituitary (acromegaly) Testicular Thyroid	<i>PRKARIA</i> (17q22-24)	160980

Table 2

Rare endocrine syndromes associated with hamartomas

Syndrome	Types of endocrine tumors	Gene (chromosomal location)	OMIM
Peutz-Jeghers	Thyroid Testicular Ovarian	<i>STK11/LKB1</i> (19q13)	175200
Tuberous sclerosis	Pancreatic neuroendocrine tumors	<i>TSC1</i> (9q34) <i>TSC2</i> (16p13)	191100
Cowden disease	Breast cancer Follicular thyroid cancer, endometrial cancer Ovarian cancer	<i>PTEN</i> (10q23.31)	158350
Neurofibromatosis type 1	Somatostatin/insulin producing NET, duodenal NET, GIST	<i>NF1</i> (17q11.2)	162200

Table 3

NF-1 diagnostic criteria

Diagnostic criteria for NF-1	
<ul style="list-style-type: none">• Six or more café-au-lait macules >5 mm in longest diameter in prepubertal and >15 mm in longest diameter in postpubertal individuals• Two or more neurofibromas of any type or one plexiform neurofibroma axillary or inguinal freckling• Optic glioma• Two or more Lisch nodules (iris hamartomas)• A distinctive bony lesion such as sphenoid dysplasia or thinning of the long bone cortex with or without pseudoarthrosis• A first-degree relative with NF1 based upon the above criteria	

Table 4

Diagnostic criteria for TSC

Major clinical features of TSC	Minor clinical features of TS
<ul style="list-style-type: none"> • Facial angiofibromas or forehead plaques • Shagreen patch (connective tissue nevus) • Three or more hypomelanotic macules • Nontraumatic ungual or periungual fibromas • Lymphangiomyomatosis • Renal angiomyolipoma • Cardiac rhabdomyoma • Multiple retinal nodular hamartomas • Cortical tuber • Subependymal nodules • Subependymal giant cell astrocytoma 	<ul style="list-style-type: none"> • Confetti skin lesions (multiple 1 to 2 mm hypomelanotic macules) • Gingival fibromas • Pits in dental enamel • Hamartomatous rectal polyps • Multiple renal cysts • Nonrenal hamartomas • Bone cysts • Retinal achromic patch • Cerebral white matter radial migration lines

Table 5

Syndromes associated with gastrointestinal stromal tumor and paraganglioma

Syndrome	Types of endocrine tumors	Gene (chromosomal location)	OMIM
Carney Triad	GIST, pulmonary chondroma, and extraadrenal paraganglioma	unknown	604287
Carney-Stratakis Syndrome	paraganglioma and GIST	<i>SDHB</i> , <i>SDHC</i> <i>SDHD</i> 1q21, 11q23,1p36.1- p35	606864

Table 6

Summary of Enteroendocrine tumor syndromes other than Carcinoid

Tumor	Clinical presentation	Percent malignant %
Insulinoma	Whipple's triad (hypoglycemic symptoms, low blood glucose, reverses with glucose intake)	<10%
Gastrinoma	Zollinger-Ellison syndrome (diarrhea, elevated gastrin, peptic ulcer, elevated gastric acid)	60–90
VIPoma (vasoactive intestinal polypeptide)	Verner-Morrison syndrome (WHDA, watery diarrhea, hypokalemia, achlorhydria) Flushing Weight loss	40–70
Glucagonoma	Diabetes Necrolytic migratory erythema Deep venous thrombosis, depression	50–80
Somatostatinoma	Diabetes Hypochlorhydria Cholelithiasis Steatorrhea Weight loss Anemia	>70
GRFoma (growth hormone releasing factor)	Acromegaly	>60
ACTHoma	Ectopic Cushing syndrome Hypertension Diabetes Weakness	>95
PTHrp NET	Hypercalcemia Nephrolithiasis	84
Calcitonin-producing NET	Unknown	>80