# 13 - 399 Pheochromocytoma

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Hartmut P. H. Neumann

Pheochromocytoma Pheochromocytomas and paragangliomas (PPGLs) are catecholamineproducing tumors derived from the sympathetic or parasympathetic nervous system. These tumors may arise sporadically or be inherited as features of multiple endocrine neoplasia type 2 (MEN 2), von Hippel–Lindau (VHL) disease, or several other pheochromocy toma-associated syndromes. The diagnosis of pheochromocytomas identifies a potentially correctable cause of hypertension, and their removal can prevent hypertensive crises that can be lethal. The clini cal presentation is variable, ranging from an adrenal incidentaloma to a hypertensive crisis with associated cerebrovascular or cardiac complications. Given the wide range of clinical signs, diagnosis may be delayed for years. ■ ■EPIDEMIOLOGY The incidence of PPGL ranges from 0.04 to 0.95 cases per 100,000 per year, with a gradual increase over time probably due to genetic familial screening, changes in imaging modalities, and more frequent A Adrenal pheochromocytoma B Extra-adrenal pheochromocytoma C Head and neck paraganglioma FIGURE 399-1 The paraganglial system and topographic sites (in red) of pheochromocytomas and paragangliomas. (Parts A and B reproduced with permission from WM Manger, RW Gifford: Clinical and experimental pheochromocytoma. Cambridge: Blackwell Science; 1996.)

diagnosis as an incidentaloma. About ~0.1% of hypertensive patients harbor a pheochromocytoma. The mean age at diagnosis is ~40 years, although the tumors can be detected from early childhood, particularly when genetically determined, until late in life. The classic “rule of tens” for pheochromocytomas states that ~10% are bilateral, 10% are extraadrenal, and 10% are metastatic.

■ ■ETIOLOGY AND PATHOGENESIS PPGLs are well-vascularized tumors that arise from cells derived from the sympathetic (e.g., adrenal medulla or sympathetic trunk) or para sympathetic (e.g., carotid body, glomus tympanicum, glomus jugulare, glomus vagale) paraganglia (Fig. 399-1). The name pheochromocytoma reflects the formerly used black-colored staining caused by chromaffin oxidation of catecholamines. The World Health Organization (WHO) applies the term pheochromocytoma to adrenal tumors (usually secret ing) and the term paraganglioma to tumors at all other sites including head and neck, thoracic, extra-adrenal retroperitoneal, and pelvic sites. Pheochromocytoma CHAPTER 399 The etiology of sporadic PPGLs is unknown. However, 25–33% of patients have an inherited condition, including germline mutations in the classically recognized RET (rearranged during transfection), VHL, NF1 (neurofibromatosis type 1), SDHB, SDHC, and SDHD (subunits of SDH) genes or in the more recently recognized SDHA, SDHAF2, TMEM127 (transmembrane protein 127), MAX (myc-associated factor X), FH (fumarate hydratase), PDH1, PDH2 (pyruvate dehydro genase), HIF1α and HIF2α (hypoxia-inducible factor), MDH2 (malate dehydrogenase), KIF1Bβ (kinesin family member), IDH1, (isocitrate dehydrogenase 1), SLC25A11 (oxoglutarate/malate), H-RAS (trans forming protein p21), and DNMTA3 (DNA methyltransferase 3 alpha) genes. Biallelic gene inactivation, a characteristic of tumor-suppressor genes, has been demonstrated for the VHL, NF1, SDHx, TMEM127, MAX, FH, PDH1, PDH2, MDH2, and KIF1Bβ genes. In contrast, RET is a protooncogene, and mutations activate receptor tyrosine kinase activity. Succinate dehydrogenase (SDH) is an enzyme of the Krebs cycle and the mitochondrial respiratory chain. The VHL protein is a component of a ubiquitin E3 ligase. VHL mutations reduce protein degradation, resulting in upregulation of components involved in cellcycle progression, glucose metabolism, and oxygen sensing. In addition to germline mutations, somatic mutations have been observed in >20 genes, broadly grouped into three different clusters of pathogenetically relevant genes: cluster 1, the pseudohypoxia group comprising mainly the genes SDHx (subunits of SDH), FH, VHL, and HIF2A; cluster 2, the kinase signaling group (RET, NF1, TMEM127, MAX, HRAS, KIF1Bβ, PDH); and cluster 3, the Wnt signaling group (CSDE1, MAML3). Vagus n. Tympanic n. Jugular p. Jugular ganglion Nodose ganglion Jugular v. Intravagal p. Glossopharyngeal n. Sup. laryngeal a. Intercarotid p. Sup. laryngeal p. Int. laryngeal a. Inf. laryngeal p. Recurrent laryngeal n. Aorticopulmonary p. Coronary p. Subclavian p. Pulmonary p. Descending aorta

TABLE 399-1 Clinical Features Associated with Pheochromocytoma, Listed by Frequency of Occurrence

1. Headaches
2. Profuse sweating
3. Palpitations and tachycardia
4. Hypertension, sustained or
5. Weight loss
6. Paradoxical response to antihypertensive drugs
7. Polyuria and polydipsia
8. Constipation
9. Orthostatic hypotension
10. Dilated cardiomyopathy
11. Erythrocytosis
12. Elevated blood sugar
13. Hypercalcemia paroxysmal

14. Anxiety and panic attacks
15. Pallor
16. Nausea
17. Abdominal pain
18. Weakness PART 12 Endocrinology and Metabolism ■ ■CLINICAL FEATURES Its clinical presentation is so variable that pheochromocytoma has been termed “the great masquerader” (Table 399-1). Among the presenting manifestations, episodes of palpitation, headache, and profuse sweating are typical, and these manifestations constitute a classic triad that is seen in roughly a third of patients with pheochromocytoma. The pres ence of all three manifestations in association with hypertension makes pheochromocytoma a likely diagnosis. However, a pheochromocytoma can be asymptomatic for years or can be identified through imaging screening in a patient presenting with a hereditary syndrome. Some tumors grow to a considerable size before patients note symptoms. The dominant sign is hypertension. Classically, patients have episodic hypertension, but sustained hypertension is also common. Catecholamine crises can lead to heart failure, pulmonary edema, arrhythmias, and intracranial hemorrhage. During episodes of hor mone release, which can occur at widely divergent intervals, patients are anxious and pale, and they experience tachycardia and palpita tions. These paroxysms generally last <1 h and may be precipitated by surgery, positional changes, exercise, pregnancy, urination (particularly with bladder pheochromocytomas), and various medications (e.g., tri cyclic antidepressants, opiates, metoclopramide). Patients may present with true panic attacks that may be mistakenly attributed to psychiatric illness. ■ ■DIAGNOSIS The diagnosis is based on documentation of catecholamine excess by biochemical testing and localization of the tumor by imaging. These two criteria are of equal importance, although measurement of cat echolamines or metanephrines (their methylated metabolites) is tradi tionally the first step in diagnosis. Biochemical Testing PPGLs synthesize and store catecholamines, which include norepinephrine (noradrenaline), epinephrine (adrena line), and dopamine. Elevated plasma and urinary levels of catechol amines and metanephrines form the cornerstone of diagnosis. The characteristic fluctuations in the hormonal activity of tumors result in considerable variation in serial catecholamine measurements. How ever, most tumors continuously leak O-methylated metabolites, which are detected by measurement of metanephrines. Catecholamines and metanephrines can be measured by differ ent methods, including high-performance liquid chromatography, enzyme-linked immunosorbent assay, and liquid chromatography/ mass spectrometry. When pheochromocytoma is suspected on clinical grounds (i.e., when values are three times the upper limit of normal), this diagnosis is highly likely regardless of the assay used. However, as summarized in Table 399-2, the sensitivity and specific ity of available biochemical tests vary greatly, and these differences are important in assessing patients with borderline elevations of different compounds. Urinary tests for metanephrines (total or fractionated) and catecholamines are widely available and are used commonly for initial evaluation. Among these tests, those for the fractionated metanephrines and catecholamines are the most sensi tive. Plasma tests are more convenient and include measurements of catecholamines and metanephrines. Measurements of plasma

TABLE 399-2 Biochemical and Imaging Methods Used for Diagnosis of Pheochromocytoma and Paraganglioma DIAGNOSTIC METHOD SENSITIVITY SPECIFICITY 24-h urinary tests Catecholamines +++ +++ Fractionated metanephrines ++++ ++ Total metanephrines +++ ++++ Plasma tests Catecholamines +++ ++ Free metanephrines ++++ +++ Imaging CT ++++ +++ MRI ++++ +++ MIBG scintigraphy ++ ++++ Somatostatin receptor scintigraphya ++ ++ 18Fluoro-DOPA PET/CT ++++ ++++ 68Gallium-DOTATOC or DOTATATE PET/CT ++++ ++++ aValues are particularly high in head and neck paragangliomas. Abbreviations: CT, computed tomography; MIBG, metaiodobenzylguanidine; MRI, magnetic resonance imaging; PET/CT, positron emission tomography plus CT. For the biochemical tests, the ratings correspond globally to sensitivity and specificity rates as follows: ++, <85%; +++, 85–95%; and ++++, >95%. metanephrines are the most sensitive and are less susceptible to falsepositive elevations from stress, including venipuncture. Although the incidence of false-positive test results has been reduced by the introduction of newer assays, physiologic stress responses and medications that increase catecholamine levels still can confound testing. Because the tumors are relatively rare, borderline elevations are likely to represent false-positive results. In this circumstance, it is important to exclude dietary or drug-related factors (withdrawal of levodopa or use of sympathomimetics, diuretics, tricyclic antidepres sants, alpha and beta blockers) that might cause false-positive results and then to repeat testing. Diagnostic Imaging A variety of methods have been used to local ize PPGLs (Table 399-2, Figs. 399-2, 399-3, and 399-4). Computed tomography (CT) and magnetic resonance imaging (MRI) are similar in sensitivity and should be performed with contrast. T2-weighted MRI with gadolinium contrast is optimal for detecting pheochromocytomas and is somewhat better than CT for imaging extra-adrenal PPGLs. About 5% of adrenal incidentalomas, which usually are detected by CT or MRI, prove to be pheochromocytomas upon endocrinologic evaluation, but the presence of pheochromocytomas is unlikely if unenhanced CT reveals an attenuation of <10 Hounsfield units (HU). Tumors also can be localized by procedures using radioactive tracers, including 131I- or 123I-metaiodobenzylguanidine (MIBG) scintigraphy, 18F-DOPA positron emission tomography (PET), 68Ga-DOTATATE PET, or 18F-fluorodeoxyglucose (FDG) PET (Fig. 399-2B and 399-4A and B). For PET-CT with both 68Ga-DOTATATE and 18F-DOPA, the sensitivity and specificity are very high (>95%). These agents are par ticularly useful in the documentation of hereditary syndromes but also in metastatic pheochromocytoma, because uptake is exhibited also in paragangliomas and metastases. Pathology PPGLs are found at the classical sites of the adrenal medulla (Fig. 399-2) and paraganglia (Fig. 399-3). Histologically, the tumors often show a characteristic “Zellballen” pattern, consisting of nests of neuroendocrine chief cells with peripheral glial-like susten tacular cells. However, a broad spectrum of architectural and cytologic features can be seen. Immunohistochemistry is positive for chromo granin and synaptophysin in the chief cells and S-100 in the susten tacular cells (Fig. 399-5A–D). Increasingly, staining with antibodies against the proteins encoded by susceptibility genes for hereditary pheochromocytomas, such as SDHB, is used to histologically demon strate defects of these proteins, thereby making germline mutations more likely (Fig. 399-5E and F).

A B FIGURE 399-2 Typical pheochromocytoma (adrenal unilateral). A. Magnetic resonance imaging. B. 18F-DOPA positron emission tomography (PET). Tumor marked by arrows. (Part A was provided courtesy of Dr. Tobias Krauss, Freiburg. Part B was provided courtesy of Dr. Juri Ruf, Freiburg.) Differential Diagnosis When the possibility of a pheochromocy toma is being entertained, other disorders to consider include essential hypertension, anxiety attacks, use of cocaine or amphetamines, mastocy tosis or carcinoid syndrome (usually without hypertension), intracranial

lesions, clonidine withdrawal, autonomic epilepsy, and factitious crises (usually from use of sympathomimetic amines). When an asymptomatic adrenal mass is identified, likely diagnoses other than pheochromocy toma include a nonfunctioning adrenal adenoma, an aldosteronoma, and a cortisol-producing adenoma (Cushing's syndrome). ■ ■TREATMENT Complete tumor removal, the ultimate therapeutic goal, can be achieved by partial or total adrenalectomy. It is important to preserve A C D FIGURE 399-3 Paragangliomas (extra-adrenal pheochromocytomas). A. Carotid body tumor. B. Thoracic tumor. C. Paraaortal tumor. D. Pelvic tumor at the anterior wall of the urinary bladder. Tumors marked by arrows. (Part A was provided courtesy of Dr. Carsten Boedeker, Stralsund. Parts B and D were provided courtesy of Dr. Tobias Krauss, Freiburg. Part C was provided courtesy of Dr. Martin Walz, Essen.)

Pheochromocytoma CHAPTER 399 the normal adrenal cortex in order to prevent Addison's disease, particularly in hereditary disorders in which bilateral pheochro mocytomas are most likely. Preoperative preparation of the patient has to be considered, and blood pressure should be consistently <160/90 mmHg. Classically, blood pressure has been controlled by α-adrenergic blockers (oral phenoxybenzamine, 0.5–4 mg/kg

of body weight). Because patients are volume-constricted, liberal salt intake and hydration are necessary to avoid severe orthostasis. Oral prazosin or intravenous phentolamine can be used to manage parox ysms while adequate alpha blockade is awaited. Beta blockers (e.g., 10 mg of propranolol three or four times per day) should not be used as first-line treatment because of the risk of increased hyper tension. Other antihypertensives, such as calcium channel blockers B

PART 12 Endocrinology and Metabolism FIGURE 399-4 Multiple and metastatic pheochromocytoma. A. Paraganglioma syndrome. A patient with the SDHD W5X mutation and PGL1 68Ga-DOTATATE positron emission tomography (PET) demonstrating tumor uptake in the right jugular glomus, the right and left carotid body, both adrenal glands, and an interaortocaval paraganglion (arrows). Note the physiologic accumulation of the radiopharmaceutical agent in the kidneys and the liver. B. 18F-DOPA PET of a patient with metastatic pheochromocytoma. Several metastases marked by arrows. (Parts A and B were provided courtesy of Dr. Juri Ruf, Freiburg.) A C B D E F FIGURE 399-5 Histology and immunohistochemistry of pheochromocytoma. A. Hematoxylin and eosin, B. chromogranin, C. synaptophysin, C and B stain chief cells; D. S-100 stains sustentacular cells. E, F. Immunohistochemistry with SDHB antibody: positive staining (granular cytoplasmic staining) indicates intact SDHB (E), whereas negative staining (endothelial cells positive as internal control) (F) indicates structurally changed or absent SDHB due to a germline mutation in the SDHB gene, which was confirmed by molecular genetic analysis of a blood sample. (Parts A–D and F were used with permission from Dr. Helena Leijon, Helsinki. Part E was provided courtesy of Dr. Kurt Werner Schmid, Essen.) A B

or angiotensin-converting enzyme inhibitors, have also been used effectively. Surgery should be performed by teams of surgeons and anesthesi ologists with experience in the management of pheochromocytomas. Blood pressure can be labile during surgery, particularly at the outset of intubation or when the tumor is manipulated. Nitroprusside infusion is useful for intraoperative hypertensive crises, and hypotension usually responds to volume infusion. The latter side effect can, however, be avoided in normotensive pheochromocytoma patients by having only standby intraoperative nitroprusside, which has been shown to be safe and avoids postoperative

hypotension often caused by alpha blockers. The long-lasting guideline for obligatory preoperative treatment with alpha blockers is under discussion and seemingly not needed. Minimally invasive techniques (laparoscopy or retroperitoneos copy) have become the standard approaches in pheochromocytoma surgery. They are associated with fewer complications, a faster recov ery, and optimal cosmetic results. Extra-adrenal abdominal and most thoracic pheochromocytomas can also be removed endoscopically. In this setting, adrenal sparing surgery should be considered. Post operatively, catecholamine normalization should be documented. An adrenocorticotropic hormone (ACTH) test should be used to exclude cortisol deficiency when bilateral adrenal cortex–sparing surgery has been performed. Head and neck paragangliomas are a challenge for surgeons, since damage of adjacent tissue, mainly vessels or cranial nerves II, VII, IX, X, XI, and XII, is a frequent permanent side effect. Careful con sideration of best management is important, and radiotherapy may be an alternative, especially for large head and neck paragangliomas. Tympanic paragangliomas are symptomatic early, and most of these tumors can easily be resected, with subsequent improvement of hear ing and alleviation of tinnitus. Asymptomatic paraganglial tumors, now often detected in patients with hereditary tumors and their rela tives, are challenging to manage. Watchful waiting strategies have been introduced, but they should consider any genetic syndrome, such as SDHB, that might be associated with a higher degree of malignancy (see below). ■ ■METASTATIC PHEOCHROMOCYTOMA About 5–10% of PPGLs are metastatic. The diagnosis of malignant pheochromocytoma is problematic. The typical histologic criteria of cellular atypia, presence of mitoses, and invasion of vessels or adjacent tissues are insufficient for the diagnosis of malignancy in pheochro mocytoma. Size >5 cm, high pheochromocytoma of the adrenal gland scaled score (PASS) and grading system for adrenal pheochromocy toma and paraganglioma (GAPP) score, and SDHB-positive status have been considered as markers of risk of recurrence, but they remain controversial. Thus, the term malignant pheochromocytoma has been replaced by metastatic pheochromocytoma as suggested by the WHO and is restricted to tumors with lymph node or distant metastases, the latter most commonly found by nuclear medicine imaging in lungs, bone, or liver locations, suggesting a vascular pathway of spread (Fig. 399-4B). Because hereditary syndromes are associated with multifocal tumor sites, these features should be anticipated in patients with germ line mutations, especially of SDHB, SDHD, VHL, and RET. However, distant metastases also occur in these syndromes, especially in carriers of SDHB mutations. Treatment of metastatic pheochromocytoma or paraganglioma is challenging. Options include tumor mass reduction, alpha blockers for symptoms, chemotherapy including tyrosine kinase inhibitors, nuclear medicine radiotherapy, and stereotactic radiation. Nuclear medicine therapy is the treatment of choice for scintigraphically documented metastases, preferably with 131I-MIBG in 100–300 mCi doses over 3–6 cycles, or somatostatin receptor ligands, e.g., DOTATOC labeled with yttrium-90 or lutetium-177. Averbuch’s chemotherapy protocol includes dacarbazine (600 mg/m2 on days 1 and 2), cyclophospha mide (750 mg/m2 on day 1), and vincristine (1.4 mg/m2 on day 1), all repeated every 21 days for 3–6 cycles. Palliation (stable disease to shrinkage) is achieved in about one-half of patients. Due to increasing insights in the genetics of pheochromocytoma and their molecular

pathways, new targeted chemotherapeutic options such as sunitinib and temozolomide are under investigation. The prognosis of metastatic pheochromocytoma or paraganglioma is variable, with 5-year survival rates of 30–60%.

■ ■PHEOCHROMOCYTOMA IN PREGNANCY Pheochromocytomas occasionally are diagnosed in pregnancy and can be very challenging to manage. The pathogenesis of adrenergic crises during pregnancy in previously asymptomatic women might be linked to human chorionic gonadotropin (hCG)-induced stimulation of epinephrine production by pheochromocytoma, as some of these express luteinizing hormone/chorionic gonadotropin (LHCG) recep tors. Endoscopic removal, preferably in the fourth to sixth month of gestation, is possible and can be followed by uneventful childbirth. Regular screening in families with inherited pheochromocytomas pro vides an opportunity to identify and remove such tumors in women of reproductive age. Pheochromocytoma CHAPTER 399 ■ ■PHEOCHROMOCYTOMA-ASSOCIATED SYNDROMES About 25–33% of patients with a PPGL have an inherited syndrome. At diagnosis, patients with inherited syndromes are a mean of ~15 years younger than patients with sporadic tumors. The best-known pheochromocytoma-associated syndrome is the autosomal dominant disorder MEN 2 (Chap. 400). Both types of MEN 2 (2A and 2B) are caused by mutations in RET, which encodes a tyrosine kinase. The locations of RET mutations correlate with the age of disease onset, the aggressiveness, and the type of MEN 2 (Chap. 400). MEN 2A is characterized by medullary thyroid carci noma (MTC), pheochromocytoma, and hyperparathyroidism. MEN 2B also includes MTC (more aggressive than in MEN 2A), pheochro mocytoma, and multiple mucosal neuromas, marfanoid habitus, and other developmental disorders, although it typically lacks hyperpara thyroidism. MTC is found in virtually all patients with MEN 2, but pheochromocytoma occurs in only ~50% of these patients. Nearly all pheochromocytomas in MEN 2 are benign and located in the adrenals, often bilaterally. Pheochromocytoma may be symptomatic before the diagnosis of MTC is made. Prophylactic thyroidectomy is being per formed in many carriers of RET mutations, and the recommended age to perform thyroidectomy usually depends on the mutation and/or the level of calcitonin; pheochromocytomas should be excluded before any surgery in these patients. VHL is an autosomal dominant disorder that predisposes to retinal and cerebellar hemangioblastomas, which also occur in the brainstem and spinal cord (Fig. 399-6). Other important features of VHL are clear cell renal carcinomas, pancreatic neuroendocrine tumors, endo lymphatic sac tumors of the inner ear, cystadenomas of the epididymis and broad ligament, and multiple pancreatic or renal cysts. Although the VHL gene can be inactivated by all types of mutations, patients with pheochromocytoma predominantly have missense mutations. About 20–30% of patients with VHL have pheochromocytomas, but in some families, the incidence can reach 90%. The recognition of pheo chromocytoma as a VHL-associated feature provides an opportunity to diagnose retinal, central nervous system, renal, and pancreatic tumors at a stage when effective treatment may still be possible. NF1 was the first described pheochromocytoma-associated syn drome. The NF1 gene functions as a tumor suppressor by regulating the Ras signaling cascade. Classic features of neurofibromatosis include multiple neurofibromas, café au lait spots, axillary freckling of the skin, and Lisch nodules of the iris. Pheochromocytomas occur in only ~1% of these patients and are located predominantly in the adrenals. Meta static pheochromocytoma is not uncommon in NF1. The paraganglioma syndromes (PGLs) have been classified by genetic analyses of families with head and neck paragangliomas. The susceptibility genes encode subunits of the enzyme SDH, a component in the Krebs cycle and the mitochondrial electron transport chain. SDH is formed by four subunits (A–D). Mutations of SDHA (PGL5), SDHB (PGL4), SDHC (PGL3), SDHD (PGL1), and SDHAF2 (PGL2) predispose to the PGLs. The transmission of the disease in carriers of


A C E G H D F B FIGURE 399-6 von Hippel–Lindau disease. Tumors and cysts marked by arrows. A. Retinal angioma (arrows with a pair of feeding vessels). All subsequent panels show findings on magnetic resonance imaging. B–D. Hemangioblastomas of the

cerebellum (large cyst and a solid mural tumor) (B) in brainstem (in part cystic) (C) and spinal cord (thoracic) (D). E. Bilateral renal clear cell carcinomas with two tumors on each side F. Multiple pancreatic cysts. G. Microcystic serous pancreatic cystadenoma (with multiple tiny spaces). H. Two pancreatic islet cell tumors. (Part A was provided courtesy of Dr. Dieter Schmidt. Part B was provided courtesy of Dr. Christian Taschner, Freiburg. Part C was provided courtesy of Dr. Sven Glaesker, Brussels. Part D was used with permission from Dr. Jan-Helge Klingler, Freiburg. Part E was provided courtesy of Dr. Cordula Jilg, Freiburg. Parts F–H were provided courtesy of Dr. Tobias Krauss, Freiburg.) SDHA, SDHB, and SDHC germline mutations is autosomal dominant. In contrast, in virtually all SDHD and SDHAF2 families, only the prog eny of affected fathers develops tumors if they inherit the mutation. PGL1 is most common, followed by PGL4; PGL2, PGL3, and PGL5 are rare. Adrenal, extra-adrenal abdominal, and thoracic pheochro mocytomas, which are components of PGL1, PGL4, and PGL5, are rare in PGL3 and absent in PGL2 (Fig. 399-4A). About one-third of patients with PGL4 develop metastases, which is the highest rate in pheochromocytoma-associated syndromes. However, the penetrance of the disease is usually low, raising questions about the optimal way to monitor asymptomatic carriers on a long-term basis. Other syndromes with metastatic pheochromocytomas are mainly VHL, NF1, and PGL1. Other familial pheochromocytoma has been attributed to heredi tary, mainly adrenal tumors in patients with germline mutations in the genes TMEM127 and MAX. Transmission is also autosomal domi nant, and mutations of MAX, like those of SDHD, cause tumors only if inherited from the father. Pituitary neuroendocrine tumors have been described as an association with SDHx (pituitary adenoma and pheochromocytoma/paraganglioma 3PA syndrome) as well as MAX mutations (MEN 5), but they seem to occur very rarely. ■ ■GENETIC SCREENING OF PATIENTS WITH PHEOCHROMOCYTOMA OR PARAGANGLIOMA Universal germline panel testing is now the gold standard to char acterize the genetic factors involved in PPGL. It usually identifies a genetic etiology in up to 30% of the cases. This rate can be even higher in patients with early age of onset, extra-adrenal location, multiple tumors, metastatic tumors, or family history of PPGL. Effective pre ventive medicine for pheochromocytoma and pheochromocytomaassociated diseases requires management according to identified germline mutations in susceptibility genes (Table 399-3). Because of the relatively high prevalence of familial syndromes among patients who present with pheochromocytoma or paraganglioma, it is useful to identify germline mutations even in patients without a known family history. Despite the use of a universal germline panel testing performed for all patients with a PPGL, a first step remains to search for clinical features of inherited syndromes and to obtain an in-depth, multigen erational family history. Each of these syndromes exhibits autosomal dominant transmission with variable penetrance, but a proband with a mother affected by paraganglial tumors is not predisposed to PLG1 and PGL2 (SDHD and SDHAF2 mutation carrier). Cutaneous neurofi bromas, café au lait spots, and axillary freckling suggest neurofibroma tosis. Germline mutations in NF1 have nearly never been reported in patients with sporadic pheochromocytomas. Thus, NF1 testing is not needed in the absence of other clinical features of neurofibromatosis. A personal or family history of MTC or an elevation of serum calcitonin strongly suggests MEN 2 and should prompt testing for RET muta tions. A history of visual impairment or tumors of the cerebellum, brainstem, spinal cord, or the kidney suggests the possibility of VHL. A personal and/or family history of head and neck paraganglioma suggests PGL1 or PGL4. Of note, sequencing protocols may not detect large deletions of one or more exons.

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