Table 24-11 Familial Syndromes Associated with Pheochromocytoma and Extra-adrenal Paragangliomas

Syndrome	Gene	Associated Lesion	Other Features
Multiple endocrine neoplasia, type 2A (MEN-2A)	*RET*	Pheochromocytoma	Medullary thyroid carcinoma Parathyroid hyperplasia
Multiple endocrine neoplasia, type 2B (MEN-2B)	*RET*	Pheochromocytoma	Medullary thyroid carcinoma Marfanoid habitus Mucocutaneous GNs
Neurofibromatosis, type 1 (NF1)	*NF1*	Pheochromocytoma	Neurofibromatosis Café-au-lait spots Optic nerve glioma
Von Hippel-Lindau (VHL)	*VHL*	Pheochromocytoma, paraganglioma *(uncommon)*	Renal cell carcinoma Hemangioblastoma Pancreatic endocrine neoplasm
Familial paraganglioma 1	*SDHD*	Pheochromocytoma, paraganglioma	
Familial paraganglioma 3	*SDHC*	Paraganglioma	
Familial paraganglioma 4	*SDHB*	Pheochromocytoma, paraganglioma	

GN, Ganglioneuroma; *NF1*, neurofibromin; *SDHB*, succinate dehydrogenase complex, subunit B; *SDHC*, succinate dehydrogenase complex, subunit C; *SDHD*, succinate dehydrogenase complex, subunit D.
Adapted with permission from Elder EE, et al: Pheochromocytoma and functional paraganglioma syndrome: no longer the 10% tumor. J Surg Oncol 89:193-201, 2005.

paraganglia, as the term implies, are distributed along the vagus nerve. The aorticosympathetic chain is found in association with segmental ganglia of the sympathetic system and therefore is distributed mainly alongside of the abdominal aorta. The organs of Zuckerkandl, close to the aortic bifurcation, belong to this group.

The most important diseases of the adrenal medulla are neoplasms, which include neoplasms of chromaffin cells *(pheochromocytomas)* and neuronal neoplasms *(neuroblastic tumors)*. Neuroblastomas and other neuroblastic tumors are discussed in Chapter 10.

Pheochromocytoma

Pheochromocytomas are neoplasms composed of chromaffin cells, which synthesize and release catecholamines and in some instances peptide hormones. It is important to recognize these tumors because they are a rare cause of surgically correctable hypertension. Traditionally, the features of pheochromocytomas have been summarized by the "rule of 10s".

- *Ten percent of pheochromocytomas are extra-adrenal*, occurring in sites such as the organs of Zuckerkandl and the carotid body. Pheochromocytomas that develop in extra-adrenal paraganglia are designated *paragangliomas* and are discussed in Chapter 16.
- *Ten percent of sporadic adrenal pheochromocytomas are bilateral*; this figure may rise to as high as 50% in cases that are associated with familial tumor syndromes (see later).
- *Ten percent of adrenal pheochromocytomas are biologically malignant*, defined by the presence of metastatic disease. Malignancy is more common (20% to 40%) in extra-adrenal paragangliomas, and in tumors arising in the setting of certain germline mutations (see later).
- *Ten percent of adrenal pheochromocytomas are not associated with hypertension*. Of the 90% that present with hypertension, approximately two thirds have "paroxysmal" episodes associated with sudden rise in blood pressure and palpitations, which can, on occasion, be fatal.

One "traditional" 10% rule that has now been modified pertains to familial cases. It is now recognized that *as many as 25% of individuals with pheochromocytomas and paragangliomas harbor a germline mutation* in one one of at least six known genes (Table 24-11). Patients with germline mutations are typically younger at presentation than those with sporadic tumors and more often harbor bilateral disease. The affected genes fall into two broad classes, those that enhance growth factor receptor pathway signaling (e.g., *RET, NF1*), and those that increase the activity of the transcription factor HIF-1α. You will recall that the VHL gene encodes a tumor suppressor protein that is needed for the oxygen-dependent degradation of HIF-1α and is mutated in patients with von Hippel-Lindau (VHL) syndrome, which is associated with a number of tumors, including pheochromocytoma. Other familial cases of pheochromocytoma are associated with germline mutations in genes encoding components of the succinate dehydrogenase complex (*SDHB, SDHC,* and *SDHD*). This complex is involved in mitochondrial electron transport and oxygen sensing, and it is believed that these mutations also lead to upregulation of HIF-1α, which appears to be a key oncogenic driver in this type of tumor.

MORPHOLOGY

Pheochromocytomas range from small, circumscribed lesions confined to the adrenal (Fig. 24-54) to large hemorrhagic masses weighing kilograms. The average weight of a pheochromocytoma is 100 gm, but weights from just over 1 gm to almost 4000 gm have been reported. The larger tumors are well demarcated by either connective tissue or compressed cortical or medullary tissue. Richly vascularized fibrous trabeculae within the tumor produce a lobular pattern. In many tumors, remnants of the adrenal gland can be seen, stretched over the surface or attached at one pole. On section, the cut surfaces of smaller pheochromocytomas are yellow-tan. Larger lesions tend to be hemorrhagic, necrotic, and cystic and typically efface the adrenal gland. Incubation of fresh tissue with a potassium dichromate solution turns the tumor a dark brown color