Familial pheochromocytoma (FP) has been attributed to hereditary, mainly adrenal tumors in patients with germ-line mutations in the genes *TMEM127*, *MAX*, and *SDHA*. Transmission is also autosomal dominant, and mutations of *MAX*, like those of *SDHD,* cause tumors only if inherited from the father.

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In addition to family history, general features suggesting an inherited syndrome include young age, multifocal tumors, extra-adrenal tumors, and malignant tumors (Fig. 407-6). Because of the relatively high prevalence of familial syndromes among patients who present with pheochromocytoma or paraganglioma, it is useful to identify germ-line mutations even in patients without a known family history. A first step is to search for clinical features of inherited syndromes and to obtain an in-depth, multigenerational 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 (*SDHD* mutation carrier). Cutaneous neurofibromas, café au lait spots, and axillary freckling suggest neurofibromatosis. Germ-line mutations in *NF1* have not been reported in patients with sporadic pheochromocytomas. Thus, *NF1* testing need not be performed 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* mutations. A history of visual impairment or

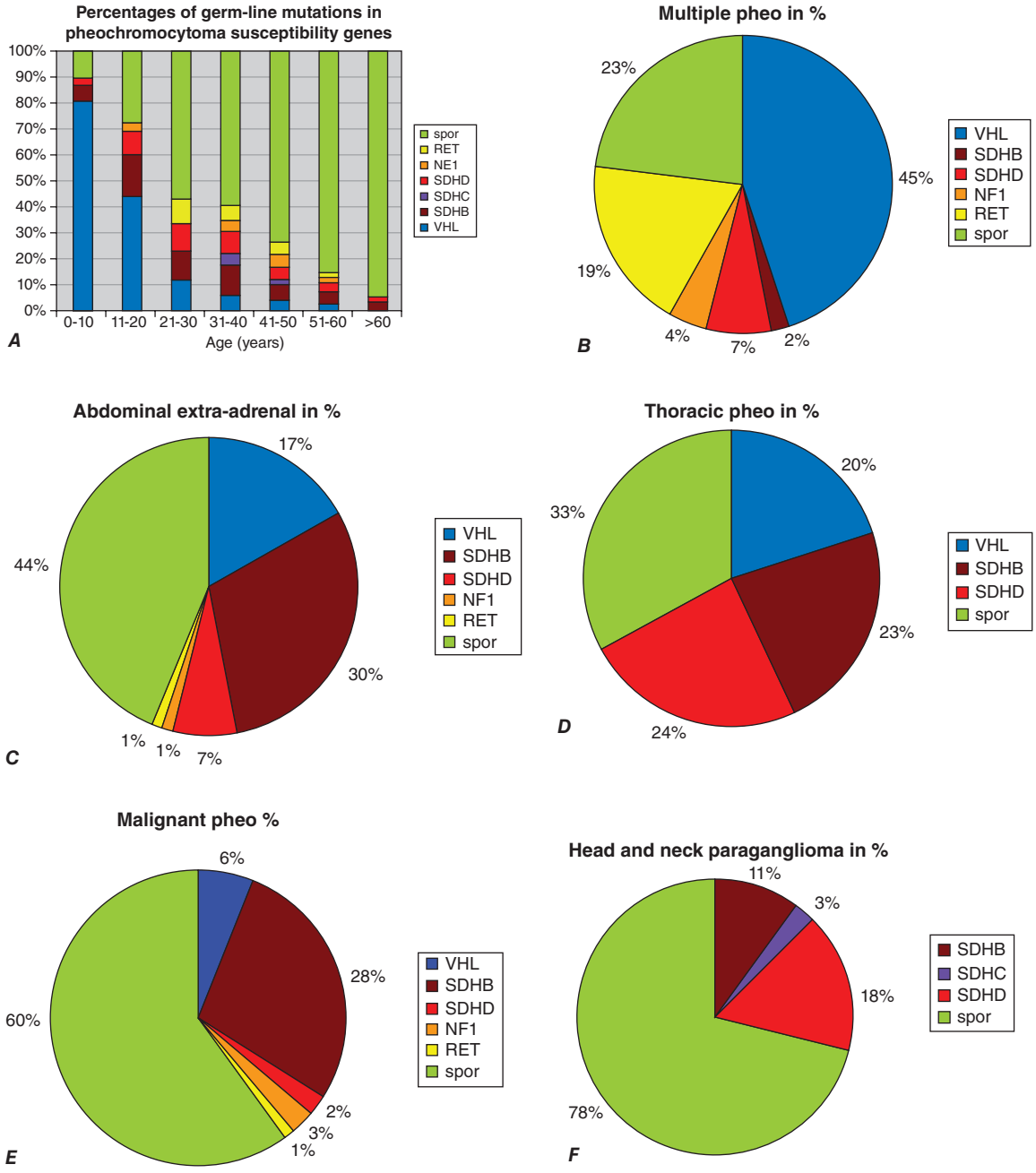

FIGURE 407-6 **Mutation distribution** in the *VHL, RET, SDHB, SDHC, SDHD,* and *NF1* genes in 2021 patients with pheochromocytomas and paragangliomas from the European-American Pheochromocytoma-Paraganglioma Registry based in Freiburg, Germany, as updated on March 1, 2014. ***A.*** Correlation with age. The bars depict the frequency of sporadic (spor) or various inherited forms of pheochromocytoma in different age groups. The inherited disorders are much more common among younger individuals presenting with pheochromocytoma. Patients with mutations in the *TMEM127, MAX,* and *SDHA* genes are not included, since they contribute <1% in decades 4–7 only. ***B–F.*** Germ-line mutations according to multiple (*B*), extra-adrenal retroperitoneal (*C*), thoracic (*D*), and malignant (*E*) pheochromocytomas and head and neck paragangliomas (*F*). *(Data from the Freiburg International Pheochromocytoma and Paraganglioma Registry, 2014.)*