Parathyroid carcinoma is often not aggressive. Long-term survival without recurrence is common if at initial surgery the entire gland is removed without rupture of the capsule. Recurrent parathyroid carcinoma is usually slow-growing with local spread in the neck, and surgical correction of recurrent disease may be feasible. Occasionally, however, parathyroid carcinoma is more aggressive, with distant metastases (lung, liver, and bone) found at the time of initial operation. It may be difficult to appreciate initially that a primary tumor is carcinoma; increased numbers of mitotic figures and increased fibrosis of the gland stroma may precede invasion. The diagnosis of carcinoma is often made in retrospect. Hyperparathyroidism from a parathyroid carcinoma may be indistinguishable from other forms of primary hyperparathyroidism but is usually more severe clinically. A potential clue to the diagnosis is offered by the degree of calcium elevation. Calcium values of 3.5–3.7 mmol/L (14–15 mg/dL) are frequent with carcinoma and may alert the surgeon to remove the abnormal gland with care to avoid capsular rupture. Recent findings concerning the genetic basis of parathyroid carcinoma (distinct from that of benign adenomas) indicate the need, in these kindreds, for family screening (see below).

GENETIC DEFECTS ASSOCIATED WITH HYPERPARATHYROIDISM

As in many other types of neoplasia, two fundamental types of genetic defects have been identified in parathyroid gland tumors: (1) overactivity of protooncogenes and (2) loss of function of tumor-suppressor genes. The former, by definition, can lead to uncontrolled cellular growth and function by activation (gain-of-function mutation) of a single allele of the responsible gene, whereas the latter requires loss of function of both allelic copies. Biallelic loss of function of a tumor-suppressor gene is usually characterized by a germline defect (all cells) and an additional somatic deletion/mutation in the tumor (Fig. 424-3).

Mutations in the *MEN1* gene locus, encoding the protein MENIN, on chromosome 11q13 are responsible for causing MEN 1; the normal allele of this gene fits the definition of a tumor-suppressor gene. Inheritance of one mutated allele in this hereditary syndrome, followed by loss of the other allele via somatic cell mutation, leads to monoclonal expansion and tumor development. Also, in ~15–20% of sporadic parathyroid adenomas, both alleles of the *MEN1* locus on chromosome 11 are somatically deleted, implying that the same defect responsible for MEN 1 can also cause the sporadic disease (Fig. 424-3*A*). Consistent with the Knudson hypothesis for two-step neoplasia in certain inherited cancer syndromes (Chap. 101e), the earlier onset of hyperparathyroidism in the hereditary syndromes reflects the need for only one mutational event to trigger the monoclonal outgrowth. In sporadic adenomas, typically occurring later in life, two different somatic events must occur before the *MEN1* gene is silenced.

Other presumptive anti-oncogenes involved in hyperparathyroidism include a still unidentified gene mapped to chromosome 1p seen in 40% of sporadic parathyroid adenomas and a gene mapped to chromosome Xp11 in patients with secondary hyperparathyroidism and renal failure, who progressed to "tertiary" hyperparathyroidism, now known to reflect monoclonal outgrowths within previously hyperplastic glands.

A more complex pattern, still incompletely resolved, arises with genetic defects and carcinoma of the parathyroids. This appears to be due to biallelic loss of a functioning copy of a gene, *HRPT2* (or CDC73), originally identified as the cause of the HPT-JT syndrome. Several inactivating mutations have been identified in *HRPT2* (located on chromosome 1q21-31), which encodes a 531-amino-acid protein called parafibromin. The responsible genetic mutations in *HRPT2* appear to be necessary, but not sufficient, for parathyroid cancer.

In general, the detection of additional genetic defects in these parathyroid tumor–related syndromes and the variations seen in

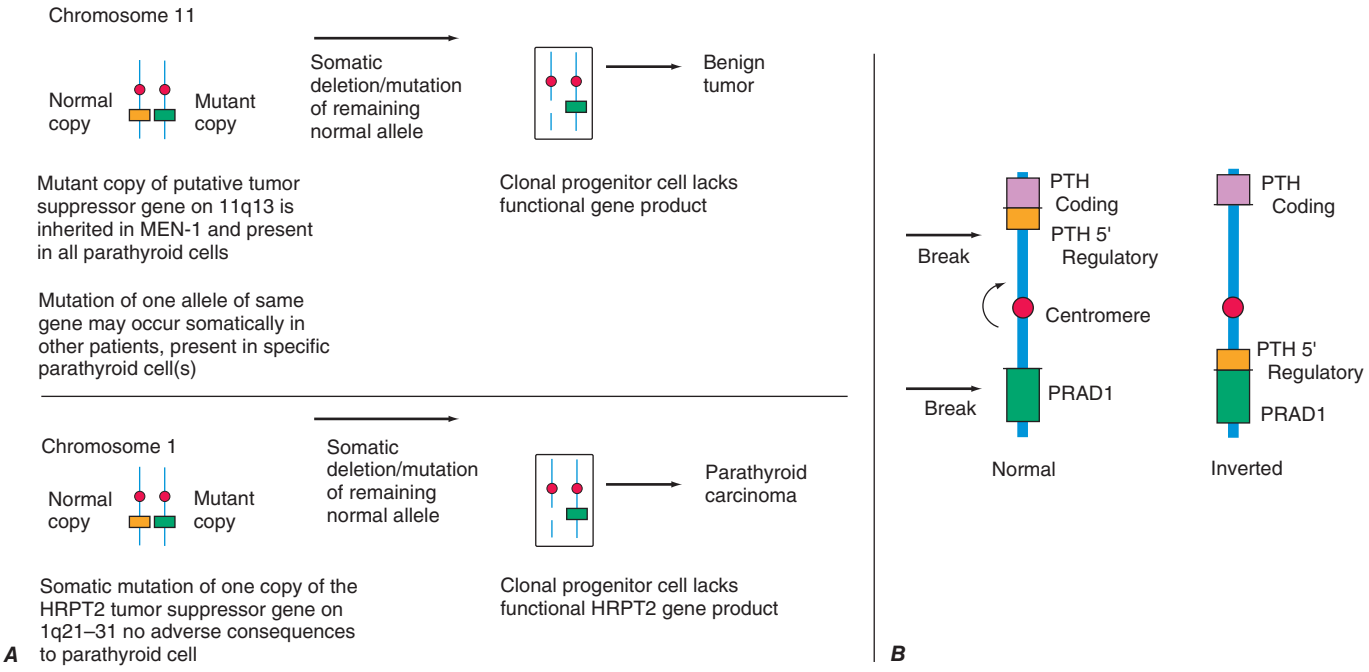

FIGURE 424-3 ***A.*** Schematic diagram indicating molecular events in tumor susceptibility. The patient with the hereditary abnormality (multiple endocrine neoplasia [MEN]) is envisioned as having one defective gene inherited from the affected parent on chromosome 11, but one copy of the normal gene is present from the other parent. In the monoclonal tumor (benign tumor), a somatic event, here partial chromosomal deletion, removes the remaining normal gene from a cell. In nonhereditary tumors, two successive somatic mutations must occur, a process that takes a longer time. By either pathway, the cell, deprived of growth-regulating influence from this gene, has unregulated growth and becomes a tumor. A different genetic locus also involving loss of a tumor-suppressor gene termed HRPT2 is involved in the pathogenesis of parathyroid carcinoma. *(From A Arnold: J Clin Endocrine Metab 77:1108, 1993. Copyright 1993, The Endocrine Society.)* ***B.*** Schematic illustration of the mechanism and consequences of gene rearrangement and overexpression of the *PRAD1* protooncogene (pericentromeric inversion of chromosome 11) in parathyroid adenomas. The excessive expression of PRAD1 (a cell cycle control protein, cyclin D_1) by the highly active parathyroid hormone (PTH) gene promoter in the parathyroid cell contributes to excess cellular proliferation. *(From J Habener et al, in L DeGroot, JL Jameson [eds]: Endocrinology, 4th ed. Philadelphia, Saunders, 2001; with permission.)*