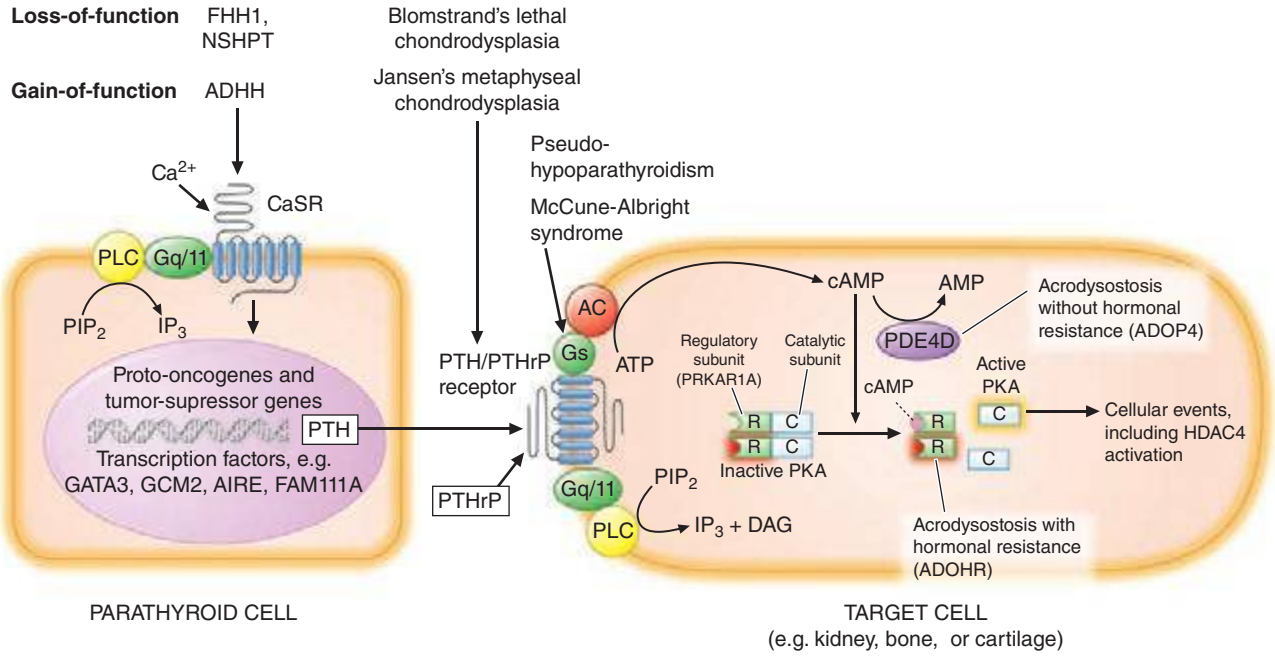

FIGURE 424-5 **Illustration of some genetic mutations** that alter calcium metabolism by effects on the parathyroid cell or target cells of parathyroid hormone (PTH) action. Alterations in PTH production by the parathyroid cell can be caused by changes in the response to extracellular fluid calcium (Ca^{2+}) that are detected by the calcium-sensing receptor (CaSR). Furthermore, PTH (or PTH-related peptide [PTHrP]) can show altered efficacy in target cells such as in proximal tubular cells, by altered function of its receptor (PTH/PTHrP receptor) or the signal transduction proteins, G proteins such as $G_s\alpha$, which is linked to adenylate cyclase (AC), the enzyme responsible for producing cyclic AMP (cAMP) (also illustrated are Gq/11, which activate an alternate pathway of receptor signal transmission involving the generation of inositol triphosphate [IP_3] or diacylglycerol [DAG]). Heterozygous loss-of-function mutations in the CaSR cause familial benign hypocalciuric hypercalcemia (FBHH), homozygous mutations (both alleles mutated), and severe neonatal hyperparathyroidism (NSHPT); heterozygous gain-of-function causes autosomal dominant hypercalciuric hypocalcemia (ADHH). Other defects in parathyroid cell function that occur at the level of gene regulation (oncogenes or tumor-suppressor genes) or transcription factors are discussed in the text. Blomstrand's lethal chondrodysplasia is due to homozygous or compound heterozygous loss-of-function mutations in the PTH/PTHrP receptor, a neonatally lethal disorder, while pseudohypoparathyroidism involves inactivation at the level of the G proteins, specifically mutations that eliminate or reduce $G_s\alpha$ activity in the kidney (see text for details). Acrodysostosis can occur with (acrodysostosis with hormonal resistance [ADOHR]; mutant regulatory subunit of PKA) or without hormonal resistance (ADOP4; mutant PDE4D). Jansen's metaphyseal chondrodysplasia and McCune-Albright syndrome represent gain-of-function mutations in the PTH/PTHrP receptor and $G_s\alpha$ protein, respectively.

difficult to distinguish from primary hyperparathyroidism. Although malignancy is often clinically obvious or readily detectable by medical history, hypercalcemia can occasionally be due to an occult tumor. Previously, hypercalcemia associated with malignancy was thought to be due to local invasion and destruction of bone by tumor cells; many cases are now known to result from the elaboration by the malignant cells of humoral mediators of hypercalcemia. PTHrP is the responsible humoral agent in most solid tumors that cause hypercalcemia.

The histologic character of the tumor is more important than the extent of skeletal metastases in predicting hypercalcemia. Small-cell carcinoma (oat cell) and adenocarcinoma of the lung, although the most common lung tumors associated with skeletal metastases, rarely cause hypercalcemia. By contrast, many patients with squamous cell carcinoma of the lung develop hypercalcemia. Histologic studies of bone in patients with squamous cell or epidermoid carcinoma of the lung, in sites invaded by tumor as well as areas remote from tumor invasion, reveal increased bone resorption.

Two main mechanisms of hypercalcemia are operative in cancer hypercalcemia. Many solid tumors associated with hypercalcemia, particularly squamous cell and renal tumors, produce and secrete PTHrP that causes increased bone resorption and mediate the hypercalcemia through systemic actions on the skeleton. Alternatively, direct bone marrow invasion occurs with hematologic malignancies such as leukemia, lymphoma, and multiple myeloma. Lymphokines and cytokines (including PTHrP) produced by cells involved in the marrow response to the tumors promote resorption of bone through local destruction. Several hormones, hormone analogues, cytokines, and growth factors have been implicated as the result of clinical assays, in vitro tests, or chemical isolation. The etiologic factor produced by activated normal lymphocytes and by myeloma and lymphoma cells, originally termed *osteoclast activation factor*, now appears to represent the biologic action of several different cytokines, probably interleukin 1 and lymphotoxin or tumor necrosis factor (TNF). In some lymphomas, there is a third mechanism, caused by an increased blood level of $1,25(OH)_2D$, produced by the abnormal lymphocytes.

In the more common mechanism, usually termed *humoral hypercalcemia of malignancy*, solid tumors (cancers of the lung and kidney, in particular), in which bone metastases are absent, minimal, or not detectable clinically, secrete PTHrP measurable by immunoassay. Secretion by the tumors of the PTH-like factor, PTHrP, activates the PTH1R, resulting in a pathophysiology closely resembling hyperparathyroidism, but with normal or suppressed PTH levels. The clinical picture resembles primary hyperparathyroidism (hypophosphatemia accompanies hypercalcemia), and elimination or regression of the primary tumor leads to disappearance of the hypercalcemia.

As in hyperparathyroidism, patients with the humoral hypercalcemia of malignancy have elevated urinary nephrogenous cAMP excretion, hypophosphatemia, and increased urinary phosphate clearance. However, in humoral hypercalcemia of malignancy, immunoreactive PTH is undetectable or suppressed, making the differential diagnosis easier. Other features of the disorder differ from those of true hyperparathyroidism. Although the biologic actions of PTH and PTHrP are exerted through the same receptor, subtle differences in receptor activation by the two ligands must account for some of the discordance in pathophysiology, when an excess of one or the other peptide occurs. Other cytokines elaborated by the malignancy may contribute to the variations from hyperparathyroidism in these patients as well. Patients