substernal locations, it is not possible to palpate all nodules. Pemberton's sign, characterized by facial suffusion when the patient's arms are elevated above the head, suggests that the goiter has increased pressure in the thoracic inlet. A TSH level should be measured to exclude subclinical hyper- or hypothyroidism, but thyroid function is usually normal. Tracheal deviation is common, but compression must usually exceed 70% of the tracheal diameter before there is significant airway compromise. Pulmonary function testing can be used to assess the functional effects of compression, which characteristically causes inspiratory stridor. CT or MRI can be used to evaluate the anatomy of the goiter and the extent of substernal extension or tracheal narrowing. A barium swallow may reveal the extent of esophageal compression. The risk of malignancy in MNG is similar to that in solitary nodules. Ultrasonography can be used to identify which nodules should be biopsied based on sonographic features (see section above on ultrasound) and size. For nodules with more suspicious imaging characteristics (e.g., hypoechogenicity, microcalcifications, irregular margins), biopsy is recommended when ≥1 cm.

TREATMENT NONTOXIC MULTINODULAR GOITER

Most nontoxic MNGs can be managed conservatively. T_4 suppression is rarely effective for reducing goiter size and introduces the risk of subclinical or overt thyrotoxicosis, particularly if there is underlying autonomy or if it develops during treatment. If levothyroxine is used, it should be started at low doses (50 µg daily) and advanced gradually while monitoring the TSH level to avoid excessive suppression. Contrast agents and other iodine-containing substances should be avoided because of the risk of inducing the *Jod-Basedow effect*, characterized by enhanced thyroid hormone production by autonomous nodules. Radioiodine is used with increasing frequency in areas where large goiters are more prevalent because it can decrease goiter size and may selectively ablate regions of autonomy. Dosage of ^{131}I depends on the size of the goiter and radioiodine uptake but is usually about 3.7 MBq (0.1 mCi) per gram of tissue, corrected for uptake (typical dose 370–1070 MBq [10 to 29 mCi]). Repeat treatment may be needed and effectiveness may be increased by concurrent administration of low-dose recombinant TSH (0.1 mg IM). It is possible to achieve a 40–50% reduction in goiter size in most patients. Earlier concerns about radiation-induced thyroid swelling and tracheal compression have diminished, as studies have shown this complication to be rare. When acute compression occurs, glucocorticoid treatment or surgery may be needed. Radiation-induced hypothyroidism is less common than after treatment for Graves' disease. However, posttreatment autoimmune thyrotoxicosis may occur in up to 5% of patients treated for nontoxic MNG. Surgery remains highly effective but is not without risk, particularly in older patients with underlying cardiopulmonary disease.

TOXIC MULTINODULAR GOITER

The pathogenesis of toxic MNG appears to be similar to that of nontoxic MNG; the major difference is the presence of functional autonomy in toxic MNG. The molecular basis for autonomy in toxic MNG remains unknown. As in nontoxic goiters, many nodules are polyclonal, whereas others are monoclonal and vary in their clonal origins. Genetic abnormalities known to confer functional autonomy, such as activating TSH-R or $G_s\alpha$ mutations (see below), are not usually found in the autonomous regions of toxic MNG goiter.

In addition to features of goiter, the clinical presentation of toxic MNG includes subclinical hyperthyroidism or mild thyrotoxicosis. The patient is usually elderly and may present with atrial fibrillation or palpitations, tachycardia, nervousness, tremor, or weight loss. Recent exposure to iodine, from contrast dyes or other sources, may precipitate or exacerbate thyrotoxicosis. The TSH level is low. The uncombined T_4 level may be normal or minimally increased; T_3 is often elevated to a greater degree than T_4. Thyroid scan shows heterogeneous uptake with multiple regions of increased and decreased uptake; 24-h uptake of radioiodine may not be increased but is usually in the upper normal range.

Prior to definitive treatment of the hyperthyroidism, ultrasound imaging should be performed to assess the presence of discrete nodules corresponding to areas of decreased uptake ("cold" nodules). If present, FNA may be indicated based on sonographic features and size cutoffs. The cytology results, if indeterminate or suspicious, may direct the therapy to surgery.

TREATMENT TOXIC MULTINODULAR GOITER

Antithyroid drugs normalize thyroid function and are particularly useful in the elderly or ill patients with limited lifespan. In contrast to Graves' disease, spontaneous remission does not occur and so treatment is long-term. Radioiodine is generally the treatment of choice; it treats areas of autonomy as well as decreasing the mass of the goiter. Sometimes, however, a degree of autonomy remains, presumably because multiple autonomous regions emerge as soon as others are treated, and further radioiodine treatment may be necessary. Surgery provides definitive treatment of underlying thyrotoxicosis as well as goiter. Patients should be rendered euthyroid using an antithyroid drug before operation.

HYPERFUNCTIONING SOLITARY NODULE

A solitary, autonomously functioning thyroid nodule is referred to as *toxic adenoma*. The pathogenesis of this disorder has been unraveled by demonstrating the functional effects of mutations that stimulate the TSH-R signaling pathway. Most patients with solitary hyperfunctioning nodules have acquired somatic, activating mutations in the TSH-R **(Fig. 405-11)**. These mutations, located primarily in the receptor transmembrane domain, induce constitutive receptor coupling to $G_{s\alpha}$, increasing cyclic AMP levels and leading to enhanced thyroid follicular cell proliferation and function. Less commonly, somatic mutations are identified in $G_{s\alpha}$. These mutations, which are similar to those seen in

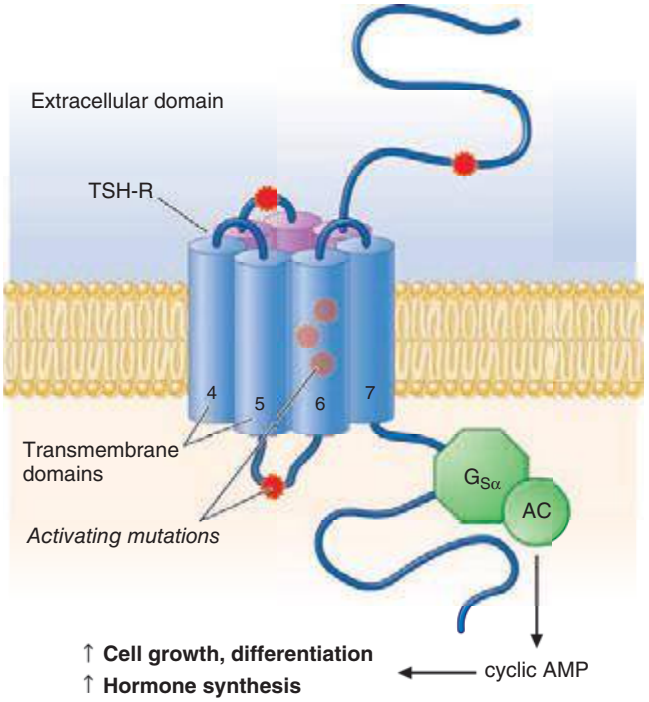

FIGURE 405-11 Activating mutations of the thyroid-stimulating hormone receptor (TSH-R). Mutations (*) that activate TSH-R reside mainly in transmembrane 5 and intracellular loop 3, although mutations have occurred in a variety of different locations. The effect of these mutations is to induce conformational changes that mimic TSH binding, thereby leading to coupling to stimulatory G protein ($G_{s\alpha}$) and activation of adenylate cyclase (AC), an enzyme that generates cyclic AMP.