TABLE 405-13 GENETIC ALTERATIONS IN THYROID NEOPLASIA

Gene/Protein	Type of Gene	Chromosomal Location	Genetic Abnormality	Tumor
TSH receptor	GPCR receptor	14q31	Point mutations	Toxic adenoma, differentiated carcinomas
$G_{s\alpha}$	G protein	20q13.2	Point mutations	Toxic adenoma, differentiated carcinomas
RET/PTC	Receptor tyrosine kinase	10q11.2	Rearrangements PTC1: inv(10)(q11.2q21) PTC2: t(10;17)(q11.2;q23) PTC3: ELE1/TK	PTC (more common in radiation-induced tumors)
RET	Receptor tyrosine kinase	10q11.2	Point mutations	MEN 2, medullary thyroid cancer
BRAF	MEK kinase	7q24	Point mutations, rearrangements	PTC, ATC
TRK	Receptor tyrosine kinase	1q23-24	Rearrangements	Multinodular goiter, papillary thyroid cancer
RAS	Signal transducing p21	NRAS 1p13.2 (most common); HRAS 11p15.5; KRAS 12p12.1	Point mutations	Follicular thyroid cancer, PTC follicular variant, adenomas
p53	Tumor suppressor, cell cycle control, apoptosis	17p13	Point mutations Deletion, insertion	Anaplastic cancer
APC	Tumor suppressor, adenomatous polyposis coli gene	5q21-q22	Point mutations	Anaplastic cancer, also associated with familial polyposis coli
p16 (MTS1, CDKN2A)	Tumor suppressor, cell cycle control	9p21	Deletions	Differentiated carcinomas
p21/WAF	Tumor suppressor, cell cycle control	6p21.2	Overexpression	Anaplastic cancer
MET	Receptor tyrosine kinase	7q31	Overexpression	Follicular thyroid cancer
c-MYC	Receptor tyrosine kinase	8q24.12-13	Overexpression	Differentiated carcinoma
PTEN	Phosphatase	10q23	Point mutations	PTC in Cowden's syndrome (multiple hamartomas, breast tumors, gastrointestinal polyps, thyroid tumors)
CTNNB1	β-Catenin	3p22	Point mutations	Anaplastic cancer
Loss of heterozygosity (LOH)	? Tumor suppressors	3p; 11q13, other loci	Deletions	Differentiated thyroid carcinomas, anaplastic cancer
PAX8-PPARγ1	Transcription factor-nuclear receptor fusion	t(2;3)(q13;p25)	Translocation	Follicular adenoma or carcinoma, rare PTC follicular variant

Abbreviations: APC, adenomatous polyposis coli; ATC, anaplastic thyroid cancer; BRAF, v-raf homologue, B1; CDKN2A, cyclin-dependent kinase inhibitor 2A; c-MYC, cellular homologue of myelocytomatosis virus protooncogene; ELE1/TK, RET-activating gene ele1/tyrosine kinase; GPCR, G protein–coupled receptor; $G_{s\alpha}$, G-protein stimulating α-subunit; MEK, mitogen extracellular signal-regulated kinase; MEN 2, multiple endocrine neoplasia-2; MET, met protooncogene (hepatocyte growth factor receptor); MTS, multiple tumor suppressor; p53, p53 tumor suppressor gene; PTC, papillary thyroid cancer; PTEN, phosphatase and tensin homologue; RAS, rat sarcoma protooncogene; RET, rearranged during transfection protooncogene; p21, p21 tumor suppressor; PAX8, paired domain transcription factor; PPARγ1, peroxisome-proliferator activated receptor γ1; TRK, tyrosine kinase receptor; TSH, thyroid-stimulating hormone; WAF, wild-type p53 activated fragment.

Source: Adapted with permission from P Kopp, JL Jameson, in JL Jameson (ed): *Principles of Molecular Medicine*. Totowa, NJ, Humana Press, 1998.

point mutations that induce constitutive activity of the tyrosine kinase (Chap. 408). MTC is preceded by hyperplasia of the C cells, raising the likelihood that as-yet-unidentified "second hits" lead to cellular transformation. A subset of sporadic MTC contains somatic mutations that activate *RET*.

WELL-DIFFERENTIATED THYROID CANCER

Papillary PTC is the most common type of thyroid cancer, accounting for 70–90% of well-differentiated thyroid malignancies. Microscopic PTC is present in up to 25% of thyroid glands at autopsy, but most of these lesions are very small (several millimeters) and are not clinically significant. Characteristic cytologic features of PTC help make the diagnosis by FNA or after surgical resection; these include psammoma bodies, cleaved nuclei with an "orphan-Annie" appearance caused by large nucleoli, and the formation of papillary structures.

PTC tends to be multifocal and to invade locally within the thyroid gland as well as through the thyroid capsule and into adjacent structures in the neck. It has a propensity to spread via the lymphatic system but can metastasize hematogenously as well, particularly to bone and lung. Because of the relatively slow growth of the tumor, a significant burden of pulmonary metastases may accumulate, sometimes with remarkably few symptoms. The prognostic implication of lymph node spread is debated. Lymph node involvement by thyroid cancer can be well tolerated but appears to increase the risk of recurrence and mortality, particularly in older patients. The staging of PTC by the TNM system is outlined in Table 405-12. Most papillary cancers are identified in the early stages (>80% stages I or II) and have an excellent prognosis, with survival curves similar to expected survival (Fig. 405-12). Mortality is markedly increased in stage IV disease, especially in the presence of distant metastases (stage IVC), but this group comprises only about 1% of patients. The treatment of PTC is described below.

Follicular The incidence of FTC varies widely in different parts of the world; it is more common in iodine-deficient regions. Currently, FTC accounts for only about 5% of all thyroid cancers diagnosed in the United States. FTC is difficult to diagnose by FNA because the distinction between benign and malignant follicular neoplasms rests largely on evidence of invasion into vessels, nerves, or adjacent structures. FTC tends to spread by hematogenous routes leading to bone, lung, and central nervous system metastases. Mortality rates associated with FTC are less favorable than for PTC, in part because a larger proportion of patients present with stage IV disease. Poor prognostic features include distant metastases, age >50 years, primary tumor size >4 cm, Hürthle cell histology, and the presence of marked vascular invasion.