Molecular Diagnostics of Thyroid Tumors
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The molecular genetics of thyroid carcinoma can be translated into clinical practice as an ancillary tool for diagnosis and prognostication.\(^1\) The two most common types of thyroid carcinoma, papillary and follicular carcinoma, harbor four nonoverlapping genetic alterations—BRAF and RAS point mutations and RET/PTC and PAX8/PPAR\(\gamma\) rearrangements in more than 70% of cases.

*BRAF* V600E mutation is the most common known genetic event in papillary thyroid carcinoma, and it represents a specific marker for papillary carcinoma and related tumor types.\(^1\) It also correlates with aggressive characteristics, such as extrathyroidal extension, advanced stage at presentation, lymph node or distant metastases, and increased tumor recurrence and tumor-related mortality; thus, it is a useful prognostic indicator.\(^2,5\) *RET/PTC* rearrangements are also found in papillary thyroid carcinomas, especially in young patients and patients with radiation exposure.\(^6-9\) *RET/PTC*-positive tumors usually present with classic papillary histology and have a high rate of lymph node metastases.\(^10\)

*RAS* (NRAS, HRAS, KRAS) point mutations are found in the follicular variant of papillary carcinomas, follicular carcinomas, and follicular adenomas.\(^1\) Papillary carcinomas with RAS mutations are usually encapsulated with a low rate of lymph node metastases.\(^10\) The presence of *RAS* mutations in cold adenomatous nodules and goiter nodules suggests that these lesions are likely true neoplasms, and they should be categorized as follicular adenomas.\(^1\)

*PAX8/PPAR\(\gamma\)* rearrangement occurs in the convention type of follicular carcinomas and oncocytic carcinomas. *PAX8/PPAR\(\gamma\)*-positive tumors are usually small, with frequent vascular invasion, and tend to occur in younger patients.\(^11,12\) Occasionally, follicular variant papillary carcinomas and follicular adenomas may also harbor the *PAX8/PPAR\(\gamma\)* rearrangement.\(^11,13\)

While FNA cytology is usually diagnostic for thyroid lesions, 10% to 40% of FNA samples may be "indeterminate for malignancy."\(^14-17\) Recent evidence suggests that molecular analysis of these FNA samples may improve the accuracy of cytologic diagnosis and guide patient management. For example, the presence of a *BRAF* mutation in an FNA sample indicates more than 99% probability of thyroid cancer, and it serves as a marker of aggressive behavior.\(^1\) Preoperatively detected *BRAF*-positive nodules should be extensively excised,\(^18\) with more aggressive treatment and follow-up.\(^19\) Detection of a *RAS* mutation in FNA samples correlates with malignancy in 74% to 88% of cases,\(^20,21\) and it is a useful marker for pre operative
diagnosis of follicular variant of papillary carcinoma and follicular carcinoma, both of which are difficult to diagnose by cytology alone.

The American Thyroid Association’s recent Revised Management Guidelines for Patients with Thyroid Nodules and Differentiated Thyroid Cancer recommends the use of molecular markers, such as BRAF, RAS, RET/PTC, and PAX8/PPARγ, for indeterminate FNA cytology to guide patient management. Molecular analysis of excised thyroid lesions has limited diagnostic value for papillary carcinomas, but the PAX8/PPARγ rearrangement is characteristically seen in follicular carcinoma, and its presence in a follicular lesion should prompt a thorough examination for histologic features of malignancy.

The most appropriate molecular analytic technique is determined by the mutation type suspected and sample type available for analysis. Freshly-collected FNA samples or snap-frozen tumor samples generally offer the highest quality DNA and RNA for molecular testing, but formalin-fixed or cytologic ethanol-fixed samples can also be used. Point mutations, such as BRAF and RAS, can be reliably detected by a variety of techniques including Sanger sequencing, pyrosequencing, and real-time PCR. The detection of chromosomal rearrangements, such as RET/PTC or PAX8/PPARγ, can be achieved by RT-PCR or by fluorescence in situ hybridization analysis.

In summary, four mutation types can be identified in papillary and follicular thyroid carcinomas: BRAF, RAS, RET/PTC, and PAX8/PPARγ. These mutations impact tumor diagnosis and prognostication, which may direct clinical management. Therefore, pathologists should perform molecular analysis of thyroid nodules when clinically indicated.

References


