Molecular Genetics of Thyroid Cancer in Children and Adolescents

Andrew J. Bauer, MD

KEYWORDS

• Thyroid cancer • Molecular markers • Oncogene • Mutation • Gene fusion
• Indeterminate cytology

KEY POINTS

- There are clinical differences for how differentiated thyroid cancer (DTC) behaves when diagnosed in pediatric patients compared with adults even within the same histologic variant.
- Pediatric patients with thyroid nodules have a similar likelihood of indeterminate cytology and a higher likelihood of malignancy.
- Mutations in *BRAF* are common in pediatric papillary thyroid carcinoma (PTC) but may not portend an increased risk of invasive or refractory disease.
- There are several familial forms of thyroid cancer that present with clinical disease within the pediatric population, including medullary thyroid cancer and DTC.
- Exploring the integrated genomic landscape of pediatric PTC holds great promise to increase the preoperative diagnosis as well as optimize stratification of care so that a more aggressive approach is pursued only for patients with an increased risk for persistent, recurrent, or refractory disease.

INTRODUCTION

In the simplest approach, thyroid cancer is divided into 2 major categories: follicular-derived tumors, including follicular thyroid carcinoma (FTC) and papillary thyroid carcinoma (PTC), and the parafollicular-derived tumor, medullary thyroid carcinoma (MTC). FTC and PTC are often classified as forms of differentiated thyroid cancer (DTC) because they typically maintain nonmalignant cellular physiology, including the ability to respond to thyroid stimulatory hormone (TSH), transport iodine via the sodium-iodine symporter, and produce thyroglobulin (Tg). In both pediatric patients

Disclosure: The author has nothing to disclose.
Division of Endocrinology and Diabetes, The Thyroid Center, The Children's Hospital of Philadelphia, The Perelman School of Medicine, The University of Pennsylvania, 3401 Civic Center Boulevard, Philadelphia, PA 19104, USA
E-mail address: bauera@chop.edu

Endocrinol Metab Clin N Am ■ (2017) ■–■
http://dx.doi.org/10.1016/j.ecl.2017.01.014 **endo.theclinics.com**

and adults, these tumors may present as sporadic lesions or be associated with a familial pattern of inheritance. In pediatrics, with decreasing frequency, DTC is most commonly sporadic, followed by radiation induced, associated with treatment of a nonthyroid malignancy, and lastly associated with a familial tumor predisposition syndrome. In contrast, MTC is most commonly associated with an autosomal dominantly inherited disorder, multiple endocrine neoplasia (MEN) type 2, and rarely presents as a sporadic tumor within the pediatric population. This article covers the genetic alterations associated with these two forms of thyroid cancer and provides recommendations for how to incorporate this information into clinical practice.

DIFFERENTIATED THYROID CARCINOMA

Thyroid tumorigenesis and progression are associated with somatic point mutations of *BRAF* and the *RAS* genes, as well as fusions involving the rearranged during transfection (*RET*) and *NTRK1* tyrosine kinases, with resultant constitutive activation of the mitogen-activated protein kinase (MAPK) and phosphoinositide 3-kinase (PI3K) signaling pathways.[1,2] With uncommon exceptions, these mutations are mutually exclusive events and there is a fairly predictable relationship between oncogenic genotype and histopathologic phenotype, with *RET-PTC* rearrangements[3,4] and B-rapidly accelerated fibrosarcoma (*RAF*) point mutations common in PTC,[5] paired-box gene 8 (*PAX8*)-peroxisome proliferator-activated receptor gamma (*PPARG*) common in FTC,[6,7] and *RAS* mutations found in both FTC and follicular variant of PTC (fvPTC).[8,9] With improved technologies, additional point mutations and fusions have been reported (**Table 1**).

The Cancer Genome Atlas (TCGA) project provided a major step forward in defining the genomic landscape of PTC via comprehensive multiplatform analysis of nearly 500 adult tumors.[10] The combined analysis of genomic variants, gene expression, microRNA (miR) expression, alterations in methylation, and proteomic profiles revealed that mutations in *BRAF* and the *RAS* genes were the most common driver events, with gene fusions involving *RET*, neurotrophic tyrosine kinase receptor (*NTRK*), and anaplastic lymphoma receptor tyrosine kinase (*ALK*) found in only 15% of tumors.[10] A thyroid differentiation score was determined by analyzing the expression of 16 thyroid-specific metabolism and function genes and, combining all the data, the investigators suggested a molecular classification into 2 distinct subgroups: *BRAF*-like PTC (BVL-PTC) and *RAS*-like PTC (RL-PTC). Tumors with *RET* fusions followed a molecular pattern and clinical phenotype within the BVL-PTC subgroup and displayed predominant activation of the MAPK signaling pathway, whereas RL-PTC tumors were associated with concurrent activation of the PI3K/AKT and MAPK signaling pathways. The importance of the TCGA results is expansive and clinically applicable with anticipated improvements in diagnostic accuracy as well as stratification of treatment, including selection of tumor-specific systemic therapy. Similar oncogenic variants are found in pediatric PTC; however, a thorough and comprehensive investigation of the genomic landscape across all molecular platforms needs to be performed to determine where crossover in molecular signaling exists before extending the TCGA data into clinical practice for children and adolescents.

GENETIC MUTATIONS AND REARRANGEMENTS OF ONCOGENES

Mutations in *BRAF* and *RAS*, and *RET-PTC* fusions, represent the most common genetic alterations in PTC and FTC. The spectrum of somatic genetic alterations seems to be different between pediatric and adult patients comparing tumors with similar histology, with gene fusions found in a higher percentage of pediatric tumors compared with point mutations. Gene fusions involving *RET* and *NTRK* and point mutations involving *BRAF*