Familial non-medullary thyroid cancer: an update on the genetic and pathologic features

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Abstract

Well differentiated thyroid carcinoma is one of the most increasingly prevalent cancers, and while many are sporadic, some are inherited. These heritable thyroid cancers are grouped as familial non-medullary thyroid carcinoma (FNMTC) and represent approximately 5–10% of non-medullary thyroid carcinomas. While the group of FNMTC is quite heterogeneous, an ever increasing number of attributable genetic changes have been described. In addition to the classic, non-syndromic FNMTC there are also several well defined and characterized genetic syndromes with thyroid cancer as a component. This review will provide an update on the current molecular understanding of both syndromic and non-syndromic heritable thyroid cancer.

Keywords follicular thyroid carcinoma; genetics; papillary thyroid carcinoma; thyroid cancer

Introduction

Thyroid cancer has one of the fastest growing incidences of any cancer type, mostly due to the increasing incidence of well differentiated thyroid carcinoma, and more specifically papillary thyroid carcinoma. It is currently estimated that 1% of the US population will develop thyroid cancer in their lifetime. Since much of this increase in cancer incidence is due to small, well differentiated thyroid cancers, there continues to be an excellent prognosis in thyroid cancer and the death rates remain stable.[1] Most thyroid cancer shows follicular cell differentiation while medullary thyroid carcinoma (MTC) with a neuroendocrine C-cell phenotype is less common.

MTC is only the third most common thyroid malignancy but is more often brought to mind when the topic of heritable thyroid cancer is raised. Approximately 25% of MTC are a result of germline mutations and heritable syndromes such as multiple endocrine neoplasia type 2 (MEN2). Less commonly, non-medullary thyroid carcinomas are part of a heritable familial genetic predisposition. Heritable or familial non-medullary thyroid carcinoma (FNMTC) can include papillary thyroid carcinoma (PTC) and its variants, follicular thyroid carcinoma (FTC), or anaplastic thyroid carcinoma (ATC). PTC and FTC are well known to develop at an increased rate in a variety of other tumour syndromes and these will be briefly discussed in this review. In addition to these more well defined eponymous syndromes, there is also strong evidence that some families have a heritable genetic trait leading to an increased risk of non-medullary thyroid carcinoma (NMTC). This review will also focus on the clinical, molecular and pathological features of this group of so called non-syndromic FNMTC.

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Non-medullary thyroid carcinoma associated with defined syndromes

Several defined syndromes exist that are associated with an increased risk of thyroid cancer. Patients with tumour syndromes such as the PTEN hamartoma syndrome (Cowden syndrome), Familial Adenomatous Polyposis (FAP), Werner syndrome (adult progeria) and Carney complex have an increased risk of NMTC and benign thyroid disease. Thyroid cancer incidence in these syndromes is increased over the general population but is not usually the most common malignancy/tumour to affect these patients. These syndromic forms of FNMTC are discussed below and are briefly outlined in Table 1.

PTEN hamartoma syndrome (Cowden syndrome)

The PTEN hamartoma syndrome is an autosomal dominant cancer predisposition syndrome linked to a variety of benign and malignant neoplasms in several organs. *PTEN* gene mutations at 10q22–23 are responsible for this genetic disease. Malignancy commonly occurs in the breast and thyroid and thyroid cancer is a major diagnostic criterion for Cowden syndrome. At least 2/3 of patients with this syndrome are affected by thyroid disease in the form of multinodular goitre, often before the age of 20 years.[2] Approximately 10% of patients with Cowden syndrome will also develop thyroid cancer in their lifetime. *PTEN* mutations are not common in sporadic thyroid carcinoma but hemizygous *PTEN* loss is described in benign thyroid tumours and more commonly in FTC.[3] Complete loss of *PTEN* expression appears to be more common in sporadic ATC.[4]

In patients with Cowden syndrome, the thyroid gland often shows enlargement with diffuse nodularity (micronodularity is common but larger nodules >2 cm are also commonly present).[2] Histologically, the nodules are primarily follicular adenomas, adenomatous nodules, and nodular hyperplasia. Background chronic lymphocytic thyroiditis is also common. Compared to thyroid nodules seen in the general population, thyroid nodules in Cowden syndrome are more numerous. It is also interesting to note that, although MTC is not a feature of Cowden syndrome, thyroid glands from these patients are reported to show C-cell hyperplasia, although this may be a reactive phenomenon.[5]

Although thyroid nodules in these patients are mostly benign, there is an increased risk of malignancy and careful histologic examination should be performed. Additionally, when thyroid cancer is found in a patient with Cowden syndrome it is always seen in a background of multiple adenomatous nodules. When considering only malignant nodules, PTC is more common than FTC but FTC is a close second and represents a higher proportion of malignant thyroid nodules in this population compared to the general population.[5,6]

Inherited syndromes associated with NMTC

Syndrome	Gene	Chromosomal location	Inheritance	Other features	Thyroid lesions	Frequency of thyroid lesions
PTEN hamartoma syndrome(Cowden disease)	PTEN	10q22—23	AD	Multiple benign and malignant tumours in a variety of organs especially the breast	MNG, hyperplasia, FA, FTC, PTC	~2/3 with thyroid disease, ~10% with thyroid carcinoma
Familial Adenomatous Polyposis	APC	5q21	AD	Many GI polyps, colon cancer	PTC	1—12% with PTC (usually women, associated with CMV-PTC)
Werner Syndrome (adult progeria)	WRN	8p11.1—21.1	AR	Premature aging, short stature, meningiomas, soft tissue sarcomas	FTC, PTC, AC	~18% of Japanese patients develop thyroid carcinoma
Carney complex	PRKAR1A	17q22—24	AD	Cardiac myxoma, spotty skin pigmentation	MNG, FA, FTC, PTC	~60% with multiple nodules, ~3% with thyroid cancer

Table 1

Familial Adenomatous Polyposis

In addition to the numerous intestinal polyps, colon cancer and other neoplasms, some patients with FAP also have an increased risk of thyroid cancer. FAP is caused by mutations in the *APC* gene at 5q21. 1—12% of patients with FAP develop thyroid carcinoma and thyroid carcinoma associated with FAP almost always occurs in women.[7] Interestingly, FAP patients developing thyroid cancer show clustering of their *APC* mutations and are significantly more likely to carry a mutation before codon 1220 outside of the normal mutation cluster region.[8] FAP patients developing thyroid carcinoma are also younger than the general population with a mean age at diagnosis in the mid 20's.[8]

PTC is the most common carcinoma type in FAP and is often multifocal. The cribriform morular variant of PTC (CMV-PTC) is associated with FAP and recognition of this variant is important as it should prompt evaluation for FAP, especially since thyroid disease is not an uncommon initial presentation for patients with FAP. Issues surrounding the diagnosis of CMV-PTC are discussed in more detail below.

Werner syndrome (adult progeria)

Werner syndrome is an autosomal recessive disorder caused by mutations in the *WRN* gene at 8p11.1—21.1. It is associated with premature aging, short stature and several neoplasms including meningiomas, soft tissue sarcomas and thyroid carcinoma. Werner syndrome is more common in Japan and Japanese patients are more likely to develop thyroid cancer than white patients with the syndrome. The histologic types of thyroid cancer seen in patients with Werner syndrome include FTC, PTC, and occasionally ATC.[9] In a series of Japanese patients, the average age of thyroid cancer diagnosis was 39 years (10 years younger than the general population), FTC was more common, and the female to male ratio, while still more common in women, was more even compared with sporadic thyroid cancer (2.3:1 vs 6.6:1).[10] While ATC may be seen in any form of FNMTC and is likely a result of transformation of a well differentiated carcinoma, in Werner syndrome it has been shown that ATC is relatively more common in Japanese patients (diagnosed in up to 13% of patients) suggesting an additional predisposition for progression to this highly aggressive cancer.[10] Approximately 18% of Japanese patients with Werner syndrome develop thyroid cancer.[10]

Carney complex

Carney complex is an autosomal dominant disease in which patients have spotty skin pigmentation, an increased risk of cardiac myxomas, and a variety of tumours involving endocrine organs. Carney complex is most commonly due to mutation of the *PRKAR1A* gene at 17q22—24 but some cases appear to be linked to an unknown gene at 2p16.[11] Thyroid nodules are common and approximately 60% of patients with Carney complex are found to have multiple thyroid nodules on ultrasound.[11] Histologically, most nodules are benign adenomas but approximately 3% of patients will develop thyroid carcinoma, including PTC and FTC, and thyroid carcinoma is one of the major diagnostic criteria for Carney complex. *PRKAR1A* gene loss or, rarely mutation of this gene, has been reported in some cases of sporadic thyroid cancer.[12]

Non-syndromic familial non-medullary thyroid carcinoma

Non-syndromic FNMTC is less well defined but there is convincing evidence that, at least in some families, a specific genetic mutation is passed on resulting in an increased risk of NMTC. The first published description of familial PTC was in 1980 and detailed two Norwegian families in which two women in different families each had multiple children and other first degree relatives with PTC.[13] No other features of a syndrome were present in these families. Additional early evidence of FNMTC came from Japan where 23 patients from 11 families were found to have thyroid carcinoma (18 PTC, two FTC, two ATC, one unknown).[14] Again, these patients were not found to have any traditional risk factors for thyroid carcinoma or known predisposing syndromes. It is estimated that approximately 5—10% of NMTC is due to a heritable genetic mutation. Most families labelled in the literature as having FNMTC show an autosomal dominant pattern of inheritance with variable penetrance.

Since the first descriptive reports of families with FNMTC there has been an increasing drive to find the causative genetic alteration