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The epidemiologic studies and genetic analyses indicating an inherited genetic predisposition to nonmedullary thyroid carcinoma are reviewed.

Familial Nonmedullary Thyroid Carcinoma

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Background: Nonmedullary thyroid carcinomas (NMTCs) originate from the thyroid epithelial cells and, until recently, were thought to arise sporadically without an inherited genetic predisposition. However, evidence of a familial predisposition to NMTC is accumulating.

Methods: This review addresses the strengths, weaknesses, and clinical implications of the observations indicating an inherited genetic predisposition to NMTC. These observations include epidemiologic studies, descriptions of large kindreds, and genetic analyses.

Results: Familial NMTC (FNMTC) may be caused by an inherited genetic predisposition and can be divided into two groups. The first group has an increased prevalence of NMTC within a familial cancer syndrome with a preponderance of nonthyroidal tumors. In the second group the predominant neoplasm is NMTC, although other neoplasms may occur with increased frequency. These disorders are the focus of this review.

Conclusions: A family history in NMTC patients should be directed at detecting those familial tumor syndromes with a preponderance of NMTC as well as those familial tumor syndromes enriched in NMTC but with a preponderance of nonthyroidal tumors. Since the recurrence rates may be greater in FNMTC than in sporadic NMTC, careful monitoring is indicated for affected individuals. The advantages and disadvantages of screening asymptomatic members of FNMTC kindreds with thyroid ultrasound are discussed, and the final decision is deferred to the treating physicians and their patients. It is hoped that positional cloning research will identify the FNMTC susceptibility genes.

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Abbreviations used in this paper: NMTC = nonmedullary thyroid carcinoma, FNMTC = familial NMTC, fPTC/PRN = familial papillary thyroid carcinoma enriched in papillary renal neoplasia, PTC = papillary thyroid carcinoma, FTC = follicular thyroid carcinoma, MEN2A = multiple endocrine neoplasia type 2A.

Introduction

Nonmedullary thyroid carcinoma (NMTC) refers to those neoplasms originating from the thyroid epithelial cell. NMTC includes papillary thyroid carcinoma (PTC), follicular thyroid carcinoma (FTC), anaplastic thyroid carcinoma, and insular thyroid carcinoma. Medullary thyroid carcinoma refers to those neoplasms arising from the calcitonin producing parafollicular cells of the thyroid that are derived from neural crest tissue. Medullary thyroid carcinomas have a familial predisposition in about 25% of cases, and the susceptibility gene

RET has been extensively investigated.¹ In contrast, the case for a familial predisposition of NMTC is only now beginning to emerge, with estimates of approximately 5% of NMTC occurring on the background of a familial predisposition. Evidence for familial NMTC (FNMTTC) comes from epidemiologic investigations, reports of large kindreds enriched in FNMTTC, and genetic linkage studies. Final proof of an inherited genetic predisposition awaits the identification of a susceptibility gene.

Based on clinical characteristics, FNMTTC can be divided into two groups. The first includes those familial tumor syndromes characterized by a preponderance of nonthyroidal tumors. These are reviewed briefly for completeness, with attention to critical points. The second group includes those familial syndromes characterized by a preponderance of NMTC. These disorders represent the major focus of this discussion.

Familial Tumor Syndromes Characterized by a Preponderance of Nonthyroidal Tumors

NMTC has been found with a greater frequency than expected in familial adenomatous polyposis, the Cowden syndrome (familial hamartoma syndrome), and the Carney complex type 1. Other possible relationships occur in a familial multinodular goiter (MNG) syndrome and in multiple endocrine neoplasia type 2A (MEN2A) (Table 1). In familial adenomatous polyposis, PTC occurs with a frequency of about 10 times that expected for sporadic PTC and has an unusual cribriform pathology.^{2,3} In the Cowden syndrome, FTC occurs with an increased frequency.⁴ Both PTC and FTC have been found in Carney complex type 1 that is caused by mutations of the protein kinase A regulatory subunit type 1-alpha gene.⁵ It is reasonable to consider genes predisposing to familial MNG as candidate genes for FNMTTC. In a familial MNG syndrome that was mapped to 14q, 2 of 18 MNG subjects had papillary lesions suggestive of PTC.⁶ Finally, one study suggests that the frequency of microscopic PTC is approximately twice as great in thyroid glands of MEN2A patients as it is in a control group of thyroid glands from MNG patients.⁷ The authors postulated that the activated RET proto-oncogene may contribute to this PTC predisposition. These microscopic PTCs are likely to carry only modest clinical significance since microscopic PTCs often remain clinically silent and since affected subjects carrying germline RET mutations undergo thyroidectomy at a young age. A single study over 20 years ago suggested an increased incidence of NMTC in the familial paraganglioma syndromes⁸ that are now known to be caused by mutations of the succinate dehydrogenase genes.⁹ However, no subsequent reports confirm this relationship. Since these familial paraganglioma

Table 1. — Nonmedullary Thyroid Carcinoma as a Minor Component of a Familial Tumor Syndrome

Disorder	Thyroid Tumors	References
Familial adenomatous polyposis	PTC with cribriform pathology	Cetta et al ^{2,3}
Cowden syndrome	FTC	Liaw et al ⁴
Carney complex type 1	PTC, FTC	Stratakis et al ⁵
Multinodular goiter at 14q	PTC	Bignell et al ⁶
Multiple endocrine neoplasia type 2A	Microscopic PTC	Biscolla et al ⁷

syndromes often present with carotid body tumors, attention to the neck may have resulted in ascertainment bias and an apparent association with NMTC.

Germline mutations of the p53 gene are responsible for the Li-Fraumeni syndrome. Sporadic anaplastic thyroid carcinoma is associated with acquired p53 gene abnormalities. Although it is reasonable to predict an increased prevalence of anaplastic thyroid carcinoma in the Li-Fraumeni syndrome, to our knowledge this has not been reported.

Familial Tumor Syndromes Characterized by a Predominance of NMTC

No FNMTTC susceptibility genes have yet been identified. Therefore, FNMTTC characterized by a predominance of NMTC has not yet been definitively proven to be a classic familial tumor syndrome. However, the evidence is accumulating to suggest that an inherited genetic predisposition is the cause of FNMTTC. This evidence is derived from different experimental designs, including epidemiologic studies, reports of extended kindreds, and genetic analyses. These findings help to guide patient care.

A 20-year accumulation of epidemiologic evidence supports a familial predisposition for NMTC. Six separate studies demonstrate that the risk of developing NMTC is about 5 times as great in first-degree relatives of affected subjects as it is in the general population.¹⁰⁻¹⁵ This familial association is consistent with an inherited genetic predisposition to NMTC. Although all of these studies were carefully performed, it should be recognized that mechanisms other than an inherited genetic predisposition would also explain the familial association. There may be ascertainment bias since members of families with NMTC may be investigated more aggressively for thyroid disease than members of the comparison control populations. Alternatively, a familial grouping of NMTC may be caused by an unsuspected or unidentified local environmental factor. Finally, a familial association may not distinguish a genetic predisposition caused by a single gene from a genetic predisposition caused by the concurrence of multiple weak susceptibility genes. Therefore, a familial association suggests an inherited susceptibility gene but does not constitute definitive proof.

Table 2. — FNMTc as the Predominant Tumor of a Familial Tumor Syndrome

Disorder	Chromosomal Location	OMIM	Tissue Pathology	References
fPTC/PRN	1q21	%606240	PTC, benign thyroid nodules, papillary renal neoplasia	Malchoff et al ^{26,27}
Thyroid carcinoma with oxyphilia (TCO)	19p13	%606383	Benign and malignant oxyphilic thyroid neoplasms	Canzian et al ²⁸
fNMTC1	2q21	%606240	PTC, benign thyroid nodules	McKay et al ²⁹
FNMTc	19p13		NMTC, benign thyroid nodules	Bevan et al ³¹

OMIM = Online Mendelian Inheritance in Man

Clusterings of FNMTc have been reported in large extended kindreds, and these findings support the hypothesis that FNMTc is caused by an inherited genetic predisposition. Sporadic NMTC is a relatively rare malignancy, with an incidence of approximately 1 per 25,000 individuals per year.¹⁶ Statistical estimates suggest that a grouping of 2 family members with NMTC could represent the concurrence of sporadic tumors but that 3 or more members in a kindred is more suggestive of a familial predisposition. Other characteristics may also suggest a familial predisposition when they occur in the setting of a small familial cluster of NMTC. These include unusual presentations of sporadic NMTC, such as in men or in children. A number of FNMTc clusterings have been reported that, because of their size or other characteristics, are likely to represent a familial predisposition to NMTC.¹⁷⁻²⁶

Genetic analyses of large FNMTc kindreds not only support the hypothesis that there exists an inherited genetic predisposition to FNMTc, but also represent the first steps in identification of the putative susceptibility genes by positional cloning methods. Linkage analyses have identified three different chromosomal regions that may harbor an FNMTc susceptibility gene (Table 2): familial PTC enriched in papillary renal neoplasia (fPTC/PRN; OMIM %606240) has been mapped to chromosomal region 1q21,²⁷ thyroid carcinoma with oxyphilia (TCO; OMIM %606383) has been mapped to chromosomal region 19p13,²⁸ and familial nonmedullary thyroid carcinoma type 1 (fNMTC1/Tas1; OMIM %606240) has been mapped to chromosomal region 2q21.²⁹ In these three disorders, NMTC inheritance appears to be autosomal dominant, and there is an increased incidence of benign thyroid nodules.

Some clinical features differ. The fNMTC1 syndrome (chromosomal region 2q21) is characterized by PTC without any distinguishing pathologic features and without an obvious increase in frequency of nonthyroidal neoplasms in kindred members. Neoplasms arising from more than one tissue type characterize many familial tumor syndromes.³⁰ The fPTC/PRN syndrome includes not only PTC and the expected benign thyroid nodules, but also papillary renal neoplasia and possibly other malignancies as well.^{26,27} Finally, FNMTc without oxyphilia has also been mapped to 19p13.³¹ Since these tumors lack the

oxyphilia found in the TCO pathology, at least two explanations exist: there may be a second FNMTc susceptibility gene in chromosomal region 19p13, or a single susceptibility gene in this chromosomal region predisposes to different thyroid tumor phenotypes.

Tumor-specific loss of heterozygosity is found in sporadic FTC with and without oxyphilia at both 19p13 and 2q21.³² These findings suggest that tumor suppressor susceptibility genes lie in these chromosomal regions and that somatically acquired disruptions of these genes as well as genetically inherited disruptions predispose to NMTC.

Clinical Characteristics of FNMTc

The clinical characteristics of FNMTc are being clarified not only by the family studies described above, but also by large epidemiologic studies. Review of the different kindreds and the genetic studies suggests that inheritance is autosomal dominant and that the penetrance is incomplete and increases with age.^{26-29,31,33} As with sporadic PTC, women are affected approximately 2 to 3 times more frequently than men.^{26,33} The age of onset of FNMTc may be younger than for sporadic NMTC.³³ Although this is the expected finding for a familial cancer syndrome, a large study from Japan found that the mean age of onset for both sporadic NMTC and FNMTc is approximately 50 years.³⁴ The pathologic subtype is most frequently PTC and occasionally FTC. A familial association has not been reported for either anaplastic thyroid carcinoma or insular thyroid carcinoma.

Many familial tumor syndromes are associated with multiple tumor types arising from different tissues of origin.³⁰ In contrast, FNMTc syndromes have not been associated with neoplasms arising from other tissues, with the exception of the fPTC/PRN syndrome, which is enriched in other papillary renal neoplasia as discussed above.²⁷ Large epidemiologic studies are somewhat more revealing. One study suggests that premenopausal breast carcinoma may occur with a greater frequency than expected in NMTC patients.³⁵ It has been hypothesized that breast carcinoma is a side effect of ¹³¹I therapy for PTC.³⁶ Alternatively, breast and thyroid carcinoma, which both arise from an epithelial

cell type, may share a common susceptibility factor, genetic or otherwise. Consistent with this explanation are the studies of malignancies in first-degree relatives of NMTC patients. Breast cancer seems to occur with a greater frequency than expected in first-degree relatives of FNMTTC patients.^{13,15} Other malignancies potentially associated with PTC include kidney, ovarian, and right-sided colon cancer.¹⁵

An increased incidence of benign neoplasia has been found in other familial tumor syndromes, especially those associated with endocrine organs. For example, in MEN2A, benign pheochromocytoma is much more common than malignant pheochromocytoma. Therefore, it is predictable that benign thyroid nodules occur with greater frequency in FNMTTC than in sporadic NMTC. One study suggests that multiple benign nodules occur in about 42% of thyroid glands from patients with FNMTTC compared to 29% of thyroid glands of patients with sporadic NMTC.³⁴

There is concern that FNMTTC might be more aggressive than sporadic NMTC, and this has led some investigators to recommend more aggressive therapy for FNMTTC.^{37,38} In contrast, a case control study from Toronto, consisting of 24 cases of FNMTTC, found no significant difference in disease-free survival between familial and sporadic NMTC.³⁹ A larger study of 258 cases of FNMTTC from a Japanese population found an increased incidence of recurrences in FNMTTC compared to sporadic NMTC but similar survival rates. The cumulative 30-year rate of recurrence in local lymph nodes was about 40% for FNMTTC compared to 20% for sporadic NMTC.³⁴ It should be noted that more frequent recurrences in FNMTTC were limited to local lymph nodes. Both recurrence rates at distal sites and survival rates were the same in FNMTTC and sporadic NMTC.³¹ One potential criticism of this study is that a familial predisposition was considered to be present when only 2 family members were affected. Using this criterion, the FNMTTC patient population may be contaminated by a relatively large number of patients with sporadic NMTC that occurred by chance alone in 2 members of the same family. Therefore, this investigation may have missed some subtle differences between FNMTTC and sporadic NMTC.

Clinical Care of FNMTTC Patients and Family Members

A family history should be obtained from all NMTC subjects. The goals are to identify that small number of patients who are affected by the familial cancer syndromes characterized by a predominance of nonthyroidal tumors, and also to identify those patients who are affected by the FNMTTC syndromes characterized by a predominance of NMTC. It should be recognized that

the presence of only 2 affected members in a kindred might represent the concurrence of 2 sporadic NMTC in the same family as opposed to indicating a FNMTTC kindred. Still, for clinical (not research) purposes, it is reasonable to conclude that those small kindreds with only 2 affected family members may represent an inherited predisposition, and family members should be screened as suggested below.

There is some evidence that recurrence rates for individuals with FNMTTC may be higher than the rates for those with sporadic NMTC, but the recurrences tend to arise in local lymph nodes. Therefore, it is anticipated that continued and careful surveillance using routine techniques will identify those recurrences and that the survival rate will be similar to that of sporadic NMTC.³¹

For kindreds affected by FNMTTC, it is generally believed that asymptomatic kindred members should be evaluated at some regular intervals, although no prospective long-term studies demonstrate benefit and the optimal frequency and type of evaluation have not been determined. At a minimum, physical examination for adults seems appropriate. Since FNMTTC does not appear to develop until after puberty, prepubertal children may not require screening. In addition to screening with physical examination, some experts prefer to perform thyroid ultrasound examinations on a regular basis, perhaps every 1 to 2 years. Since this relatively aggressive approach carries with it the potential for finding clinically unimportant benign disease that prompts further testing and perhaps patient harm, others suggest that screening be carried out by physical examination. One recent uncontrolled study provides data derived from the use of thyroid ultrasound.³¹ In this study, 149 first- and second-degree relatives of FNMTTC subjects were evaluated by thyroid ultrasound. The yield was 77 individuals with at least 1 nodule. All nodules were reportedly aspirated, 18 subjects underwent thyroidectomy based on aspiration results, and 15 (10% of those screened) were confirmed to have NMTC (14 PTC and 1 FTC) at surgical resection. Three of the 18 subjects undergoing surgery had benign nodules. Therefore, in this study the yield of NMTC in asymptomatic relatives of FNMTTC subjects seems to be greater than expected in the general population, where the overall prevalence is expected to be about 0.6%.¹⁶ However, there was no appropriate control group such as one composed of relatives of sporadic NMTC subjects. Therefore, whether thyroid ultrasound identified more thyroid cancers than would otherwise have been found in a similarly screened control population is unclear. Additionally, there are no data to demonstrate that this relatively aggressive approach will improve outcome. Finally, since the average size of the NMTC was about 9 mm,³⁴ it can be argued that at least some of these NMTCs could have been found on physical examination without ultrasound and that the smaller

neoplasms were unlikely to be harmful to the patient, until reaching the limit of detection by physical examination. In summary, arguments can be made both for and against the use of thyroid ultrasound to screen asymptomatic members of FNMTc kindreds. No definitive conclusion can be reached, so this decision is best left to the clinician and the patient.

In general, thyroid nodules in those individuals belonging to FNMTc kindreds should be aspirated, just as all thyroid nodules should be aspirated. This is straightforward for all nodules greater than 1 cm in diameter; most experts feel that these should be aspirated regardless of family history. For nodules less than 1 cm in diameter, the decision to aspirate is not clear. The smaller the nodule, the more difficult it is to obtain an adequate sample on aspiration, and the less likely it is that this will represent a thyroid carcinoma requiring immediate attention. Regardless of whether they are aspirated or not, these small nodules should be monitored on a regular basis, and aspiration should be undertaken when they enlarge to greater than 1 cm.

Conclusions

Current studies suggest that FNMTc is an autosomal dominant familial tumor syndrome accounting for about 5% of all NMTC. NMTC also occurs with increased frequency in other familial tumor syndromes such as familial adenomatous polyposis and the Cowden syndrome. Therefore, a careful family history is indicated in all NMTC subjects to identify these two groups of syndromes. Since no specific FNMTc susceptibility genes have been identified, genetic analysis is not yet clinically available. However, there is likely to be more than one susceptibility gene. The decision to screen members of FNMTc kindreds with thyroid ultrasound is neither recommended nor discouraged. FNMTc subjects should be followed closely for recurrence since recurrence rates may be about twice as high for FNMTc as they are for sporadic NMTC.

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