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In Our View . . .

Differentiated Thyroid Carcinoma: A Polygenic Disease

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Differentiated thyroid cancer is a rare disease and until recently was considered to be sporadic. However, increasing evidence has been found for a genetic basis of this disease. In approximately 5% of patients the differentiated thyroid cancer is dominantly inherited. Several families with different syndromes, of which differentiated thyroid cancer is a feature, have already been described. However, until now, single genes explain only a minority of cases. We hypothesize that differentiated thyroid cancer is a polygenic disease. Data from epidemiologic studies, about occult and multifocal carcinomas and the different response to specific risk factors contribute to this hypothesis.

Introduction

SEVERAL SUBTYPES of malignant thyroid tumors can be distinguished: the differentiated (papillary and follicular) carcinoma originating from the follicular epithelium, the medullary carcinoma consisting of C cells, and the anaplastic carcinoma, often considered to represent the terminal stage in the dedifferentiation of a follicular or papillary carcinoma.

Differentiated thyroid carcinoma is a sporadic and rare disease, with an age-adjusted incidence rate from 0.9–5.2 per 100,000 cases per year (1). However, in approximately 5% of the cases a familial presentation is present, with a more aggressive phenotype than its sporadic counterpart (2). Patients with familial differentiated thyroid carcinoma present at an earlier age, often exhibit more multifocality of the tumor, and have more relapses during follow-up (3). In recent years, in several families germline mutations responsible for differentiated thyroid cancer have been found, but no single gene could be held responsible (4–7). In two syndromes associated with differentiated thyroid cancer, Cowden syndrome and familial adenomatous polyposis, two different genes, PTEN and APC, respectively, were also identified as responsible for the clinical features.

Medullary thyroid carcinoma accounts for 5% to 10% of all thyroid cancers and is hereditary in 20%–30% of the cases. Germline mutations of the *RET* proto-oncogene (10q11.2) are associated with the multiple endocrine neoplasia type 2 (MEN 2A and 2B) and the familial medullary thyroid carcinoma (8). The anaplastic form of thyroid carcinoma is not reported to be hereditary (9).

In sporadic cases of differentiated thyroid cancer several arguments exist for a genetic predisposition of a more complex kind. In this article we review the literature and conclude that differentiated thyroid carcinoma can be considered as a polygenic disease.

Arguments for Polygenicity of Differentiated Thyroid Carcinoma

Strong arguments for a genetic basis of the disease can be found in epidemiologic data, in the occurrence of occult carcinomas, in the occurrence of multifocality of the tumor, and in the risk factors.

Epidemiology

The existence of genetic risk factors for differentiated thyroid carcinoma has been demonstrated by epidemiologic studies. In the Utah population database, the familial relative risk for differentiated thyroid carcinoma was shown to be the highest of 28 distinct cancer sites, 8.60 (95% confidence interval [CI] 4.68–13.7), which means that first-degree relatives of patients with thyroid cancer have a chance of developing thyroid cancer that is much higher than in the normal population (10). For comparison, the familial relative risk for developing breast cancer is only 1.83 (CI 1.65–2.01). In addition, the familial relative risk of thyroid cancer in a Swedish nationwide family cancer database was also high, 14.8 in male offspring and 7.3 in female offspring of female probands. Females had a three times higher background rate of thyroid cancer, as was also observed in other parts of the world (11).

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In the Swedish Family-Cancer database, the familial standardized incidence ratios were 7.8 and 2.5 for male and female papillary and follicular thyroid carcinoma, with a gender ratio of 2.8. Papillary and follicular thyroid carcinoma were not associated with other cancers in parents in this database (12), although in the Utah database significant familial associations were found between breast and colon cancer (10). Moreover, the practice of prophylactic colectomies in APC mutation carriers may have flawed a possible association. Also, in the Norwegian cancer registration an increased risk for nonmedullary thyroid cancer was found among more than 5,000 relatives in 970 families (SIR male 5.2 [CI 2.1–10.7] SIR female 4.0 [CI 2.1–7.1]) (13), but in these data the increased risk in the papillary cancer was more clear than in the follicular type. Although the contribution of familial syndromes of differentiated thyroid cancer such as Cowden and familial adenomatous polyposis cannot be excluded, it is unlikely that these syndromes are the only explanation for the high familial risk of thyroid cancer.

Occult carcinomas

Many autopsy studies are performed in different countries and reveal occult differentiated thyroid cancer in 2%–36% of thyroid glands (14). Studies of surgical thyroidectomy specimens have reproduced many of the findings of autopsy series, with occult thyroid carcinoma found in 9%–19% of these glands (14,15). These cancers are papillary carcinomas, by definition smaller than 1.0 cm in diameter. The differences in the incidence of occult carcinoma result from various study techniques and variable geographic origin. However, unlike the marked female preponderance for clinical disease of thyroid cancer, the gender distribution of occult thyroid cancer is nearly equal (16). The prevalence in adults in autopsy series is virtually identical across age groups. The high number of occult carcinomas is in contrast to the low incidence of clinical differentiated thyroid carcinomas. This suggests that papillary microcarcinomas may develop in young adults, but that most do not progress to a clinical cancer or perhaps even regress spontaneously (17).

Multifocality

The proportion of multifocal differentiated thyroid cancer in autopsy studies is 20%–50% (14). The estimated frequency of multifocal cases is highly variable and depends on the size of the primary tumor and on the number of sections of the thyroid tissue (20%–80%, the latter is found in cases of multiple millimetric sections) (18,19). Multiple intrathyroidal cancers are frequently observed in papillary, and much less frequently in follicular thyroid carcinoma. These multiple cancers are considered to be intrathyroidal metastases, but it might well be that these cells are not metastases but multifocal tumors. The multifocality of the tumor may be an indication for a genetic first mutation followed by multiple second hits. The low prevalence of loss of heterozygosity in papillary thyroid carcinomas supports this, because a high rate of loss of heterozygosity is more compatible to clonality than with multifocality (20).

Risk factors

Epidemiologic studies indicate a number of risk factors for

differentiated thyroid carcinoma: a previous history of radiation exposure, family history, underlying thyroid diseases, hormonal and reproductive factors, body size, and dietary iodine intake. The only clear etiologic factor in the development of differentiated thyroid cancer is a previous history of exposure to external irradiation during childhood (21). In a pooled analysis of seven studies, the risk of developing a thyroid carcinoma after irradiation under the age of 5 years is twofold higher than in children treated with irradiation between 5 and 9 years of age and fivefold higher than in children treated between 10 and 14 years of age (22). In Japanese atomic bomb survivors, the excess risk of differentiated thyroid cancer was 9.5, 3.0, 0.3 and 0.2, respectively, for the following four age categories 0–9, 10–19, 20–39, and over 40 years of follow-up since 1945 (23). The high susceptibility of young children to the carcinogenic effects of radiation to the thyroid thus contrasts with a low susceptibility in adults. This is consistent with experimental studies in animals and suggests greater radiation effects in humans during periods of rapid cell proliferation, as observed during the development of the thyroid gland.

Genetic predisposition because of a defect in DNA repair mechanisms and dietary and hormonal factors may modify the risk of developing a thyroid tumor after radiation exposure. Several clinical data support these assumptions: patients with one radiation-related tumor (thyroid, salivary, parathyroid, benign neural, or depending on radiation fields, brain and breast tumors) are more likely to develop another radiation-related tumor. In sibling pairs who were both exposed to radiation, development of a thyroid tumor occurred more often than expected by chance (24,25). The risk of developing a thyroid tumor for subjects undergoing radiotherapy during childhood for a cancer (other than a neuroblastoma) was 3–10 times higher than in children who received ionizing irradiation for benign conditions. Furthermore, children who received radiotherapy for a neuroblastoma had a fivefold risk of developing a thyroid cancer compared to those who were treated with radiotherapy for an other cancer (22). The dose effect is similar, suggesting a single predisposition common for neuroblastoma and thyroid carcinoma.

What is Known About Differentiated Thyroid Tumor Genetics?

Currently, research into a specific germline mutation as a basis for the development of familial differentiated thyroid carcinoma has yielded inconclusive results. Several genes have already been implicated, but no single locus has yet been identified as main cause for the occurrence of differentiated thyroid cancer (Table 1).

Germline mutations

In two familial syndromes in which differentiated thyroid carcinoma is involved, namely Cowden syndrome and familial adenomatous polyposis, two genes have been identified. Classic Cowden syndrome is characterized by multiple hamartomas and a high risk of benign and malignant breast tumors and thyroid tumors. In 80% of these patients germline mutations in *PTEN*, a tumor-suppressor gene (10q23.3) are present (30). However, if no hamartomas are present, *PTEN* germline mutations are only found in 5% of the families with breast and thyroid tumors (32). In familial adenomatous polyposis, characterized by predisposition for

TABLE 1. PROPOSED LOCI AS GENETIC BASIS IN SEVERAL INHERITED SYNDROMES IN WHICH DIFFERENTIATED THYROID CARCINOMAS ARE DESCRIBED

Chromosomal localization	Gene	Number of known families	Phenotype
1q21	?	1	PTC, PRCC (7)
19p13.2	<i>TCO</i>	1	benign thyroid nodules, PTC (5)
14q31	<i>MNG1</i>	1	multinodular goiter, PTC (4)
5q21-22	<i>APC</i>	>	familial polyposis coli, PTC (26)
5q21-22/?	<i>APC</i> /?	>	Gardner syndrome: polyps in small and large intestine, osteomas, fibromas, lipomas, PTC (27)
5q21-22/?	<i>APC</i> /?	>	Turcot's syndrome: polyposis coli, brain tumors, PTC (27)
2q16/17q22-24	?/ <i>PRKAR1A</i>	>	Carney complex: skin pigmentation, myxomas, schwannomas, hypercortisolism, pituitary adenomas, testicular tumors, FTC (28,29)
10q23.3	<i>PTEN</i>	>	Cowden syndrome: hamartomas, benign thyroid nodules, FTC, breast cancer, endometrial cancer (30)
t(3;8)(p14.2;q24.1)	?	1	PTC, CRCC (31)

PTC, papillary thyroid carcinoma; FTC, follicular thyroid carcinoma; CRCC, clear cell renal carcinoma; PRCC, papillary renal cell carcinoma; > numerous families described.

colorectal carcinoma and in minor cases also differentiated thyroid carcinoma, mutations in the *APC* gene are present (5q21-22) (26). Linkage analysis, however, excluded the *APC* gene as a susceptible gene for familial papillary carcinoma (33).

On the other hand, in most families with familial differentiated thyroid cancer, the search for responsible genes is less successful. A putative locus for multinodular goiter (*MNG1*) was mapped to 14q31 in a large family, with 18 cases of multinodular goiter in which 2 individuals also had papillary thyroid carcinoma, but *MNG1* does not account for the differentiated thyroid cancer in this family (4). Another locus called thyroid cell oxyphilia (*TCO*), mapped to chromosome 19p13.2, may be responsible for predisposition to thyroid tumors in a family with 6 individuals with multinodular goiter and 3 individuals with papillary thyroid carcinoma. There were, however, insufficient number of patients to demonstrate linkage (5). In contrast, *MNG1* and *TCO* were excluded as strong susceptibility loci in a large family with papillary carcinoma, as were six other candidate genes (*RET*, *TRK*, *MET*, *TSH-R*, *APC*, *PTEN*) (34). Moreover, *MNG1*, *TCO*, and also *RET* were excluded as susceptible loci for familial differentiated thyroid carcinoma in 56 families with 150 individuals (35). The *RET*-proto-oncogene was earlier also excluded as the disease-causing gene in 7 families with 15 individuals with papillary thyroid cancer (36). Recently, in a large kindred with a tumor syndrome characterized by papillary thyroid cancer, nodular thyroid disease, and papillary renal neoplasia, a predisposing gene on chromosome 1q21 has been mapped (7). Also a gene on 3p14 or 8q24, might be considered as another gene in a family with renal clear cell cancer and papillary thyroid cancer (31).

Somatic mutations

The somatic gene abnormalities found in thyroid tumor tissue may be of help in elucidating underlying inherited abnormalities. If one of the two alleles is already mutated, a

second hit in the normal allele is then required for the subsequent transformation in a tumor cell (37). Differentiated thyroid carcinoma is a result of abnormal growth and differentiation of thyroid follicular cells. Tumor growth occurs when the normal equilibrium of regulatory pathways is disrupted, either through enhancement of stimulatory pathways or deficient inhibitory pathways. Most benign and malignant thyroid tumors have a monoclonal origin, suggesting that random mutational events account for their onset, for instance activation of oncogenes or inactivation of tumor suppressor genes such as *p53*.

In nonradiation-associated human thyroid tumors several abnormalities can be found (Table 2). Except for *TRK* and *MET*, all these mutations have higher frequencies in radiation-induced thyroid carcinoma (21). Simultaneous alterations of *ras*, *Gsa*, *TSH-R*, *RET/PTC*, *TRK* were only found in 5 of 114 thyroid tumors, indicating that these genes may play independent roles in the tumorigenic process (41). Activating point mutations of the *ras* genes are detected in a high percentage of thyroid tumors of all histologic types and they

TABLE 2. SOMATIC MUTATIONS FOUND IN NONRADIATION ASSOCIATED HUMAN THYROID TUMORS (1,21,38-40)

	Somatic mutation	%
Oncogenes:	<i>MET</i>	50%–70% ^a
	<i>ras</i>	40%
	<i>RET/PTC</i>	3%–40% ^a
	<i>TRK</i>	0%–15%
	<i>TSH-R</i>	<10%
	<i>Gsa</i>	<10%
Tumor suppressor genes:	<i>PPARγ</i>	62% ^b
	<i>p53</i>	<10%
	<i>PTEN</i>	5%–25% ^b

^aSomatic mutations only found in papillary thyroid carcinoma.
^bSomatic mutations only found in follicular thyroid carcinoma.

are therefore considered as an early event in thyroid tumorigenesis (42). Other genetic abnormalities, which capitalize on genetic instability induced by *ras* mutation are then needed for tumor progression and determine the histologic type of the thyroid tumor.

Gross somatic genetic analysis have demonstrated loss of heterozygosity of markers localized on various regions of chromosome 10 in thyroid tumors (20,43) and preliminary loss of heterozygosity studies of sporadic thyroid tumors suggest contiguous area of deletion centromeric to the *PTEN* locus, suggesting the existence of other tumor-suppressor genes in this area (44). Also, others have described the loss of heterozygosity of this region in thyroid tumors (45,46). Recently, it was shown that inactivation of *PTEN* function is a critical step in the development and/or progression of thyroid tumors (47). The involvement of *PTEN* in the pathogenesis of sporadic nonmedullary thyroid carcinoma has been further confirmed by *PTEN* expression in these tumors (40) and expression of *PTEN* in thyroid cancer cell lines (48).

Comparison genome hybridization (CGH) techniques applied in the field of thyroid cancer may reveal somatic genetic alterations that will offer new interesting loci for further research. A loss of chromosome 22 was particularly common in follicular thyroid carcinoma when investigated by CGH (49). In a CGH study of papillary carcinomas also a recurrent pattern of aberrations was detected localizing to identical chromosomal loci (50). Especially the loss of chromosome 22 was unique for younger patients and associated with more lymphogenic metastases.

Further Elucidation of Genetic Basis of Sporadic Differentiated Thyroid Carcinoma

In addition to the familial syndromes with differentiated thyroid cancer, there are, as illustrated above, several arguments that genetic factors may play a role in the development of sporadic differentiated thyroid cancer. The main arguments for a genetic role in differentiated thyroid cancer are derived from the frequent presence of occult microcarcinoma and the multifocality of the tumor. Until now, research that focused on the underlying genetic origin did not lead to elucidation of a single locus for differentiated thyroid cancer. Loci such as *RET*, *MNG1*, and *TCO* were excluded as susceptible genes by linkage analysis (34–36). This does not, however, exclude that specific loci play a meaningful role. This may, in our opinion, be because of the linkage analysis as analytical approach, which has been used until now. With linkage analysis, cosegregation of genetic markers of diseases in families is analyzed for approximately 300 genetic markers over the whole genome. However, if several high-frequency, low-penetrant genes contribute to differentiated thyroid cancer, such linkage analysis has little power because the disease-causing allele is present in more than one founder. In case of involvement of several genes in different pathways linkage analysis only yields results in large families where genetic heterogeneity is absent.

Linkage analysis followed by association analysis is an interesting strategy, if low-frequency alleles with high penetrance as well as high frequency alleles with low penetrance are present. The advantage of this strategy in a founder area is that rare alleles coalesce in a short time frame to common ancestors and that coalescence of frequent alleles takes place

in a subgroup with a short coalescence time. This offers an advantage for association-based research (51).

The strategy of investigation is to cover the region where candidate genes are present with a set of 4–6 closely linked markers, in linkage disequilibrium. This allows determination of common ancestry for the chromosomal region of interest (identity by descent), and improves the ability to find association, because haplotype association is less dependent on allele frequency match between marker and disease alleles. Association-based methods offer the most feasible approach to find genes with low-penetrant and high-frequency risk alleles. Mapping of frequent genes by association analysis has been shown to be possible by using partial coalescence to a limited set of ancestors (51–53). For rare gene mutations such as *BRCA1* and 2 (54,55) and cystic fibrosis (56) it has already been demonstrated that carriers of an identical mutation share DNA around this mutation due to non-recombination because of a common ancestor.

Association analysis on a genome-wide scale is being developed with different technical approaches (DNA pooling, array genotyping, etc.). With association studies, the so-called trio design is preferred, which means that the DNA of the patient is compared to the DNA of the relatives, e.g., parents or the DNA of the partner and a child. Thus, the DNA of the parent, which is transmitted to the patient, is compared to the DNA of the parents, which is not transmitted. The advantage of this approach is that the trio design eliminates bias better than a case control design. With this trio approach, the information obtained in phase (in which alleles are on the same chromosomes) more than compensates for the extra DNA typing required in comparison to case control studies (57,58). In addition, recently developed laboratory techniques allow large scale rapid genotyping. For this reason, it is to be expected that association analysis will be of great value in elucidating the genetic base of differentiated thyroid cancer.

Conclusions

Differentiated thyroid cancer is a rare disease for which increasing evidence for a genetic basis is recognized. Nevertheless, no single defect has yet been found. Taking into account the data from epidemiologic studies, data about occult and multifocal carcinomas, and the occurrence of specific risks factors, we hypothesize that differentiated thyroid carcinoma is a polygenic disease. Systematic association analysis is an interesting method for further elucidating the genetic background of the disease.

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