Short Communication

Genetic and Biological Subgroups of Low-Stage Follicular Thyroid Cancer

Christopher A. French,* Erik K. Alexander,† Edmund S. Cibas,* Vania Nose,‡ Julia Laguette,* William Faquin,§ Jeff Garber,‖ Francis Moore, Jr.,‖ Jonathan A. Fletcher,* P. Reed Larsen,‖ Todd G. Kroll**
From the Division of Endocrinology, Departments of Medicine,§ Surgery,‖ and Pathology,* Brigham and Women’s Hospital, Boston, Massachusetts; the Department of Pathology,‡ Children’s Hospital, Boston, Massachusetts; the Department of Pathology,¶ Massachusetts General Hospital, Boston, Massachusetts; and Harvard Vanguard Medical Associates,¶ Harvard Medical School, Boston, Massachusetts; and the Departments of Pathology and Laboratory Medicine and Hematology and Oncology,** Winship Cancer Institute, Emory University School of Medicine, Atlanta, Georgia

Investigations of cancer-specific gene rearrangements have increased our understanding of human neoplasia and led to the use of the rearrangements in pathological diagnosis of blood cell and connective tissue malignancies. Here, we have investigated 3p25 rearrangements of the peroxisome proliferator-activated receptor γ (PPARγ) gene in follicular epithelial tumors of the human thyroid gland. Eleven of 42 (26%) low-stage follicular carcinomas, 0 of 40 follicular adenomas, 1 of 30 Hurthle cell carcinomas, 1 of 90 papillary carcinomas, and 0 of 10 nodular goiters had 3p25 rearrangements by interphase fluorescence in situ hybridization. All 11 follicular carcinomas with 3p25 rearrangement exhibited strong, diffuse nuclear immunoreactivity for PPARγ, consistent with expression of PPARγ fusion protein. Twelve of 42 (29%) low-stage follicular carcinomas had 3p25 aneusomy without PPARγ rearrangement (P = 0.01), suggesting that PPARγ rearrangement and aneuploidy are independent early events in follicular cancer. Eleven of 12 follicular carcinomas with 3p25 aneusomy exhibited no PPARγ immunoreactivity, supporting the existence of two independent pathways. Follicular carcinoma patients with PPARγ rearrangement more frequently had vascular invasion (P = 0.01), areas of solid/nested tumor histology (P < 0.001), and previous nonthyroid cancers (P < 0.001) compared with follicular carcinoma patients without PPARγ rearrangement. Our experiments identify genetic subgroups of low-stage follicular thyroid cancer and provide evidence that follicular carcinomas with PPARγ rearrangement are a distinct biological entity. The findings support a model in which separate genetic alterations initiate distinct pathways of oncogenesis in thyroid carcinoma subtypes. (Am J Pathol 2003, 162:1053–1060)

Chromosomal rearrangements that create abnormal gene fusions are some of the most early and specific genetic alterations identified in cancer.1,2 Such rearrangements in leukemias play a primary role in establishment and maintenance of malignancy3–7 and in induction of clinical remission by drugs that target activities of the encoded fusion oncoproteins.5,7,8 Gene rearrangements are now used commonly in the molecular diagnosis of cancer.

Aneuploidy is another frequent genetic abnormality in cancer. It results from full or partial aneuploies in which the copy number of entire chromosomes or chromosomal subregions is altered. Aneuploidy per se has been proposed to be an early and genetically destabilizing force in cancer development.9–13 Increasing aneuploidy is associated with cancer progression, but the molecular mechanisms related to aneuploidy in cancer are poorly understood.

Chromosomal rearrangements at 3p25 have been reported in human tumors arising from thyroid follicular epithelial cells.14–22 One such rearrangement, t(2;3)(q13;p25), results in a PAX8-PPARγ gene fusion,21 and is the predominant member of a family of PPARγ rearrangements in follicular thyroid carcinoma.20,21 Even so, there

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Address reprint requests to Todd G. Kroll, M.D., Ph.D., Department of Pathology and Laboratory Medicine, Emory University School of Medicine, 146 Whitehead Building, 615 Michael St., Atlanta, GA 30322. E-mail: tkroll@emory.edu.
is a striking disparity in the overall number of rearrange-
ments that have been discovered in carcinomas com-
pared to leukemias and sarcomas. Two adult carcino-
mas, both arising within the thyroid gland, have been
shown to harbor specific gene rearrangement fami-
lies. Thus, the thyroid provides a tractable car-
inoma model with which to investigate gene rearrange-
ment mechanisms.

Here, we have used interphase fluorescence in situ
hybridization (FISH) and immunohistochemistry to define
the prevalence, specificity, and clinicopathological cor-
relates of 3p25 genetic alterations in human follicular
thyroid tumors. Our findings suggest that distinct genetic
pathways exist in early follicular thyroid cancer and that
PPARγ rearrangements characterize a specific follicular
carcinoma entity. The results highlight the thyroid as a
natural cancer model with which to investigate both gene
rearrangement and aneuploidy mechanisms in epithelial
malignancy.

Materials and Methods

Pathological Diagnoses

We retrieved pathology materials from all thyroidectomy
specimens diagnosed with follicular thyroid carcinoma at
Brigham and Women’s Hospital (BWH), Boston, MA, in
the 13-year period 1988 to 2000. Original pathological
diagnoses were rendered by individual staff pathologists
at BWH. More than 40% of cases had been reviewed by
multiple BWH pathologists and ~15% had been re-
viewed by outside pathologists in expert consultations.
All cases were re-examined independently and blindly
with respect to molecular and clinical features by three
pathologists (TGK, CAF, and VN) using current morpho-
logical criteria. Four follicular carcinomas were re-
classified as papillary carcinomas because well-devel-
oped nuclear clearing, grooves, and/or focal papillary
architecture were seen. Seven follicular carcinomas were
reclassified as follicular adenomas because unequivocal
capsular penetration or vascular invasion was not
present. The remaining 42 follicular carcinomas and ad-
ditional study specimens, including 90 papillary carcino-
mas, 40 follicular adenomas, 15 Hurthle cell carcinomas,
and 10 multinodular goiters from BWH, and 15 Hurthle
cell carcinomas from the Massachusetts General Hospi-
tal (MGH), were included in our final series. Some fea-
tures of the 6 follicular carcinomas, 20 follicular adeno-
as, 10 papillary carcinomas, and 10 multinodular
goiters have been reported previously. The work was
approved by the joint BWH/MGH institutional review
board.

Cytogenetics and FISH

Karyotyping was performed on Giemsa-banded meta-
phase spreads as described. Formalin-fixed, paraaffin-
embedded sections were prepared for FISH according to
a procedure modified from Bull and Harnden. Briefly, 3-
to 4-μm sections were deparaffinized in xylene and mi-
crowaved for 30 to 60 minutes at 98°C in 100 mmol/L of
Tris and 50 mmol/L of disodium ethylenediaminetetraace-
tic acid, pH 8. The tissue was digested with Digest-All III
pepsin (Zymed, South San Francisco, CA) two times at
37°C (15 to 30 minutes each), washed, and postfixed in
10% phosphate-buffered formalin for 1 minute. Slides
were denatured at 94°C for 3 to 5 minutes with biotin- and
digoxigenin-labeled 3p25 YAC probes (753f7 and
932f3), incubated for 18 to 48 hours at 37°C, washed at
72°C in 0.5 × standard saline citrate for 5 minutes, and
incubated with fluorescein isothiocyanate-anti-digoxige-
nin (Roche, Indianapolis, IN) and 594 rhodamine strepta-
vidin (Molecular Probes, Eugene, OR) detection reagents
in CAS block (Zymed).

Immunohistochemistry

Immunohistochemistry was performed using the mono-
clonal antibody E8 raised against a human PPARγ syn-
thetic peptide antigen (Santa Cruz Biotechnology, Santa
Cruz, CA). E8 (1:300) was incubated overnight at 4°C on
paraffin-embedded tissue sections after microwave anti-
gen retrieval (10 mmol/L citrate buffer, pH 6, at 98°C for
30 minutes). Immune complexes were detected with the
ENVISION nonbiont system (DAKO, Carpinteria, CA) to
circumvent known endogenous thyroid biotin-like activi-
ties. Controls for antibody specificity included preincuba-
tion of E8 with blocking synthetic peptide (Santa Cruz
Biotechnology) and exclusion of E8 on tumor and normal
thyroid sections. Positive and negative control tissue sec-
tions (containing or lacking PPARγ rearrangement by
molecular analyses) were included in each run. Consis-
tent, diffuse PPARγ nuclear immunoreactivity in tumor
relative to normal thyroid tissues in the same sections
was scored into three categories for comparative pur-
poses: category 1, immunoreactivity in tumor nuclei com-
parable or less than that in normal thyroid nuclei; cate-
gory 2, immunoreactivity in tumor nuclei elevated mildly
over normal thyroid nuclei; category 3, immunoreactivity
in tumor nuclei elevated highly over normal thyroid nuclei.
Only category 3 tumors had PPARγ rearrangement. Focal
PPARγ nuclear immunoreactivity, seen rarely in small cell
clusters and microfolllicles within tumors or reactive thy-
rocytes, and cytoplasmic PPARγ immunoreactivity, which
was generally low, focal, and variable, were disregarded
in our analyses.

Clinical and Pathological Features and
Statistical Analyses

Tumor pathology data and clinical preoperative and fol-
low-up data were obtained by report and chart reviews
and by contact with the patient’s primary endocrinologist
and/or primary care physician. Values for continuous
variables were calculated as the mean ± SD, and values
for categorical variables were calculated as percent-
ages. Statistical differences were assessed using the
Student’s t-test for continuous data and the chi-square or
Fisher’s exact test for categorical data. All tests were
two-tailed. Tumor capsular thickness was scored subjec-
tively as mild, moderate, or thick and objectively using a stage micrometer. Neither method yielded a statistical difference between tumors with or without PPAR
alterations.

**Results**

**Detection of 3p25/PPARγ Rearrangement and 3p25 Aneusomy**

The single follicular thyroid carcinoma karyotyped in our series contained t(2;3)(q13;p25) (Figure 1A, black arrowheads), a chromosomal rearrangement identified previ-

ously in follicular thyroid tumors. Recent studies have shown that t(2;3)(q13;p25) forms a PAX8-PPARγ gene fusion that is present in a subset of follicular carcinomas. Here, we used interphase FISH with probes flanking the PPARγ gene to investigate these 3p25 rearrangements.

3p25 rearrangements were observed by FISH in 11 of 42 (26%) low-stage follicular carcinomas, 0 of 40 follicular adenomas, 1 of 30 Hurthle cell carcinomas, 1 of 90 papillary carcinomas, and 0 of 10 multinodular goiters (Figure 1B, Table 1). The FISH assay also detected 3p25 genetic imbalances (3p25 aneusomy) in 12 of 42 (29%) follicular thyroid carcinomas (Figure 1C, Table 1). 3p25 aneusomy consisted of trisomy (five cases), trisomy with focal monosomy (one case), and tetrasomy (six cases). No follicular carcinoma had both 3p25 aneusomy and 3p25 rearrangement ($P = 0.01$). In total, 23 of 42 (55%) follicular thyroid carcinomas had 3p25 genetic alterations.

**Detection of PPARγ Fusion Protein by Immunohistochemistry**

Strong, diffuse nuclear immunoreactivity for PPARγ was observed in all 11 follicular thyroid carcinomas with 3p25 rearrangement but not in normal thyroid tissues or thyroid tumors such as follicular adenomas without PPARγ rearrangement (Figure 2A). On the other hand, 11 of 12 follicular carcinomas with 3p25 aneusomy exhibited no nuclear PPARγ immunoreactivity (Figure 2A). Mildly elevated nuclear PPARγ immunoreactivity relative to normal thyroid tissue was seen in a small subset (6 of 42) of follicular carcinomas without PPARγ rearrangement (one with 3p25 aneusomy). Cytoplasmic PPARγ immunoreactivity was infrequent, low, and focal in both tumor and normal thyroid tissues and was disregarded in our analyses. In summary, 18 of 42 (43%) follicular thyroid carcinomas had elevated nuclear PPARγ expression. Strong, diffuse nuclear PPARγ expression was observed in all 11 cases with 3p25 rearrangement.

**Clinical and Pathological Correlations in Follicular Carcinoma Patients**

We compared the clinical and pathological features of patients with follicular thyroid carcinomas containing or lacking 3p25/PPARγ rearrangement and 3p25 aneusomy. Clinical features that did not differ statistically ($P > 0.05$) in these groups included patient sex, age at diagnosis, mean tumor size, TMN stage at diagnosis (98% stage I or II), and frequency of regional lymph node spread (Table 1). Follicular carcinoma patients with PPARγ rearrangement had previous nonthyroid cancers more frequently than follicular carcinoma patients without PPARγ rearrangement ($P < 0.01$, Table 1). One patient (36 years of age) had Hodgkin’s disease and a carcinoid tumor metastatic to lung. A second patient (25 years of age) had a testicular germ cell cancer. A third patient (36 years of age) had Hodgkin’s disease and a lung adeno-

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**Figure 1.** 3p25 genetic abnormalities in follicular thyroid carcinoma. A: Chromosomal rearrangements such as t(2;3)(q13;p25) (black arrowheads) are present in a subset of follicular thyroid carcinomas. B: A 3p25 FISH assay with DNA probes flanking the PPARγ gene demonstrates 3p25 rearrangement (white arrowheads) in a paraffin-embedded follicular thyroid carcinoma. C: The FISH assay also detects 3p25 aneusomy (tetrasomy in this tumor) in the presence or absence of 3p25 rearrangement.
Table 1. Clinical and Pathologic Features of Follicular Carcinoma Patients with 3p25/PPARγ Rearrangement and 3p25 Aneusomy

<table>
<thead>
<tr>
<th>Clinical features</th>
<th>All follicular carcinomas</th>
<th>Follicular carcinomas with 3p25/PPARγ rearrangement</th>
<th>Follicular carcinomas without 3p25/PPARγ rearrangement</th>
<th>P value</th>
<th>Follicular carcinomas with 3p25 aneusomy</th>
<th>Follicular carcinomas without 3p25 aneusomy</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>42 (100%)</td>
<td>11 (26%)</td>
<td>31 (74%)</td>
<td>0.01</td>
<td>12 (29%)</td>
<td>30 (71%)</td>
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<tr>
<td>Age at diagnosis (years)</td>
<td>40.6 ± 16.5</td>
<td>35.6 ± 9.7</td>
<td>42.4 ± 8.1</td>
<td>0.23</td>
<td>46.5 ± 24.3</td>
<td>38.5 ± 11.8</td>
<td>0.15</td>
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<tr>
<td>Tumor size (cm)</td>
<td>3.5 ± 1.8</td>
<td>2.8 ± 0.7</td>
<td>3.8 ± 2.0</td>
<td>0.17</td>
<td>4.0 ± 2.6</td>
<td>3.3 ± 1.4</td>
<td>0.25</td>
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<td>TNM stage at diagnosis</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>I</td>
<td>67%</td>
<td>82%</td>
<td>62%</td>
<td>0.62</td>
<td>59%</td>
<td>70%</td>
<td>0.1</td>
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<tr>
<td>II</td>
<td>29%</td>
<td>16%</td>
<td>32%</td>
<td>0.25</td>
<td>25%</td>
<td>30%</td>
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</tr>
<tr>
<td>III</td>
<td>2%</td>
<td>0%</td>
<td>3%</td>
<td>8%</td>
<td>0%</td>
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<tr>
<td>IV</td>
<td>2%</td>
<td>0%</td>
<td>3%</td>
<td>8%</td>
<td>0%</td>
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<td>Lymph node involvement</td>
<td></td>
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<tr>
<td>Positive</td>
<td>0%</td>
<td>0%</td>
<td>3%</td>
<td>8%</td>
<td>0%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Negative</td>
<td>100%</td>
<td>100%</td>
<td>97%</td>
<td>92%</td>
<td>100%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prior nonthyroid cancer</td>
<td>3 (7%)</td>
<td>3 (27%)</td>
<td>0%</td>
<td>&lt;0.01</td>
<td>0%</td>
<td>3%</td>
<td>&lt;0.01</td>
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<tr>
<td>Pathologic features</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Vascular invasion</td>
<td>21 (50%)</td>
<td>9 (82%)</td>
<td>12 (39%)</td>
<td>0.01</td>
<td>5 (42%)</td>
<td>16 (53%)</td>
<td>0.5</td>
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<td>Solid/nested histology</td>
<td>22 (52%)</td>
<td>11 (100%)</td>
<td>11 (35%)</td>
<td>&lt;0.001</td>
<td>4 (33%)</td>
<td>21 (70%)</td>
<td>0.04</td>
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<tr>
<td>Capsular invasion</td>
<td>38 (90%)</td>
<td>11 (100%)</td>
<td>27 (87%)</td>
<td>0.21</td>
<td>10 (83%)</td>
<td>28 (93%)</td>
<td>0.56</td>
</tr>
<tr>
<td>Capsular penetration</td>
<td>30 (71%)</td>
<td>7 (64%)</td>
<td>23 (74%)</td>
<td>0.51</td>
<td>8 (67%)</td>
<td>22 (73%)</td>
<td>0.72</td>
</tr>
<tr>
<td>Thick tumor capsule</td>
<td>18 (43%)</td>
<td>6 (55%)</td>
<td>11 (35%)</td>
<td>0.27</td>
<td>3 (25%)</td>
<td>15 (50%)</td>
<td>0.18</td>
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</table>

Discussion

Our experiments provide evidence that PPARγ gene rearrangement and 3p25 aneusomy arise independently in early follicular thyroid carcinoma subgroups. Twenty-three of 42 (55%) follicular carcinomas had either PPARγ rearrangement or 3p25 aneusomy but none had both. Gene rearrangements are pathogenic aberrations in many blood cell cancers,2,32 in which they are early and perhaps even initiating events. PPARγ rearrangements seem to provide this type of oncogenic stimulus in follicular carcinomas.21 Aneuploidy is another early genetic alteration in cancer and it may promote genetic instability.3,33 Our findings suggest that PPARγ rearrangement and aneuploidy have an either/or relationship in early follicular carcinomas and that they are independent genetic events in separate pathways of thyroid tumorigenesis. RAS mutations, other early genetic alterations in follicular carcinoma,34–36 also appear to arise independently of PPARγ rearrangement (M. Nikiforova, R. Lynch, P. Biddinger, E. Alexander, G. Dorn, G. Tallini, T. Kroll, and Y. Nikiforov, unpublished data). Moreover, papillary carcinomas (thought to arise from the same follicular cells as follicular carcinomas) frequently have rearrangements of the RET37–39 or NTRK140 genes. Thus, various early genetic alterations appear to identify alternative oncogenic pathways within the thyroid. This pattern appears different from the single pathway of step-wise genetic progression envisioned for colorectal and pancreatic carcinomas, which nearly all contain APC10,42,43 or KRAS44 mutations, respectively.

Although PPARγ rearrangement and aneuploidy appear to arise independently in early follicular carcinomas, they can co-exist16,18 (TG Kroll and JA Fletcher, unpublished data). In two such published cases, PPARγ rearrangement and aneuploidy appeared together in recurrent16 and metastatic18 follicular cancers. Hence, it is possible that PPARγ rearrangement, aneuploidy, and other genetic alterations are rarely associated in low-stage tumors but can be acquired sequentially to create follicular cancers with more aggressive clinical behavior.

Considering the overall data, it seems most appropriate to consider follicular carcinomas with PPARγ rearrangement a distinct thyroid cancer entity. Characteristic pathological features of this entity appear to be vascular...
mechanisms of PPARγ deregulation exist in thyroid cancer and this may explain, at least in part, the various growth effects of PPARγ ligands on thyroid cancer cell lines in vitro and in vivo. Alternate mechanisms of PPARγ deregulation could include cryptic rearrangements, point mutations, or deletions that do not disrupt the physical relationship of our FISH probes or epigenetic/regulatory factors that affect PPARγ transcription, translation, or degradation.

An interesting clinical feature of follicular carcinoma patients with PPARγ rearrangement was an apparent increase in previous nonthyroid cancers (P < 0.001). The robustness of this correlation is uncertain because of low patient numbers but it raises the possibilities that PPARγ rearrangement might be associated with cancer predisposition and/or previous cancer therapy. All three patients had previous cancers treated commonly with irradiation, but we could document a definite history of irradiation only in one.

We detected PPARγ rearrangements in a significant fraction of follicular carcinomas but not other thyroid tumors, supporting their high specificity. PPARγ rearrangements were absent from most Hurthle cell carcinomas, supporting the idea that follicular and Hurthle cell carcinomas should be considered separate thyroid cancer classes. Although not observed in our series, some follicular adenomas with t(2;3)(q13;p25)/PAX8-PPARγ have been reported. We suggest that these morphological follicular adenomas are best considered early in situ follicular carcinomas with malignant potential. Several observations are compatible with the possibility. First, gene rearrangements involving transcription factors are early alterations in many blood cell and connective tissue malignancies and their detection (even by polymerase chain reaction) often defines malignancy. Secondly, the majority of thyroid tumors so far shown to have PPARγ rearrangements are bona fide follicular carcinomas with vascular invasion, our best pathological indicator of malignancy in absence of local-regional spread or metastases. Advanced stage follicular carcinomas with PPARγ rearrangement have been observed (T. Dwight and C. Larsson, unpublished data). Thirdly, a clonal alteration such as PPARγ rearrangement is expected in some morphological follicular adenomas in which vascular invasion and capsular penetration are not yet developed or are missed by standard histological sectioning. Fourth, the high percentage of follicular carcinoma cells containing PPARγ rearrangements and the gross pathology patterns argue against follicular carcinomas arising often from benign thyroid (adenomatous) nodules. Finally, cytogenetic, comparative genomic hybridization, and loss of heterozygosity studies suggest that follicular adenomas and carcinomas are overall genetically distinct thyroid tumor groups.

We have also observed at low frequency papillary thyroid carcinomas with PPARγ rearrangement and expect more to be identified. It is therefore noteworthy that a minority (3 of 11) of our follicular carcinomas with PPARγ rearrangement exhibited identifiable but incompletely developed papillary carcinoma-like nuclear
changes (clearing and focal grooves). However, all three tumors with such features were encapsulated follicular-patterned lesions with vascular invasion—classic follicular carcinoma characteristics. None were felt to be suspicious for papillary carcinoma on preoperative cytology in which such nuclear changes are most sensitive and specific for papillary carcinoma. Even so, these observations suggest that follicular carcinomas with PPARγ rearrangements do exhibit some morphological variation.

Well-differentiated follicular thyroid tumors with mixtures of papillary, follicular, and/or Hurthle cell morphologies are not uncommon62–64 and they highlight an overlapping morphological spectra that confounds attempts to diagnose follicular-patterned thyroid lesions in a precise and accurate way.65,66 This histological overlap among thyroid carcinoma subtypes poses challenges in evaluating molecular genetic correlates. RET rearrangements were originally thought specific for papillary thyroid carcinoma,67,68 but have recently been identified in up to 50% of benign and malignant Hurthle cell tumors.69–71 Apparently identical RET rearrangements have also been demonstrated in follicular thyroid tumors with very different morphological and biological patterns.72–77 These observations suggest that multiple genetic and/or epigenetic events collaborate to determine overall thyroid cancer phenotype.78 It seems likely that such alterations will ultimately prove useful in classifying thyroid tumors into more definitive biological and clinical subgroups.

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References

27. Rosai J, Carcangiu M, DeLellis R: Tumors of the Thyroid Gland. Washington DC, Armed Forces Institute of Pathology, 1992
29. Marques AR, Espadinha C, Catarino AL, Moniz S, Pereira T, Sobrinho LG, Leite V: Expression of PAX8-PPARgamma1 rearrangements in
both follicular thyroid carcinomas and adenomas. J Clin Endocrinol Metab 2002, 87:3947–3952
32. Rowley JD: Molecular genetics in acute leukemia. Leukemia 2000, 14:513–517
33. Thiagalingam S, Laken S, Willson JK, Markowitz SD, Kinzler KW, Vogelstein B, Lengauer C: Mechanisms underlying losses of het-
42. Fearon ER, Vogelstein B: A genetic model for colorectal tumorigen-
44. Hruban RH, Wilentz RE, Kern SE: Genetic progression in the pro-
49. van Heerden JA, Hay ID, Goeliner JR, Salomao D, Ebersold JR, Bergstrahl EJ, Grant CS, Jenkins RB, Eberhardt NL: Frequent loss of heterozygo-
sity on chromosomes 3p and 17p without VHL or p53 mutations suggests involvement of unidentified tumor suppressor genes in follicular thyroid carcinoma. J Clin Endocrinol Metab 1997, 82:3684–3691
tions of 340 thyroid hyperplasias and adenomas revealing correla-
55. Frisk T, Kytola S, Wallin G, Zedenius J, Larsson C: Low frequency of numerical chromosomal aberrations in follicular thyroid tumors de-
56. Hemmer S, Wasenius VM, Knuttila S, Joensuu H, Franssila K: Com-
parison of benign and malignant follicular thyroid tumours by com-
59. Grebe SK, McIver B, Hay ID, Wu PS, Maciel LM, Drabkin HA, Goeliner JR, Grant CS, Jenkins RB, Eberhardt NL: Frequent loss of heterozygo-
sity on chromosomes 3p and 17p without VHL or p53 mutations suggests involvement of unidentified tumor suppressor genes in follicular thyroid carcinoma. J Clin Endocrinol Metab 1997, 82:3684–3691
60. Ye HJ, Marsh DJ, Zedenius J, Dwight T, Delbride L, Robinson BG, Eng C: Fine-structure deletion mapping of 10q22-24 identifies regions of loss of heterozygosity and suggests that sporadic follicular thyroid adenomas and follicular thyroid carcinomas develop along distinct neoplastic pathways. Genes Chromosom Cancer 1999, 26:322–329
63. Chan JK: Strict criteria should be applied in the diagnosis of encapsu-