Balanced Translocation (3;7)(p25;q34): Another Mechanism of Tumorigenesis in Follicular Thyroid Carcinoma?

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ABSTRACT: Alterations of 3p are the most frequently observed changes in follicular thyroid carcinomas. Loss of 3p25–pter has been speculated to be a critical event in the malignant transformation of a subset of thyroid follicular neoplasms. The present report describes a minimally invasive follicular thyroid carcinoma (FTC) with a balanced t(3;7)(p25;q34) and dic(15;22)(p11;p11) as the only abnormalities. The alterations were present in all metaphases analyzed and were demonstrated by G-banding, spectral karyotyping (SKY), and fluorescence in situ hybridization (FISH). This study represents the second case of FTC where 3p25 is involved in a balanced translocation. The findings support the existence of a gene locus in this region which is involved in the tumorigenesis of thyroid carcinoma. © 2000 Elsevier Science Inc. All rights reserved.

INTRODUCTION

Tumors of the thyroid gland are common in the general population, but only a small proportion is malignant. Follicular thyroid carcinoma (FTC) is the second most frequent of the thyroid malignancies, constituting approximately one fifth of the cases. Cytogenetic profiles on FTC are limited in the literature [1–7]. Karyotypes reported for 38 FTC cases have revealed that numerical chromosomal aberrations occur frequently [2–7]. However, in contrast to follicular adenomas, complex structural rearrangements are common in follicular carcinomas [2, 4, 7], although simple deletions/rearrangements have also been seen [3, 5]. Among these structural aberrations, alterations of 3p are the most commonly observed, and include both deletions and translocations [2, 3, 5–7]. Molecular studies have corroborated the cytogenetic findings, with consistent observation of loss of heterozygosity for polymorphic markers in this region. Based on these findings, it was proposed that a locus important in FTC tumorigenesis was located at 3p25–pter. Here, we report a second case of FTC where 3p25 is involved in a balanced translocation.

MATERIALS AND METHODS

Case Report

A 70-year-old man presented with a solid nodule in the right lobe of the thyroid gland. A right lobectomy was performed, which identified a tumor of approximately 8 cm in diameter and weighing 154 g. Microscopic examination revealed a nodular tumor with insular/trabecular cell arrangement that was classified as a minimally-invasive follicular thyroid carcinoma. The tumor cell nuclei were large with varying degree of atypia, and mitoses were regularly seen. The growth pattern was expansive within a capsule; however, in some parts of the tumor invasion of the capsule was seen. Immunostaining revealed the tumor cells to show strong thyroglobulin reactivity; 2–10% of the cells were Ki-67-positive, indicating a low proliferation rate. Informed consent was obtained from the patient, and tumor and blood samples were collected for cytogenetic analyses.

Cell Culture and Karyotyping

Fresh tumor tissue was minced and treated with collagenase I (1,400 U/mL) for 30 minutes. The cells were then disaggregated, and cultured for 5–7 days in RPMI 1640 medium supplemented with 15% fetal bovine serum, 1% L-glutamine, and 1% penicillin and streptomycin at 37°C in a humidified atmosphere of 5% CO₂. After harvesting, metaphase chromosomes were prepared, and G-banded for karyotyping. As a control, lymphocytes were cultured using a PHA method and karyotyped. The clonality criteria and the description of karyotypes followed the recommendations of the ISCN 1995 [8].
SKY and FISH Analysis

Spectral karyotyping (SKY) and fluorescence in situ hybridization (FISH) analysis were performed on metaphase slides from the cultured tumor cells [9]. The SKY was done according to the protocol recommended by the manufacturer (Applied Spectral Imaging, ASI, Migdal Haemek, Israel). Image acquisitions were performed using a SD200 Spectracube system (ASI) mounted on a Zeiss Axioskop microscope with a custom-designed optical filter (SKY-1, Chroma Technology, Brattleboro, VT, USA). The conversion of emission spectra to the display colors was achieved by assigning blue, green, and red colors to specific sections.

Figure 1  Panel (A) shows the G-banded karyotype of the follicular thyroid carcinoma with the detected t(3;7) (p25;q34) and dic(15;22)(p11;p11), illustrated as idiograms. Panel (B) displays the SKY karyotype of the same tumor, with the chromosomes shown in SKY classification colors.
of the emission spectrum. The whole chromosome painting probes for chromosomes 3, 7, 15, and 22 were labeled directly by nick translation using SpectrumOrange-dUTP (Vysis, Downers Grove, IL, USA), FITC-dUTP, or Texas-Red-dUTP (DuPont, Boston, MA, USA). Fluorescence in situ hybridization was performed essentially as described [10], and the results were analyzed using a Zeiss Axioplan 2 (Carl Zeiss Jena GmbH, Jena, Germany) epifluorescence microscope and Sensys (Photometrics, Tucson, AZ, USA) charge-couple-device camera interfaced to a IPlab Spectrum 10 workstation (Signal Analytics Corporation, Vienna, VA, USA).

RESULTS AND DISCUSSION

A total of 30 tumor metaphases were analyzed by G-banding. All were found to have the same karyotype of 46,XY, t(3;7)(p25;q34),dic(15;22)(p11;p11) (Fig. 1A). However, the constitutional karyotype was normal (46,XY), demonstrating that the chromosomal alterations occurred somatically. The SKY analysis performed on tumor metaphases identified the same abnormal karyotype as was detected by G-banding (Fig. 1B). Furthermore, the composition of the derivative chromosomes involved in the t(3;7) and dic(15;22) was confirmed by FISH chromosome painting.

To our knowledge, Jenkins et al. [2] reported the first balanced translocation t(1;3)(p13;p25) in an FTC. In the present case, we found another balanced translocation that also involved 3p25. Taken together, these findings suggest that a 3p gene locus involved in FTC tumorigenesis may reside in band p25. However, the nature of this putative gene is unknown. The observation of balanced translocations would suggest a mechanism involving activation of a proto-oncogene, similar to the situation in papillary thyroid carcinomas (PTC). As seen in some FTCs, RET oncogene activation may occur as a result of gene rearrangements, resulting in a chimeric fusion gene [11–14]. Table 1 shows the structural rearrangements involving 3p and 7q which have been reported in the literature [2, 3, 5–7]. A balanced translocation involving the same band of chromosome 7 as in our case was reported by Teyssier et al. [3]. Thus, a putative proto-oncogene can be residing at either 3p or 7q. However, the structural abnormalities involving 3p are more common than those of 7q.

On the other hand, loss of 3p is also seen in FTCs. Although the reported frequencies are variable, 3p deletions represent consistent findings, demonstrated by cytogenetic as well as molecular genetic methods. These findings would indicate the inactivation of a tumor suppressor gene rather than a dominant mechanism. Furthermore, it is also possible that more than one gene in 3p is involved in FTC tumorigenesis.

Recently, Belge et al. [15] reported 12 cases with dicentric chromosomes or telomeric associations. Among these cases, two goiters and one adenomatous goiter demonstrated a tas(15;22). In the present case, a dic(15;22) was found; however, no evidence of nodular goiter was seen in multiple sections of this tumor. Some studies also reported acrocentric chromosomes, especially of chromosome 22, in both neoplastic and other thyroid lesions [5, 15]. This may suggest that dic(15;22) is an early event in the malignant transformation of thyroid neoplasms.

Based on the present findings and data previously reported in the literature, we suggest that oncogene activation could be an important event in the pathogenesis of FTC. Obviously, more FTCs need to be analyzed to shed light on their tumorigenesis; whether a tumor suppressor gene or an oncogene at 3p is involved is yet to be established.

This work was supported by the Swedish Cancer Foundation, the Torsten and Ragnar Söderberg Foundations, and the Cancer Society in Stockholm (no. 99:114).

REFERENCES


Table 1 Structural abnormalities involving 3p and 7q in follicular thyroid carcinomas

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<td>Jenkins et al. [2]</td>
<td>t(13)(p13;p25)</td>
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