**Topic:** CLONAL ORIGIN OF MULTIFOCAL PAPILLARY THYROID CANCER

**Title:** The heterogeneous distribution of BRAF mutation supports the independent clonal origin of distinct tumor foci in multifocal papillary thyroid carcinoma.

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**SUMMARY**

**Context:** Papillary thyroid carcinoma (PTC) is frequently multifocal. Independent PTC foci may occur either from intraglandular metastases from a single dominant tumor or as unrelated neoplastic clones. In rare cases, the simultaneous presence of PTC foci of different histo-pathological subtypes points to independent sites of tumor formation.

**Objectives:** The authors examined the pattern of BRAF mutations in noncontiguous tumor foci and node metastases from 69 patients affected by multcentric PTC. These included 19 cases characterized by the simultaneous presence of different PTC histo-pathological variants.

**Design:** BRAF (exon 15) mutation was examined by PCR-single strand conformational polymorphism followed by DNA sequencing in laser-capture microdissected tissue samples.

**Results:** Discordant patterns of BRAF mutation were found in about 40% of the multifocal PTCs. In node metastases, BRAF mutations were, in most but not all the cases, concordant with the dominant tumor. A discordant pattern of BRAF mutation was also found in about 50% of the cases in which multiple foci of different histo-pathological variants were present.

**Conclusions:** The heterogeneous distribution of BRAF mutations suggests that discrete tumor foci in multifocal PTC may occur as independent tumors. This information has to be considered in the design of targeted therapeutic approaches with BRAF pathway inhibitors.

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**COMMENT**

Papillary thyroid carcinoma (PTC) is the most common cancer of the thyroid gland, accounting for ~85-90% of all cases. PTC often presents as a multcentric tumor, with the lesions representing multiple non-contiguous foci of tumor disseminated in one or both lobes. In the literature, the prevalence of multifocality varies widely, with prevalence figures ranging between 18% & 87% of the cases. These cases are characterized (in general) by one ‘dominant’ tumor, and multiple additional smaller foci, often microcarcinomas. One of the features of PTC that has puzzled me during my entire professional life is the fact that even though multifocality seems to be frequent, one rarely observes recurrences in the remaining lobe after removal of the main lesion by hemithyroidectomy. Thyroid carcinogenesis is a multi-step process where normal thyrocytes evolve to become carcinomatous cells. For PTC, the two well-recognized genetic oncogenic steps are “RET rearrangements” and “somatic BRAF point mutations”, found in 20%-40% and 40% respectively of sporadic PTC. BRAF is a member of the
Raf family, and the gene encodes for a cytoplasmic kinase, which signals along the MAPK (mitogen-activated protein kinase) pathway. MAPKs transmit intracellular signals by sequential phosphorylation events, and play a major role in carcinogenesis. Recent experimental evidence indicate that toxicity due to H$_2$O$_2$ might play a role in the initiation of such events.

In present article, the dominant tumor of patients affected by multifocal PTC showed a BRAF point mutation (V600E) in 31 out of 50 cases, i.e. a surprisingly high figure of 62%. Furthermore, the analysis of the BRAF mutational status supported the hypothesis that individual tumors in multifocal PTC could occur as independent tumors in 20 of 50 cases, i.e. 40% of cases. These findings may have important direct implications for the stratification of patients with regard to targeted therapeutic approaches.

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See Figure below

![Figure 3](image-url)

Fig. 3. Schematic representation of the variable distribution of the BRAF V600E mutation in the 50 patients affected by multifocal PTC. Shaded shapes indicate presence of BRAF mutation, and clear shapes indicate wild-type (WT) BRAF. Number: 1, absence of BRAF mutation in the dominant tumor, additional foci and metastasis; 2, presence of BRAF mutation in the dominant tumor, additional foci and metastasis; 3, presence of BRAF mutation only in the dominant tumor; 4, presence of BRAF mutation in the dominant tumor and the corresponding metastasis; 5, presence of the BRAF mutation exclusively in the node metastasis; 6, absence of the BRAF mutation in the node metastasis; and 7, presence of the BRAF mutation exclusively in the additional focus.