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Medullary and Non-medullary Thyroid Cancer in a Family

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Acta Oncologica Vol. 43, No. 7, pp. 680–681, 2004

Received 8 March 2004
Accepted 7 July 2004

We report an unusual family which suggests that susceptibility to medullary and non-medullary thyroid cancer (MTC, NMTC) may be related. The index case, a woman aged 59, presented with a 3 cm nodule in the right lobe of her thyroid gland. Thyroid function tests were within normal limits. The patient's past medical history was unremarkable. Furthermore, she was normotensive and had no clinical features suggestive of Cowden's disease. Ultrasound examination showed the thyroid lesion was solid and a biopsy was diagnostic of a diagnosis of MTC. The patient underwent a right lobectomy of the thyroid gland with complete excision of isthmus, histology confirming the biopsy diagnosis.

Her sons, aged 39 and 35 years, underwent screening for C-cell hyperplasia. Both had repeated exaggerated response to pentagastrin stimulation displaying more than 20-fold increases in circulating calcitonin. In addition each had normal thyroid function, and was normotensive with normal 24 h urinary catecholamine levels. There was no history of radiation exposure in either the mother or her two sons.

Using venous blood as a source of DNA the index case was screened for a germline mutation in *RET*. This analysis showed that the index case possessed the V804L mutation within exon 14 that has been implicated as a cause of MEN-2A, MEN-2B and FMTC (1–4).

The index case's two sons were screened for the germline V804L mutation. Neither was a carrier of this mutation or another mutation in exon 10, 11, 13, 14, 15, or 16 of the RET gene. These findings raised the possibility that the index case might carry two different *RET* mutations, the second mutation not being detected in the first screen. To examine this possibility DNA was screened for additional mutations by directly sequencing all exons of *RET*. Intriguingly this analysis failed to demonstrate any additional sequence changes. One of the sons was subsequently noted on examination to have a swelling in the left lobe of his thyroid. An FNA (fine needle aspiration) was reported as showing a follicular-papillary lesion. The individual underwent a total thyroidectomy and central compartment excision. Pathological examination of the excised thyroid gland showed two separate malignancies, a 60 mm Hurthle cell carcinoma and a 7 mm micro-papillary carcinoma. Detailed review of histology showed no significant evidence of C-cell hyperplasia.

A recent study of familial thyroid cancer risks based on the Swedish Family-Cancer Database showed that the risk of NMTC in relatives of MTC cases is similarly elevated to that observed in relatives of NMTC cases (5). This suggests that part of the familial risk of all thyroid cancers has a common aetiology. Certain variants of *RET* might therefore confer an increased risk of NMTC only in concert with other non-RET genes, which confer susceptibility to NMTC. Supporting this hypothesis is the observation that specific RET-haplotypes appear to be over-represented in NMTC cases (6). In addition, in a mouse model of FMTC, follicular tumours resembling human papillary thyroid carcinoma (PTC) have been shown to develop (7). Feldman et al. (3) reported two families in which four out of 21 members with the V804M mutation had concomitant PTCs at thyroidectomy. Similarly, Brauckhoff et al. (2) reported three patients with the mutations 790, 791, and V804L who underwent prophylactic thyroidectomies and were found to have PTCs. Furthermore, in a systematic survey of 104 patients carried out by these workers 9% of patients with the 'low risk' codon 790, 791, and 804 mutations who underwent surgery had concomitant PTCs. Perhaps of greater significance is the recent report of a large multigenerational FMTC family in whom the *RET* A891S mutation segregated with MTC, but individuals who did not carry the mutation developed PTCs (8).

The possibility that aggregation of phenotypes in the family we report could be coincidental cannot be entirely excluded but on the basis of the frequency of the tumours in the population the probability of this seems remote. Notwithstanding this exclusion the observations in the family we report, and published data, suggest that susceptibility to all types of thyroid cancer in some families may be a composite of more than one gene mutation.

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 ISSN 0284-186X
DOI: 10.1080/02841860410018539

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