One hundred and seven family members with the rearranged during transfection V804M proto-oncogene mutation presenting with simultaneous medullary and papillary thyroid carcinomas, rare primary hyperparathyroidism, and no pheochromocytomas: Is this a new syndrome—MEN 2C?

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Background. The rearranged during transfection (RET) V804M proto-oncogene mutation is rare and associated with medullary thyroid carcinoma (MTC). We present 40 members from a total cohort of 107 family members with this mutation.

Methods. Family members were tested for RET mutations, calcitonin levels, and screened for pheochromocytoma and primary hyperparathyroidism (PHPT). Thyroidectomies were performed on 15 members. Surgery and pathology reports were obtained and reviewed. A pedigree was constructed.

Results. A high penetrance was found for MTC and simultaneous papillary thyroid carcinoma (PTC; 40%). The incidence of PHPT was low (13%). There were no findings of pheochromocytoma. The course in the first family generation was indolent, with late onset of MTC. The second generation experienced earlier disease development; onset occurred earliest in the third generation. The second generation experienced a higher incidence of PTC than the first.

Conclusion. This is the largest family with this mutation reported to date. However, it does not fit the classic familial MTC or MEN 2A cancer syndrome. Considering that PTC is not an incidental finding, but the result of an inherited RETV804 M mutation, we propose to identify this phenotypic expression as a unique syndrome consistent with manifestations of MTC, PHPT, and PTC. (Surgery 2009;146:998-1005.)

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The REarranged during Transfection (RET) proto-oncogene codes for a transmembrane receptor that has tyrosine kinase activity and is located on chromosome 10q11.2. RET is activated as a dominant oncogene by DNA rearrangement and was described by Takahashi et al in 1985. The RET proto-oncogene is essential for the development of the sympathetic, parasympathetic, and enteric neurons. It is necessary for the development of calcitonin-secreting thyroid C-cells, but it is not detectable in normal thyroid follicular cells. RET proto-oncogene mutations result in development of medullary thyroid carcinoma (MTC) and have
been found in cases of papillary thyroid carcinoma (PTC).\textsuperscript{1} Ninety-eight percent of inherited MTC cases, and 30–50\% of sporadic MTC cases result from point mutations in the RET proto-oncogene.\textsuperscript{1} In 1993, Donis-Keller et al\textsuperscript{3} and Mulligan et al\textsuperscript{4} independently identified the association of RET proto-oncogene mutations with multiple endocrine neoplasia (MEN) 2A syndrome. In 1994, Eng et al\textsuperscript{5} and Carlson et al\textsuperscript{6} separately identified the association of codon 918 missense mutation in exon 16 of the RET proto-oncogene in families with MEN 2B syndrome. MTC, a tumor of parafollicular thyroid C-cells, may occur sporadically or as part of MEN 2A, MEN 2B, and familial MTC (FMTC) cancer syndromes. MEN 2A is characterized by MTC in 95\% of cases, parathyroid hyperplasia or adenoma in 15–30\%, and pheochromocytoma in 50\%. MEN 2B is similar, but has no hyperparathyroidism and presents with characteristic developmental abnormalities such as marfanoid habitus and ganglioneuromatosis of the intestinal tract.\textsuperscript{1,3,6}

Germline mutations in the extracellular cysteine-rich domain of the RET proto-oncogene were described in exon 10, codons 609, 611, 618, 620, and exon 11, codon 634, resulting in the majority of MEN 2A and FMTC cases. Mutations within intracellular tyrosine kinase domain of RET in exon 13, codon 768 and exon 14, codon 804 have also been described in association with MEN 2A and FMTC syndromes. Mutations of exon 16, codon 918 within the intracellular tyrosine kinase catalytic core are associated with the MEN 2B syndrome.\textsuperscript{3–7} The Seventh International Workshop on MEN classified RET proto-oncogene mutations according to MTC risk and utilized a genotype–phenotype correlation between mutation and symptom development as the basis for age of thyroidectomy. Level 1 mutations (the least high risk) have the lowest risk for MTC development and include codons 768, 790, 791, 804, and 891, with recommended thyroidectomy by age 10. Some authors recommend thyroidectomy by age 5, but others suggest following patients using a pentagastrin-stimulated test. Level 2 mutations (high risk) carry an intermediate risk for MTC and include codons 634, 650, 609, 611, 618, and 620, with recommended total thyroidectomy by age 5. Level 3 mutations (the highest risk) are characterized by early development of metastatic MTC and include codons 883, 918, and 922, with recommended total thyroidectomy within the first 6 months of life. The youngest age at diagnosis and malignant transformation was reported according to codon and risk categories.\textsuperscript{8} The V804M mutation results from replacement of the nucleotide valine (GTG) with methionine (ATG) in exon 14 codon 804.\textsuperscript{9} However, it is rare, and case reports are limited. In fact, the phenotype described in families with the RET V804M mutation seems to be inconsistent in the literature and described as FMTC or MEN 2A syndromes.\textsuperscript{10,16}

This paper presents findings from 107 family members, the largest family with the RET V804M mutation reported to date. Forty members tested positive for the familial mutation, and many have developed MTC or C-cell hyperplasia (CCH). The family has the highest reported incidence of PTC. Several members developed primary hyperparathyroidism (PHPT), but no pheochromocytomas were detected. This family does not fit the classic FMTC or MEN 2A cancer syndrome phenotypes.

**PATIENTS AND METHODS**

**Patients.** One hundred and seven (107) members of an Italian family (origin from Florence/Calabria) with the RET V804M proto-oncogene mutation were evaluated retrospectively. Diagnostic studies, operative, and pathology reports from our hospital and external facilities were obtained with family members’ help and permission. Cases were made anonymous for review. All were screened for RET proto-oncogene mutations, serum calcitonin, calcium, PTH, and carciñoembryonic antigen levels, catecholamines, and metanephrines in the blood and urine. Thyroid ultrasonography (US) was performed; some patients had adrenal gland imaging. Those treated in our facility received genetic counseling. Individuals with elevated calcitonin levels and some carriers with no evidence of clinical disease had thyroidectomy with or without neck dissection at our facility or others along the east coast of the United States. Two large family branches underwent surgery in our hospital, with choice of procedure based on pre-operative diagnostic data. Patients with evidence of MTC on fine-needle aspiration (FNA) biopsy and high calcitonin level underwent total thyroidectomies with central and ipsilateral lateral neck dissection. Mutation carriers with no clinical disease (low or normal calcitonin level, normal thyroid US or negative [FNA] biopsy results) underwent total thyroidectomies. Patients with evidence of PHPT underwent 4 parathyroid gland explorations with biopsies of glands and intra-operative frozen sections. Our hospital employed intra-operative PTH monitoring. PTH and calcium levels were examined 2 weeks and 6 months postoperatively. Endocrine surgeons performed procedures on the majority of patients using a similar approach. Patients
with pre-operative evidence of disease in some community settings received only total thyroidec-
tomies without neck dissection.

Genetic testing. Testing for the RET proto-
oncogene mutation was performed through stan-
dardized blood tests sent to the Mayo Clinic
Medical, Quest Diagnostics, and Lab Corp Labo-
ratories. Sequencing was completed on exons 10,
11, 13, 14, 15, and 16 of the RET proto-oncogene
through amplification of genomic DNA using
polymerase chain reaction followed by nucleotide
sequence analysis on an automated capillary DNA
sequencer. The mutation detected was V804M,
which changes the normal valine at amino acid
position 804 to methionine. Molecular analysis was
performed on 1 patient with PTC to test for a
RET/PTC rearrangement. A pedigree was con-
structed and analyzed. Test results and genetic
counseling were provided to family members who
also received a letter describing the MEN syn-
drome and recommended testing.

Pathology. Pathologic evaluation and staining
were performed using a standardized approach in
external institutions. In our facility, all surgical
specimens were processed in the Department of
Pathology using standardized methods. The glands
were grossly evaluated and sliced entirely. Conven-
tional hematoxylin and eosin, thyroglobulin im-
munohistochemistry, and staining of thyroid
tissues for calcitonin were performed. The diagno-
ses of MTC and PTC were based on World Health
Organization standards.

Statistical analysis. Patient characteristics were
summarized using median and percentages. The
exact 95% confidence intervals were calculated for
proportions. The association between age and
calcitonin level was assessed by using the Spearman
rank correlation coefficient.

RESULTS

To date, 40 of 107 family members tested
positive for the RET V804M proto-oncogene mu-
tation (Fig 1). The RET mutation status on some
third- and fourth-generation members is pending.
Eight of 10 first-generation members were positive
(Table I). One of the 2 deceased member’s status is

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Table I. RET mutation status

<table>
<thead>
<tr>
<th>Generation</th>
<th>Total</th>
<th>Positive*</th>
<th>Negative</th>
<th>Pending/unknown</th>
<th>Died</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>From positive parents</td>
<td>From negative parents</td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>10</td>
<td>8 (89%)</td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>II</td>
<td>27</td>
<td>17 (77%)</td>
<td>5</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>III</td>
<td>66</td>
<td>15 (68%)</td>
<td>7</td>
<td>23</td>
<td>21</td>
</tr>
<tr>
<td>IV</td>
<td>4</td>
<td>0 (0%)</td>
<td>0</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Total</td>
<td>107</td>
<td>40</td>
<td>13</td>
<td>28</td>
<td>26</td>
</tr>
</tbody>
</table>

*Percentage was based on the patients at risk.

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Fig 1. Pedigree of family. Circles represent females and squares represent males. Those who were tested and found to
carry the RET V804M mutation are shown with a “+” sign in the upper right-hand corner of their symbol, those who
tested negative are represented with a “−” sign. No sign in the upper right-hand corner indicates they have not been
tested to date. The symbols of members affected with MTC are filled with black; if they have CCH, the upper half of
their symbols are filled with black. PTC is represented with a gray dot in the center of the symbol. A hash mark—
“/”—through a symbol indicates the person is deceased. The present ages of the family members are located just below
their symbol.
unknown because she had no children. The other deceased first-generation member is presumed to be positive because his offspring were positive. Based on pathology reports and elevated calcitonin levels, all 7 living first-generation mutation carriers are symptomatic. In the second generation, 17 of 22 (77%) at-risk members tested positive. Nine of 17 carriers underwent operations and were symptomatic. In the third generation, 15 of 22 (68%) members tested positive. One 10-year-old, third-generation boy had a total thyroidec-
tomy and was diagnosed with CCH. In the first generation, age at time of diagnosis fell between 71 and 83 years (median, 75). In the second generation, age at diagnosis was between 41 and 64 (median, 45). The majority of family members were diagnosed in 2008. Total thyroidectomies with or without central and/or lateral neck lymph node dissection were performed on 15 family members (Table II). Five members in the first generation and 5 in the second had MTC. Three from the first generation had multifocal MTC. Two in the first and 2 in the second had a combination of MTC and CCH. One in the first generation and 5 in the second had PTC resulting in an incidence of 40%. Three patients with CCH and 3 patients with MTC had PTC. Several PTCs were microcarcinomas; some were multifocal. Two second-generation patients had large PTC requiring postoperative $^{131}$I therapy; 1 had a 2-cm PTC that was multifocal and bilateral. A first-generation patient had an 0.5-cm PTC and lymph node metastasis with PTC. Two second-generation patients had primary hyperparathyroidism; both had 1 parathyroid adenoma removed and both had PTC (1 micro and 1 macro). No patients had a pheochromocytoma. The association between age at diagnosis and calcitonin level increased with age (Spearman's rho = 0.57; P = .03; Fig 2).

Several family members presented for evaluation and treatment to our hospital. The proband (refer to 1:1 in Fig 1) was a 74-year-old man evaluated for the RET V804M proto-oncogene mutation because his sister, treated for MTC, had a RET proto-oncogene mutation. He had no symptoms except for a 30-pound weight loss. His calcitonin level was 622 pg/mL (normal, <16) and carcinoembryonic antigen was 1.4 ng/mL (normal, 0–3.0). Calcium, PTH, catecholamines, and metanephrines in the blood and urine, and serum chromogranin A were normal. Thyroid US showed bilateral hypoechoic nodules; the largest was 1.7 × 1.2 × 1.2 cm. Computed tomography showed no adrenal masses. US-guided FNA biopsy of the dominant thyroid nodule showed positive findings of malignant cells stained for calcitonin. A total thyroidectomy was performed with central and right modified radical neck lymph node dissection. Pathology showed a 1.5-cm MTC in the right lobe, 0.5 cm in the left, and multiple metastatic lymph nodes.

This patient’s 47-year-old daughter (2:1) tested positive for the V804M mutation. Her pre-operative calcium-stimulated calcitonin level was normal; she was negative for PHPT and a pheochromocytoma. Pre-operative US was normal. Prophylactic total thyroidectomy was performed with findings of CCH. Three of her 5 children tested positive for the V804M mutation. A 75-year-old brother (1:2) was asymptomatic but positive for the mutation, with a calcitonin level of 34 pg/mL (normal, <10). He tested negative for pheochromocytoma and PHPT. Thyroid US showed bilateral thyroid nodules <1.0 cm. He underwent total thyroidectomy with findings of a 1.0 × 0.8-cm left lobe MTC and negative lymph nodes.

A 45-year-old daughter (2:4) tested positive for a mutation. Her calcitonin level was 10 pg/mL (normal, <5). Calcium level was normal at 10.5 ng/mL (normal, 8.5–10.6), with an elevated PTH of 97 pg/mL (normal, 12–65). She tested negative for a pheochromocytoma. Thyroid US showed bilateral thyroid nodules with a dominant nodule on the right side measuring 2.7 × 2.2 cm.

**Table II.** Phenotypes from 15 subjects

<table>
<thead>
<tr>
<th>Pathology</th>
<th>Proportion</th>
<th>Percentage (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MTC</td>
<td>10/15</td>
<td>67% (38%, 88%)</td>
</tr>
<tr>
<td>CCH</td>
<td>5/15</td>
<td>33% (12%, 62%)</td>
</tr>
<tr>
<td>PTC</td>
<td>6/15</td>
<td>40% (16%, 68%)</td>
</tr>
<tr>
<td>Hyperparathyroidism</td>
<td>2/15</td>
<td>13% (2%, 40%)</td>
</tr>
<tr>
<td>Pheochromocytoma</td>
<td>0/15</td>
<td>0% (0%, 22%)</td>
</tr>
</tbody>
</table>

CCH, C-cell hyperplasia; MTC, medullary thyroid carcinoma; PTC, papillary thyroid carcinoma.

**Fig 2.** Association between age and calcitonin levels.
US-guided FNA biopsy was negative for malignant cells. She underwent total thyroidectomy and parathyroid exploration with a finding of right inferior parathyroid adenoma. Three remaining parathyroid glands were biopsied and found to be normal. Pathology was consistent with CCH and a 2.0 × 1.5-cm follicular variant of the PTC in the right lobe, a <2-mm PTC in the left lobe, and a single parathyroid adenoma. To rule out an acquired RET mutation resulting in PTC, her 2-cm PTC tumor tissue was analyzed for RET/PTC-1 and RET/PTC rearrangements; none were found. Phosphoglycerate kinase (PGK) was present in the tumor, indicating adequate preservation of mRNA, and, therefore, accurate results. Her 2 children tested positive for the V804M mutation. Other family members were treated in other facilities.

Family members were questioned for history of other cancers. Two family members had different cancers. A first generation 74-year-old was recently operated on for renal cell carcinoma. A third-generation 15-year-old was recently diagnosed with a myosarcoma. No family treated in our facility had any other abnormal findings, such as skin abnormalities, neurologic dysfunction, or mental problems. They were appropriately developed for age, with normal height and weight. A questionnaire was distributed and the responses demonstrated normal development of all family members.

DISCUSSION

This paper is the first to describe the largest family ever studied with the RET V804M proto-oncogene mutation. Our analysis reveals the highest penetrance, not only for MTC, but also for PTC in patients with this mutation. First generation family members showed that 8 of 10 were carriers. We find this noteworthy, given that with autosomal-dominant inheritance, only 50% may be expected to carry the mutation. Also important is the 40% incidence of simultaneous PTC and MTC/CCH. Few published reports describe the simultaneous occurrence of MTC (or CCH) and PTC, and even fewer identify presentation of MTC and PTC in patients with RET proto-oncogene mutations. 13,19,20 To date, 7 cases in 4 families demonstrate the occurrence of MTC and PTC and the V804M mutation. 13,19,20 Including our family, a total of 13 cases will have been reported. Feldman et al 13 described 5 patients with simultaneous PTC and MTC/CCH from 2 families with the V804M mutation. They found increased incidence and predisposition to PTC among young carriers, and recommended prophylactic thyroidectomy in childhood. His findings are consistent with our observations.

The V804M mutation combined with a secondary germ-line or somatic mutation has been considered a possible cause of disease manifestation and/or aggression. 16,20,21 A CDKN2A in combination with V804M was described in a patient with melanoma who subsequently developed MTC, CCH, multifocal PTC, and PHPT, but tested negative for a pheochromocytoma. 20 The more aggressive MTC phenotype is the result of a combination of a somatic M918 T and the V804M mutation. 21 Conversely, some reports indicate that the V804M must be inherited in a homozygous manner for disease manifestation. 22 In our cohort, all symptomatic and affected persons were heterozygous for the V804M mutation.

Based on age distribution, it seems that the first generation has a later onset but more aggressive presentation of MTC (several had metastases) in contrast with the second generation (4 of 8 patients). One patient had both MTC and PTC metastases to the lymph nodes. A similar case with simultaneous metastasis from PTC and MTC was reported by Papi et al. 19 We speculate that the diagnosis of MTC and a more aggressive presentation at a later age is related to the time of diagnosis. If identified earlier, it may not have progressed. The second and third generations in our study show an earlier onset of disease. We again attribute this to the earlier timing of MTC/CCH discovery, when all family members were screened. The fact that the youngest patient with CCH was diagnosed at age 10 might indicate that the disease presents earlier in subsequent generations, consistent with the genetic phenomenon of anticipation. A similar phenomenon was observed by Fattoruso et al. 16 This finding has significant impact on treatment planning and prognosis. Most of the individuals in our study who carried the RET V804M mutation displayed late onset of C-cell disease and an indolent course. However, CCH has been reported as early as age 5, and aggressive metastatic MTC has been reported in 2 children 6 years of age, 1 of whom died of metastatic disease at age 12. 10,11,15

Our family cohort exhibits unique findings of PTC, with even a higher incidence of PTC in the second generation (5 vs 1 member). As reported by Miccoli et al. 23 the frequency of incidental small PTC was about 10% in the series of 998 patients operated on for benign thyroid disease. The frequency of simultaneous MTC/CCH and PTC in our study was 40%. Some patients experienced more clinically significant, large multifocal PTC (1 with lymph node metastasis). The simultaneous presence of MTC/CCH and PTC shows no specific pattern in the literature. 10,17,19 Some reports
suggest that RET proto-oncogene chromosomal rearrangements result in chimeric sequences (RET/PTC) that cause the development of sporadic PTC.\(^1\) Absence of RET/PTC chimeras in 1 patient with large PTC and CCH indicates an inherited rather than acquired mutation resulted in PTC. Hyperparathyroidism was also discovered in 2 of our second-generation family members. Only 3 patients with an association of PHPT and the RET V804M mutation have been described in the literature.\(^11,12,20\)

To date, no family members in our study have a pheochromocytoma. With the classic presentation of MEN 2A, we would expect a 50% incidence.\(^1,7\) One case report describes a pheochromocytoma in a patient with MTC and PHPT who had the RET V804M mutation.\(^24\) Coexisting somatic mutations could explain the finding of pheochromocytoma.

Current recommendations for treatment of clinically evident MTC include total thyroidectomy and bilateral central neck, level 6 and 7, lymph node dissection. Ipsilateral lateral neck dissection should be added if the primary tumor is >1 cm in size or evidence exists of positive nodes in the central neck. A contralateral lateral neck dissection should be considered for bilateral tumors or extensive lateral adenopathy on primary tumor side. Prophylactic total thyroidectomy is advocated for mutation carriers. Central neck lymphadenectomy is debatable.\(^25\)

In conclusion, the current phenotypic criteria for MEN 2A and FMTC syndromes are inconsistent with our study cohort that exhibits a rare RET V804M proto-oncogene mutation described in only a few published case reports. A high penetrance is seen for MTC with simultaneous PTC along with evidence of PHPT, but no pheochromocytoma. We therefore question whether this mutation represents a distinct syndrome with a combination of MTC/CCH, PHPT, and PTC without pheochromocytoma. We also consider the influence of other genetic abnormalities on the phenotype, including additional mutations or polymorphisms. Based on our data, literature reports, and the consensus statement from the Seventh International Workshop on MEN and EUROMEN data, we recommend either thyroidectomy at age 5 for all V804M mutation carriers, or basal and stimulated calcitonin level testing at the time of genetic diagnosis to determine the timing for thyroidectomy. Finally, we strongly suggest establishing a registry of rare RET mutations to further our understanding and improve the management of patients.

The authors thank Megan Tackney, Lisa S., Patricia D., and the family members for their enthusiastic support and help in collecting the data, as well as staff members of the Department of Surgery and Pathology of the Jersey Shore University Medical Center, who helped and assisted in our project.

REFERENCES

DISCUSSION

Dr Ashok R. Shaha (New York, NY): The case that we published on 804 mutations was very interesting because the index patient was a 73-year-old. And out of the 4 children aged between 40 and 50 we elected to operate on them, 3 of them had the 804 mutation, 1 patient had C-cell hyperplasia at the age of 43. So the recommendation you are making that we should offer it at age 5 could be questioned whether these patients could be followed with calcitonin or—and operated at—is always a question, especially—anyone there operated at age 5 with a high complication rate.

Dr Alexander L. Shifrin (Neptune, NJ): The data are not available yet, but some patients presented at an early age and some patients have been followed for a long time. And, actually, you presented 1 of these patients who have had additional mutation. One of your papers was recently published with one V804 mutation, and one additional mutation that was presented as a different phenotype. These additional mutations would influence the phenotype in contrast to just the single V804M mutation.

Dr Electron Kebebew (San Francisco, CA): Just a quick question whether you did your analysis sort of age at presentation. So many of the penetrants are age dependent as well as whether you are going to see the hyperparathyroidism as well as the incidental papillary.

It looked like from your presentation most of the ones that had incidental papillary were older than 45. So how do you know it’s not just transparency and how meticulously the pathologist is looking at the thyroid gland. I don’t know if you had a chance to do an age-based analysis when medullary thyroid cancer is developing, or the risk of it, or papillary thyroid carcinoma and primary hyperparathyroidism.

Dr Alexander L. Shifrin (Neptune, NJ): This family presented to our center within the last 2 years, and all the studies and testing was completed within the last 2 years. The first generation, which presented mostly with MTC, all of the members which are known, besides one who is negative for mutation, all had metastatic MTC. One patient only had PTC in the first generation, but 5 out of the second generation, somewhere between age 40s and 50s, had PTC. Three of these patients also had C-cell hyperplasia and 2 had MTC. Obviously, what will happen in the future, if we just follow those patients and see what happens with the third generation, we don’t know. And what age of the development will be is unclear at this time.

Dr Electron Kebebew (San Francisco, CA): I think it would be worthwhile to look at that first generation sort of age at onset. I think that information should be available to you.

Dr Alexander L. Shifrin (Neptune, NJ): Unfortunately, they have only presented to us in the last 2 years and they didn’t know about mutation before that, or their diagnoses.

Dr Sareh Parangi (Boston, MA): I was curious to see in that first generation did calcitonin correlate to disease—in that patient group? Or did you notice any difference in calcitonin secretion or levels?

Dr Alexander L. Shifrin (Neptune, NJ): Yes, the difference in presentation as metastatic disease versus no metastatic disease and extent of the disease. But we do not know about time of the onset. Because, as I mentioned, they were discovered in the last 2 years. Many family members were in denial that they could have the mutation until 1 of the members had surgery and then told everybody and they started getting tested. And the level of calcitonin correlates with the extent of the disease.

Discussant from the floor: I just thought I would add that we presented a family from Iowa a couple of months ago at the Society of Surgical Oncology who had 3 members who had concurrent medullary thyroid cancer and papillary thyroid cancer who had prophylactic or therapeutic thyroidectomy for the C609Y mutation. So I’m
not sure if this is a specific finding for the 804 mutation, I know it’s relatively rare in the literature, but in that family there were 3 individuals who also had that.

**Dr Alexander L. Shifrin** (Neptune, NJ): I think in addition to 804, there’s something else going on besides just the 804 mutation. There are probably some additional genetic mutations or germline mutations that influence in that expression of the disease. We are completing additional studies to investigate that.

**Dr Orlo H. Clark** (San Francisco, CA): Have you looked at the pathology of the medullary thyroid cancer? Is it mixed? Are the cells mixed, which they sometimes are—histopathologically? Are they separate? What are the actual sizes of the papillary cancers and how operative are they multifocal?

**Dr Alexander L. Shifrin** (Neptune, NJ): Thanks Dr Clark for your interesting question. You mentioned about the cells, most of them were diagnosed as a follicular variant of the PTC. I did not look at the specific description of the cells. I have only looked at thyroid tumor slides of the patients that I operated on. I have not looked specifically at this point, but plan to. The sizes of the PTC were variable between micropapillary to large size, 2-cm tumor, which was multifocal and bilateral. One patient had medullary and PTCs with metastases from PTC into the lymph nodes on the same side of the neck. We are in the process of investigation of RET/PTC chimeras in these patients and in the process of doing a study on polymorphisms influencing this phenotype.