gene carriers.[3] Although discussed at the AAES meeting where the paper was initially presented (cf. discussion accompanying their article), the authors did not consider these alternative explanations.

Without evidence of a common molecular origin of PTC and MTC, calls for a novel "MEN 2C" syndrome seem premature. To better appreciate the authors' reasoning, additional clinicopathologic information is needed for the 15 thyroidectomized V804M gene carriers, preferably in the form of a table. Ideally, such a table should list the size and number of all PTC, the number of involved and removed nodes, the presence or absence of concomitant C-cell disease, the patients' age at the time of thyroidectomy, as well as the indication for thyroidectomy.

Furthermore, the authors are kindly asked to clarify what they consider as "evidence of primary hyperparathyroidism." Specifically, did this evidence require presence of hypercalcemia, or solely a demonstration of increased parathyroid hormone levels? If such evidence was based on increased parathyroid hormone levels or parathyroid histopathology alone, this may explain the authors' 13% rate of primary hyperparathyroidism (2 of the 15 thyroidectomized patients), which is much higher than the rates reported for many V804M RET families.[4,5]

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Response to "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?"

To the Editors:

We thank Drs Machens and Dralle for reviewing our recent publication "One hundred and seven family members with the RET 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?"[1] Their contribution, as world-renowned experts in medullary thyroid carcinoma (MTC) and multiple endocrine neoplasia (MEN) syndrome are very valuable to this topic. They bring up important points and some potential limitations of our study. We provide the additional information that they have suggested.

We agree that the title may imply that all 107 family members have the V804M RET mutation. As reported, only 40 of the 107 members of the family have been documented to carry the RET V804M mutation. We chose to include the total number of family members in the title to illustrate that this is the largest family with the RET V804M mutation reported to date. We did not state in the title that we had identified a new syndrome, but rather the possibility of a new syndrome, and we presented this as a question to promote provocative discussion.

The large number of carriers (68–89%) in the first 3 generations is indeed striking in contrast to the expected 50%, but we do not believe selection bias played a role in our multi-institutional series. We disclosed all available data. As recommended in current MTC: Management and Guidelines of American Thyroid Association,[2] once a germline RET mutation has been identified in a family, RET mutation analysis should be offered to all first-degree relatives (recommendation 9), and those patients should be tested for the presence of MTC/C-cell hyperplasia (CCH) primary hyperparathyroidism (PHPT), and pheochromocytoma. In our family, carriers were evaluated with neck ultrasonography and if thyroid nodules were detected, they underwent fine-needle aspiration biopsy, regardless of serum calcitonin level. The same diagnostic approach is used routinely for noncarriers of the RET mutation with thyroid nodules. We do not agree with the separation of 2 symptomatic patients and 4 incidental patients with papillary thyroid carcinoma (PTC), because the purpose of our paper is to show an increased chance of PTC in persons with V804M mutation.[1,3] Pathologists in our institution provide routine careful examination of each thyroid specimen for PTC, CCH/MTC, or other pathology regardless of the gene study as this information is not always available for them at the time of the operation or pathologic evaluation. Indeed, it is possible that other

Table. Pathologic findings in 15 patients with the RET V804M proto-oncogene mutation

Generation/gender/age at diagnosis (y)	*Pathologic findings*
I/F/83	MTC (multifocal bilateral <2 cm, T1)
	CCH
I/F/76	MTC
I/M/75	MTC (1 × 0.8 cm, negative lymph nodes)
I/M/74	MTC (right lobe, 1.5 cm; left lobe, 0.5 cm; lymph nodes, multiple metastasis)
I/F/71	MTC (multifocal 1.4 cm on the left and 0.3 cm on the right)
	CCH
	PTC (0.5-cm follicular variant)
	Lymph nodes metastasis: 1 PTC, 1 MTC (total 19 lymph nodes removed)
II/F/61	CCH
	PTC (0.6-cm occult sclerosing variant, not encapsulated, moderately differentiated)
II/F/44	MTC
	PTC
II/M/48	MTC (multifocal microscopic, microinvasive, 0.1 cm each)
	CCH
	PTC (0.1 cm, follicular variant)
II/F/44	MTC
II/F/41	MTC (0.1 cm)
	CCH
II/F/46	CCH
	PTC (multifocal: 2 cm, follicular variant on the right and 0.2 cm on the left)
	PHPT (PTH, 97 pg/mL [normal, 12–65]; Ca, 10.5 mg/mL [normal, 8.5–10.6]; pathology consistent with adenoma)
II/F/47	CCH
II/M/46	MTC (0.3 cm)
	CCH
II/F/44	CCH
	PTC (0.1 cm)
	PHPT (PTH, 68 pg/mL [normal, 12–65]; Ca, 9.9 mg/mL [normal, 8.5–10.6]; pathology consistent with adenoma)
III/M/10	CCH

CCH, C-cell hyperplasia; *F*, female; *M*, male; *MTC*, medullary thyroid carcinoma; *PHPT*, primary hyperparathyroidism; *PTC*, papillary thyroid carcinoma; *PTH*, parathyroid hormone.

institutions may look more carefully to find CCH/MTC/PTC if they knew that a patient was a carrier for an RET mutation.

We provide additional information on 15 patients (Table). We did our best to obtain complete details; however, we need to respect patient confidentiality and their wishes to protect their personal information, which explains the lack of some details in this table.

We agree with Drs Machens and Dralle that, to deem "MEN 2C" a new syndrome, a common molecular origin of PTC and MTC should be determined. As pointed out in their studies, somatic secondary hit mutations and modifying factors impact the individual tumor phenotype from an inherited genetic mutation.[4] This very concept is integral to our ongoing investigations.

Regarding the question about our diagnosis of primary hyperparathyroidism: 2 patients from the second generation (44 and 46 years old) had identical diagnostic findings of normocalcemic hyperparathyroidism (Table), defined by abnormally increased PTH levels and upper limit of normal calcium levels. Similar findings were also reported in 1 of 3 cases of PHPT described in V804M carriers.[5-7]

Both patients had parathyroid exploration with findings of 1 enlarged parathyroid gland consistent with parathyroid adenoma by pathologic evaluation. In our institution, we performed biopsies of the remaining 3 parathyroid glands to confirm their benign appearance.

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