# The Clinical Spectrum of Multiple Endocrine Neoplasia Type 2a Caused by the Rare Intracellular *RET* Mutation S891A

Klaus-Martin Schulte, Andreas Machens, Laura Fugazzola, Alan McGregor, Salvador Diaz-Cano, Louise Izatt, Simon Aylwin, Nadia Talat, Paolo Beck-Peccoz, and Henning Dralle

Departments of Endocrine Surgery (K.-M.S., N.T.), Endocrinology (A.M., S.A.), and Pathology (S.D.-C.), King's College Hospital, and Department of Genetics (L.I.), Guy's and St. Thomas' Hospital, King's Health Partners, London SE5 9RS , United Kingdom; Dipartimento di Scienze Mediche (L.F., P.B.-P.), Università degli Studi di Milano and Endocrine Unit, Fondazione Istituto di Rocvero e Cura a Carattere Scientifico Ca' Granda, I-20122 Milan, Italy; and Department of Surgery (A.M., H.D.), Martin-Luther-University of Halle, D-06108 Halle, Germany

**Background:** Germline missense mutations of the *RET* protooncogene cause a clinical spectrum called multiple endocrine neoplasia (MEN) type 2. A strong genotype-phenotype correlation results in major implications for the clinical approach. More information on less common mutations is needed to advance specific guidance.

**Patients and Methods:** We report individualized patient information on 36 carriers of the intracellular *RET* gene mutation S891A from three centers and clustered data of 38 former patients reported in the literature in nine additional studies.

**Results:** S891A mutation accounts for up to 5% of all patients to date reported with *RET* mutations and 16% of those hitherto reported with intracellular mutations. S891A mutation caused medullary thyroid cancer (MTC) in 69.4%, pheochromocytoma in 2.8%, and parathyroid hyperplasia in 8.3% of the 36 patients of this case series and in 63.5, 4.1, and 4.1%, respectively, for the entire groups of 74 patients. The youngest age of onset for MTC in this group was 17 yr (median, 46 yr; range, 17–80 yr), for pheochromocytoma 46 yr (median, 46 yr), and for parathyroid hyperplasia 17 yr (median, 20 yr, range, 17–46 yr). Persistence of MTC was described in 14.3% of patients with available follow-up. Additional findings included corneal nerve thickening in three of 74 patients (4.1%).

**Conclusion:** This intracellular mutation can initiate the full spectrum of MEN2a, initiates MTC at an early age, and causes recurrence and death if undertreated. We recommend stringent adherence to established guidance in MEN2a in this rare mutation. **(*J Clin Endocrinol Metab* 95: E92–E97, 2010)**

The *RET* gene on chromosome 10q11.2 encodes a tyrosine kinase with essential function in growth regulation of endocrine tissues including calcitonin (Ct)-producing parafollicular C-cells, parathyroid chief cells, and adrenomedullary cells. The resulting endocrine tumors constitute the core spectrum of multiple endocrine neoplasia (MEN) type 2 (1). In contrast to extracellular mutations in codons 609–634, intracellular mutations do not target cysteine codons. Lesser constitutive *RET* kinase activation results in lesser transforming capacity (2). Early reports stress association with familial medullary thyroid cancer (FMTC). Accumulating evidence shows their capacity to induce the wider spectrum of MEN2a (3, 4). S891A mutation accounts for less than 5% of all patients

ISSN Print 0021-972X ISSN Online 1945-7197
Printed in U.S.A.

doi: 10.1210/jc.2010-0375 Received February 16, 2010. Accepted May 25, 2010.
First Published Online June 16, 2010

Abbreviations: CCH, C-cell hyperplasia; CNT, corneal nerve thickening; Ct, calcitonin; FMTC, familial medullary thyroid cancer; PH, parathyroid hyperplasia; Pg, pentagastrin; PHEO, pheochromocytoma; PTC, papillary thyroid cancer; MEN, multiple endocrine neoplasia; MRND, modified radical neck dissection.

to date reported with *RET* mutations and 16% of those hitherto reported with intracellular mutations. Specifically, it was found in three of 141 German *RET* families (2.1%) (5) or 17 of 356 Continental European *RET* families (4.8%) (6). We here establish the phenotype of the hitherto rarely reported intracellular *RET* mutation S891A.

## Subjects and Methods

### Subjects

Patients (n = 36) were identified from existing databases by the teams in London, Halle, and Milan. Patients of the Milan (7) and Halle (8) groups have been subject to previous publication. One patient (KMS-10) had died after repeated operations for MTC in another hospital more than 10 yr before establishment of the diagnosis of familial disease.

Clustered data on other patients with *RET* S891A mutations were identified searching the NCBI resources PubMed and Google Scholar with a cutoff date in December 2009 (http://www.ncbi.nlm.nih.gov/pubmed/) using the terms *RET* mutation and intracellular. This retrieved 81 publications. All publications with information relating to codon S891A were subjected to forward and backward quotation searches using the Thompson resource ISI Web of Knowledge (http://apps.isiknowledge.com/). This identified a total of nine publications (3, 9–15) containing data on 38 more patients with S891A mutation. Data in these publications are clustered but suitable for analysis (as presented in Table 2).

### *RET* mutation analysis

Genetic testing was arranged for affected or at-risk family members after genetic counseling and fully informed consent. Sequence analysis of selected exons 10, 11, 13, 14, 15, and 16 was done in accredited genetic testing laboratories.

### Clinical evaluation

All 35 patients of this case series with proof of mutation underwent evaluation for MTC, pheochromocytoma (PHEO), and primary hyperparathyroidism. KMS-10 died without recognition of her MEN2a syndrome. The suspicion of MTC was evaluated by basal Ct in all patients. Serum levels of carcinoembryonic antigen were determined in 22 patients. Ultrasound of the thyroid, fine-needle aspiration biopsy, $^{99m}$technetium scintiscan, or dimercaptosuccinic acid scan was performed in 33 of 35 patients (94%). The suspicion of PHEO was evaluated by triple 24-h urine collection and analysis of excreted amounts of catecholamines. Specific imaging was performed in eight of 35 patients (22.8%).

Primary hyperparathyroidism was defined as raised corrected serum calcium and PTH level and was evaluated in 16 of 35 patients (45.7%).

Details of investigations in formerly reported patients are not known (3, 9–15).

Pentagastrin (Pg) stimulation was performed with an indwelling catheter, and Ct was measured at −10, 0, 2, 5, and 10 min (Milan) or 0, 2, and 5 min (Halle) after an iv bolus of 0.5 $\mu$g/kg Pg.

### Histopathology

All cases were classified according to the World Health Organization classification criteria (16). Standard criteria were used to identified for C-cell hyperplasia (CCH) (50 or more C-cells in at least one low-power field, ×100). TNM (tumor-node-metastasis staging) of MTC and papillary thyroid cancer (PTC) was performed according to the International Union Against Cancer sixth edition system 2006.

PHEO was diagnosed based on histopathological findings as a tumor of chromaffin cells of the adrenal medulla of at least 1 cm in diameter.

Histopathological parathyroid hyperplasia (PH) was defined by enlarged glands (more than 60 mg) with diffuse or nodular growth patterns, variable amount of mature adipose tissue, and mild nuclear pleomorphism in the absence of histologically normal or atrophic parenchyma. In case of nodular configuration, internodular transition was identified.

## Results

The clinical presentation of 36 patients with detailed information is shown in Table 1. A summary of these 36 and 38 previous patients is shown in Table 2.

### Thyroid disease, surgery, and related outcomes in the 36 patients of this case series

#### *Thyroidectomy*

Among carriers of the S891A mutation, 29 patients underwent at least a total thyroidectomy, 22 with central neck dissection (level VI). Eight patients from Milan did not undergo surgery (Table 1).

#### *MTC and C-cell-associated pathology*

Histopathological proof of CCH and MTC was found in 23 and 21, respectively, of the 29 patients treated by surgery. MTC is likely present in an additional three Milan patients with elevated basal Ct and pathological Pg tests or elevated carcinoembryonic antigen levels. MTC may hence be present in as many as 25 of the 36 patients or 69.4% with an age range of 17–80 yr. Age-related penetrance is shown in Table 3.

#### *Lymph node metastasis pattern of MTC*

The extent of lymph node dissection varied between centers. Six of 10 London patients underwent ipsilateral modified radical neck dissection (MRND) level II-V, and 4 of these also underwent contralateral MRND. Three of 8 patients from Halle underwent bilateral MRND because of high basal Ct, significant Ct rise of Pg stimulation, or established macroscopic cancer.

#### *Persistent/recurrent MTC*

Persistent measurable Ct levels were identified in two of 10 patients from London, in two of eight from Halle, and in seven of 11 patients from Milan, giving a total of 11 of 29 patients, or 37.9%. Redo modified radical bilateral

**TABLE 1.** *RET* S891A mutation: clinical presentation, treatment, and outcome of 36 patients with *RET* S891A mutation (individual data)

| Patient | Age at Dx (yr) | Gender | Pre-op Ct (times upper normal limit) | Pg test | CCH | MTC | Persistent MTC | Total thyroidectomy | Level VI LN+/all resected[a] | Level II–V LN+/all resected[a] | pT stage | pN stage | PTC | PTC stage | Parathyroid pathology | PHEO |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| KMS-1 | 17 | F | 5.3 | NP | Yes | Yes | No | Yes | 0/30 | 0/10 | T1m | N0 | No | | Hyperplasia | No |
| KMS-2 | 46 | F | 189.3 | NP | Yes | Yes | Yes | Yes | 1/7 | 0/55 | T1m | N1a | No | | Hyperplasia | Yes |
| KMS-3 | 52 | M | 1.7 | NP | Yes | No | No | Yes | 0/8 | 0/50 | T0 | N0 | No | | Normal | No |
| KMS-4 | 20 | M | 0.0 | NP | Yes | No | No | Yes | 0/0 | 0/36 | T0 | N0 | No | | Hyperplasia | No |
| KMS-5 | 55 | M | 1.5 | NP | No | Yes | No | Yes | 0/8 | 0/48 | T1 | N0 | Yes | pT1mN0 | Normal | No |
| KMS-6 | 80 | F | 110.9 | NP | Yes | Yes | No | Yes | 0/0 | 0/0 | T1m | N0 | No | | Normal | No |
| KMS-7 | 17 | M | NA | NP | Yes | No | No | Yes | 0/37[b] | | T0 | N0 | No | | Normal | No |
| KMS-8 | 20 | M | NA | NP | Yes | No | No | Yes | 0/87[b] | | T0 | N0 | No | | Normal | No |
| KMS-9 | 24 | F | 3.0 | NP | Yes | Yes | No | Yes | 0/17 | 0/20 | T1m | N0 | No | | Normal | No |
| KMS-10 | 69 | F | NA | NP | No.speci | Yes | Yes | Yes | No.speci | No.speci | T4a | No.speci | No.speci | | No.speci | No |
| Fug-I/7 | 85 | F | 6.1 | NP | No.speci | Yes[c] | Yes | No | 0/0 | 0/0 | | Nx | No.speci | | No.speci | No |
| Fug-II/10 | 60 | F | 10.0 | NP | No.speci | Yes[c] | Yes | No | 0/0 | 0/0 | | Nx | No.speci | | No.speci | No |
| Fug-II/11 | 65 | M | 7.7 | NP | Yes | Yes | Yes | Yes | Yes | 0/0 | T1m | N0 | No | | Normal | No |
| Fug-II/14 | 53 | F | 3.6 | + | No.speci | Yes[c] | Yes | No | 0/0 | 0/0 | | Nx | No.speci | | No.speci | No |
| Fug-II/16 | 61 | F | 41.0 | NP | Yes | Yes | Yes | Yes | Yes | 0/0 | T1m | N1a | No | | Normal | No |
| Fug-II/18 | 56 | F | 12.7 | NP | Yes | Yes | No | Yes | Yes | 0/0 | T1 | N1a | No | | Normal | No |
| Fug-II/19 | 60 | M | 8.8 | NP | Yes | Yes | Yes | Yes | Yes | 0/0 | T2 | N0 | No | | Normal | No |
| Fug-II/22 | 51 | F | 7.5 | NP | Yes | Yes | No | Yes | Yes | 0/0 | T1m | N0 | No | | Normal | No |
| Fug-III/2 | 42 | F | 0.0 | + | Yes | Yes[c] | No | Yes | Yes | 0/0 | T1m | N0 | No | | Normal | No |
| Fug-III/3 | 41 | M | 0.0 | + | Yes | Yes | No | Yes | Yes | 0/0 | T1m | N0 | No | | Normal | No |
| Fug-III/4 | 34 | M | 0.0 | + | Yes | Yes | No | Yes | Yes | 0/0 | T1m | N0 | Yes | pT1N0 | Normal | No |
| Fug-III/8 | 27 | M | NA | NP | Yes | Yes[d] | No | Yes | Yes | 0/0 | T1m | N0 | Yes | pT1mN0 | Normal | No |
| Fug-III/12 | 40 | M | 0.0 | + | No.speci | Yes | Yes | No | 0/0 | 0/0 | – | Nx | No.speci | | No.speci | No |
| Fug-III/23 | 30 | M | 0.0 | + | Yes | Yes | No | Yes | 0/0 | 0/0 | T1m | N0 | No | | No.speci | No |
| Fug-III/24 | 55 | F | 0.0 | + | Yes | Yes | No | Yes | Yes | 0/0 | T1m | N1a | No | | No.speci | No |
| Fug-III/13 | 29 | M | 0.0 | – | No.speci | No.speci | No.speci | No | 0/0 | 0/0 | | Nx | No.speci | | No.speci | No |
| Fug-IV/2 | 19 | M | 0.0 | – | No.speci | No.speci | No.speci | No | 0/0 | 0/0 | | Nx | No.speci | | No.speci | No |
| Fug-IV/5 | 24 | F | 0.0 | – | No.speci | No.speci | No.speci | No | 0/0 | 0/0 | | Nx | No.speci | | No.speci | No |
| HAL-A1 | 4 | F | 1.0 | + | Yes | No | No | Yes | 0/0 | 0/0 | T0 | Nx | No | | Normal | No |
| HAl-B1 | 6 | M | 0.0 | + | Yes | No | No | Yes | 0/0 | 0/0 | T0 | Nx | No | | Normal | No |
| HAL-B2 | 8 | M | 4.6 | NP | Yes | No | No | Yes | 0/0 | 0/0 | T0 | Nx | No | | Normal | No |
| HAL-B3 | 17 | M | 2.3 | NP | No | Yes | No | Yes | 0/9 | 0/0 | T1m | N0 | No | | Normal | No |
| HAL-B4 | 10 | F | 1.3 | + | Yes | No | No | Yes | 0/0 | 0/0 | T0 | Nx | No | | Normal | No |
| HAL-B5 | 46 | M | 1.4 | NP | No | Yes | No | Yes | 0/5 | 0/25 | T1m | N0 | Yes | pT1N0 | Normal | No |
| HAL-B6 | 78 | F | 72.6 | + | No | Yes | Yes | Yes | 1/15 | 0/30 | T1m | N1a | No | | Normal | No |
| HAL-C1 | 59 | F | 11.6 | NP | No | Yes | Yes | Yes | 0/12 | 2/54 | T1m | N1b | No | | Normal | No |
| Total | Mean 41 | 18 M, 18 F | Mean 14.0 | | 23[e] (63.9%) | 25 (69.4%) | 11 (30.6%) | 29 (80.1%) | 2/96 | 2/328 | T1–T4 | | 4 (11.1%) | 4 = T1N0 | 3 (8.3%) | 1 (2.8%) |

Dx, Diagnosis; F, female; M, male; LN, lymph node; NA, not available; NP, not performed, No.speci, no specimen; pN, lymph node status; pT, tumour stage; +, positive test; –, negative test.

[a] LN+ includes positive lymph nodes proven on histopathology; all resected includes all lymph node resected.

[b] The origin of dissected lymph node is clustered.

[c] Patient had clinically proven MTC but refused to undergo surgery.

[d] Patient had clinically proven MTC and died of progressive colon cancer with metastases.

[e] Because CCH is an exclusive histopathology, finding the actual percentage of CCH per removed thyroid is 79.3%.

**TABLE 2.** Clinical presentation and treatment in 74 patients with *RET* S891A mutation

| Study | Total patients | No. affected patients [n (%)] | No. asymptomatic gene carriers [n (%)] | Mean age at Dx (yr) | Tx [n (%)] | Central LN [n (%)] | Lateral LN [n (%)] | MTC [n (%)] | CCH [n (%)] | PTC [n (%)] | PH [n (%)] | PHEO [n (%)] | CNT [n (%)] | Extra-regional metastases of MTC | Other cancers |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Present | 36 | 33 (92) | 3 (8) | 41 | 29 (81) | 19 (53) | 9 (25) | 25 (86) | 23 (79) | 4 (14) | 3 (10) | 1 (3) | ND | No | Colon |
| Jimenez *et al.* (9) | 6 | 3 (50) | 3 (50) | 45 | 3 (50) | 1 (17) | 1 (17) | 2 (67) | 2 (67) | 0 | 0 | 1 (17) | No | Hepatic | Gastric |
| Hofstra *et al.* (10) | 5 | 3 (60) | 2 (40) | 47 | 3 (60) | ND | ND | 3 (100) | 1 (33) | 0 | 0 | 0 | ND | No | No |
| Dang *et al.* (11) | 3 | 3 (100) | 0 | ND | ND | ND | ND | 3 (100) | ND | ND | ND | ND | 1 (33) | ND | ND |
| Elisei *et al.* (3) | 14 | 6 (43) | 8 (57) | 44 | 6 (43) | ND | ND | 6 (100) | ND | ND | ND | ND | ND | ND | ND |
| Yip *et al.* (12) | 3 | 3 (100) | 0 | ND | 3 (100) | ND | ND | 3 (100) | DC | 0 | 0 | 0 | 2 (66) | Bones, lung, breast | No |
| Asari *et al.* (13) | 1 | 1 (100) | 0 | ND | 1 (100) | ND | ND | 1 (100) | 0 | 0 | 0 | 1 (100) | ND | ND | ND |
| Paszko *et al.* (15) | 2 | 2 (100) | 0 | ND | 2 (100) | 2 (100) | 0 | 2 (100) | 0 | 0 | 0 | 0 | ND | No | No |
| Wohllk *et al.* (14) | 4 | 2 (50) | 2 (50) | 49.0 | 2 (50) | ND | ND | 2 (100) | 2 (100) | 0 | 0 | 0 | ND | No | No |
| Total | 74 | 56 (75.7) | 18 (24.3) | 41.2 | 49 (66.2) | 22 (29.7) | 10 (13.5) | 47 (63.5) | 28[a](37.8) | 4 (5.4) | 3 (4.1) | 3 (4.1) | 3 (4.1) | 2 (2.7) | 2 (2.7) |

DC, Data clustered; Dx, diagnosis; LN, lymph node; ND, no data; n, number of patients; Tx, total thyroidectomy.

[a] Because CCH is an exclusive histopathology, finding the actual percentage of CCH per removed thyroid is 57.1%.

**TABLE 3.** Age-related penetrance of 36 patients with *RET* S891A mutation

| | Age range (yr) | | | |
|---|---|---|---|---|
| | 0–20 | 21–40 | 41–60 | >60 |
| Cancer (n) | 2 | 5 | 12 | 6 |
| Gene carriers (n) | 10 | 7 | 13 | 6 |
| Age-related penetrance (%) | 20.0 | 71.4 | 92.3 | 100.0 |

n, Number of patients.

neck dissection in one patient from London, who initially presented with PHEO and MTC stage pT1 (m) N1a (1/62) Mx, found one additional lymph node metastasis in 111 lymph nodes and resulted in biochemical cure. The mother of this patient (KMS-10) had elsewhere undergone more than five neck operations before dying from locoregional MTC recurrence at age 69. Her sister displayed a persistently 1- to 3-fold elevated Ct at 20 months follow-up.

### *PHEO*

Clinical evidence of catecholamine excess was identified in one of 36 patients (KMS-2). She was the London index case and presented at age 46 with severe arterial hypertension, spells, and headaches. Twenty-four-hour urine epinephrine output was elevated 21-fold, and norepinephrine was elevated 11-fold, with a normal dopamine. Computed tomography and [$^{123}$I]meta-iodobenzylguanidine scanning identified a PHEO, which was removed laparoscopically combined with a total thyroidectomy and bilateral MRND. Histology demonstrated a locally invasive PHEO sized 45 × 30 × 25 mm, extending through the adrenal capsule in multiple areas, and infiltrating the periadrenal soft tissue. Tumor cells were arranged in a nested pattern and with basophilic granular cytoplasm with fewer than one mitotic figure per 50 high-power fields and no necrosis or lymphovascular or perineural invasion. Ki 67 showed a proliferation fraction of less than 1%.

### *Parathyroid disease*

Calcium levels were normal in 17 patients and borderline normal in one patient (2.6 mM; normal, 2.2–2.6 mM). All patients had normal PTH levels. Histology identified PH in three of 10 patients from London in whom at least one parathyroid had been removed on grounds of macroscopic enlargement. All patients remain eucalcemic and euparathyroid on follow-up.

### *PTC*

PTC was observed in four of 29 patients (13.8%) with surgical specimens. PTC presented as microcarcinoma, in some cases multifocal, without lymph node metastases.

### *Corneal nerve thickening (CNT)*

Corneal nerve thickening (CNT) was confirmed in three of 74 patients (4.1%).

### *Other solid cancers*

One colon cancer was identified among the 36 patients of this case series.

## Discussion

The mutation S891A is uncommon and located in the second intracellular tyrosine kinase domain TK2 of the *RET* protooncogene. It belongs to those *RET* mutations with low (E768D, V804L, S891A and A919P) rather than high (A883F, M918T and E768D) transforming activity (17). This publication characterizes the phenotype of the S891A mutation.

Histopathology revealed CCH in 23 of 28 specimens (Table 1). MTC was found in 25 of 29 mutation carriers (86.2%) in the present case series if three nonoperated patients with 3.6- to 10.0-fold elevated basal Ct and one patient with 8-fold Ct rise after Pg are included (Table 1). MTC was described in 22 of 38 former patients (57.9%) (3, 9–15) or 47 of 74 (63.5%) of all reported S891A mutation carriers. It is noteworthy that five patients without CCH yet manifested with MTC. Patient KMS-5 had a single focus of a 2-mm microinvasive MTC in the absence of CCH. Four patients from Halle without CCH showed seven, four, two, and two microcancers, respectively. This is clearly different from patients with extracellular mutations where multiple foci of CCH precede and outnumber foci of microscopic MTC. CCH in extracellular mutations are monoclonal, genetically heterogeneous, and consistent with an intraepithelial neoplasia, due to embryonic clonal expansion before divergence of each thyroid lobe. The pattern of MTC appearing without background CCH in 25.0% of our patients points toward a different pathway.

Outcome in the London patient with initial Ct persistence is encouraging. Redo surgery identified MTC in only one more of 111 cervical lymph nodes, and Ct became undetectable. Absence of lymph node metastasis in most patients with established MTC indicates a mitigated propensity of lymphatic spread. For the S891A mutation, the guidelines of the American Thyroid Association for class-A mutations should be followed (18). Given the moderate metastatic potential, secondary surgical cure can be attempted in cases with persistent Ct.

PTC and microcancer are increasingly frequent findings (Supplemental Appendix 1, published on The Endocrine Society's Journals Online web site at http://jcem.endojournals.org). We observed four cases of multifocal PTC in 74 patients at risk, or merely 5.4%, close to the expected background frequency. There is no epidemiological support for a causal relationship but a strong argument for a chance coincidence (19).

We confirm that intracellular *RET* mutations can induce PHEO. Former reports on PHEO in such mutations include fewer than 20 patients (Supplemental Appendix 1). Jimenez *et al.* (9) identified the first PHEO associated with S891A mutation. This review of 74 patients identified three patients, or 4.1% of patients, to have a PHEO, one new and two former patients (9, 13). PHEO needs to be an integral part of clinical screening of patients with S891A mutations.

PTH excess is rare if not absent in this mutation. Although three patients had histopathological PH, none met endocrine criteria for primary hyperparathyroidism.

CNT was initially thought to be an exclusive feature of the MEN2b due to mutations in codon 918, where it is routinely observed. However, it can be observed outside the context of identified *RET* mutation and has been found in more than 60% of patients with MEN2a. CNT has been observed in a minority of patients with intracellular *RET* mutations. Details can be found in the internet repository (Supplemental Appendix 1). Association of S891A mutation with CNT was first reported in 1999 (11), followed by additional patients in 2008 (12) (Table 2). Moderate degrees of CNT are hard to detect unless using slit lamp examination. CNT is hence likely underreported.

Our report shows that mutation S891A can produce the phenotype of MEN2a, including metastatic MTC, invasive PHEO, and CNT. PH seems to be of little functional consequence.

## Acknowledgments

We gratefully acknowledge the contribution of Dr. Muriel Buxton-Thomas, M.D., F.R.C.P., F.R.C.R., (Nuclear Medicine, King's College Hospital, King's Health Partners, London, UK) for input in diagnostic imaging and patient care.

Address all correspondence and requests for reprints to: Dr. Klaus-Martin Schulte, M.D., F.R.C.S., Department of Endocrine Surgery, King's College Hospital, Denmark Hill, London SE5 9RS, United Kingdom. E-mail: klaus-martin.schulte@nhs.net.

Disclosure Summary: The authors have nothing to disclose.

## References

1. **Eng C, Smith DP, Mulligan LM, Nagai MA, Healey CS, Ponder MA, Gardner E, Scheumann GF, Jackson CE, Tunnacliffe A, *et al*** 1994 Point mutation within the tyrosine kinase domain of the *RET* protooncogene in multiple endocrine neoplasia type 2B and related sporadic tumours. Hum Mol Genet 3:237–241

2. **Machens A, Dralle H** 2007 Genotype-phenotype based surgical concept of hereditary medullary thyroid carcinoma. World J Surg 31: 957–968
3. **Elisei R, Romei C, Cosci B, Agate L, Bottici V, Molinaro E, Sculli M, Miccoli P, Basolo F, Grasso L, Pacini F, Pinchera A** 2007 RET genetic screening in patients with medullary thyroid cancer and their relatives: experience with 807 individuals at one center. J Clin Endocrinol Metab 92:4725–4729
4. **Brauer VF, Scholz GH, Neumann S, Lohmann T, Paschke R, Koch CA** 2004 RET germline mutation in codon 791 in a family representing 3 generations from age 5 to age 70 years: should thyroidectomy be performed? Endocr Pract 10:5–9
5. **Machens A, Dralle H** 2008 Familial prevalence and age of RET germline mutations: implications for screening. Clin Endocrinol (Oxf) 69:81–87
6. **Machens A, Lorenz K, Dralle H** 2009 Constitutive RET tyrosine kinase activation in hereditary medullary thyroid cancer: clinical opportunities. J Intern Med 266:114–125
7. **Fugazzola L, Cerutti N, Mannavola D, Ghilardi G, Alberti L, Romoli R, Beck-Peccoz P** 2002 Multigenerational familial medullary thyroid cancer (FMTC): evidence for FMTC phenocopies and association with papillary thyroid cancer. Clin Endocrinol (Oxf) 56:53–63
8. **Machens A, Lorenz K, Dralle H** 2009 Individualization of lymph node dissection in *RET* (rearranged during transfection) carriers at risk for medullary thyroid cancer: value of pretherapeutic calcitonin levels. Ann Surg 250:305–310
9. **Jimenez C, Habra MA, Huang SC, El-Naggar A, Shapiro SE, Evans DB, Cote G, Gagel RF** 2004 Pheochromocytoma and medullary thyroid carcinoma: a new genotype-phenotype correlation of the *RET* protooncogene 891 germline mutation. J Clin Endocrinol Metab 89:4142–4145
10. **Hofstra RM, Fattoruso O, Quadro L, Wu Y, Libroia A, Verga U, Colantuoni V, Buys CH** 1997 A novel point mutation in the intracellular domain of the *ret* protooncogene in a family with medullary thyroid carcinoma. J Clin Endocrinol Metab 82:4176–4178
11. **Dang GT, Cote GJ, Schultz PN, Khorana S, Decker RA, Gagel RF** 1999 A codon 891 exon 15 *RET* proto-oncogene mutation in familial medullary thyroid carcinoma: a detection strategy. Mol Cell Probes 13:77–79
12. **Yip L, Cote GJ, Shapiro SE, Ayers GD, Herzog CE, Sellin RV, Sherman SI, Gagel RF, Lee JE, Evans DB** 2003 Multiple endocrine neoplasia type 2: evaluation of the genotype-phenotype relationship. Arch Surg 138:409–416; discussion 416
13. **Asari R, Scheuba C, Kaczirek K, Niederle B** 2006 Estimated risk of pheochromocytoma recurrence after adrenal-sparing surgery in patients with multiple endocrine neoplasia type 2A. Arch Surg 141: 1199–1205; discussion 1205
14. **Wohllk N, Becker P, Youlton R, Cote GJ, Gagel RF** 2001 [Germline mutations of the *ret* proto-oncogene in Chilean patients with hereditary and sporadic medullary thyroid carcinoma]. Rev Med Chil 129:713–718 (Spanish)
15. **Paszko Z, Sromek M, Czetwertynska M, Skasko E, Czapczak D, Wisniewska A, Prokurat A, Chrupek M, Jagielska A, Kozlowicz-Gudzinska I** 2007 The occurrence and the type of germline mutations in the *RET* gene in patients with medullary thyroid carcinoma and their unaffected kindred's from Central Poland. Cancer Invest 25:742–749
16. **DeLellis RA LR, Heitz PU, Eng C (Eds)** 2004 World Health Organization Classification of Tumours. Pathology and genetics of tumours of endocrine organs. Lyon, France: IARC Press
17. **Iwashita T, Kato M, Murakami H, Asai N, Ishiguro Y, Ito S, Iwata Y, Kawai K, Asai M, Kurokawa K, Kajita H, Takahashi M** 1999 Biological and biochemical properties of *Ret* with kinase domain mutations identified in multiple endocrine neoplasia type 2B and familial medullary thyroid carcinoma. Oncogene 18:3919–3922
18. **Kloos RT, Eng C, Evans DB, Francis GL, Gagel RF, Gharib H, Moley JF, Pacini F, Ringel MD, Schlumberger M, Wells Jr SA** 2009 Medullary thyroid cancer: management guidelines of the American Thyroid Association. Thyroid 19:565–612
19. **Kim WG, Gong G, Kim EY, Kim TY, Hong SJ, Bae Kim W, Shong YK** 2010 Concurrent occurrence of medullary thyroid carcinoma and papillary thyroid carcinoma in the same thyroid should be considered as coincidental. Clin Endocrinol (Oxf) 72:256–263