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Letter to the Editor: The Somatic RET M918T Variant May Modify the Natural History of Germline RET L790F MEN2-Related Medullary Thyroid Carcinoma

Nicolas Sahakian, Pauline Romanet, Delphine Mirebeau-Prunier, Cinzia Paladino, Frederic Castinetti, Anne A. Barlier

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1 **Letter to the editor: The somatic *RET* M918T variant may modify the natural history of germline**
2 ***RET* L790F MEN2-related medullary thyroid carcinoma**

3
4 **Running title:** Somatic *RET* variant may modify MEN2-MTC outcome

5
6 **Authors:** Nicolas Sahakian^{1*}, Pauline Romanet^{2#*}, Delphine Mirebeau-prunier^{3, 4}, Nunzia Cinzia
7 Paladino⁵, Frederic Castinetti^{1**}, Anne Barlier^{2**}

8 *Co-first, **Co Senior, #corresponding author

9
10 **Affiliations:**

11 ¹ Aix Marseille Univ, APHM, INSERM, MMG, La Conception University Hospital, Department of
12 Endocrinology, Marseille, France. nicolas.sahakian@ap-hm.fr, frederic.castinetti@ap-hm.fr

13 ² Aix Marseille Univ, APHM, INSERM, MMG, La Conception University Hospital, Laboratory of
14 Molecular Biology, Marseille, France. pauline.romanet@ap-hm.fr, anne.barlier@ap-hm.fr

15 ³ Service de Biochimie et biologie Moléculaire, Centre Hospitalier Universitaire d'Angers, 49933,
16 Angers, France. deprunier@chu-angers.fr

17 ⁴ Université d'Angers, Inserm U1083, CNRS UMR 6015, MITOVASC, 49000, Angers, France.

18 ⁵ APHM, Department of Endocrine Surgery, La Conception University Hospital, Marseille, France.
19 nunzia.paladino@ap-hm.fr

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23
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25 Dear Editor,

26

27 Twenty to 25% of medullary thyroid carcinoma (MTC) are due to germline *RET* activating pathogenic
28 variants as part of multiple endocrine neoplasia type 2 (MEN2). MEN2 is characterized by a strong
29 genotype-phenotype correlation. Patients are stratified into three risk grades for aggressive MTC
30 (moderate, high, and highest risk) based on germline *RET* variations. For instance, the c.2370G>C,
31 p.Leu790Phe variant (*RET*-L790F) is considered to be of moderate risk of aggressive MTC, while the
32 germline c.2753T>C, p.Met918Thr *RET* variant (*RET*-M918T) presents the highest risk¹.

33

34 A 35-year-old woman presented with a suspicious 13 mm thyroid nodule and right laterocervical
35 nodes. Calcitonin and carcino-embryonic antigen (CEA) levels were 2300 pg/mL (N < 10) and 21
36 ng/mL (N < 3.5), respectively, in favor of MTC. ¹⁸F-dihydroxyphenyl-alanine positron emission
37 tomography showed high uptake in the thyroid nodule and laterocervical nodes, while millimetric
38 lung nodules did not show any uptake. Total thyroidectomy with neck dissection revealed a
39 pT3N1bMx MTC. Ki-67 was 10%. Germline genetic screening identified a *RET*-L790F pathogenic
40 variant. During the follow-up, she presented with a locoregional progression with laterocervical
41 nodes. Both calcitonin and CEA increased with a doubling time of 12 and 15 months, respectively.
42 Imaging identified a suspicious left iliac bone lesion 23 months after the diagnosis, treated by
43 cryoablation. As the patient progressed with distant metastases, somatic analysis was performed on
44 the thyroid specimen (T-site), showing a somatic *RET*-M918T. No variations were founded on cancer-
45 related genes *ALK*, *FGFR1*, *FGFR2*, *FGFR3*, *HRAS*, *KRAS*, *JAK1*, *JAK2*, *JAK3* and *MET*. At last follow-up,
46 six years after surgery, calcitonin and CEA were 6566 pg/mL and 84.2 ng/mL, respectively (figure 1).
47 As imaging showed a stable metastatic disease, the multidisciplinary team recommended a wait-and-
48 watch approach with no systemic treatment. Catecholamines, calcium and PTH levels all remained
49 normal. Family screening revealed four *RET*-L790F carriers aged 12 to 68 years old, with normal
50 calcitonin and neck ultrasound. No thyroidectomy was performed.

51

52 Most studies reporting the natural history of *RET*-L790F-related MTC suggest of an indolent disease.
53 A French multicentric study involving 77 *RET*-L790F MEN2A patients reported no distant metastases,
54 and lymph node invasion in only 10/55 (18.2%) operated patients (mean age, 32 years of age). After
55 a follow-up of 89 months, most patients were cured². On the other hand, several studies reported
56 that somatic *RET*-M918T is a main driver of tumorigenesis in non-hereditary MTC, leading to a more
57 advanced stage at diagnosis and a worse outcome³. Concomitant somatic and germline *RET*
58 mutations in MEN2-related MTC have been rarely reported. Lombardo *et al.* described a 12-year-old
59 girl exhibiting an extensive and invasive MTC despite a germline moderate risk 804 *RET* variant,
60 leading to the identification of a somatic *RET*-M918T⁴. A somatic *RET*-M918T was also identified in 4
61 MEN2A MTCs with germline 634, 618, and 620 variants⁵. More recently, no somatic *RET* mutation
62 has been identified, but a somatic variant in *FTL3* (a transcription factor involved in growth and
63 differentiation) in a *RET*-L790F carrier with metastatic progression further years after the diagnosis of
64 a loco-regionally advanced MTC⁶.

65

66 To our knowledge, this is the first report highlighting the potential additional role of a somatic *RET*-
67 M918T in a patient with a germline *RET*-L790F, who developed rapidly metastatic disease. Further
68 studies should determine whether MEN2 patients with an atypical MTC phenotype should be tested
69 from a somatic viewpoint, and how this could individualize our follow-up strategies in MEN2
70 patients.

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74
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79
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85
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87 revised in 2013 and was approved to the APHM RGPD IRB. The patient has given consent for the
88 publication of this case report

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90 **Corresponding author:**

91 Dr Pauline ROMANET, MD, PhD, Laboratory of molecular biology, Conception University Hospital,
92 13005 Marseille, France.

93 Mail: pauline.romanet@univ-amu.fr

94
95 **Figures**

96
97 **Figure 1:** Evolution of calcitonin and CEA levels and treatments from the time of diagnosis to last
98 follow-up.

99
100 **References**

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