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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

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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

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22 mutation; medullary thyroid carcinoma

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 risk<sup>1</sup>.

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. <sup>18</sup>F-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 cured<sup>2</sup>. 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 outcome<sup>3</sup>. 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*-M918T<sup>4</sup>. A somatic *RET*-M918T was also identified in 4  
61 MEN2A MTCs with germline 634, 618, and 620 variants<sup>5</sup>. 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 MTC<sup>6</sup>.

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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85  
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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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