

## RET Y791F: alone or accompanied?

Rodrigo A. Toledo<sup>1</sup>, Delmar M. Loureço Jr.<sup>1</sup>, Cleber Camacho<sup>2</sup>,  
Susan Lindsey<sup>3</sup>, Janete Cerutti<sup>1</sup>, Rui M. B. Maciel<sup>3</sup>, Sergio P. A. Toledo<sup>1</sup>

Dear Editor,

We read with interest the article “Diagnosis, treatment, and follow-up of medullary thyroid carcinoma: recommendations by the Thyroid Department of the Brazilian Society of Endocrinology and Metabolism” recently published in this Journal (1).

The article was written by Brazilian endocrinologists and surgeons and consists of a consensus of the Thyroid Department of the Brazilian Society of Endocrinology and Metabolism (SBEM). As a full version of it is also available in Portuguese language and free for download, it is definitely a valuable reference to Brazilian doctors in residency trainings and medical specialists in the fields of endocrinology, surgery, oncology and others.

Virtually all individuals carrying a germline mutation in the *RET* proto-oncogene will develop medullary thyroid carcinoma (MTC) and therefore total prophylactic thyroidectomy is indicated at early ages, based on the specific *RET* mutations (1-3).

In this context, we would like to make a comment regarding to the Y791F variant located at the exon 13 of *RET*. Although initial data regarding this variant indicated that it could be a weak mutation associated with mild forms of the disease (4,5), recent studies have shown no association of this variant with an increased susceptibility to MTC. Erlic and cols. (6) and Toledo and cols. (7) have analyzed the frequencies of *RETY791F* in large cohorts of tumor free individuals and showed that the variant behaves as a rare non-pathogenic polymorphism rather than a disease-causing mutation. In addition, a thorough review of the literature does not document a link of Y791F (alone) with familial MTC. On the contrary, the reported Y791F carriers who inadvertently underwent thyroidectomy presented no histopathological signs of disease (5,6).

These data indicate that thyroidectomy should not be recommended to cases with genetic testing results showing *RET* Y791F (alone). However, especial attention should be taken by Brazilian doctors, geneticists and surgeons, as the *RET* Y791F variant has been identified in combination with the strong *RET*C634Y (exon 11) mutation in more than 15 Brazilian families with MTC/MEN2 (7,8). Noteworthy, this combination changes completely the clinical scenario, and patients with *RET*C634Y/Y791F should be treated accordingly to the recommendations to cases carrying *RET* C634 mutations, in which early total thyroidectomy is needed to be performed (1-3). Therefore, when receiving a genetic testing showing the presence of the *RETY791F* variant, it is crucial to make sure that the remaining exons of the gene were completely sequenced as well, to fully certify whether is a Y791F-alone or a *RET*C634Y/Y791F patient (6).

In conclusion, we would like to congratulate the authors for the SBEM consensus and invite all the Brazilian medical doctors and geneticists to read our extended study and review of the literature about *RETY791F*, a variant that need to be well understood by the health professionals of our country to the better management of Brazilian patients with MTC and their relatives (6).

<sup>1</sup> Faculdade de Medicina da Universidade de São Paulo (FMUSP), São Paulo, S, Brasil  
<sup>2</sup> Programa de Pós-Graduação em Medicina, Universidade Nove de Julho (Uninove), São Paulo, S, Brasil  
<sup>3</sup> Escola Paulista de Medicina, Universidade Federal de São Paulo (Unifesp), São Paulo, SP, Brasil

**Correspondence to:**

Rodrigo A. Toledo  
Dr. Arnaldo, 455  
05409011 – São Paulo, SP, Brasil  
toledorodrigo@usp.br  
toledorodrigo79@gmail.com

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