LETTER TO THE EDITOR

Penetrance of pheochromocytoma in *RET* G533C carriers differs between South America and Europe

Dear Editor,

In a recent issue of *Endocrine-Related Cancer*, Castinetti *et al.* reported a different natural history of pheochromocytoma in multiple endocrine neoplasia type 2 (MEN 2) patients between Europe and South America (Castinetti *et al.* 2017). The authors retrospectively collected data about the pheochromocytoma in MEN 2 patients carrying *RET* mutations on exons 10 and 11 in 14 countries from South America, Southern Europe, Western Europe and Central Europe. They showed that pheochromocytoma penetrance is lower (53%) in South America compared to South Europe, Western Europe and Central Europe (75–81%). Furthermore, there was a different significance for unilateral and bilateral pheochromocytoma penetrance between South America and the other three areas. Nearly 50% of the Central Europe patients will have a pheochromocytoma by the age of 33 years, while the same percent will have a pheochromocytoma by the age of 43 years in South America. The delay was even higher for bilateral pheochromocytoma in Europe vs South America. The authors suggested that *RET* mutation is not the only determinant of the penetrance of pheochromocytoma and that its natural history could be influenced by genetic or environmental factors.

As we understand that these findings are of clinical importance, we sought to verify whether genetic or environmental factors might have a modifying effect on the disease penetrance for other *RET* mutations. We retrospectively reviewed the published data on 183 patients carrying *RET* G533C mutation on exon 8 in South America (Brazil) and Europe (Greece and Ireland). This rare mutation was first reported in a Brazilian family of Caucasian origin with ancestors from Catalonia, Spain, who immigrated to Brazil at the end of the 19th century (Da Silva *et al.* 2003, Oliveira *et al.* 2011, Signorini *et al.* 2014). To date, this is the largest reported family with a

RET mutation and MEN 2A, whose family members have been followed for over 15 years. Four hundred and thirty two of 728 recruited relatives were genetically tested for the *RET* G533C mutation, 119 being G533C carriers. At the last follow-up, the median age of the 60 G533C carriers who underwent thyroidectomy was 45 years (ranges 6–75 years) and the mean age of the 59 patients awaiting surgery was 17 years (ranges 4–39 years). Among all patients who underwent surgery, 46 patients had medullary thyroid carcinoma, 11 patients had C-cell hyperplasia and 1 patient had pheochromocytoma (Da Silva *et al.* 2003, Oliveira *et al.* 2011, Signorini *et al.* 2014). During this long-term follow-up (mean follow-up period of 12.9), genetic and clinical characteristics of these patients have been described in detail (Oliveira *et al.* 2011, Signorini *et al.* 2014). Importantly, the large majority (43/46; 93%) of the patients who underwent surgery and were diagnosed with medullary thyroid carcinoma are over the age of 30 years, which is the youngest age reported in a patient with pheochromocytoma in Greece.

In 2007, Kaldrymides *et al.* reported a Greek patient with MEN 2A harbouring the same *RET* G533C mutation (5), followed by other reports (Kaldrymides *et al.* 2006, Bethanis *et al.* 2007). Interestingly, in three Greek families, pheochromocytoma was the first clinical manifestation (Bethanis *et al.* 2007, Peppas *et al.* 2008). A few years later, Sarika *et al.* identified the G533C mutation in 11 families with MEN 2 in Greece. Pheochromocytoma was described as the first clinical manifestation in one of these families. The authors also identified G533C mutation in ten cases with apparently sporadic medullary thyroid carcinoma (Sarika *et al.* 2012, 2015). In 2013, Castro *et al.* published the first *RET* 533 family from the United States, with ancestors from Greece, presenting with MEN 2A in several affected members

Table 1 Prevalence of pheochromocytoma in *RET* G533C carriers in two continents.

	South America*	Europe (Greece)**	P value
Total individuals screened for <i>RET</i> mutation	432	222 [§]	–
# of <i>RET</i> G533C carriers	119/432 (27.5%)	64/222 (28.8%)	ns
# cases of MTC	46/119 (38.6%)	34/64 (53.1%)	ns
# cases of pheochromocytoma	1/119 (0.84%)	6/64 (9.4%)	0.0079
Mean age at diagnosis in years (range)	63 [†]	43.5 (30–66)	–
Unilateral	1/1 (100%)	4/6 (66.7%)	ns
Bilateral	0/1 (0%)	2/6 (33.3%)	ns
Initial manifestation	0/1 (0%)	5/6 (83.3%)	ns

*Da Silva *et al.* (2003), Signorini *et al.* (2014); **Kaldrymes *et al.* (2006), Bethanis *et al.* (2007), Peppas *et al.* (2008), Sarika *et al.* (2012, 2015); [§]including 129 sporadic cases; [†]only one pheochromocytoma case was described among 119 carriers.
ns, not significant.

(Castro *et al.* 2013). Remarkably, not only the prevalence of pheochromocytoma in this family was higher than the prevalence previously reported in Brazil, but also three patients presented with pheochromocytoma as their initial manifestation. Finally, Casey *et al.* reported a case in Ireland of MEN 2A and *RET* G533C mutation diagnosed with pheochromocytoma as the first clinical manifestation (Casey *et al.* 2013). Even if there were variances in screening methods, the evident difference observed in the initial presentation of the disease is remarkable.

Until now, these are the only studies that report G533C mutation on *RET* gene in MEN 2 families or apparently sporadic medullary thyroid carcinoma cases. Although it has been reported that G533C was identified in one family in South Portugal and a few families in France (Sarika *et al.* 2015), no information is available in the literature. As far as we know, there is no other kindred with *RET* G533C mutation in the United States (John C Morris and Samuel Wells, personal communications).

In this study, we observed a significant difference in the prevalence of pheochromocytoma in patients from South America when compared to Europe ($P=0.0079$) (Table 1). Notably, the primary ancestors of both South American and Europe populations were from Greece. Moreover, in Europe and North America, the pheochromocytoma was the first clinical manifestation in most families, whereas in South America, pheochromocytoma was diagnosed 5 years after the diagnosis of medullary thyroid carcinoma. Actually, the median age at diagnosis in Europe was 43.5 years, while in South America, the patient has presented with pheochromocytoma at the age of 63 years (Table 1). Moreover, logistic regression analysis showed that the chance of having a pheochromocytoma in a Greek family, compared to the Brazilian family, was 12.2 ($P=0.022$), 95% CI (1.4–103.8) (IBM Corp, Released 2017: IBM SPSS Statistics for Windows, version 25.0). Therefore, this analysis suggests that the risk for pheochromocytoma

development in patients with *RET* G533C mutation could also be affected by additional mutations or polymorphism within *RET* gene or in other genes or even environmental factors (modifying factors).

In summary, similar to those reported by Castinetti *et al.*, our results highlight the fact that *RET* germline mutation may not be the only determinant of the natural history of pheochromocytoma in MEN 2 patients with G533C, particularly after our recent data suggesting that Brazilian and Greek patients carrying the same *RET* G533C mutation originate from a common ancestor (Cunha *et al.* 2017, Machens *et al.* 2018).

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Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of this article.

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