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G534E Variant in *HABP2* and Nonmedullary Thyroid Cancer

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Dear Editor:

Recently, using next-generation sequencing (NGS) and functional studies, it has been suggested that the germline c.1601G>A variant (p. G534E, rs7080536) in *HABP2* is implicated in familial nonmedullary thyroid cancer (NMTC) (1). However, the role of this variant in NMTC has been questioned due to the high reported frequencies in several public databases (2–4). Most of the subsequent replication studies have failed to confirm a causal role of G534E in NMTC (5–8). In order to contribute to the clarification of the role of G534E variant in NMTC, we have tested the presence of this variant by Sanger sequencing in 16 Spanish families with NMTC (12 patients with papillary thyroid cancer [PTC], two with follicular thyroid cancer [FTC], and two with both PTC and FTC), including 33 affected and 44 unaffected individuals. These families were defined by the occurrence of thyroid cancer in two or more first- or second-degree relatives. In addition, we have included 62 juvenile patients with sporadic NMTC (50 PTC and 12 FTC) in the study. The age at the time of diagnosis ranged from 5 to 26 years (average age for PTC 15.5 years; average age for FTC 18.2 years), and none of them had a record of head and/or neck irradiation. Written informed consent was obtained from all the participants for clinical and molecular genetic studies. Our study complies with the tenets of the Declaration of Helsinki.

The analysis of the familial NMTC cases demonstrated two heterozygous carriers of the variant, both in the same family. However, they showed no segregation between the disease and the G534E variant. Furthermore, one of the two PTC patients in this family did not carry the *HABP2* variant, and one variant carrier was an unaffected individual, who is currently 62 years old. We also detected a monoallelic G534E variant in two juvenile patients with sporadic PTC, and it could not be detected in any of the juvenile patients with FTC. The minor allele frequency (MAF) values were 2% considering exclusively juvenile PTC patients, and 1.6% including the total cohort of juvenile NMTC patients. In addition, when analyzing the data obtained from 267 healthy Spanish controls without thyroid cancer (9) to examine the frequency of this variant in our own population, no homozygous subjects were detected and only six heterozygous individuals (2.24%) could be identified, resulting in a MAF of 1.12%. Based on these results, no statistically significant differences were observed when comparing control individuals with allelic and genotype distributions of either juvenile PTC patients (Fisher's exact test two-tailed p-values = 0.3675 and 0.6168, respectively) or the total cohort of juvenile NMTC patients (Fisher's exact test two-tailed p-values = 0.6493 and 0.6481, respectively). Moreover, the A allele frequencies obtained both in juvenile patients and in controls were similar to those reported for the general population in public databases and for Europeans from different sources (HapMap-CEU; www.ncbi.nlm.nih.gov/projects/SNP/snp_ref.cgi?rs=7080536).

In conclusion, our study suggests that the G534E variant in *HABP2* is not associated with NMTC in the Spanish population. Although NGS is a very powerful tool, which has completely changed our way of identifying disease-associated mutations, it is important to be cautious before assuming a role of detected sequence variants in the pathogenesis of a disease.

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Author Disclosure Statement

No competing financial interests exist.

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