HABP2 as genetic susceptibility factor for Familial Differentiated Thyroid Carcinoma

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Introduction
Hyaluronic Acid Binding Protein 2 (HABP2) is an extra-cellular matrix protein involved in cell proliferation. Recently, HABP2 was proposed to be the responsible protein for the familial clustering of differentiated thyroid carcinoma (DTC). However, its involvement was questioned by subsequent studies revealing a high prevalence of HABP2 polymorphisms (SNPs) in the general population, leaving its pathogenic role uncertain.1,3,4,5.

Objectives
To identify genetic HABP2 variants/mutations in a series of FDTC patients and investigate their involvement in the disease.

Patients and Methods
The whole coding region of HABP2 (13 exons) was PCR-amplified and directly sequenced from genomic DNA of six index patients with FDTC (Figure 1).

Prevalence of identified variants was investigated in the Spanish population from 368 alleles of healthy control individuals. Public SNP databases were used to estimate variant prevalence in Caucasian populations. Presence of the variants was investigated in all members of Family 1 and segregation analyses performed in affected and healthy individuals. Germline mutations were screened in lymphocyte DNA. BRAF and RAS "hotspot" mutations in DTC were studied from the paraffin-embedded thyroid tissue from index patient, through the immunofluorescent mutation test Cobas®4800.

Disclosure statement
The authors report no conflicts of interest in this study.

Results
Two germline heterozygous HABP2 variants (p.E393Q and p.G534E) located in exons 10 and 13, respectively, were investigated in 3 affected members (index patient, mother, aunt) from Family 1 and in 5 additional healthy members of the kindred (Figure 2). Both variants are present in SNP databases (rs11575688, rs7080356) with MAF’s (Minor Allele Frequency) between 0.32-1.34% and 0.82-2.79%, respectively. In Spanish control alleles, the prevalence of p.E393Q is 0.5% and of p.G534E 5.1%.

However, pathogenicity programs predict that the p.G534E variant is possibly damaging. Although 3/8 individuals in the pedigree harbored both variants, their presence does not co-segregate with the phenotype. Additionally, the index patient presented the most prevalent somatic mutation of BRAF (p.V600E) in FTC.

Conclusions
HABP2 p.G534E variant is prevalent (5,1%) in the normal Spanish population, however, p.E393Q is rare (<1%). Neither co-segregated with the FDTC phenotype in the family.

Our findings do not support a relevant role of HABP2 in the increased susceptibility of FTC. Therefore, other germline defects must be responsible for the familial clustering of DTC in this pedigree.

The finding of the most prevalent BRAF mutation (p.V600E) in thyroid DNA of VI.2 supports Knudson’s "double-hit" hypothesis of cancer, suggesting the involvement of more than one gene in the expression of FTC.

References