Common genetic variants in pituitary - thyroid axis genes and the risk of differentiated thyroid cancer

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Thyroid hormone receptors, THRA and THRB, together with the thyrotropin receptor, TSHR, are key regulators of thyroid function. Alterations in the genes of these receptors (*THRA, THRB* and *TSHR*) have been related to thyroid diseases, including thyroid cancer. Moreover, there is evidence suggesting that genetic predisposition to differentiated thyroid cancer (DTC) is related to common genetic variants with low penetrance effect that interact with each other and with environmental factors. In this study we have investigated the association of single nucleotide polymorphisms (SNPs) in the *THRA* (one SNP), *THRB* (three SNP) and *TSHR* (two SNP) genes with the risk of DTC.

A case-control association study was conducted with 398 patients with sporadic DTC and 479 healthy controls from a Spanish population. Among the polymorphisms studied, only *THRA*-rs939348 was found to be associated with an increased risk of DTC (recessive model, OR = 1.80, 95% CI = 1.03-3.14, p = 0.037). Gene-gene interaction analysis using the genotype data of the present study together with our previous genotype data on *TG* and *TRHR*, indicated a combined effect of the pairwises: *THRB*-*TSHR* (*P*interaction = 0.0056, *THRB*-rs844107 with *TSHR*-rs8019570), *THRB*-*TG* (*P*interaction = 0.04, *THRB*-rs844107 with *TG*-rs2076740), and *THRB*-*TRHR* (*P*interaction = 0.006, *THRB*-rs3752874 with *TRHR*-rs4129682) for DTC risk in a Spanish population.

Our results confirm that *THRA* is a risk factor for DTC, and we show for the first time the combined effect of *THRB* and *TSHR*, *TG* or *TRHR* in DTC susceptibility, supporting the importance of gene-gene interaction in thyroid cancer risk.