Mismatch repair SNPs and thyroid cancer susceptibility: a potential role for the MSH6 rs1042821 (Gly39Glu) polymorphism

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Background: Exposure to ionizing radiation (IR) is the best-established risk factor for thyroid cancer (TC) but genetic variation could also play a role. The DNA mismatch repair (MMR) pathway counters carcinogenesis through the suppression of genetic instability and several lines of evidence suggest that altered function or expression of MMR proteins may also be implicated in TC pathogenesis. Objective: We aimed to evaluate the potential modifying role of a panel of eight MMR single nucleotide polymorphisms (SNPs) on the individual susceptibility to non-familial differentiated TC. Design: A small-scale hospital-based case-control study was performed in a Caucasian Portuguese population, comprising 106 histologically confirmed differentiated TC patients and 212 age and gender matched controls. DNA mismatch repair SNPs rs1799977 (MLH1), rs26279 and rs184967 (MSH3), rs5745325 and rs5745549 (MSH4), rs5742933 (PMS1), rs175080 (MLH3) and rs1042821 (MSH6) were genotyped using the TaqMan allelic discrimination assay and the genotype-associated TC risk was estimated by multivariate logistic regression analysis. Results: The homozygous variant genotype of rs1042821 (MSH6) was significantly associated with increased differentiated TC risk, both under a codominant model (Glu/Glu vs. Gly/Gly: adjusted OR=3.42; 95%CI=1.04-11.24; p=0.04) and a recessive model (Glu/Glu vs. [Gly/Glu + Gly/Gly]: adjusted OR=3.84; 95%CI=1.18-12.44; p=0.03). This association was also observed after histological and gender stratification, both in the follicular subset (adjusted OR=20.98; 95%CI=1.08-406.53; p=0.04 – codominant model; adjusted OR=23.70; 95%CI=1.25-449.32; p=0.04 – recessive model) and in the female subset (adjusted OR=4.78; 95%CI=1.17-19.56; p=0.03 – codominant model; adjusted OR=5.42; 95%CI=1.34-21.92; p=0.02 – recessive model). No significant associations were observed for the remaining SNPs. Conclusion: Our data supports the idea that the MSH6 rs1042821 SNP may contribute to differentiated TC susceptibility, particularly of the follicular type. The risk increase is also apparent in women. Acknowledgement: This study was supported by Project PTDC/SAU-OSM/105572/2008 from Fundação para a Ciência e Tecnologia (FCT).