THE INFLUENCE OF NONCODING RET POLYMORPHISMS ON THE PATHOGENESIS OF MEDULLARY THYROID CARCINOMA

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Background/Purpose: Besides mutations in the *RET* proto-oncogene, single nucleotide polymorphisms (SNPs) contribute to the pathogenesis of medullary thyroid carcinoma (MTC) with modifying function. In Hirschsprung's disease (HSCR), SNPs from intron 1 and other noncoding regions play the key role. We focused our investigation on these regions in patients with sporadic MTC and the influence on clinical features of tumor.

Methods: DNAs of 345 patients with sporadic MTC, 162 patients with HSCR and 205 healthy controls were isolated from peripheral leukocytes. Polymorphisms in noncoding regions (rs1864410, rs2435357, rs2506004, rs2565200, rs2435355) were determined using TaqMan Genotyping Assays and statistically evaluated by chi-square test.

Results: The increased risk of studied SNPs ($p<0.000001$) was observed in our cohort of patients with HSCR vs. controls. Comparing MTC and control cohorts, significant differences in frequencies of SNPs were revealed only in rs2435355 ($p=0.03$) where the minor allele was underrepresented in MTC. The minor alleles of rs1864410, rs2435357, rs2506004 were significant in comparison of patients with/without local recurrence, patients with recurrence/disease-free status and TNM classification. These minor alleles were underrepresented in patients: without local recurrence ($p=0.03$), with disease-free status ($p=0.01$), with T1 vs. T2-4 ($p=0.03$) and with N0 vs. N1 (0.04).

Discussion & Conclusion: Noncoding regions of the *RET* proto-oncogene play an important role in HSCR. In MTC, the distribution of investigated SNPs significantly differed only in rs2435355 from controls, but the possible modifying effect of rs1864410, rs2435357, rs2506004 was also registered. In this study, the minor alleles of these 3 SNPs were associated with worse progress of the disease, especially recurrence of the disease and TNM classification.

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