ADVERSE EFFECTS OF TERT-CLPTM1L AND DOUBLE-STRAND BREAKS REPAIR CONTRIBUTE TO RISK FOR NASOPHARYNGEAL CARCINOMA

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BACKGROUND AND AIMS: The genetic etiology of NPC and mechanisms for inherited susceptibility remain unclear. Only modest low-penetrance effects of cancer-predisposing common variant SNPs were previously identified in the few large-scale NPC association studies reported. Most NPC association studies focused on single or limited candidate genes with modest sample sizes. Systematic and comprehensive study designs for evaluation of higher order gene-gene interactions are scanty. A large-scale NPC case-control SNP association study was performed to examine the genetic risk factors for NPC development. In order to elucidate the genetic susceptibility for NPC, we hypothesized that heritable risk is attributable to cumulative effects of common low-risk variants, especially for genes in DNA repair pathways.

MATERIAL AND METHODS: Genotype screening of 377 SNPs and validation in an 81-SNP panel of DNA repair and other genes in 2349 individuals from Hong Kong (1177 cases and 1172 controls) using iPLEX Gold assays with the MassARRAY platform were performed for association analyses for risk allele identification and pathway-based studies for NPC. All statistical tests were two-sided.

RESULTS: Three SNPs (rs401681, rs6774494, rs3757318) corresponding to TERT/CLPTM1L (OR 0.77, 95% CI 0.68-0.88), MDS1-EVI1 (OR 0.79, 95% CI 0.69-0.89), and CCDC170 (OR 0.76, 95% CI 0.66-0.86) conferred modest protective effects individually for NPC risk by the logistic regression (pBonferroni <0.05) (Table II). Stratification of NPC according to familial status identified rs2380165 in BLM (OR 1.49, 95% CI 1.28-1.78) association with family history-positive NPC (FH+NPC) patients (pBonferroni <0.05) (Table III). Higher order multiple SNPs pathway-based analysis revealed that the combined adverse effects of TERT-CLPTM1L and double-strand break repair (DSBR) (HR, NHEJ, FA-BS, and FA-HR pathways) conferred significant elevated risk up to OR 5.6 (95% CI 2.67-11.78) in FH+NPC and 2.4 (95% CI 1.28-4.48) in sporadic NPC patients carrying five adverse alleles in TERT/NHEJ and TERT/FA/BS pathways, respectively. (Fig. 2,3) CONCLUSIONS: Three SNPs corresponding to MDS1-EVI1, TERT/CLPTM1L, and CCDC170 conferred modest protective effects individually for NPC risk in Hong Kong patients. Importance of pathway-based analysis for the cumulative increased risk associations with TERT locus and DNA repair pathways for DBS repair play a critical role in determining genetic susceptibility to NPC. A SNP in BLM is associated with FH+NPC patients. Pathway-based analysis also showed that the cumulative effect is more pronounced in FH+NPC patients.