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(RainDance and SOLiD sequencing). We compared MPN cases that are homozygous for risk allele (GG-MPN cases) with the ones that are homozygous for wild type allele (CC-MPN cases). We found that there is no excess of single nucleotide variants in the JAK2 locus in GG-MPN cases compared to CC-MPN cases using ancestral sequence as reference. However, we further explored the existence of selection pressure at JAK2 using HapMap phase III data and detected an excess of derived alleles at JAK2 when compared to ancestral repeats. To identify the functional variant(s) that results in haplotype-specific mutation acquisition in MPN cases, we are analyzing sequence specific differences (such as motif /regulatory elements) between these two groups of patients. Our study is helpful to understand the etiology of MPN phenotype and predisposition.

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GENETIC VARIANTS OF TNF- α -308G>A AND IL-8 -251T>A ARE ASSOCIATED WITH SUSCEPTIBILITY OF SPORADIC COLORECTAL CANCER IN MALAYSIAN PATIENTS

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Colorectal cancer (CRC), the incidence of which has been increasing worldwide for the past few years, represents a significant cause of morbidity and mortality. Even though the mechanism of CRC development is still unknown, both environmental factors and genetic susceptibility are believed to contribute to the onset of CRC. Recently, chronic inflammation has been linked to increased risk to various types of cancers including CRC. If inflammation constitutes one of the molecular networks underlying susceptibility to CRC, genes which mediate inflammatory response might be a group of candidate genes for CRC predisposition. Allelic variants of the genes involved in inflammatory pathways could be logical candidates as genetic determinants of CRC risk. Tumor Necrosis Factor alpha (TNF-α), Interleukin-8 (IL-8) and Intercellular Adhesion Molecule 1 (ICAM-1) are genes involved in mediating inflammatory response. Polymorphisms have been identified in these genes. So a case control study was designed to investigate the TNF- α -308 G>A, IL-8 -251 T>A and ICAM-1 K469E polymorphic genotype frequencies in healthy controls and CRC patients in Malaysian population and to determine the influence of the polymorphic genotypes on sporadic CRC susceptibility risk. Subjects were recruited from Hospital University Sains Malaysia (HUSM), and other government hospitals under Ministry of Health, Malaysia. In this case control study, we included 146 histopathologically confirmed CRC patients (80 males, 66 females, 57.26 years) and 146 healthy normal controls (76 males, 70 females, 48.91 years). Peripheral blood samples of study subjects were collected, genomic DNA extracted and amplified using appropriate primers and genotyped employing PCR-RFLP followed by sequencing. Genotypes were categorized into homozygous wildtype, heterozygous and homozygous variants. The strength of association between polymorphic genotypes and colorectal cancer susceptibility risk was assessed by Odd Ratio (OR) with corresponding 95 % CI. On comparing the frequencies of TNF-α -308 G>A genotypes of patients and controls, the homozygous variant -308AA was significantly higher in CRC patients (P=0.017) compared to controls. For IL-8 -251 T>A, the frequencies of homozygous variant -251 AA was significantly higher in CRC patients compared to controls, with P value of 0.033. However, for ICAM-1 K469E, the genotype frequencies were not significantly different between cases and controls. On investigating the association of the variant genotypes with susceptibility risk, the homozygous variant of TNF-α -308G>A with OR=3.0077 and the heterozygous and homozygous variants of IL-8 -251T>A with OR of 2.1 and 4.0 respectively, emerged as high risk genotypes. However, ICAM-1 K469E showed no CRC risk association. When analyzed in combination, the homozygous variant genotypes TNF-α -308 AA/ IL-8 -251AA showed remarkably higher CRC susceptibility risk with OR 11.375, (CI 1.1718-110.4238, P=0.036). These results suggest that genetic polymorphisms of inflammation response gene IL-8T251A and TNF-α -308G > A are significantly associated with susceptibility risk in Malaysian CRC patients and could be considered as a potential predisposition risk factors for CRC in Malaysian population. Results are also in favor of inflammation mediated colorectal carcinogenesis pathway.

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CYCLOOXYGENASE-2 (PTGS2) -765 G>C POLYMORPHISM: SUSCEPTIBILITY AND PROGNOSTIC IMPLICATIONS IN BREAST CARCINOMA

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Cyclooxygenase-2 (COX-2) is involved in carcinogenesis, immune response suppression, apoptosis inhibition, angiogenesis, and tumor cell invasion and metastasis. The gene for COX-2, designated as PTGS2, carries a common functional polymorphism at position 765 in the 5' transcriptionnal regulatory region, which has been associated with susceptibility to malignant disease. In the current study, we investigated the susceptibility and prognostic implications of the genetic variation in PTGS2 in breast carcinoma. We used the RFLP-PCR to characterize the variation of PTGS2 for 409 unrelated Tunisian patients with breast carcinoma and 305