RESEARCH COMMUNICATION

Association of Arg72Pro of *P53* Polymorphism with Colorectal Cancer Susceptibility Risk in Malaysian Population

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Abstract

Background: Colorectal cancer (CRC) results from the interaction between environmental exposures and genetic predisposition factors. Aims: A case control study was designed and to investigate the genotype frequencies of *P53* Arg72Pro polymorphism in Malaysian CRC patients and healthy controls and to determine the associated risk of this polymorphism with CRC predisposition. Methods: In this case-control study, peripheral blood samples of 202 sporadic CRC patients and 201 normal controls were collected, DNA extracted and genotyped using the polymerase chain reaction - restriction fragment length polymorphism (PCR-RFLP) technique. Results: Genotype analysis showed the frequency of homozygous variant (Pro/Pro) genotype (21%) to be significantly higher in cases compared to controls (13%), (p=0.013). On examining the association between variant genotypes and CRC risk, the Pro/Pro homozygous variant genotype showed significantly higher risk association with CRC susceptibility (OR: 2.047, CI: 1.063-4.044, p=0.033). When stratified according to age, we observed that, individuals aged above 50 years and carriers of pro/pro genotype had significantly higher risk with OR: 3.642, CI: 1.166-11.378, p=0.026. Conclusions: Our results suggest that the codon 72 SNP which results in amino acid substitution of Arginine to Proline in cell cycle regulatory gene P53, is associated with sporadic CRC risk and carriers of Pro/Pro genotype and more than 50 years old may have high susceptibility.

Keywords: Colorectal cancer - TP53 codon 72 - Malaysia

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Introduction

Colorectal cancer (CRC) is the second to fourth most common cancer in developed countries. Worldwide, 875,000 or more people are diagnosed with CRC annually (de la Chapelle, 2004). The incidence of CRC is increasing in developing countries including Malaysia. In Malaysia, CRC has become the second commonest cause of cancer related mortality after breast cancer and has become the most common cancer in men and second in women (Malaysia Cancer Statistics, 2006). Being a complex and multifactorial disease, its etipathogenesis involve interaction between environmental and genetic factors. Age, gender environmental factors such as diet, tobacco smoke and alcohol consumption (Giovannucci, 2001; Terry et al., 2001; Neagoe et al., 2004; Yeh et al., 2005; Stern et al., 2007) in interaction with genetic factors have been shown to increase the risk of colorectal cancer (de la Chapelle, 2004)

Tumour suppressor genes play important role in mediating cellular responses to genotoxic insults through its effects on gene transcription, DNA synthesis and repair, genomic stability and apoptosis (Vogelstein and Kinzler, 1992). The most common mutated gene in various cancers is *P53* gene which is involved in 50% cancers. Being a guardian of the genome, p53 is involved in G1 arrest which facilitate DNA repair during replication or in induction of apoptosis and cell cycle regulation. In sporadic colorectal cancer, 75% of the tumours had been reported to have inactivation of p53 (Kressner et al., 1999). This inactivation could be single base substitution or loss of alleles with inactivation by viral or cellular proteins (Tommasino et al., 2003).

Genetic variation like Single Nucleotide Polymorphisms (SNPs) in candidate genes such as DNA damage and tumour suppressor genes are thought to play an important role in individual variation in colorectal cancer susceptibility. Genetic association studies have focused on SNPs as important tools for targeting the genes responsible for cancer susceptibility (Cao et al., 2009). A SNP at the codon 72, located at exon 4 of *P53* gene (Lima-Ramos et al., 2008) has been studied significantly for its association with various types of cancer such as colorectal, breast and other types of cancer (Tenesa et al., 2008;

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