Cancer Epidemiology 37 (2013) 634–638

Contents lists available at SciVerse ScienceDirect

Cancer Epidemiology

The International Journal of Cancer Epidemiology, Detection, and Prevention

journal homepage: www.cancerepidemiology.net

# The functional −94 insertion/deletion ATTG polymorphism in the promoter region of *NFKB1* gene increases the risk of sporadic colorectal cancer

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ARTICLE INFO

*Article history:*
Received 10 January 2013
Received in revised form 12 May 2013
Accepted 28 May 2013
Available online 24 June 2013

*Keywords:*
Colorectal cancer
*NFKB1*
Polymorphism
Predisposition
Risk
rs28362491
Susceptibility

ABSTRACT

*Objective*: To investigate the allele and genotype frequencies of *NFKB1* −94 ins/del ATTG (rs28720239) polymorphism and to evaluate the association between the polymorphism and colorectal cancer (CRC) risk in Malaysian population. *Methods*: Genomic DNA was extracted from the peripheral blood samples of 474 study subjects, which consisted of 237 histopathologically confirmed CRC patients and an equal number of cancer-free controls. The *NFKB1* −94 ins/del ATTG (rs28720239) polymorphism was genotyped using polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) method and confirmed by DNA sequencing. The association between the polymorphic genotypes and CRC risk was evaluated by deriving odds ratios (ORs) and 95% confidence intervals (CIs) using unconditional logistic regression analysis. *Results*: The frequencies of wildtype (del/del), heterozygous (del/ins) and variant (ins/ins) genotypes in CRC patients were 31.7%, 53.6% and 14.8%, respectively, while those in cancer-free controls were 35.0%, 58.2% and 6.8%, respectively. The frequency of the variant genotype was significantly higher in cases compared to controls ($P < 0.01$). Evaluation of the risk association of the polymorphic genotypes revealed that the variant genotype could contribute to a significantly increased risk of CRC (OR = 2.42, 95% CI = 1.24–4.73, $P < 0.01$). *Conclusions*: The variant allele of *NFKB1* −94 ins/del ATTG (rs28362491) polymorphism is associated with higher risk of sporadic CRC in Malaysian population.

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## 1. Introduction

Colorectal cancer (CRC) is the third most common cancer in men and the second most common cancer in women worldwide [1]. Over the past few years, the incidence of CRC has been increasing, and it contributes to a significant burden of cancer-related morbidity and mortality. Among the known risk factors for CRC include lifestyle habits (such as tobacco smoking and alcohol consumption) and dietary habits (such as high consumption of red meat and low consumption of fibrous food), but these alone are not sufficient to result in colorectal carcinogenesis. CRC is a multifactorial disease caused not only by environmental factors, but also by various genetic factors as well as interactions between the two [2,3]. Mutations in high penetrance genes such as *APC* and DNA mismatch repair (MMR) genes could represent a strong genetic determinant in the pathogenesis of hereditary forms of CRC. However, these mutations account for only less than 5% of all CRC cases [4].

Over the past decades, low penetrance genetic polymorphisms have emerged as important players in the pathogenesis of various types of cancers, including CRC [5,6]. Such genetic polymorphisms play a role in predisposing an individual to CRC by influencing the risk of developing the cancer, although typically the risk modification is modest. Such genetic polymorphisms are relatively common in the general population. Hence, they contribute to a higher attributable risk of cancer compared to high penetrance genes [7]. Genetic polymorphisms of genes whose protein products are involved in colorectal carcinogenic pathways could therefore modulate CRC risk.

Nuclear factor-kappa B (NF-κB) family constitutes a class of pleiotropic transcription factors which act as central regulators to many genes known to be implicated in cancer initiation and progression [8,9]. These include genes involved in the inflammatory pathway, immune response, cell proliferation, and apoptosis, among others [10]. The p105/p50 isoforms of NF-κB is encoded by the *NFKB1* gene, which is located on chromosome 4q24. Recently, a functional polymorphism in the promoter region of *NFKB1* gene has been described, namely the −94 ins/del ATTG (rs28362491) polymorphism, which could potentially influence the transcription of the gene and therefore, the level and function of NF-κB protein

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http://dx.doi.org/10.1016/j.canep.2013.05.007