

## RESEARCH ARTICLE

# Distribution and Haplotype Associations of XPD Lys751Gln, XRCC1 Arg280His and XRCC1 Arg399Gln Polymorphisms with Nasopharyngeal Carcinoma in the Malaysian Population

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### Abstract

**Background:** DNA repair pathways play a crucial role in maintaining the human genome. Previous studies associated DNA repair gene polymorphisms (XPD Lys751Gln, XRCC1 Arg280His and XRCC1 Arg399Gln) with nasopharyngeal carcinoma. These non-synonymous polymorphisms may alter DNA repair capacity and thus increase or decrease susceptibility. The present study aimed to determine the genotype distribution of XPD codon 751, XRCC1 codon 280 and codon 399 polymorphisms and haplotype associations among NPC cases and controls in the Malaysian population. **Materials and Methods:** We selected 157 NPC cases and 136 controls from two hospitals in Kuala Lumpur, Malaysia for this study. The polymorphisms studied were genotyped by PCR-RFLP assay and allele and genotype frequencies, haplotype and linkage disequilibrium were determined using SNPstat software. **Results:** For the XPD Lys751Gln polymorphism, the frequency of the Lys allele was higher in cases than in controls (94.5% versus 85.0%). For the XRCC1 Arg280His polymorphism, the frequency of Arg allele was 90.0% and 89.0% in cases and controls, respectively and for XRCC1 Arg399Gln the frequency of the Arg allele was 72.0% and 72.8% in cases and controls respectively. All three polymorphisms were in linkage disequilibrium. The odds ratio from haplotype analysis for these three polymorphisms and their association with NPC was 1.93 (95% CI: 0.90-4.16) for haplotype CGC vs AGC allele combinations. The global haplotype association with NPC gave a p-value of 0.054. **Conclusions:** Our study provides an estimate of allele and genotype frequencies of XRCC1 Arg280His, XRCC1 Arg399Gln and XPD Lys751Gln polymorphisms in the Malaysian population and showed no association with nasopharyngeal cancer.

**Keywords:** Single nucleotide polymorphism - haplotype - linkage disequilibrium - DNA repair genes - Malaysia

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### Introduction

Numerous genetic association studies have recently focused on genetic polymorphisms and cancer risk. These studies attempted to identify the effects of candidate genes in cell-cycle control, carcinogen metabolism and DNA repair. Because of their crucial role in preserving human genome integrity, certain SNPs in these genes that alter the expression and functional properties of the corresponding proteins support the hypothesis of SNPs as genetic risk factors (Hall et al., 2009).

Polymorphisms in DNA repair genes such as Xeroderma pigmentosum group D (XPD) and X-ray cross-complementing group 1 (XRCC1) genes alter the DNA repair capacity by modifying the biological responses to exogenous and endogenous DNA insults, at both cellular and tissue levels, and hence the susceptibility in developing cancer or age-related diseases (Ladiges, 2006;

Manuguerra et al., 2006; Sterpone and Cozzi, 2010).

XPD gene is located in chromosome 19q13.3 (Benhamou and Sarasin, 2002). This gene encodes a protein that participates in at least three crucial cellular mechanisms: a) repair of damaged DNA in nucleotide excision repair (NER) pathway, b) general transcription and c) cell cycle regulation through its interaction with cyclin-activating kinase (CAK), a pivotal activator of cyclin dependent kinases (CDKs) (Cameron et al., 2010; Compe and Egly, 2012). XRCC1 gene located on chromosome 19q 13.2 encodes a protein that acts as a scaffold protein through its interaction with poly (ADP-ribose) polymerase (PARP), DNA polymerase  $\beta$  and DNA ligase III $\alpha$  in base excision repair (BER) pathway (Ladiges, 2006).

Many studies have reported possible links between XPD codon 751, XRCC1 codon 280 and codon 399 polymorphisms with other cancers and nasopharyngeal

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