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***XPC* Lys939Gln polymorphism, smoking and risk of sporadic colorectal cancer among Malaysians**

**Abdul Aziz AA *et al*.** *XPC* polymorphism and colorectal cancer risk

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**Abstract**

**AIM:** To investigate the risk association of xeroderma pigmentosum group C (*XPC*) Lys939gln polymorphism alone and in combination with cigarette smoking on colorectal cancer (CRC) predisposition.

**METHODS:** Peripheral blood samples of the study subjects (*n* = 510 255 CRC patients and 255 controls) were collected, DNA extracted and genotyping of this polymorphism was performed using Polymerase Chain Reaction - Restriction Fragment Length Polymorphism technique. The association between polymorphic genotype and CRC predisposition was determined by computing odds ratio (OR) and assuming 95%CI.

**RESULTS:** The frequency of homozygous variant (Gln/Gln) genotype was significantly higher in cases compared to controls (16.0% *vs* 10.2%, *P* = 0.049). On examining the association between variant genotype and CRC, the Gln/Gln genotype of *XPC* showed significantly higher risk association with CRC susceptibility (OR: 1.884, 95%CI: 1.082-3.277, *P* = 0.025). In case of allele frequencies, variant allele C showed significantly increased risk of CRC susceptibility (OR: 1.375, 95%CI: 1.050-1.802, *P* = 0.020). Moreover, the risk was markedly higher for those who were carriers of Gln/Gln variant genotype and were cigarette smokers, as well (OR: 3.409, 95%CI: 1.061-10.949, *P* = 0.032).

**CONCLUSION:** *XPC* Gln/Gln genotype alone and in combination with smoking enhances CRC predisposition risk among Malaysians.

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**Key words:** DNA repair; Xeroderma pigmentosum group C Lys939Gln polymorphism; Cigarette smoking; Colorectal cancer; Susceptibility risk

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**INTRODUCTION**

Colorectal cancer (CRC) which is the third commonest cancer and the fourth cancer that cause deaths is a major public health problem worldwide[1]. In Malaysia, CRC has become the first commonest cancer among male and second among female[2]. Development of CRC is a complex, multistep process involving interaction between environmental and genetic factors. Environmental factors such as dietary and life style habits, smoking, alcohol consumption, and obesity interact with host’s genetic factors especially genetic variations and may modulate the risk of CRC[3]. Genetic variation such as single nucleotide polymorphisms (SNPs) may increase the sensitivity to environmental carcinogens and may act as cancer predisposition factors. Environmental sensitive genetic polymorphisms acting together with environmental factors are well documented candidates for cancer susceptibility.

DNA damage repair genes maintain integrity of the genome against endogenous and exogenous factors. The xeroderma pigmentosum group C (*XPC*) gene is a DNA repair gene involved in nucleotide excision repair (NER) mechanism which repair bulky DNA lesions such as pyrimidine dimers, ultraviolet light induced damage, photo products, intrastrand cross links, larger chemical adducts and other genotoxic agent[4]. Genetic variations in *XPC* gene has been reported to modulate an individual’s susceptibility of developing cancer[5,6]. *XPC* Lys939Gln polymorphism which leads to amino acid change from lysine to glutamine at codon 939 is the most common SNP studied in *XPC* gene and have been shown to be associated with increased risk of several cancers such as skin[7], breast[8] and bladder cancers[9,10].

However there are only limited reports available on the association of this polymorphism with CRC susceptibility risk. A case-control study was undertaken in order to investigate the association of this polymorphism alone and/also in concert with cigarette smoking on CRC susceptibility risk. This polymorphism is believed to alter the gene expression and modulate the DNA repair function of the protein product as it is located at the coding sequence of *XPC* gene. Thus, we hypothesized that *XPC* Lys939Gln polymorphism may have an effect on modulating the susceptibility to CRC, and cigarette smoking may further enhance the effect on CRC risk.

**MATERIALS AND METHODS**

***Study subjects***

The study was approved by Research Review Board and Ethics Committee of Universiti Sains Malaysia, Kelantan and Ministry of Health, Malaysia. For this Hospital based case control study, subjects were recruited from various hospitals in Malaysia like Hospital Universiti Sains Malaysia, Hospital Raja Perempuan Zainab II and Hospital Sultanah Bahiyah, Kedah, Malaysia. Genotyping was carried out at the Human Genome Center, Universiti Sains Malaysia. Two hundred and fifty five (255) sporadic CRC patients and 255 healthy normal controls were recruited as study subjects. Cases were histopatologically confirmed sporadic CRC patients, with age more than 25 years and who did have previous colon/rectal or other cancers. Cases with known (as indicated in the pathology reports) familial adenomatous polyposis, ulcerative colitis or Crohn’s disease or any other previous malignancy were excluded. Controls were normal healthy individuals who were biologically unrelated to the study patients, aged more than 25 years and were cancer free participants. Epidemiological data was collected from patients using a pre-structured questionnaire which included socio-demographic status, physical status, dietary factors, occupation, tobacco/alcohol habits, previous illness, radiation exposure etc.

***Genotyping***

Genotyping of *XPC* Lys939Gln polymorphism was carried out by employing Polymerase Chain Reaction-Restriction Fragment Length Polymorphism. Briefly, PCR primers for the *XPC* Lys939Gln (F: 5’-GGCTTCCTGGTATCTGATTACT-3’R:5’- CTCAGTTTGCCTTCTCAGCA-3’) were used to generate a 402 bp product containing the polymorphic site. The PCR reactions were carried out in a 25 µL volume of 1X PCR Buffer, 2.0 mmol/L of MgCl2, 0.5 mmol/L dNTPs, 0.4 mmol/L of each primers and 1 U of amplitaq gold polymerase with a denaturation of 94 ℃ for 5 min, followed by 35 cycles at 94 ℃ for 30 s, 57 ℃ for 30 s and 72 ℃ for 30 s and finally 5 min at 72 ℃. Following amplification, PCR products were digested using *PvuII* restriction enzyme for 1 h at 37 ℃ and electrophoresed on 2% agarose gel. The wild-type homozygous was identified by a single band at 402 bp level, the heterozygous by 3 bands at 402, 276 and 126 bp levels and homozygous variant by 2 bands at 276 and 126 bp levels (Figure 1).

***Statistical analysis***

The sample size was calculated using power and sample size (PS) software version 2.1.31 by using two proportion uncorrected 2 test with 80% power of study and 95%CI. The difference in distribution of genotypes, gender and age between cases and controls were assessed using 2 test. The odds ratios and 95%CI were calculated by using binary logistic regression to evaluate the risk association. All statistical tests were two sided, and statistical significance was determined as *P* < 0.05. SPSS (version 18) was utilized for statistical analysis.

**RESULTS**

The distribution of demographic characteristics of study subjects is shown in Table 1. This case-control study recruited 510 study subjects involving 255 histopathologically confirmed sporadic CRC patients and 255 healthy normal individuals. Out of the 255 sporadic CRC patients, 139 (54.5%) were males and 116 (45.5%) were females. Among the 255 normal controls, 115 (45.1%) were males and 140 (54.9%) were females. The ages of the sporadic CRC patients ranged from 27 to 93 years old with a mean age of 53.17 ± 7.074 years and for healthy normal controls group, the age ranged from 26 to 84 years old with a mean age of 46.47 ± 12.020 years.

The frequencies of homozygous wildtype (Lys/Lys), heterozygous (Lys/Gln) and homozygous variant (Gln/Gln) genotypes were 108 (42.4%), 106 (41.6%) and 41 (16.0%), respectively among CRC cases. In controls, the frequencies were 129 (50.6%) for homozygous wildtype, 100 (39.2%) for heterozygous and 26 (10.2%) for homozygous variant genotypes. The frequency of homozygous variant (CC) genotype was significantly higher in cases compared to the controls (*P* = 0.049). Table 2 shows the genotype and allele frequencies of *XPC* Lys939Gln polymorphism in cases and controls.

Binary logistic regression analysis was performed in order to find the risk association. Table 3 shows the risk association between the *XPC* Lys939Gln polymorphism and CRC susceptibility. It can be clearly seen that, the homozygous variant genotype was significantly associated with increased risk of CRC susceptibility with OR: 1.884, 95%CI: 1.082-3.277, *P* = 0.025. Variant allele C was found to be significantly associated with increased risk of CRC predisposition with OR: 1.375, 95%CI: 1.050-1.802, *P* = 0.020. Furthermore, the study subjects were stratified into smokers and non-smokers and risk association was evaluated. Results showed that, for those with homozygous variant genotype (CC) and who were smokers, the risk was significantly higher with OR: 3.409, 95%CI: 1.061-10.949, *P* = 0.032. In case of non-smokers group, no significant high risk association was observed between *XPC* Lys939Gln polymorphism and CRC susceptibility.

**DISCUSSION**

To date, a variety of chemical carcinogens have been identified to cause DNA damage in humans. DNA damage repair genes are responsible for maintaining the integrity of human genome through different pathways, locations and types of damage through base excision repair, NER, double strand break and mismatch repair pathways[4]. Gene involved in NER pathway such as *XPC* commonly repairs lesions induced by numerous exogenous agents such as those derived from food and smoking, including 2-amino-1-methyl-6-phenylimidazo [4,5-β] pyridine and benzo [α] pyrene diol-epoxide[11].

The *XPC* gene, located on chromosome 3p25, contains 16 exons and 15 introns and encodes a 940 amino acid protein[12]. Several polymorphic variants in the *XPC* gene have been identified and *XPC* Lys939Gln is one of the three most common SNPs. This case-control study investigated the genotype and allele frequencies of *XPC* Lys939Gln polymorphism, and the risk association with sporadic CRC susceptibility. Results from the present study showed that, the genotype frequency of *XPC* homozygous variant genotype was significantly higher in cases as compared to controls (16.0% *vs* 10.2%, *P* = 0.049). On evaluation of the risk association, a significant high risk association between homozygous variant genotype (CC) and CRC susceptibility was observed (OR: 3.409, *P* = 0.032). This result is in favour of a study by Yasuda *et al*[13], which demonstrated that a single amino acid alteration could be sufficient to compromise *XPC* function, thereby enhancing the risk for CRC development. Our results are in agreement with few other reports by Qiu *et al*[5], Zhang *et al*[6] and Gil *et al*[14] which revealed that, *XPC* is one the most important genes modulating an individual’s risk of developing sporadic cancer.

Carcinogens ingested through dietary and life style habits as well from environment play major role in damaging DNA. Cigarette smoking is one of the life style factors that play an important role in the exposure of an individual to the carcinogens present in cigarette smoke. Carcinogens contained in tobacco smoke such as polycycliaromatic hydrocarbon, heterocyclic amines, nitrosamines and aromatic amines are harmful to human colon and rectum. Cigarette smoking has been reported to lead to the formation of DNA adducts and cause damage of the DNA in human colon[15,16]. All these carcinogens can reach colorectal mucosa, though direct ingestion or via circulatory system, and has been demonstrated to induce bulky adducts in crypt cells and contribute to the formation of mutations in the colon[17,18]. In the present study, combination of smoking habits and variant genotype of *XPC* enhanced the CRC susceptibility risk to 3-fold times higher and indicates that, smoking habits enhanced the risk of CRC predisposition. Although non-smokers showed OR value of 1.256, it was not statistically significant.

 *XPC* gene encodes an important protein involved in the recognition of DNA damage in NER pathway. This protein binds to HR23B protein to form XPC-HR23B that recognizes DNA lesion and repairs the DNA damage along with other DNA repair protein[19,20]. Polymorphism in the coding sequence of *XPC* gene has been demonstrated to alter the gene expression and thereby modulate the DNA repair function[21]. *XPC* Lys939Gln polymorphism is located in coding sequence of *XPC* gene. The nucleotide change from A to C, lead to amino acid change from lysine to glutamine in the coding sequence of *XPC* gene and has been reported to lead to reduced repair capacity. This genetic variation also has been reported to result in reduced specificity of this gene in recognition and repair of the DNA damage as well as protein expression, thus allowing more somatic DNA mutations or alterations to occur[21, 22].

XPC protein plays a crucial role in repairing the DNA damage caused by tobacco smoke. Individuals with *XPC* variant genotype might be possessing deficient DNA repair capability. Accordingly the XPC protein product might be less efficient in repairing the DNA lesions induced by tobacco smoke, and thereby could be enhancing the susceptibility risk, favouring the development of CRC.

Previous studies focusing on the role of *XPC* variant in the modulation of an individual’s risk of developing CRC are scarce and results reported were inconsistent. Berndt *et al*[22] in American population found a OR value of 1.19 for the variant genotype’s risk association with CRC susceptibility, however the result was statistically insignificant (*P* = 0.50). On the contrary, a study conducted by Hansen *et al*[23] on Polish population observed no significant a risk association between this polymorphism and CRC susceptibility. However, when the variant genotype in conjunction with red meat consumption was evaluated, the risk was reported to be significantly higher (OR: 3.7) for an individual, who carried homozygous variant (CC) genotype and consumed 100g red meat per day.

A recent study by Wu *et al*[24] on 421 CRC patients and 845 controls, had shown that, homozygous variant (CC) genotype was significantly associated with higher risk for CRC susceptibility in Chinese population with OR: 1.5, 95%CI: 1.0-2.2, *P* = 0.035. Moreover, combination (AC + CC) genotypes under homozygous wildtype model also showed significant high risk association with OR: 1.3, 95%CI: 1.0-1.7, *P* = 0.039. When those study subjects were stratified into tea drinkers and non-tea drinkers, the results showed that, individuals who were non-tea drinkers and carried combination of (AC + CC) genotypes, had increased risk of CRC susceptibility with OR: 3.0 , 95%CI: 1.9-4.7, *P* < 0.001.

Apart from CRC, this polymorphism was reported to be associated with risks of other cancers such as head and neck[25], lung[10], breast[8] and bladder[26]. Besides that, abnormal expression of *XPC* gene has been shown in hepatocarcinogenesis[27]. Variant allele of *XPC* gene is associated with lower DNA repair capacity (DRC). Several studies showed that, the Lys939Gln polymorphism, had an interaction with other SNPs located in same gene such as Ala499Val, PAT (-/+) and also IVS11 C/A polymorphisms. According to Khan *et al*[28], *XPC* Lys939Gln polymorphism is in linkage disequilibrium with *XPC* PAT polymorphism as well as C/A polymorphism at 25 positions of intron 11 of *XPC*. This caused the exon 12 to be skipped and deleted, resulting in the losses of *XPC* cDNA function, thus reducing the DNA repair activity.

Researchers have shown that carriers of C variant allele of *XPC* Lys939Gln polymorphism exhibited significantly more DNA damages induced by BPDE[21,29,30]. Moreover, combinations of haplotype C + C (Lys939Gln, PAT +, Ala499Val) has been reported to cause poor DRC thus increasing the risk of CRC. On the contrary, haplotype T-A (Ala499Val-PAT-Lys939Gln) has been demonstrated to be associated with the least DNA damages[21,24]. Also, a study has shown that accumulation or presence of increased risk alleles in *XPC* gene might reduce DRC and thus increase the CRC risk[31].

The difference in results on risk association between the present study and other previous studies might be explained by difference in genetic background of study subjects groups or populations, and also differences in exposure to environmental and lifestyle factors. Smaller sample size and or inadequate controlling for certain confounder factors such as gender and age also might have contributed to differing results and lack of association.

From the present study, it is reasonable to suggest that *XPC* gene, especially the *XPC* variant genotype may modulate the DRC of the host cell and thus play an important role in sporadic colorectal carcinogenesis. The risk could be much higher for individuals who possess the variant genotype and who are cigarette smokers as well. The results also highlight the potential role of NER pathway (especially of *XPC*) in modulation of an individual’s risk of sporadic CRC. Further studies exploring the interaction of *XPC* Lys939Gln with other SNPs of *XPC* gene and also with other genes involved in DNA repair pathways, either singly or in combination, and also correlating with environmental interactions such as alcohol consumption, and dietary habits as well as clinicopathological characteristics, would be beneficial in deriving more accurate risk predictive markers.

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**COMMENTS**

***Background***

Colorectal cancer (CRC) which ranks the first commonest cancer among male and second among female in Malaysian population, has become a major public problem. Environmental factors such as dietary carcinogens, tobacco smoke etc interacting with host’s genetic factors may modulate the risk of CRC. However, the genetic predisposition factors associated with colorectal carcinogenesis remains largely undetermined. Identification of the host’s genetic predisposition factors may help in understanding of the carcinogenic process. So, it was of interest to explore the contribution of single nucleotide polymorphisms (SNPs) in DNA repair gene, singly and also in combination with tobacco smoke, as predisposition factor for CRC susceptibility.

***Research frontiers***

Exposure to mutagens and carcinogens through diet, tobacco smoke etc can cause varying degrees of DNA damage and can cause mutations in humans, if left unrepaired. Damages in DNA are repaired by various DNA repair genes belonging to distinct pathways. The Xeroderma pigmentosum group C (*XPC*) gene is a DNA repair gene involved in the nucleotide excision repair (NER) pathway which repairs bulky lesions such as pyramidine dimers, ultraviolet light induced damage, photo products, intrastrand cross links, large chemical adducts and other genotoxic agents. A single nucleotide polymorphism Lys939Gln located at coding region of *XPC* gene has been associated with lower DNA repair capacity and had been shown to be associated with increased risk of cancers of the skin, breast and bladder. This study was designed to determine the frequencies and influence of the *XPC* Lys939Gln polymorphic genotype separately and also in combination with smoking, on sporadic CRC susceptibility risk in a Malaysian population.

***Innovations and breakthroughs***

Even though the incidence of CRC is increasing in Malaysia, there is paucity of information on the nature of genetic predisposition factors that contribute to susceptibility to CRC in Malaysia population. This study reports the risk association of *XPC* Lys939Gln polymorphism with CRC in Malaysian patients. Only limited reports are available on the association of *XPC* Lys939Gln polymorphism with CRC susceptibility risk. Furthermore, no previous reports are available on Malaysian population. To the best of our knowledge, this seems to be the first report of an association of genetic variation of *XPC* with CRC susceptibility risk in Malaysian population. The observation that genetic variation of *XPC* gene influences one’s susceptibility to CRC implies the importance of NER pathway in the modulation of an individual’s risk for CRC development. This study provide support to the hypothesis that genetic variation in *XPC* gene, acting together with environmental factors, contribute to CRC development and may be considered as candidate marker for CRC predisposition risk in Malaysian population.

***Applications***

The present study observed that the genetic variation Lys939Gln of *XPC* gene influences CRC predisposition risk in Malaysian population. Further SNP mapping studies utilizing high throughout genotyping methods could facilitate the analysis of multiple polymorphisms within DNA repair genes. Genotyping of Malaysian CRC patients for polymorphism(s) in DNA repair genes will help in understanding the specific polymorphism(s), which act as predisposing genotype(s) in CRC susceptibility. This will lead to advancement of knowledge on genetic predisposing factors related to CRC susceptibility in Malaysian population. Identification of genetic factors associated with CRC predisposition risk, will help in better understanding of the colorectal carcinogenic process and in the design of appropriate diagnostic, therapeutic and preventive strategies. Moreover, in future, the study can be extended to a population level, to identify individuals with high risk predisposition genotypes. Once the high risk individuals are identified, appropriate preventive screening strategies can be devised for them. Regular, frequent and effective screening for CRC is not currently available at the population level. The public perception of genetic determinism is that, if the polymorphic at risk, genotype status of an individual is known, the cancer predisposition status of that individual can be predicted and appropriate surveillance programs can be initiated. By this, morbility and mortality of CRC can be reduced at the population level.

***Peer review***

This case-control study investigated the association between SNPs and cigarette smoking on sporadic CRC susceptibility risk in Malaysian population. The genotype and allele frequencies of *XPC* Lys939Gln were investigated in 255 CRC patients and 255 healthy controls. Homozygous variant (CC) genotype frequency was found to be significantly higher in CRC cases compared to controls. When the risk association was evaluated singly, the homozygous variant *XPC* CC genotype was associated with an increased risk of CRC susceptibility. Moreover, when the risk was evaluated after stratifying the study subjects into smokers and non-smokers, the combination of smoking habits and variant genotype of *XPC* was found to enhance the CRC susceptibility risk to 3-fold times higher. These results prompt us to suggest that genetic variation Lys939Gln in *XPC* gene might modify the effect of smoking and contribute to sporadic colorectal cancer etiology.

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**P-Reviewer** Gusella M **S-Editor** Wen LL  **L-Editor**  **E-Editor**

**Lane M Lane1 Lane 2 Lane 3 Lane 4 Lane 5**

402bp

276bp

126bp

Lane M

: 100bp DNA ladder

Lanes 2 & 3

: Homozygous

wildtype

Lane 1

: Heterozygous

Lanes 4 & 5

: Homozygous variant

**Figure 1** **Gel picture showing the different categories of xeroderma pigmentosum group C Lys939Gln polymorphism genotype.**

**Table 1 Demographic characteristics of study population *n* (%)**

|  |  |  |  |
| --- | --- | --- | --- |
| **Variable** | **Cases*****n* =255**  | **Controls*****n* = 255**  | ***P*-value** |
| **Gender** |  |  |  |
| Male | 139 (54.5) | 115 (45.1) | 0.0341 |
| Female | 116 (45.5) | 140 (54.9) |
| **Mean age** | 53.17 ± 7.07 | 46.47 ± 12.02 |  |
| **Cigarette smoking** |  |  |  |
| Yes | 110 | 48 | <0.0011 |
| No | 145 | 207 |

1*P*-value < 0.05, statistically significant.

**Table 2 Genotype and allele frequencies of xeroderma pigmentosum group C Lys939Gln polymorphism in study subjects *n* (****%)**

|  |  |  |  |
| --- | --- | --- | --- |
|  | **Cases*****n* = 255**  | **Controls*****n* = 255**  | ***P*-value** |
| **Genotype** |  |  |  |
| Homozygous wildtype (AA) | 108 (42.4) | 129 (50.6) | 0.062 |
| Heterozygous (AC) | 106 (41.6) | 100 (39.2) | 0.588 |
| Homozygous variant (CC) | 41 (16.0) | 26 (10.2) | 0.0491 |
| **Allele** |  |  |  |
| A | 322 (63.1) | 358 (70.0) | 0.294 |
| C | 188 (36.9) | 152 (30.0) |

1*P*-value < 0.05, statistically significant.

**Table 3 Xeroderma pigmentosum group C Lys939Gln polymorphism, smoking and colorectal cancer susceptibility risk**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | **Cases** | **Controls** | **OR** | ***P*-value** |
| **Genotype** |  |  |  |  |
| Lys/Lys (AA) | 108 | 129 | **1 (Reference)1** |  |
| Lys/Gln (AC) | 106 | 100 | 1.266 (0.871-1.841) | 0.216 |
| Gln/Gln (CC) | 41 | 26 | 1.884 (1.082-3.277) | 0.0252 |
| **Allele** |  |  |  |  |
| A | 322  | 358  | **1 (Reference)1** | - |
| C | 188  | 152  | 1.375 (1.050-1.802) | 0.0202 |
| **Non-smoker** |  |  |  |  |
| AA | 64 | 104 | **1 (Reference)1** |  |
| AC | 64 | 81 | 1.284 (0.817-2.018) | 0.278 |
| CC | 17 | 22 | 1.256 (0.620-2.542) | 0.526 |
| **Smoker** |  |  |  |  |
| AA | 44 | 25 | **1( Reference)1** |  |
| AC | 42 | 19 | 1.256 (0.605-2.609) | 0.541 |
| CC | 24 | 4 | 3.409 (1.061-10.949) | 0.0322 |

1Homozygous wildtype genotype served as reference category; 2*P* value < 0.05, statistically significant. OR: Odds ratio.