Acta Oncologica, 2008; 47: 379–384

informa
healthcare

ORIGINAL ARTICLE

The xeroderma pigmentosum group C gene polymorphisms and genetic susceptibility of nasopharyngeal carcinoma

ZHI-HUI YANG[1,4], WEI-BO LIANG[1], JING JIA[1], YE-SHENG WEI[2], BIN ZHOU[1] & LIN ZHANG[1,3]

[1]*Department of Forensic Biology, West China School of Preclinical and Forensic Medicine, Sichuan University, Chengdu 610041, Sichuan, China,* [2]*Department of Immunology, West China School of Preclinical and Forensic Medicine, Sichuan University, Chengdu 610041, Sichuan, China,* [3]*State Key Laboratory of Biotherapy, Ministry of Education, Chengdu 610041, Sichuan, China and* [4]*Department of Pathology, Luzhou Medical College, Luzhou 646000, Sichuan, China*

Abstract

Aims. Nasopharyngeal cancer (NPC) is a multi-factorial disease, and the genetic background may be a crucial etiologic factor. The xeroderma pigmentosum complementation group C (XPC) is mainly involved in DNA damage repair, and the sequence variants in XPC gene may modulate DNA repair capacity and consequently lead to an individual's susceptibility to NPC. The aims of this study were to examine the association between XPC Val499Ala, Lys939Gln, PAT polymorphisms and the genetic susceptibility of nasopharyngeal carcinoma (NPC) in Chinese population. *Methods.* We analyzed the three XPC gene polymorphisms in 153 patients with NPC and 168 age- and sex-matched controls in a Chinese population, using a polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) procedure. *Results.* There were significant differences in the genotype and allele distribution of XPC Val499Ala among cases and controls. The 499Val allele carriers were associated with a significantly increased risk of NPC compared with the non-carriers (OR = 1.603; 95%CI, 1.160 ~ 2.216, p = 0.005). Consistent with the results of the genotype analysis, the 499Val/939Lys/PAT–haplotype was associated with a significantly increased risk of NPC as compared with the 499Ala/939Lys/PAT–haplotype (OR = 1.901; 95% CI, 1.284 ~ 2.814, p = 0.002).The interaction between the Val499Ala polymorphism and gender or smoking status did not been found in NPC risk. *Conclusions.* Our data demonstrated that XPC 499Val allele and its haplotype were strongly associated with NPC, which indicated that Val499Ala polymorphism may be a contributing factor in the NPC development.

Nasopharyngeal carcinoma (NPC) has a marked geographic and ethnic distribution. It is rare among Caucasians in Western Europe and North America, with the incidence usually less than 1/1 000 000 [1]. The disease is predominantly endemic in Southeast Asia and southern China. In these high-risk areas, the incidence is 10–50/100 000 [2]. Previous studies have demonstrated that NPC is a multi-factorial disease. Epstein-Barr virus (EBV) infection, environmental factor and individual genetic susceptibility are widely recognized as the risk factors in the development of NPC. But, the molecular mechanism of NPC carcinogenesis remains unclear.

The XPC protein is one of the DNA-repairing enzymes, which is absolutely necessary in nucleotide excision repair (NER) pathway that is responsible for bulky adducts and UV-induced DNA damage repair. It binds tightly with HR23B (one of 2 human homologs of Saccharomyces cerevisiae NER factor RAD23) to form XPC–HR23B complex [3], which acts as an early damage detector and a molecular matchmaker for recruitment of other components of the repair apparatus to the damaged DNA in global genomic NER [4,5]. The normal function of the XPC is essential in maintaining genomic integrity and preventing cellular neoplastic transformation [6]. DNA repair gene polymorphisms have been reported that could lead to the deficiency of DNA repair capacity, and subsequently contribute to genomic instability and an individual's susceptibility to cancer. The most extensively polymorphisms studies of XPC are Val499Ala (a T -to- C transition in exon8), Lys939Gln (a A -to- C transition in exon15) and Poly-AT (PAT, an insertion of 83 bases

Correspondence: Lin Zhang, Department of Forensic Biology, West China School of Preclinical and Forensic Medicine, Sichuan University, Chengdu 610041, Sichuan, China. Tel: +86 28 85469033. Fax: +86 28 85405541. E-mail: kjc@scu.edu.cn

(Received 13 April 2007; accepted 28 June 2007)

ISSN 0284-186X print/ISSN 1651-226X online
DOI: 10.1080/02841860701558815

of A and T with a concurrent 5 base deletion in intron 9). Recently, genetic polymorphisms of the XPC gene have been implicated in the susceptibility to a range of cancers, including bladder cancer [7], squamous cell carcinoma of the head and neck [8] and lung cancer [9]. However to our knowledge, there are no studies about XPC gene polymorphisms and NPC susceptibility. In the current study, we evaluated whether XPC Val499Ala, Lys939Gln, PAT polymorphisms contribute to NPC risk in a Chinese population.

Materials and methods

Subjects

The case group consisted of 153 diagnosed patients with histologically confirmed NPC in Sichuan Province, China, from January 2005 to May 2006. Patients with secondary and recurrent tumors were excluded. The control group comprised 168 healthy volunteers who visited the general health check-up and they matched to the cases by age, gender and smoking status in frequency. These cancer-free controls were genetically unrelated to the cases and all subjects were of the Han ethnic group. Data on age, gender, smoking status and amount were derived from questionnaires through personal interviews by two trained investigators. For each subject, the results of the questionnaires from the two investigators were required to be consistent. After informed consent obtained, and with the approval of the ethics committee of Chinese Human Genome, each study participant donated 2–5 ml of blood in EDTA tubes and stored at -20°C. Genomic DNA was extracted from peripheral blood by proteinase K digestion and phenol/chloroform extraction.

Genotyping

Genotyping for polymorphisms of XPC Val499Ala, Lys939Gln, PAT were detected by using PCR-RFLP technique. Polymerase chain reaction (PCR) assays were used to amplify exon8, exon15 and intron9 of XPC containing the polymorphisms interested. The primers used to identify the polymorphism were as follows: 5′-TAA GGA CCC AAG CTT GCC CG-3′and 5′-CCC ACT TTT CCT CCT GCT CAC AG-3′for exon8 [9]; 5′-GAT GCA GGA GGT GGA CTC TCT -3′And 5′-GTA GTG GGG CAG CAG CAA CT-3′for exon15 [7]; 5′-TAG CAC CCA GCA GTC AAA G-3′and 5′-TGT GAA TGT GCT TAA TGC TG-3′ for intron9 [8]. Each PCR (25 μl vol) generally comprised 50–100 ng genomic DNA, 0.4 pmol/L of each primer, 0.1 mmol/L of dNTP mix, 0.2 U Taq DNA polymerase (Invitrogen, Shanghai, China), 1.5 mmol/L $MgCl_2$ and 1.0 × PCR buffer. Thermal cycling conditions were an initial denaturation at 94°C for 4 min, 35 cycles of denaturation at 94°C for 35 s, 45 s of annealing (64°C for Val499Ala and Lys939Gln, 67°C for PAT) and 55 s of elongation at 72°C, followed by a final extension at 72°C for 7 min. The various PCR products were digested with specific restriction enzymes. Ten microliters of PCR products were digested respectively with 5 units of Pvu II (for codon 939), Sac II (for codon 499) [FERMENTAS, Chengdu, China] at 37°C for 4 h. The products were then resolved on 8% polyacrylamide gel. For quality control, the three PCR-RFLP assays were repeated on 20% of the samples and the replicates were 100% concordant.

Statistical analysis

Differences in genotype distributions and allele frequencies in the NPC cases and the controls were compared for statistical significance using the Pearson χ^2 test or Fisher's Exact Test. The odds ratios (OR) with 95% confidence intervals (CI) were used to estimate the association of certain polymorphism and NPC. Hardy-Weinberg equilibrium was tested by a goodness-of-fit χ^2 to compare the observed genotype frequencies within the case-control groups to the anticipated genotype frequencies calculated from the observed allele frequency. Statistical significant was set at $p < 0.05$, all analysis were conducted using the SPSS 11.5 statistical package. The linkage disequilibrium (LD) of the three loci, haplotypes and their frequencies were estimated by using the SHEsis software [10] (available at http://202.120.7.14/analysis/myAnalysis.php).

Results

Characteristics of the study population

Select characteristics of the 153 NPC cases and 168 cancer-free controls are summarized in Table I. The mean ages of cases and controls (mean $\pm$ SD) were almost identical (49.8 ± 10.5 versus 48.3 ± 11.2). There were slightly more males among the cases (70.4%) than in controls (68.3%), but this difference was not statistically significant ($p > 0.05$). As expected, the smoking history and current smoking status among patients and controls were quite similar.

Polymorphisms of XPC Val499Ala, Lys939Gln, PAT

The association between XPC Val499Ala, Lys939Gln, PAT polymorphisms and NPC risk were summarized in Table II. The genotype distributions of all the polymorphisms studied were in

Table I. Characteristics of the study population.

Variable	NPC patients (n = 153)	Controls (n = 168)
Age (years)	48.7 ± 9.2	47.9 ± 10.1
Sex		
Male	110 (71.9)[a]	118 (70.2)
Female	43 (28.1)	50 (29.8)
Smoking status		
Current	64 (41.8)	69 (41.1)
Former	45 (29.4)	53 (31.5)
Never	44 (28.8)	46 (27.4)
Clinical stages		
Stage I & II	19 (12.4)	–
Stage III & IV	134 (87.6)	–
Histological type (%)		
Poorly differentiated SCC	126 (82.4)	–
undifferentiated cancer	24 (15.7)	–
Others	3 (1.9)	–

[a]Numbers in parenthesis, percentage. SCC, squamous cell carcinoma; others include poorly differentiated adenocarcinoma (n = 1), and moderately differentiated SCC (n = 2).

accordance with Hardy-Weinberg equilibrium (HWE). The genotype frequencies of Val499Ala were 18.3% (Val/Val), 47.7% (Val/Ala) and 34.0% (Ala/Ala) among cases and 7.7% (Val/Val), 47.1% (Val/Ala), 45.2% (Ala/Ala) among control subjects. There were significant differences in the genotype and allele frequencies of the Val499Ala polymorphism between NPC patients and control groups ($\chi^2 = 9.871$, $p = 0.007$ and $\chi^2 = 8.225$, $p = 0.004$ respectively). The frequency of 499Val allele was markedly higher in the cases than in the controls (42.2% versus 31.2%), subjects with the 499Val allele were at statistically significant increased risk of NPC relative to subjects with the 499 Ala allele (OR = 1.603; 5%CI, 1.160 ~ 2.216, $p = 0.005$). The genotype frequencies and allelic frequencies of Lys939Gln and PAT polymorphisms among cases were similar to those of controls in this investigation, and any significant association of the two polymorphisms and NPC risk was not found.

Frequency distributions of XPC haplotypes and their associations with NPC

The three polymorphisms were in strong LD. The parameter of linkage disequilibrium D' was 0.980(Val499Ala and Lys939Gln), 0.942(Val499Ala and PAT), 0.971(Lys939Gln and PAT). Eight haplotypes were observed in this study, and their frequency distributions among cases and controls were shown in Table III. To avoid possible errors in either haplotype analysis or the estimation process, five haplotypes that had a frequency of <2% were combined for further analysis. The frequency of 499Val/939Lys/PAT−(TA−) was significantly higher in the cases than in the controls (41.5% versus 30.4%), which was associated with a significantly

Table II. Frequency distributions of XPC polymorphisms among cases and controls and their associations with NPC.

Polymorphisms	Cases n = 153 (%)	Controls n = 168 (%)	OR (95%CI)	P
Val499Ala(T→C)				
Genotypes				
Ala/Ala	52 (34.0)	76 (45.2)	1.00 (Ref)	–
Val/Ala	73 (47.7)	79 (47.1)	1.151 (0.770 ~ 1.723)	0.537
Val/Val	28 (18.3)	13 (7.7)	3.148 (1.492 ~ 6.640)	0.002
Alleles				
Ala	177 (57.8)	231 (68.8)	1.00 (Ref)	–
Val	129 (42.2)	105 (31.2)	1.603 (1.160 ~ 2.216)	0.005
Lys939Gln(A→C)				
Genotypes				
Lys/Lys	66 (43.1)	74 (44.0)	1.00 (Ref)	–
Lys/Gln	75 (49.1)	72 (42.9)	1.168 (0.735 ~ 1.865)	0.555
Gln/Gln	12 (7.8)	22 (13.1)	0.612 (0.281 ~ 1.331)	0.251
Alleles				
Lys	207 (67.6)	220 (65.5)	1.00 (Ref)	–
Gln	99 (32.4)	116 (34.5)	0.907 (0.653 ~ 1.260)	0.616
PAT				
Genotypes				
PAT+/PAT+	12 (7.8)	24 (14.3)	1.00 (Ref)	–
PAT+/PAT−	78 (51.0)	72 (42.9)	2.167 (1.010 ~ 4.649)	0.062
PAT−/PAT−	63 (41.2)	72 (42.9)	1.750 (0.809 ~ 3.784)	0.187
Alleles				
PAT+	102 (33.3)	120 (35.7)	1.00 (Ref)	–
PAT−	204 (66.7)	216 (64.3)	1.111 (0.802 ~ 1.539)	0.561

Table III. Frequency distributions of XPC haplotypes and their associations with NPC.

Haplotype*	Cases (n = 306) (%)	Controls (n = 336) (%)	OR (95%CI)	P
CA−	74 (24.2)	113 (33.6)	1.00 (Ref)	–
CC+	95 (31.0)	115 (34.2)	1.261 (0.846 ~ 1.881)	0.265
TA−	127 (41.5)	102 (30.4)	1.901 (1.284 ~ 2.814)	0.002
TC+,TC−, CA+, CC−, TA+	10 (3.3)	6 (1.8)	2.545 (0.887 ~ 7.300)	0.111

*The order of the polymorphisms was as follows: Val499Ala, Lys939Gln, PAT.

increased risk of NPC as compared with the 499Ala/939Lys/PAT−(CA−) haplotype (OR = 1.901; 95% CI, 1.284 ~ 2.814, p = 0.002).

Stratification analysis of XPC Val499Ala polymorphism and NPC risk

To estimate the interaction between XPC Val499Ala polymorphism genotypes and smoking status or gender, stratified OR was calculated. The risk for XPC 499 genotypes among various smoking status (current, former and never) or gender (male and female) were presented in Table IV. The XPC 499Val/Ala and Val/Val genotypes were not associated with a significantly increased risk of NPC in male or current smoker groups compared to Ala/Ala genotype (OR = 1.545, 95%CI, 0.891 ~ 2.676; p = 0.129 and OR = 1.670, 95%CI, 0.825 ~ 3.381; p = 0.161 respectively), and the interaction between XPC Val499Ala genotypes and gender or smoking status did not been found in the NPC risk.

Discussion

To our knowledge, the present study is the first to examine the Val499Ala, Lys939Gln, PAT polymorphisms of the XPC gene in patients with NPC in a Chinese population. In this study, we have demonstrated that the Val499Ala polymorphism and the XPC haplotype were significantly associated with the NPC risk, and no statistically significant association between XPC Val499Ala polymorphism and NPC risk was found when stratifying the gender and smoking status. These findings indicated that Val499Ala may be a contributing factor in the NPC development.

In the current study, the frequency of 499Val allele among the healthy Chinese population was 0.312, which was comparable to those in healthy Korean [11] and SNP500 Cancer database (http://snp500cancer.nci.nih.gov/home.cfm; dbSNP ID: rs2228000, 0.289 and 0.235 respectively). The allele frequencies of XPC 939Gln and PAT+ in Korean and American population were 0.394, 0.372 and 0.383, 0.408 respectively [11,12], which were similar to those frequencies observed in this study (0.345 and 0.357 respectively). We also found that the Val499Ala, Lys939Gln, PAT polymorphisms were in LD, the magnitude of the LD among these three polymorphisms in our study subjects were in agreement with previous studies [9,11,13]. The frequencies of three common haplotypes 499Val/939Lys/PAT−, 499Ala/939Lys/PAT− and 499Ala/939Gln/PAT+ respectively in controls were 0.304, 0.336 and 0.342 respectively, which were similar to those in Korean (0.271, 0.370 and 0.359 respectively) [14].

XPC is a part of the XPC-HR23B complex that identifies target lesions in the NER repair pathway [4]. It is suggested that the normal XPC gene is critical for the cells to complete excision repair of bulky DNA lesions [15]. Mice defective in the XPC gene are highly prone to cancers of lung and liver,

Table IV. Stratification analysis of XPC Val499Ala polymorphism in relation to NPC by gender and smoking.

Variable	Genotypes	Cases n = 153 (%)	Controls n = 168 (%)	OR (95%CI)	P
Sex					
Female	Ala/Ala	19 (12.4)	29 (17.3)	1.00 (Ref)	–
	Val/Ala+Val/Val	24 (15.7)	21 (12.5)	1.744 (0.766 ~ 3.973)	0.215
Male	Ala/Ala	33 (21.6)	47 (28.0)	1.00 (Ref)	–
	Val/Ala+Val/Val	77 (50.3)	71 (42.2)	1.545 (0.891 ~ 2.676)	0.129
Smoking status					
Never	Ala/Ala	14 (9.2)	18 (10.6)	1.00 (Ref)	–
	Val/Ala+Val/Val	30 (19.6)	28 (16.7)	1.378 (0.578 ~ 3.281)	0.514
Former	Ala/Ala	17 (11.1)	27 (16.1)	1.00 (Ref)	–
	Val/Ala+ Val/Val	28 (18.3)	26 (15.5)	1.710 (0.762 ~ 3.838)	0.225
Current	Ala/Ala	21 (13.7)	31 (18.5)	1.00 (Ref)	–
	Val/Ala+ Val/Val	43 (28.1)	38 (22.6)	1.670 (0.825 ~ 3.381)	0.161

when exposed to chemical carcinogens, and highly vulnerable to skin cancer following exposure to UV radiation [16,17], which suggested that XPC plays an important role to preventing carcinogenesis. The XPC gene polymorphisms may alter an individual's capacity of repairing damaged DNA and therefore may lead to genetic instability and carcinogenesis. Qiao et al. (2002a) and Qiao et al. (2002b) [18,19] showed that the XPC PAT+allele reduced repair the UV-DNA damage in the host cell reactivation assay. Vodicka et al. [20] observed that XPC 939Gln variant elevated chromatid aberrations and might influence base excision repair activity in an irradiation-specific DNA repair.

A number of molecular epidemiologic studies on the XPC genotypes and cancer susceptibility have been reported. Lee et al. [11] and Son et al. [14] showed that the XPC Val499Ala was not associated with lung cancer risk in Korean populations, in contrast to these Hu et al. [9] and our current study revealed that the XPC 499Val allele was associated with a significantly increased risk of lung cancer and NPC respectively in Chinese populations. Consistent with our results, Hirata et al. [21] showed that Lys939Gln may not be linked to susceptibility for renal cell carcinoma in a Japanese population, Hu et al. [9] and Son et al. [14] showed that Lys939Gln was not associated with the lung cancer development in a Chinese and Korean population respectively. However, Vogel et al. [22] showed that 939 Gln allele had significantly increased the risk of lung cancer in a Danish population. Sanyal et al. [7] suggested that the homozygote individuals for the 939Gln allele were at an almost 2-fold increased risk of bladder cancer in a Swedish population. In contrast to two previous studies [12,14] and the current study, Marin et al. [23] found that the PAT+/+ subjects were at significantly increased risk for lung cancer in a Spanish population, and Blankenburg et al. [13] demonstrated that PAT+ was associated with an increased risk of melanoma a German population.

DNA repair protein XPC is a major player in the NER pathway and essential for genomic integrity. It is plausible that variations in DNA repair genes may result in individuals with a low repair capacity, which may lead to individuals more sensitive to DNA damage and therefore more prone to cancer. However, the association of DNA repair gene XPC Val499Ala, Lys939Gln, PAT polymorphisms and cancer risk was not uniform, even conflicting in specific population and various case-control studies. Although it is hard to decipher the reasons for these discrepancies, but several possibilities should be considered. First, it may be due to the genetic trait differences, DNA repair gene polymorphisms were distinct in specific population, various ethnicity and geographic region. For example, a protective haplotype in one population may increase the cancer risk in another population due to other linked polymorphisms that exhibit a stronger effect on the susceptibility to cancer [17]. Furthermore, the presence of variants in metabolism and other critical DNA repair genes may alter the influence of variants in the XPC genes, and the presence of an allelic variant that induces subtle differences in protein activity may result in different cancer risks depending on the exposure or the metabolic pathways available in different tissues [24]. In addition, cancer is a multi-factorial disease, and the individuals' exposure to various environmental factors and genetic susceptibility may result in different DNA damage and influence the DNA repair protein activity, as Lunn et al. [25] suggested that the XPD Lys751Gln polymorphism Lys allele may have different effects in different types of DNA damage in the initiation of different cancers. In the end, the inadequate study design such as non-random sampling and a limited sample size should be also considered. The possible selection bias that might have been present in the hospital-based, case-control study is a relevant issue.

In conclusion, to our knowledge, this is the first study of the association of XPC Val499Ala, Lys939Gln, PAT polymorphisms, their haplotypes and NPC risk. Our results showed that the XPC codon 499Val allele and 499Val/939Lys/PAT−(TA−) haplotype were associated with a significantly increased risk of NPC, which suggested that the XPC gene polymorphisms may be involved in the development of NPC. However, the molecular mechanism by which the XPC gene polymorphisms are associated with NPC is unclear, so additional studies will be needed to explore further, whether XPC polymorphisms are an independent risk factor or an indirect marker of different genetic and environmental factors. Further studies on the XPC sequence variants and their biologic functions are also needed to characterize the molecular mechanisms by which XPC is involved in susceptibility to NPC in diverse ethnic populations.

Acknowledgements

This study was supported by Sichuan Key Science and Technologic Programs (No. 06Z09-005) and Chengdu Technologic Programs (No. 06GGYB349 SF-034).

References

[1] Chen JY, Chen CJ, Liu MY, Cho SM, Hsu MM, Lynn TC, et al. Antibody to Epstein-Barr virus-specific DNase as a

marker for field survey of patients with nasopharyngeal carcinoma in Taiwan. J Med Virol 1989;27:269–73.
[2] Tiwawech D, Srivatanakul P, Karaluk A, Ishida T. The p53 codon 72 polymorphism in Thai nasopharyngeal carcinoma. Cancer Lett 2003;198:69–75.
[3] Matutani C, Araki M, Sugawasa K, van der Spek PJ, Yamada A, Uchida A, et al. Identification and characterization of XPC binding domain of hHR23B. Mol Cell Biol 1997;17: 6915–23.
[4] Sugasawa K, Ng JMY, Masutani C, Iwai S, van der Spek PJ, Eker AP, et al. Xeroderma pigmentosum group C protein complex is the initiator of global genome nucleotide excision repair. Mol Cell 1998;2:223–32.
[5] Yokoi M, Masutani C, Maekawa T, Sugasawa K, Ohkuma Y, Hanaoka F. The xeroderma pigmentosum group C protein complex XPC-HR23B plays an important role in the recruitment of transcription factor IIH to damaged DNA. J Biol Chem 2000;275:9870–5.
[6] Charames GS, Bapat B. Genomic instability and cancer. Curr Mol Med 2003;3:589–96.
[7] Sanyal S, Festa F, Sakano S, Zhang Z, Steineck G, Norming U. Polymorphisms in DNA repair and metabolic genes in bladder cancer. Carcinogenesis 2004;25:729–34.
[8] Shen H, Sturgis EM, Khan SG, Qiao Y, Shahlavi T, Eicher SA, et al. An intronic poly (AT) polymorphism of the DNA repair gene XPC and risk of squamous cell carcinoma of the head and neck: A case-control study. Cancer Res 2001;61: 3321–5.
[9] Hu Z, Wang Y, Wang X, Liang G, Miao X, Xu Y, et al. DNA repair gene XPC genotypes/haplotypes and risk of lung cancer in a Chinese population. Int J Cancer 2005;115: 478–83.
[10] Shi YY, He L. SHEsis, a powerful software platform for analyses of linkage disequilibrium, haplotype construction, and genetic association at polymorphism loci. Cell Res 2005; 15:97–8.
[11] Lee GY, Jang JS, Lee SY, Jeon HS, Kim KM, Choi JE, et al. XPC polymorphisms and lung cancer risk. Int J Cancer 2005;115:807–13.
[12] Nelson HH, Christensen B, Karagas MR. The XPC poly-AT polymorphism in non-melanoma skin cancer. Cancer Lett 2005;222:205–9.
[13] Blankenburg S, Konig IR, Moessner R, Laspe P, Thoms KM, Krueger U, et al. Assessment of 3 xeroderma pigmentosum group C gene polymorphisms and risk of cutaneous melanoma: A case-control study. Carcinogenesis 2005;26: 1085–90.
[14] Son JW, Lee YS, Choi JE, Kam S, Jung TH, Kim IS, et al. No apparent association of XPC haplotype with lung cancer risk. Lung Cancer 2003;41:S112.
[15] Berneburg M, Lehmann AR. Xeroderma pigmentosum and related disorders: Defects in DNA repair and transcription. Adv Genet 2001;43:71–102.
[16] Cheo DL, Burns DK, Meira LB, Houle JF, Friedberg EC. Mutational inactivation of the xeroderma pigmentosum group C gene confers predisposition to 2 acetylaminofluorene-induced liver and lung cancer and to spontaneous testicular cancer in $Trp53^{-/-}$ mice. Cancer Res 1999;59: 771–5.
[17] Friedberg EC, Bond JP, Burns DK, Cheo DL, Greenblatt MS, Meira LB, et al. Defective nucleotide excision repair in Xpc mutant mice and its association with cancer predisposition. Mutat Res 2000;459:99–108.
[18] Qiao Y, Spitz MR, Shen H, Guo Z, Shete S, Hedayati M, et al. Modulation of repair of ultraviolet damage in the host-cell reactivation assay by polymorphic XPC and XPD/ERCC2 genotypes. Carcinogenesis 2002;23:295–9.
[19] Qiao Y, Spitz MR, Guo Z, Hadeyati M, Grossman L, Kraemer KH, et al. Rapid assessment of repair of ultraviolet DNA damage with a modified host-cell reactivation assay using a luciferase reporter gene and correlation with polymorphisms of DNA repair genes in normal human lymphocytes. Mutat Res 2002;509:165–74.
[20] Vodicka P, Kumar R, Stetina R, Sanyal S, Soucek P, Haufroid V, et al. Genetic polymorphisms in DNA repair genes and possible links with DNA repair rates, chromosomal aberrations and single-strand breaks in DNA. Carcinogenesis 2004;25:757–63.
[21] Hirata H, Hinoda Y, Matsuyama H, Tanaka Y, Okayama N, Suehiro Y, et al. Polymorphisms of DNA repair genes are associated with renal cell carcinoma. Biochem Biophys Res Commun 2006;342:1058–62.
[22] Vogel U, Overvad K, Wallin H, Tjonneland A, Nexo BA, Raaschou-Nielsen O. Combinations of polymorphisms in XPD, XPC and XPA in relation to risk of lung cancer. Cancer Lett 2005;222:67–74.
[23] Marin MS, Lopez-Cima MF, Garcia-Castro L, Pascual T, Marron MG, Tardon A. Poly (AT) Polymorphism in intron 11 of the XPC DNA repair gene enhances the risk of lung cancer. Cancer Epidemiol Biomarkers Prev 2004;13:1788–93.
[24] Yu HP, Wang XL, Sun X, Su YH, Wang YJ, Lu B, et al. Polymorphisms in the DNA repair gene XPD and susceptibility to esophageal squamous cell carcinoma. Cancer Genet Cytogen 2004;154:10–5.
[25] Lunn RM, Helzlsouer KJ, Parshad R, Umbach DM, Harris EL, Sanford KK. XPD polymorphisms: Effects on DNA repair proficiency. Carcinogenesis 2000;21:551–5.