Very low prevalence of XPD K751Q polymorphism and its association with XPD expression and outcomes of FOLFOX-4 treatment in Asian patients with colorectal carcinoma

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Xeroderma pigmentosum group D (XPD) participates in DNA unwinding during nucleotide excision repair, which may alter the efficacy of platinum-based chemotherapy. We analyzed the influence of codon 751 Lys→Gln polymorphism of *XPD* on its protein expression levels, clinico-pathological features, and outcome of 188 Chinese patients with metastatic colorectal carcinoma (CRC) that had been treated with first-line Oxaliplatin + Leucovorin + 5-Fluorouracil (FOLFOX-4) chemotherapy. The results showed that in comparison with Caucasian populations, a remarkably lower prevalence of Lys/Gln genotype was noted (16%, *n* = 30). No between-group difference in XPD protein expression of patients with or without this polymorphism was noted (56.5% *vs* 59.7%; *P* = 0.783). Patients with Gln751 allele have a significantly lower response to FOLFOX-4 treatment (36.7% *vs* 58.2%, *P* = 0.03), and shorter progression-free (7 *vs* 11 months; *P* < 0.01) and overall (14 *vs* 22 months; *P* < 0.01) survivals. The incidence of grade 3/4 oxaliplatin-neuropathies was very similar in both groups (13.3% *vs* 16.5%; *P* = 0.67). By adjusted analysis, this polymorphism was further identified as an independent prognostic factor (*P* = 0.03). These data suggest that Asian populations have a significantly lower prevalence of codon 751 Lys/Gln polymorphism in XPD, which could be a key determinant for good response to oxaliplatin-based treatment and favorable outcomes. (*Cancer Sci* 2009; 100: 1261–1266)

Oxaliplatin, a cytotoxic platinum compound, is one of the most important chemotherapeutic agents for treating metastatic colorectal cancer (CRC) patients.[1] By causing intrastrand cross-links in DNA, oxaliplatin results in structural DNA damage and apoptosis of tumor cells.[2] At least four pathways have been postulated for repairing DNA damage, among which the nucleotide excision repair (NER) pathway plays a major role in repairing platinum-DNA lesions, and counteracts against platinum effects in various tumor cells.[3] Overexpression and polymorphisms of genes involved in the NER pathway result in resistance to platinum-based chemotherapy in a variety of malignant diseases, including CRC.[4–6] In addition, single nucleotide polymorphism of genes involved in the NER pathway affects DNA repair capacity, and therefore influences the risk for the development of certain malignant diseases.[7,8]

Xeroderma pigmentosum group D (XPD), also known as the excision repair cross-complementing group 2 (ERCC2), possesses both single-strand DNA-dependant adenosine triphosphate enzyme (ATPase) and 5′-3′ DNA helicase activities and is thought to participate in DNA unwinding during NER and transcription.[9,10] XPD is an important component of the NER pathway and is capable of reversing ionizing radiation-induced damage and platinum-DNA damage.[11,12] One common single nucleotide polymorphism which occurs at codon 751 of *XPD* resulting in lysine to glutamine substitution (K751Q) has been proposed to predict responses as well as survival to platinum-based chemotherapy in CRC patients.[13] Interestingly, discrepancies existed in the influence of K751Q polymorphism of XPD on NER capacity.[14,15] It has been shown that this polymorphism may alter *XPD* mRNA secondary structure and reduce constitutive mRNA levels, indicating that this polymorphism potentially affects local folding as well as mRNA stability.[14] In lung cancer patients, the risk for suboptimal DNA repair capacity was higher for those with the Gln/Gln genotype.[16] However, possessing a Lys/Lys genotype was identified to increase the risk of suboptimal DNA repair to X-ray-induced chromatid aberrations in another study.[17] Whether this polymorphism may account for an altered susceptibility to oxaliplatin-based chemotherapy in CRC patients is of interest.

Ethnic difference in genetic polymorphisms significantly affects the response and toxicity to chemotherapeutic agents for treating CRC, including fluoropyrimidine regimens and irinotecan.[18–20] With regard to genes involved in the NER pathway, a remarkably lower percentage of C→T polymorphism of *ERCC1* codon 118 has been demonstrated in Asian populations and may account for an increased susceptibility to platinum-based chemotherapy.[6,21] It has been shown that Asian populations seem to have a lower prevalence of the XPD Gln751 allele, but the sample size is quite small.[22] In another study, the allele frequency of XPD Gln751 showed marginal racial differences only.[23] Whether the prevalence of Gln751 allele is indeed lower in Chinese populations deserves further studies.

Based on these earlier findings, we propose that codon 751 Lys→Gln polymorphism of XPD may account for altered susceptibility to oxaliplatin-based chemotherapy in CRC patients. To examine the ethnic difference of this polymorphism in Asian populations and its influence on XPD protein expression levels and outcome to Oxaliplatin + Leucovorin + 5-Fluorouracil (FOLFOX-4) treatment, a study has been conducted.

Materials and Methods

Patient characteristics. To understand the impact of XPD Lys751Gln polymorphism on its expression level and outcomes of FOLFOX-4 treatment, we examined 217 Chinese patients with unresectable metastatic CRC, who had received FOLFOX-4 as a first-line treatment from June 2003 to December 2007. Among them, 188 patients were enrolled and analyzed (patients'

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Table 1. Clinico-pathological features of metastatic colorectal cancer patients with or without *XPD* codon 751 Lys→Gln polymorphism (*n* = 188)

Characteristics	Lys/Lys (wild-type) (%)	Lys/Gln (%)	*P*-values
All patients	158[100]	30[100]	
Age (years)			
<50	56 (35.4)	12 (40.0)	0.63
≥50	102 (64.6)	18 (60.0)	
Gender			
Male	87 (55.1)	17 (56.7)	0.87
Female	71 (44.9)	13 (43.3)	
Performance status			
0	118 (74.7)	20 (66.7)	0.36
1, 2	40 (25.3)	10 (33.3)	
Primary tumor			
Colon	96 (60.8)	19 (63.3)	0.79
Rectum	62 (39.2)	11 (36.7)	
Histological differentiation			
Well/moderate	131 (82.9)	26 (86.7)	0.61
Poorly/unknown	27 (17.1)	4 (13.3)	
Invasive extent			
T1-2	43 (27.2)	6 (20.0)	0.41
T3-4	115 (72.8)	24 (80.0)	
Lymph node involvement			
N0	39 (24.7)	11 (36.7)	0.17
N1–3	119 (75.3)	19 (63.3)	
Serum CEA level (ng/mL)			
≤6	22 (13.9)	5 (16.7)	0.70
>6	136 (86.1)	25 (83.3)	
Grade 3/4 oxaliplatin-neuropathy			
Presence	26 (16.5)	4 (13.3)	0.67
Absence	132 (83.5)	26 (86.7)	
TSER 28-bp polymorphism			
2R/2R	1 (0.6)	0 (0)	0.76
2R/3R	51 (32.3)	9 (30.0)	
3R/3R	106 (67.1)	21 (70.0)	

CEA, carcinoembryonic antigen; TSER 28-bp polymorphism, germ-line polymorphisms of the number of 28-base pair tandemly repeated sequences in the 5′-enhancer region of the thymidylate synthase gene; XPD, xeroderma pigmentosum group D.

characteristics are shown in Table 1). The remainders were excluded. They either lacked measurable lesions ($n = 9$), or had not had primary tumor removed for determining accurate T and N stages ($n = 7$), or died before blood sampling ($n = 6$), or were unwilling to participate ($n = 4$), or were lost in follow-up ($n = 3$). The FOLFOX-4 regimen consisted of oxaliplatin (Sanofi-Aventis, Paris, France) (85 mg/m^2, 1-h infusion, day 1) and Leucovorin (LV) (200 mg/m^2, 2-h infusion, day 1 and 2), before bolus 5-Fluorouracil (5-FU) (400 mg/m^2, day 1 and 2) and infusional 5-FU (600 mg/m^2, 22-h infusion immediately after bolus 5-FU, days 1 and 2) were administered every 2 weeks. Patients with or without XPD codon 751 Lys→Gln polymorphism were followed up at a similar intensity with a median duration of 18 months.

The responses of treatment were evaluated on the basis of standard Response Evaluation Criteria In Solid Tumors (RECIST) criteria. Patients with complete response (CR), partial response (PR), or stable disease remained in the protocol until progressive disease or unacceptable toxicity was documented. Common toxicities were assessed at baseline, and after two, four, and six courses of treatment according to the National Cancer Institute Common Toxicity Criteria (NCI-CTC). Treatment was delayed until recovery if grade 3–4 toxicity occurred, and the doses of oxaliplatin and 5-FU were reduced by 20% in subsequent cycles. In the case of intolerable toxicity or failure on front-line FOLFOX-4, the treatment was discontinued, and irinotecan-based or fluoropyrimidine-only regimens were subsequently administered according to physicians' decision. During treatments, chest X-ray, ultrasonography of the abdomen, or computed tomography scan was conducted every 2 months. An institutional review board approved this study and informed consent was given by all patients before blood testing for genotyping.

Examination of XPD codon 751 Lys→Gln polymorphism. Genomic DNA was extracted from patients' leukocytes obtained via 0.5-mL whole blood using standard phenol-chloroform procedures subject to *XPD* codon 751 testing. The XPD K751Q polymorphism was examined by polymerase chain reaction–restriction fragment length polymorphism (PCR-RFLP) method as previously described.[17] 0.1-μg genomic DNA, forward primer 5′-CCT CTC CCT TTC CTC TGT TC-3′, and reverse primer 5′-CAG GTG AGG GGG ACA TCT-3′ were used for PCR amplification. After initial denaturation at 94°C for 4 min, the reaction was carried out at 94°C denaturation for 30 s, 60°C annealing for 30 s, and 72°C extension for 1 min for a total of 30 cycles. PCR products, after being digested by *Mbo*II restriction enzyme (New England Biolabs, Beverly, MA, USA) at 37°C for 2 h, were separated on 2% Nusieve ethidium bromide–stained agarose gels.

Examination of the number of a 28-bp tandemly repeated sequence in the 5′-enhancer region of the thymidylate synthase gene. Since 5-FU has been used in combination with oxaliplatin for treating these patients, and germ-line polymorphisms of the number of a 28-bp tandemly repeated sequence in the 5′-enhancer region of the thymidylate synthase gene (*TSER*) remarkably affect the response and survival of CRC patients who receive 5-FU,[18] the influences of this polymorphism on patients with or without XPD Lys751Gln polymorphism deserved further analysis. Genomic DNA was prepared from patients' leukocytes accordingly and a set of primers for amplification of the TSER was used according to a method previously described.[24] The sequences of the forward and reverse primers were 5′-GTG GCT CCT GCG TTT CCC CC-3′ and 5′-CCA AGC TTG GCT CCG AGC CGG CCA CAG GCA TGG CGC GG-3′, respectively. Amplification was performed for 30 cycles, including denaturation at 94°C for 1 min, annealing at 60°C for 1 min, and extension at 72°C for 2 min between the initial denaturation at 94°C for 2 min and a final extension at 72°C for 5 min. Finally, the amplified DNA fragments were analyzed by eletrophoresis on a 4% agarose gel to determine the number of a 28-bp tandemly repeated sequence over the TSER.

Immunohistochemical staining. To examine the influence of codon 751 Lys→Gln polymorphism of XPD on its protein expression, we obtained paraffin-embedded colorectal tumor tissues from 100 CRC patients, whose tumor tissues were available and who agreed to release their tumor tissues for examination. These tissues were subjected to immunohistochemical staining. Tumor tissue sections were stained with a mouse monoclonal anti-XPD antibody (ProteinTech Group, Chicago, IL, USA), using a streptavidin-biotin-immunoperoxidase kit (BioGenex, San Roman, CA, USA) according to the manufacturer's instructions. An experienced pathologist examined these slides microscopically, and both the intensity and distribution of the immunohistochemical staining signals were analyzed. Only nuclear immunoreactivity was considered positive for XPD. The staining intensity was graded on a scale of 0–3. The percentage of stained tumor cells (0–100%) was counted and a final semiquantitative score calculated by intensity multiplying by distribution ranging from 0 to 300. The median value therefore is used as the cut-off point for separating XPD-positive from -negative tumors.

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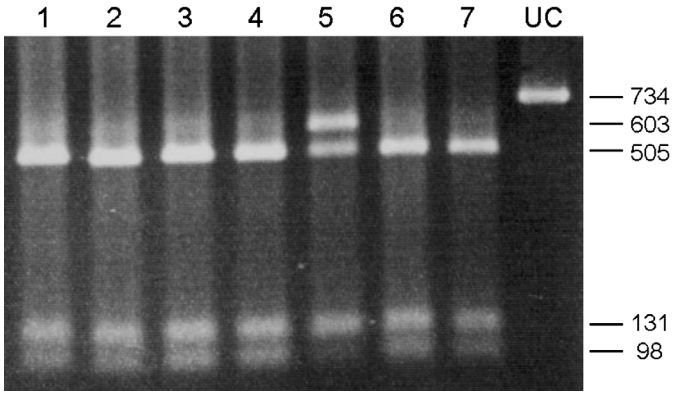


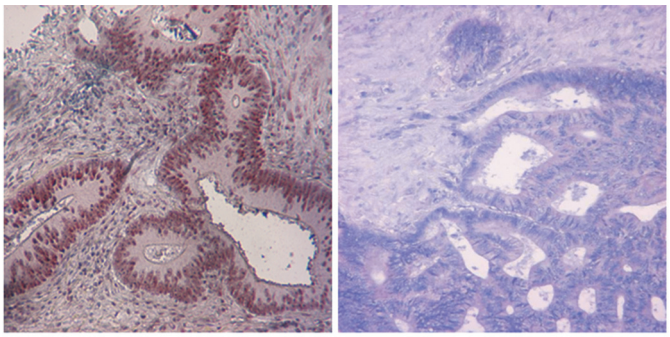
Fig. 1. Representative polymerase chain reaction–restriction fragment length polymorphism (PCR-RFLP) patterns of different xeroderma pigmentosum group D (*XPD*) codon 751 genotypes examined by patients' blood samples. Genomic DNA obtained from patients' white blood count (WBC) was subjected to PCR amplification using 5′-CCT CTC CCT TTC CTC TGT TC-3′ and 5′-CAG GTG AGG GGG ACA TCT-3′ as forward and reverse primers, respectively. PCR products after being digested by *Mbo*II were separated by agarose gels electrophoresis. Lanes 1, 2, 3, 4, 6, and 7 represent Lys/Lys, while lane 5 represents Lys/Gln. Lane UC indicates that PCR product has not been digested.

Statistical analysis and survival curve plotting. All statistical analyses were performed using the SPSS software system (version 14.0; SPSS, Chicago, IL, USA). The progression-free and overall survival curves were also plotted using the Kaplan–Meier product limit method, and the statistical differences in survival among subgroups were compared by log-rank test. The correlations between XPD codon 751 Lys→Gln statuses and XPD protein expression, clinico-pathological characteristics, and response to FOLFOX-4 treatment were analyzed separately. The statistical differences of these correlations have been determined by χ^2-test. To assess the independent prognostic values of this polymorphism, we used Cox's proportional hazards regression analysis (multivariate) which included XPD codon 751 status and other clinico-pathological parameters. Two-sided *P*-values less than 0.05 were considered statistically significant.

Results

Significantly lower prevalence of XPD K751Q polymorphism is identified in Asian populations. Representative PCR-RFLP patterns of different *XPD* codon 751 genotypes examined by patients' blood samples are shown in Fig. 1. We found that the incidences of codon 751 Lys/Lys, Lys/Gln, and Gln/Gln genotypes are 84% ($n = 158$), 16% ($n = 30$), and 0% ($n = 0$), respectively, in CRC patients. To our interest, in comparison with Caucasian populations reported by previous studies,[22] a significantly lower percentage of Lys/Gln (16%), and Gln/Gln (0%) genotypes in our patients was clearly demonstrated, indicating the existence of ethnic difference in this polymorphism. In addition, there are no between-group differences in age, gender, performance status, histological differentiation, invasive extent, lymph node involvement, serum carcinoembryonic antigen (CEA) level, or number of a 28-bp tandemly repeated sequence in TSER of patients with or without this polymorphism (Table 1).

No between-group difference in XPD protein expression in tumor tissues of patients with or without XPD K751Q polymorphism. Since it has been shown that codon 751 Lys→Gln polymorphism was predicted to alter *XPD* mRNA secondary structure and thereby reduce constitutive mRNA levels, indicating that this polymorphism potentially affects mRNA stability,[14] a decreased XPD protein expression was proposed in patients with this polymorphism. As shown in Figure 1, the intensive nuclear signals stood for positive staining for XPD. However, by analyzing 100 CRC patients' tumor tissues, we found that there is no between-group difference in XPD protein expression levels of patients with or without this polymorphism as the percentage of positive XPD staining in patients with Lys/Lys or Lys/Gln genotypes is 59.7% and 56.5%, respectively ($P = 0.783$; Fig. 2).



	XPD (+)	XPD (–)	*P*
XPD-751 Lys/Lys	46	31	0.783
XPD-751 Lys/Gln	13	10	

Fig. 2. Representative immunohistochemical staining patterns of xeroderma pigmentosum group D (XPD) in patients' tumor tissues with original magnifications of ×400. Tumor tissues from 100 colorectal carcinoma patients have been stained with a mouse monoclonal anti-XPD antibody, using a streptavidin-biotin-immunoperoxidase kit according to the manufacturer's instructions. Positive XPD staining is defined as intense nuclear signals. The statistical difference of the correlation between *XPD* codon 751 statuses and XPD nuclear staining patterns was determined by χ^2-test. The *P*-value defines the difference in XPD expression between patients with or without Lys→Gln polymorphism.

Table 2. The response to FOLFOX-4 treatment in metastatic colorectal cancer patients with different *XPD* codon 751 Lys→Gln statuses ($n = 188$)

Response	Lys/Lys (wild-type) (%)	Lys/Gln (%)	*P*-values*
All patients enrolled	158 (100)	30 (100)	
OR (CR + PR)	92 (58.2)	11 (36.7)	0.03
CR	4 (2.5)	1 (3.3)	
PR	88 (55.7)	10 (33.3)	
SD	55 (34.8)	16 (53.3)	
PD	11 (7.0)	3 (10.0)	

**P* represents the comparison of overall response rate between patients with different *XPD* codon 751 polymorphisms.
CR, complete remission; FOLFOX-4, Oxaliplatin + Leucovorint + 5-Fluorouracil; OR, overall response; PD, progressive disease; PR, partial remission; SD, stable disease; XPD, xeroderma pigmentosum group D.

XPD K751Q polymorphism leads to poor response and unfavorable prognosis of patients treated with FOLFOX-4, without affecting the incidence of oxaliplatin-induced neuropathy. In comparison with Lys/Lys (wild-type), patients with codon 751 Lys/Gln genotype in XPD have a significantly lower response to FOLFOX-4 treatment (36.7% *vs* 58.2%, $P = 0.03$) (Table 2). Accordingly, a shorter progression-free (7 months *vs* 11 months; $P < 0.01$) as well as overall (14 months *vs* 22 months; $P < 0.01$) survival is observed in patients with Lys/Gln genotype (Fig. 3), which is consistent with previous findings.[13] By adjusted analysis, this polymorphism is further identified as an independent prognostic factor ($P = 0.03$; Table 3).

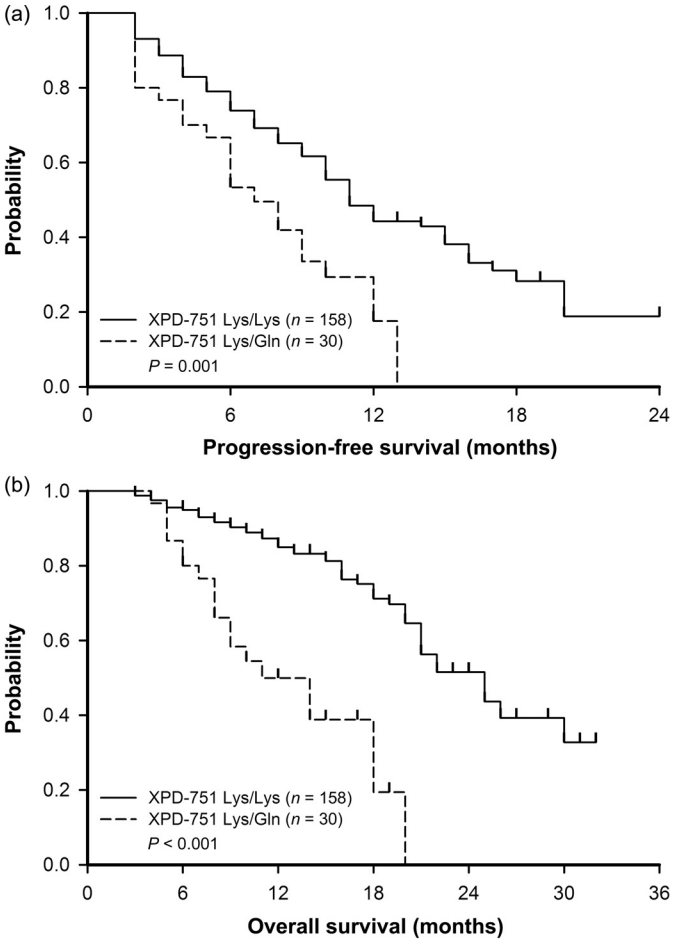


Fig. 3. Patients with codon 751 Lys→Gln polymorphism of the xeroderma pigmentosum group D (*XPD*) gene have a shorter progression-free as well as overall survival after being treated with Oxaliplatin + Leucovorin + 5-Fluorouracil (FOLFOX-4). (a) Progression-free survival curves of 188 patients with *XPD*-118 Lys/Lys or Lys/Gln genotypes have been plotted by Kaplan–Meier method ($P < 0.01$; log-rank test). (b) A similar method has been used to plot overall survival curves of patients with different *XPD* codon 751 genotypes ($P < 0.01$).

Table 3. Analysis of factors that may affect the survival of patients with metastatic colorectal carcinoma receiving FOLFOX-4 ($n = 188$)

Characteristics	*P*-values (univariate)	*P*-values (multivariate)
Age (years)		
<50 *versus* ≥50	0.42	0.67
Gender		
Male *versus* female	0.91	0.74
Performance status		
0 *versus* 1, 2	0.22	0.19
Primary tumor		
Colon *versus* rectum	0.65	0.72
Histological differentiation		
Well–moderate *versus* poorly	0.70	0.53
Invasive extent†		
T1-2 *versus* T3-4	0.28	0.11
Nodal status†		
Negative *versus* positive	0.12	0.38
Metastasis at diagnosis†		
No *versus* Yes	0.02	0.04
Serum CEA level (ng/mL)		
≤6 *versus* >6	0.56	0.28
TSER 28-bp polymorphism		
2R/2R *versus* 2R/3R or 3R/3R	0.08	0.11
XPD codon 751 polymorphism		
Lys/Lys (wild-type) *versus* Lys/Gln	0.02	0.03

†According to international TNM staging system for colorectal carcinoma.
CEA, carcinoembryonic antigen; FOLFOX-4, Oxaliplatin + Leucovorin + 5-Fluorouracil; TSER 28-bp polymorphism, germ-line polymorphisms of the number of 28-base pair tandemly repeated sequences in the 5′-enhancer region of the thymidylate synthase gene; XPD, xeroderma pigmentosum group D.

Later on, we supposed that patients with this polymorphism, by enhanced excision repair of platinum-DNA lesions, might account for a lower incidence of severe oxaliplatin-related peripheral sensory neuropathy. However, as shown in Table 1, the incidence of grade 3 or 4 neuropathies after six courses of FOLFOX-4 treatment is very similar in both groups of patients (13.3% *vs* 16.5%; $P = 0.67$).

Discussion

In 2001, Park *et al*. first reported that codon 751 Lys→Gln polymorphism of XPD correlated with clinical response and survival to oxaliplatin-based chemotherapy in patients with advanced colorectal cancer.[13] Of the 71 Caucasian patients enrolled in their study, the percentage of Lys/Lys, Lys/Gln, and Gln/Gln genotypes were 31%, 55%, and 14%, respectively. Moreover, a marked decrease in the response, progression-free survival, and overall survival were found in the patients with Gln751 allele, while the Gln/Gln group was associated with the poorest prognosis.[13] Concordantly, in another study ($n = 107$) similar percentages of Lys/Lys, Lys/Gln, and Gln/Gln genotypes were demonstrated in Caucasian populations.[25] In the current study, a larger sample size ($n = 188$) of Chinese patients were enrolled and survival benefit was clearly demonstrated in patients with Lys/Lys genotypes (Fig. 3), which was in good agreement with previous studies. However, the percentage of patients with Gln751 allele is quite low (16%), and no patient showed a homozygous Gln/Gln genotype.

In the current study, we noted that XPD K751Q polymorphism, although showing no correlation to protein expression level, was a marker of response to oxaliplatin-based chemotherapy. The mechanisms underlying discordant mRNA expression and corresponding protein levels have been discussed in previous studies,[26,27] and protein half-life as well as post-translational mechanisms were postulated to account for this phenomenon. Wolfe *et al*. demonstrated a 1.5-fold decrease in XPD mRNA copy number in patients with the K751Q polymorphism, accompanied by alterations in protein folding properties.[14] Lunn *et al*. further demonstrated that in X-ray-irradiated lymphocytes, a suboptimal DNA repair capacity was observed in the Lys/Lys genotype.[17] Based on these prior studies, we suggested that the changes in XPD protein folding properties, rather than protein expression levels, may account for a different response to platinum-based chemotherapy. From clinical viewpoint, a clear association between this polymorphism and varied response to oxaliplatin was demonstrated in the current and previous studies,[13,25] indicated that this polymorphism might have an influence on DNA repair capacity.

With the exception of FOLFOX-4, XPD K751Q polymorphism has similar effects on other types of chemotherapy. In non-small cell lung cancer patients treated with cisplatin-containing regimens, those with the Lys/Lys genotype have the best survival after chemotherapy, and those with the Gln/Gln genotype have the worst survival.[28] Concordantly, in acute myeloid leukemia

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patients treated with anthracycline-based chemotherapies, those with the Lys/Lys genotype were identified as having better response rates and favorable disease-free as well as overall survival rates.[29] However, in gastric cancer patients treated with 5-FU and LV as the agents for adjuvant concurrent chemoradiotherapy (CCRT), the Lys/Lys genotype was identified as a predictor for unfavorable outcomes.[30] Whether this is due to the CCRT not containing platinum drugs, or simply due to different tumor types, deserves further studies. With regards to irinotecan-based regimens, it has been shown that XPD K751Q polymorphism has no influence on its efficacy for treating metastatic CRC patients.[25]

Ethnic difference has a profound influence on the response as well as survival to chemotherapy in certain malignant diseases. For example, the prevalence of homozygous triple-repeat polymorphism in the TSER was twice as common in Chinese as in Caucasian subjects, which may account for an impaired response to fluoropyrimidine regimens.[18] The UGT1A1*28 polymorphism is rare in Asian populations,[19] but the UGT1A1*6 polymorphism is very common in Asian populations,[20] leading to altered risk of developing severe neutropenia after being treated with irinotecan. In addition, due to a significantly higher incidence of epidermal growth factor receptor mutations, the gefitinib becomes very effective in Asian patients with non-small cell lung cancer.[31] It has been shown that Asian populations seem to have a lower prevalence of XPD Gln751 allele; however, the sample size is quite small ($n = 11$).[22] In the current study, a significantly larger sample size ($n = 188$) of Asian patients were analyzed, and a remarkably lower percentage of Lys/Gln (16%) and Gln/Gln (0%) genotypes was found. Interestingly, ethnic difference in codon 118 C→T polymorphism of *ERCC1* has also been observed in our previous study, which indicated that Asian populations have a significantly higher prevalence of C/C genotype in codon 118.[6] These results implicated that Asian populations might have a suboptimal NER system; however, no data have shown a better response from Asian people to FOLFOX compared to Caucasian populations. Whether such ethnic difference in polymorphisms may account for better response and outcomes in Asian patients after being treated with platinum-based chemotherapy deserves further studies.

Neurotoxicity is the principle and dose-limiting toxicity of oxaliplatin and the incidence of oxaliplatin-induced severe neurotoxicity has varied from 12% to 18% in different clinical trials.[32–34] The feasibility of using genomic polymorphism in predicting the development of severe neuropathy in patients treated with oxaliplatin is of extreme interest. It has been shown that the 105Val allele variant of the glutathione S-transferase P1 gene confers a decreased risk of developing severe oxaliplatin-related cumulative neuropathy.[35] But codon 118 C→T polymorphism of *ERCC1*, although leading to a higher ERCC1 expression and consequential excision repair, was not associated with a lower incidence of severe oxaliplatin-related neuropathy.[6] The influence of XPD codon 751 Lys→Gln polymorphism on the incidence of severe oxaliplatin-related neuropathy remains unclear. As the Lys/Lys751 genotype of XPD led to a suboptimal capacity of nuclear excision repair,[17] we supposed that Lys→Gln polymorphism would also be associated with a lower incidence of severe neuropathy after oxaliplatin treatment. However, the negative result in the present study (Table 1) might indicate different XPD expression and oxaliplatin metabolism between peripheral nerve and tumor tissues. Another explanation is that oxaliplatin neurotoxicity is mediated by a different mechanism to that of the platinum-DNA lesions. For example, an oxaliplatin metabolite, such as oxalate, may alter the properties of voltage-gated sodium channels or slow down the clearance of platinum compounds from the peripheral nervous system,[36] which warrants further studies.

In summary, we found that Asian populations have a significantly lower prevalence (16%) of the Lys/Gln genotype in codon 751 of *XPD*. This polymorphism has no influence on XPD protein expression levels. However, this polymorphism might be a key determinant for decreased response to FOLFOX-4 treatment and unfavorable outcomes for patients with metastatic CRC.

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