RESEARCH ARTICLE

Associations of *ABCB1* and *XPC* Genetic Polymorphisms with Susceptibility to Colorectal Cancer and Therapeutic Prognosis in a Chinese Population

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Abstract

Associations between *ABCB1* and *XPC* genetic polymorphisms and risk of developing colorectal cancer (CRC) as well as clinical outcomes in CRCs with chemotherapy were investigated. A case-control study was performed on the *ABCB1* C3435T, G2677T/A and *XPC* Lys939Gln polymorphisms in 428 CRC cases and 450 hospital-based, age and sex frequency-matched controls using polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) assays. We observed that the *ABCB1* 3435CT or CC+CT variants were significantly linked with increasing risk of developing CRC (adjusted OR (95% CI): 1.814 (1.237-2.660), *P*=0.0022; adjusted OR (95% CI): 1.605 (1.117-2.306), *P*=0.0102, respectively). Moreover, the distribution frequency of *XPC* AC genotype or AC+CC genotypes also showed a tendency towards increasing the suscepbility for CRC (*P*=0.0759 and *P*=0.0903, respectively). Kaplan-Meier curves showed that the *ABCB1* C3435T variant was associated with a tendency toward longer progression-free survival (PFS) (n=343, Log-rank test: *P*=0.063), and the G2677T/A variant genotypes (GT+TT+GA+AA) with a tendency for longer OS in postoperative oxaliplatin-based patients (n=343, Log-rank test: *P*=0.082). However, no correlation of the *XPC* Lys939Gln polymorphism was found with PFS and OS in patients with postoperative oxaliplatin-based chemotherapy (n=343). Our study indicated that *ABCB1* polymorphisms might be candidate pharmacogenomic factors for the prediction of CRC susceptibility, but not for prognosis with oxaliplatin chemosensitivity in CRC patients.

Keywords: *ABCB1 - XPC* - genetic polymorphisms - colorectal cancer - susceptibility - prognosis

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Introduction

Colorectal cancer (CRC) is the third most common malignancies in the world. The incidence or mortality of CRC has been rapidly increasing due to the changing lifestyles, environmental exposure, and inherited genetic background (Pourhoseingholi, 2012). Aside from the traditional risk factors, a number of studies have provided evidence those germline polymorphisms in genes encoding xenobiotics and drug transporters or DNA repair pathway is considered as a potential factor that may influence the risk of developing CRC and its clinical outcome associated with the carcinogenesis(Gervasini et al., 2006; Andersen et al., 2009; Engin et al., 2010;Wu et al., 2011; Kang et al., 2013).

ATP-binding cassette (ABC) transporters, which mediate efflux of a wide variety of endogenous substrates, xenobiotics, and chemotherapeutic agents, are known to mediate multidrug resistance in many tumors (Gottesman et al., 2002; Leonessa and Clarke, 2003; Ferguson et al., 2005).

P-glycoprotein (P-gp), encoded by the ATP-binding cassette B1 (*ABCB1*) gene, is an efflux transporter located on the luminal side of intestinal epithelial cells, which protects the gut from endogenous and exogenous toxins. The most frequent two variant alleles of *ABCB1* gene (C3435T and G2677T/A) have been shown to be associated with altered P-gp (Kim et al., 2001; Samanian et al., 2011). Kim et al. (2011) reported that C3435T TT genotype was associated with lowered intestinal P-glycoprotein expression. Meanwhile, Samanian et al. observed that the GG2677 genotype was correlated with highest while the AT 2677 genotype was associated with the lowest levels of P-gp expression in Iranian CRC patients. Furthermore, recent studies also demonstrated that *ABCB1* polymorphisms contribute to the susceptibility of CRC in different populations, but these results were inconsistence. Khedri et al. found that the *ABCB1* C3435T T allele and the TT genotype were significantly increased in patients with CRC compared with controls in an Iranian population. However, Andersen et al. reported that carriers of the variant allele of MDR1 C3435T had a lower risk of

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CRC than homozygous C allele carriers (Andersen et al., 2009). Moreover, Bae et al found no association of the *ABCB1* C3435T polymorphism with CRCs in Koreans (Bae et al., 2006). In addition, the G2677T polymorphism was reported to be significantly associated with CRCs with high microsatellite instability (Samanian et al., 2011). The association of *ABCB1* gene polymorphisms with the development and prognosis of CRCs has not been explored in a Chinese population yet.

The nucleotide excision repair (NER) pathway is the primary mechanism for removal of bulky adducts from DNA, and thus NER pathway plays an important role in the cellular defence against a large variety of structural unrelated DNA lesions, including bulky adducts, cross links, oxidative DNA damage, alkylating damage and thymidine dimers (Kusumoto et al., 2001; Sugasawa et al., 2002). If these DNA lesions are left unrepaired, they may contribute to mutagenesis and oncogenesis. The *XPC* gene is located at chromosome 3p25, is one of the eight core genes in the NER pathway and plays an important role in the early steps of global genome NER, especially in damage recognition, open complex formation and reparation (Janicijevic et al., 2003; Nishi et al., 2005). Previously studies have shown that polymorphisms of the NER pathway genes may alter the DNA repair capacity and thus could play an important role in carcinogenesis (Friedberg, 2001). Only few studies have investigated the association of Lys 939Gln polymorphism of *XPC* with CRC risk, and the findings were inconclusive (Hansen et al., 2007; Engin et al., 2010; Wu et al., 2011; Liu et al., 2012). Wu et al. found that the *XPC* Lys939Gln CC genotype was associated with a significantly increased risk of CRC compared with the AA genotype (Wu et al., 2011). Similarly, Liu et al. observed that individuals with at least one copy of the *XPC* Lys939Gln (AC or CC genotype) had an increased risk for CRC (Liu et al., 2012). However, in Denmark population, there are no significant association oberved between Lys939Gln and CRC risk, whereas they found a significant interaction between Lys939Gln and consumption of red meat, with a 3.7-fold increase in CRC risk per 100 g red meat intake per day among carriers of the homozygous variant, but virtually no effect of red meat intake among carriers of the wild type allele (Hansen et al., 2007). Similary, Engin et al. also found the *XPC* Lys939Gln was not associate with the risk of CRC, despite the increased oxidative stress in cancer patients (Engin et al., 2010).

Against this background, we analyzed the common genetic polymorphisms in the genes for the drug transporter MDR1 and in the NER pathway *XPC*, and attempted to elucidate the association between these polymorphisms and CRC susceptibility and clinical outcomes after oxaliplatin-based chemotherapy.

Materials and Methods

Subjects

This study included 480 patients with CRC who were admitted to the Oncological surgery of Xinxiang Central Hospital between 2008 and 2012. Approximately 89% of contacted patients consented to enrollment in the study. Finally, 428 patients were included in the study. The principal clinical characteristics were obtained from the interviewer-administered health risk questionnaires and medical records. Tumor differentiation or pathological grade of these CRC patients was performed according to the World Health Organization criteria and DUKE's criteria, respectively. The patients received several chemotherapy regimens, including oxaliplatin-based chemotherapy (Folfox regimen: oxaliplatin, leucovorin plus 5-FU; Xelox regimen: oxaliplatin plus capecitabine), LV5-FU2 (leucovorin plus 5-FU), or FU alone (fluorouracil).

We also included 450 unrelated ages- and sex- matched healthy controls. The population had no known medical illness or hereditary disorders, and was not taking any medications. Before its commencement, this study was approved by the Research Ethics Committee of Xinxiang Central Hospital, and informed consent was obtained from each participant.

Genotyping Assay

Genomic DNA was isolated from a leukocyte cell pellet of each blood sample, using the TIANGEN DNA Blood Mini Kit (TIANGEN BIOTECH (Beijing) CO., LTD, Beijing, China) according to the manufacturer's instructions. The *ABCB1* and *XPC* genetic polymorphisms were genotyped by PCR–RFLP assay. PCR was performed using 100 ng of genomic DNA, 300 nM of each primer, 200 nM dNTPs, and 0.5 U Taq polymerase in PCR buffer (TaKaRa Biotechnology (Dalian) Co., Ltd, Dalian, China) in a total volume of 25 μl. For *ABCB1* C3435T, the 244-base pair (bp) PCR products were digested with Mbo I (Promega Corporation, U.S.A.) at 37 oC overnight. The T allele was uncut, and the C allele was cut into 175-bp and 69-bp bands. For *ABCB1* G2677T, the 224-bp PCR products were digested with Ban I (Promega Corporation, U.S.A.) at 50 oC for 3 hours. The T allele was uncut, and the G allele was cut into 198-bp and 26-bp bands. For *ABCB1* G2677A, the 220-bp PCR products were digested with Bsr I (Promega Corporation, U.S.A.) at 37 °C overnight. The G allele was uncut, and the A allele

Table 1. Frequency Distribution of ABCB1and XPC Genotypes and Their Associations with CRC Risk

Genotypes	Cases No. (%)	Controls No. (%)	Adjusted OR (95% CI)[a]	P^b
All patients	428(100.0)	450(100.0)		
ABCB1 C3435T				
TT	57(13.32)	89(19.78)	1.00[Ref]	
CT	230(53.74)	198(44.00)	1.814(1.237-2.660)	0.0022
CC	141(32.94)	163(36.22)	1.351(0.904-2.018)	0.1419
CC+CT	371(86.68)	361(80.22)	1.605(1.117-2.306)	0.0102
ABCB1 G2677T/A				
GG	49(11.45)	40(8.89)	1.00[Ref]	
GT/GA	211(49.30)	223(49.55)	1.295(0.819-2.047)	0.2684
TT/AA	190(44.39)	165(36.67)	1.064(0.667-1.697)	0.7951
GT+GA+TT+AA	400(93.46)	388(86.22)	1.185(0.763-1.841)	0.4489
XPC Lys939Gln				
AA	174(40.65)	142(31.55)	1.00[Ref]	
AC	212(49.53)	225(50.00)	1.300(0.973-1.739)	0.0759
CC	64(14.95)	61(13.55)	1.168(0.771-1.768)	0.4632
AC+CC	276(64.49)	286(63.55)	1.270(0.963-1.674)	0.0903

OR, indicates odds ratio; CI, confidence interval; ABCB1, C3435T, Ile1145Ile; G2677T/A, Ala893Ser/Thr; XPC Lys939Gln, Nucleotide A to C; Ref, reference category; The significance levels are $P < 0.05$ for all the bold values; [a]Adjusted OR and 95% CI values were calculated by unconditional logistic regression adjusted for age, sex,smoking status; [b]P values were calculated from 2-sided chi-square tests for either genotype distribution or allele frequency

Table 2. Association Between ABCB1and XPC Polymorphisms and Clinicopathological Features in CRC Patients

Characteristics	ABCB1 C3435T			ABCB1 G2677T/A			XPC Lys939Gln		
	TT No.(%)	CC+CT No.(%)	*P*	GG No.(%)	GT+TT+GA+AA No.(%)	P	AA No.(%)	AC+CC No.(%)	*P*
Gender			0.146			0.025			0.051
Men	40(15.2)	223(84.8)		18(6.8)	245(93.2)		78(29.7)	185(70.3)	
Women	17(10.3)	148(89.7)		22(13.3)	143(86.7)		64(38.8)	101(61.2)	
Age			0.013			0.604			0.305
≤60	19(9.1)	189(90.9)		21(10.1)	187(89.9)		74(35.6)	134(64.4)	
>60	38(17.3)	182(82.7)		19(8.6)	201(91.4)		68(30.9)	152(69.1)	
First-degree family history of CRC				0.139			0.493		0.408
No	47(12.4)	331(87.6)		34(9.0)	344(91.0)		128(33.9)	250(66.1)	
Yes	10(20.0)	40(80.0)		6(12.0)	44(88.0)		14(28.0)	36(72.0)	
Smoking			0.822			0.76			0.974
Ever	46(13.1)	304(86.9)		32(9.1)	318(90.9)		116(33.1)	234(66.9)	
Never	11(14.1)	67(85.9)		8(10.3)	70(89.7)		26(33.3)	52(66.7)	
Prime cancer			0.872			0.655			0.633
rectum	27(13.0)	180(87.0)		18(8.7)	189(91.3)		71(34.3)	136(65.7)	
colon	30(13.6)	191(86.4)		22(10.0)	199(90.0)		71(32.1)	150(67.9)	
Tumor size			0.551			0.118			0.799
<4cm	18(14.88)	103(85.12)		12(9.92)	109(90.08)		47(38.84)	74(61.16)	
≥4cm	39(12.70)	268(87.30)		28(9.12)	279(90.88)		95(30.94)	212(69.06)	
Tumor differentiation			0.547			0.664			0.644
Grade 1	5(16.7)	25(83.3)		2(6.7)	28(93.3)		12(40.0)	18(60.0)	
Grade 2	45(12.5)	314(87.5)		33(9.2)	326(90.8)		116(32.3)	243(67.7)	
Grade 3	7(17.9)	32(82.1)		5(12.8)	34(87.2)		14(35.9)	25(64.1)	
Pathological grade			0.692			0.256			0.468
Dukes A	16(14.68)	93(85.32)		8(7.34)	101(92.66)		40(36.70)	69(63.30)	
Dukes B	20(11.63)	152(88.37)		17(9.88)	155(90.12)		50(29.07)	122(70.93)	
DukesC	19(15.32)	105(84.68)		15(12.10)	109(87.90)		45(36.29)	79(63.71)	
DukesD	2(8.70)	21(91.30)		0(0.00)	23(100.00)		7(30.43)	16(69.57)	
Lymph node metastases			0.367			0.191			0.634
No	24(11.8)	180(88.2)		23(11.3)	181(88.7)		70(34.3)	134(65.7)	
Yes	33(14.7)	191(85.3)		17(7.6)	207(92.4)		72(32.1)	152(67.9)	
Relapse			0.439			0.913			0.785
No	51(12.9)	343(87.1)		37(9.4)	357(90.6)		130(33.0)	264(67.0)	
Yes	6(17.6)	28(82.4)		3(8.8)	31(91.2)		12(35.3)	22(64.7)	

[a]*P* was obtained from two-sided chi-square test

was cut into 206-bp and 14-bp bands. PCR products of *XPC* Lys939Gln were digested with PvuII overnight at 37 °C. The variant C allele had a PvuII restriction site, 2 bands (150 and 131bp) were generated, while the wild A allele had a single band with a size of 281bp. Samples were coded for case-control status, and at least 10% of the samples were randomly selected and subjected to repeat analysis as quality control for verification of genotyping procedures. Two researchers independently performed RFLP and reviewed all genotyping results.

Statistical analysis

SPSS software package version 16.0 (SPSS Inc, Chicago, IL, U.S.A.) was used to perform statistical analyses. All statistical significance was set at $P < 0.05$ and all tests were 2-sided. The chi-square (Pearson χ^2 test) or Fisher exact test was used to determine the differences in distributions of demographic, epidemiologic, and clinical variables between groups. The population genetic analysis program SNPAlyze 2.2 (Dynacom Co. Ltd., Yokohama, Japan) based on the expectation-maximization was used for linkage disequilibrium analysis, haplotype inference, and Hardy-Weinberg equilibrium (HWE) test. The associations between genotypes and CRC risk were assessed using Odd ratios (ORs) and 95% confidence intervals (CIs) from both univariate and multivariate logistic regression analyses with adjustment for age and smoking status. The progression-free survival (PFS) was calculated as the time between the first day of treatment and an occurrence of relapse, death, or last known follow-up. The overall survival (OS) was calculated as the time between the first day of treatment and death, or last known follow-up. Univariate or multivariate Cox proportional hazards regression models were performed to obtain the adjusted hazard ratio (HR) and 95% CI for potential prognostic factors for the survival in CRC patients. The Kaplan–Meier method and the log-rank test were used to analyze the associations of the survival time with demographic characteristics, clinical features, and polymorphisms.

Results

The 428 patients enrolled in this study which included 263 (61.4%) men and 165 (38.6%) women. The mean age at diagnosis (SD) was 58.1(12.2), and at the range of 25~80 years old. Among 428 patients, most of the patients were in grade 2 (G2, moderate, 83.9%), 39 patients were in grade 3 (G3, poor, 9.1%),and only 30 patients were in grad 1(G1, Well, 7%) according to tumor differentiation

Table 3. Cox Regression Analysis of Potential Factors for Progression-free Survival and Overall Survival in Colorectal Carcinoma Patients with Oxaliplatin-Based Chemotherapy

Variables	Progression-free Survival				Overall survival			
	Univariate		Multivariate		Univariate		Multivariate	
	HR(95%CI)[a]	P^a	HR(95%CI)[b]	P^b	HR(95%CI)[a]	P^a	HR(95%CI)[b]	P^b
Gender		0.278				0.618		
Men	1				1			
Women	1.177(0.877-1.580)		-	-	1.191(0.600-2.367)		-	-
Age		0.142				0.298		
≤58	1				1			
>58	1.236(0.931-1.641)		-	-	1.440(0.725-2.861)		-	-
First-degree family history of CRC			0.106			0.078		0.426
No	1				1		1	
Yes	1.416(0.928-2.161)		-	-	2.227(0.914-5.425)		1.469(0.571-3.780)	
Smoking		0.762				0.01		0.031
Never[a]	1				1		1	
Ever	1.054(0.750-1.481)		-	-	2.427(1.233-4.776)		2.192(1.074-4.477)	
Prime cancer		<0.001		0.027		0.153		
Rectum	1		1		1			
Colon	2.532(1.887-3.398)		1.433(1.041-1.972)		0.596(0.293-1.231)		-	-
Tumor size		<0.001		0.047		0.445		
≤ 4.0 cm	1		1		1			
> 4.0 cm	1.639(1.367-1.966)		1.262 (1.004-1.587)		1.171(0.781-1.754)		-	-
Tumor differentiation		0.11				0.175		
G1	1				1			
G2 or G3	1.287(0.944-1.755)		-	-	1.650(0.800-3.405)		-	-
Pathological grade		0		<0.001		0.022		0.038
Dukes A or Dukes B	1		1		1		1	
Dukes C or Dukes D	2.200(1.884-2.569)		2.035(1.703-2.431)		1.464(1.057-2.028)		1.407(1.019-1.944)	
Lymph node metastases		0		0.073		0.786		
non-metastases	1		1		1			
metastases	3.656(2.599-5.142)		1.501(0.963-2.340)		1.095(0.569-2.109)		-	-
ABCB1 C3435T		0.607						
TT	1		1		1			
CT	0.571(0.396-0.825)	0.03	0.508(0.350-0.738)	<0.001	1.116(0.348-3.581)	0.853	-	-
CC	0.889(0.689-1.149)	0.369			1.210(0.570-2.568)	0.62	-	-
CC+ CT	0.847(0.598-1.199)	0.349	-	-	0.765(0.220-2.667)	0.675	-	-
ABCB1 G2677T/A							-	-
GG	1				1			
GT+GA	0.978(0.548-1.744)	0.939	-	-	3.216(0.712-14.523)	0.129	-	-
TT+AA	0.852(0.631-1.151)	0.297	-	-	2.209(0.865-4.757)	0.104	-	-
GT+TT+GA+AA	0.839(0.592-1.189)	0.324	-	-	3.474(0.794-15.193)	0.098	-	-
XPC Lys939Gln								
AA	1				1			
AC	1.104(0.758-1.608)	0.604	-	-	1.657(0.209-13.157)	0.633	-	-
CC	0.939(0.703-1.253)	0.667	-	-	1.297(0.455-3.699)	0.626	-	-
AC+CC	0.847(0.598-1.199)	0.35	-	-	1.599(0.212-12.066)	0.649	-	-

HR, Hazard Ratio; [a]*P* value, HR and 95% CI were assessed using univariate Cox regression analysis; [b]*P* value, HR and 95% CI were assessed using multivariate Cox regression analysis

classification. 50 patients (11.7%) of the patients had the first-degree family history of CRC. The results of Duke's pathological grade for tumors were as follows: Dukes A for 109 (25.4%), Dukes B for 172 (40.2%), Dukes C for 124 (29.0%), Dukes D for 23 (5.4%) patients. 224 (52.3%) of the cases had lymph node metastases. The vast majority of CRC patients (80.1%) received oxaliplatin-based chemotherapy, whereas 9.8% of the them underwent fluorouracil chemotherapy. The variables of age, sex and smoking status were adjusted for any residual confounding effects in later logistic regression analyses.

Table 1 summarizes the genotype and allele frequencies of the *ABCB1* C3435T, G2677T/A and *XPC* Lys939Gln polymorphisms between CRC patients and controls. The genotype distributions in the control group did not significantly differ from Hardy-Weinberg equilibrium. A significant increased in the frequency of the CT genotype of the C3435T polymorphism was observed in CRC patients compared with controls (CT vs TT: *P*=0.0022; adjusted OR=1.814, 95% CI: 1.237-2.660). There was a significant difference in the CC+CT genotypes of the C3435T between CRC patients and controls and appeared to be associated with a increased risk of CRC (*P*=0.0102; adjusted OR=1.605, 95% CI: 1.117-2.306) (Table 1). However, there were no significant associations between *ABCB1* G2677T/A polymorphisms and the risk of CRCs (Table 1). For *XPC* Lys939Gln polymorphism, the heterozygous variant AC genotype and variant genotypes (AC+CC) showed a tendency for a higher risk of developing CRC compared with the GG genotype (adjusted OR=1.300, 95% CI: 0.973-1.739, *P*=0.0759; adjusted OR=1.237, 95% CI: 0.963-1.674, *P*=0.0903, respectively) (Table 1).

Next, we further investigated the correlation of *ABCB1* C3435T, G2677T/A and *XPC* Lys939Gln polymorphisms with clinicopathological features of 428 CRC patients using χ^2 test (Table 2). We observed that the distribution frequency of the *ABCB1* C3435T polymorphisms was

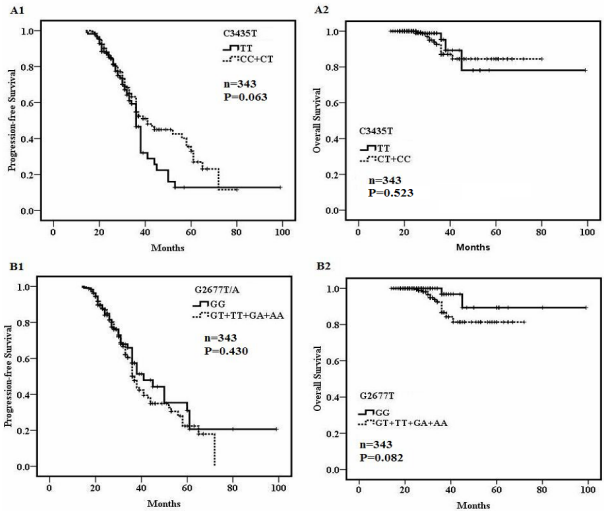

Figure 1. Kaplan-Meier Survival Curves Illustrating the Progression-free Survival (PFS) and Overall Survival (OS) in CRC Patients with the ABCB1 C3435T, G2677T/A Polymorphisms after Postoperative Oxaliplatin-based Chemotherapy (n=343). A1, B1 progression-free survival (PFS); A2, B2: overall survival (OS)

associated with age (≤60 or>60 years old). The frequency (9.1%) of C3435T TT genotype in the patients with younger patients (≤60 years old) was significantly lower than that (17.3%) in patients with more than 60 years old (*P*=0.013). (Table 3). Moreover, a higher frequency of the *ABCB1* G2677T/A GG genotype was observed in female patients (13.3%) compared with patients with male patients (6.8%) (*P*=0.025) (Table 2). In addition, there was a tendency towards higher distribution frequency of the *XPC* Lys939Gln polymorphisms observed in the female CRCs than those male CRCs (*P*=0.051) (Table 3). However, no significant correlation of genotype distributions of *ABCB1* C3435T, G2677T/A and *XPC* Lys939Gln polymorphisms were found with smoking status, first-degree family history of CRC, tumor differentiation, pathological grade, relapse situation, prime cancer (rectal cancer or colon cancer) (Table 3).

We further evaluated the correlation of *ABCB1* C3435T, G2677T/A and *XPC* Lys939Gln polymorphisms with the prognosis of CRC patients with postoperative oxaliplatin-based chemotherapy. For patients with postoperative oxaliplatin-based chemotherapy (n=343), the *ABCB1* C3435T CC+CT genotype was associated with a tendency toward a longer PFS compared with the TT genotype (Log-rank test: *P*=0.063; Figure 1 A1). The estimated median PFS was 41 months for patients with CC + CT genotype (95% CI=35.98-46.04) and 36 months for patients with TT genotype (95% CI=34.19-37.81). However, no correlation of *ABCB1* C3435T polymorphism was found with OS (Log-rank test: P=0.523; Figure 1 A2) in patients with postoperative oxaliplatin oxaliplatin-based chemotherapy (n=343).

For the *ABCB1* G2677T/A polymorphism, no significant association of the *ABCB1* G2677T/A genotypes were observed with PFS in patients with postoperative oxaliplatin-based chemotherapy (n=343, Log-rank test: *P*=0.430; Figure 1 B1). However, the variant *ABCB1* G2677T/A GT+TT+GA+AA genotypes showed a tendency towards longer OS in postoperative oxaliplatin treated patients (n=343, Log-rank test: *P*=0.082; Figure 1 B2). In addition, no correlation of the *XPC* Lys939Gln polymorphism was found with PFS (Log-rank test: *P*=0.867) and OS (Log-rank test: *P*=0.523) in patients with postoperative oxaliplatin-based chemotherapy (n=343).

A descriptive Cox proportional hazard model was performed to estimate the independent impact of each variable on PFS and OS (Table 3). Multivariate Cox regression identified that the prime cancer (rectum vs colon), tumor size (≤ 4cm vs > 4cm), pathological grade (Dukes A/Dukes B vs Dukes C/ Dukes D) had independent influence on the PFS of the patients with oxaliplatin oxaliplatin/5-FU -based chemotherapy (n=343). Furthermore, Smoking status (ever) and pathological grade (Dukes C/ Dukes D) were a predictive prognostic factor for a shorter OS (OR=2.192, 95%CI: 1.074-4.477; *P*=0.031; OR=1.407, 95%CI: 1.019-1.944; *P*=0.038, respectively) in patients with oxaliplatin-based chemotherapy (n=343).

Discussion

P-gp, *ABCB1* encoded transporter, is expressed not only in normal human tissues but also in multidrug-resistant cancer cells, which contributs to the absorption and distribution of xenobiotics, toxins and drugs. The polymorphisms of *ABCB1* C3435T, G2677T/A have been shown involving in altered expression or transporter activity of P-gp (Kim et al., 2001; Fromm, 2002; Leschziner et al., 2007; Samanian et al., 2011), and maybe associated with the susceptibility for developing cancer, but their biological significance is not fully understood yet. In the present study investigating 428 CRC patients and 450 cancer-free controls, we found that heterogeneous CT genotype or combined variants CC+CT genotypes of C3435T in *ABCB1* was associated with significantly increased risk of developing CRC. In agreement with our results, Andersen and co-workers found that carriers of C allele of the C3435T polymorphism had an increased risk of CRC in Norwegian Caucasian population (Andersen et al., 2009). On the contrary, in an Iran population investigation, T allele of the *ABCB1* C3435T polymorphism showed significantly increased risk of CRC (Khedri et al., 2011), while others did not find any statistically significant associations (Bae et al., 2006; Samanian et al., 2011). Regarding *ABCB1* G2677T/A genotypes and risk for CRC, we did not find any correlation between CRC risk and the investigated G2677T/A genotypes, likewise, De Iudicibus et al. found no relation between *ABCB1* G2677T/A polymorphism and CRC patients (De Iudicibus et al., 2008).These data suggest that the role of the *ABCB1* polymorphisms in cancer risk may vary with ethnicity, a possibility that warrants further investigation.

Risk factors contribute to CRC risk through multiple genetic alterations and DNA repair plays an important role in maintaining genome integrity. Moreover, recent year studies have established that the polymorphisms in DNA repair genes can either change protein coding or alter the levels of transcription or translation, consequently,

which can reduce DNA repair capacity and induce genetic instability or carcinogenesis. Few studies have investigated the associations between *XPC* Lys939Gln and risk of CRC, and these findings were inconsistent (Hansen et al., 2007; Engin et al., 2010; Wu et al., 2011; Liu et al., 2012). Overall, the *XPC* Lys939Gln was found to be associated with CRC risk in two case-control studies (Wu et al., 2011; Liu et al., 2012) while others did not find any statistically significant associations (Hansen et al., 2007; Engin et al., 2010). In this study, although there were no statistically significant association observed between *XPC* Lys939Gln polymorphism and CRC risk, it is worth to note that current data regarding *XPC* Lys939Gln polymorphism showed a tendency for a higher risk of developing CRC in heterozygous AC genotypes (P=0.0759) or AC+CC variants carriers (P=0.0903). Thus, it might be stated that the associated between *XPC* Lys939Gln polymorphism and cancer risk was varied in different ethnicity, and need further research to establish it.

CRC treatment strategies mainly include surgical excision and adjuvant chemotherapy according to different tumor stage of CRC patients. Oxaliplatin is the third-generation platinum derivative compound that has found a place in the routine treatment of CRC. Despite reducing recurrence after chemotherapy, multi-drug resistance to chemotherapeutic agents remains a big problem in the treatment of CRC patients (Robert et al., 2005; Kerb, 2006). Therefore, we further analyzed the relationship between *ABCB1* and *XPC* polymorphisms and the prognosis of CRC patients with postoperative oxaliplatin-based chemotherapy. Likewase, Chai et al. and Liu et al. (2006) found no relation between *ABCB1* C3435T, G2677T/A or *XPC* Lys939Gln polymorphisms and prognosis in Chinese people. We only observed that *ABCB1* C3435T variants carriers were associated with a tendency toward longer PFS, meanwhile G2677T/A variants were observed in a tendency for longer OS in postoperative oxaliplatin-based patients. However, no statistcally significant correlation of the *XPC* polymorphism was found with prognosis in patients with postoperative oxaliplatin-based chemotherapy.

Although numerous studies have investigated the relevance between the polymorphisms of the drug resistance-associated genes or DNA repair pathway genes and CRC risk and prognosis, the roles of these genes in carcinogenesis remain unclear and need to be further elucidated. The present study is one of studies to address the potential association between *ABCB1* and *XPC* polymorphisms and CRC risk and prognosis in a larger and well charactererized population.Nonethelss, several potential limitations should be considered in this study. In the case-control study, the cohort was included only in Chinese Han population in Northeast areas, and the results should be replicated in other enthcities or geographic areas. Although relatively large sample size, our data might not have adequate statistical power to detect weak genetic-disease associations or gene-environment interactions. Further studies estimating the effect of gene-gene and gene-environment interactions may provide a comprehensive understanding of the roles of *ABCB1* and *XPC* polymorphisms invovled in the initiation of cancer. Therefore, functional studies in vitro or in vivo to identify the physiological and molecular mechanism are also warranted.

In conclusion, this hospital-based case-controlled study indicates that in the Chinese population, *ABCB1* C3435T polymorphism was significantly associated with the susceptibility to CRC, but not found *ABCB1* and *XPC* polymorphism were associated with chemotherapeutic progosis of CRC patients with oxaliplatin-based chemotherapy. Additional investigations are warranted to confirm our findings in predicting the cancer risk and prognosis of CRC patients with chemotherapy.

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