Contribution of XPD and XPF Polymorphisms to Susceptibility of Non-Small Cell Lung Cancer in High-Altitude Areas

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Keywords

Non-small cell lung cancer · XPD · XPF · Susceptibility · Cisplatin-based chemotherapy

Abstract

Background: We aimed to explore the relation of XPD and XPF variants with non-small cell lung cancer (NSCLC) risk and the effect of these variants on the sensitivity to cisplatin-based chemotherapy among the Chinese Han population in high-altitude areas. **Methods:** Eight single-nucleotide polymorphisms (SNPs) in XPD and XPF were genotyped by Agena MassARRAY platform among 506 NSCLC cases and 510 healthy controls. Correlation of XPD and XPF gene polymorphisms with NSCLC susceptibility and the response of cisplatin-based chemotherapy were analyzed with logistic regression by calculating odds ratios (ORs) and 95% confidence intervals (CIs). **Results:** XPD rs13181 (OR = 1.53, 95% CI: 1.04–2.24, $p = 0.029$) and rs1052555 (OR = 1.63, 95% CI: 1.05–2.53, $p = 0.029$) possibly contributed to the increased risk of lung adenocarcinoma, while XPD rs238406 (OR = 0.63,

95% CI: 0.43–0.94, $p = 0.024$) was a protective factor for lung squamous cell carcinoma. Age, gender, BMI, smoking, and drinking might affect the correlation of XPD and XPF polymorphisms with NSCLC risk. More importantly, XPD rs13181 (OR = 2.91, $p = 0.015$), XPD rs1052555 (OR = 2.67, $p = 0.022$), and XPF rs231127 (OR = 4.15, $p = 0.008$) were associated with treatment response in NSCLC patients underwent cisplatin-based chemotherapy. **Conclusion:** This study found that XPD and XPF variants might contribute to NSCLC risk and the response of cisplatin-based chemotherapy among the Chinese Han population in high-altitude areas.

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Introduction

There were an estimated 2.1 million new cases and 1.8 million deaths for lung cancer worldwide in 2018, which accounted for close to 1 in 5 (18.4%) cancer deaths [1]. In China, lung cancer is the most commonly diagnosed and was identified as the leading cause of cancer death (17.1%

for incidence and 21.7% for mortality, respectively) [2]. Among them, two-thirds of lung cancer deaths occur in males and about 55% of which are due to active smoking. Other factors such as alcohol, poor diet, occupational exposures, and air pollution may also had effect on the occurrence and development of lung cancer, especially non-small cell lung cancer (NSCLC) [3]. Existing studies have revealed the strong association between genetic variations and the susceptibility to NSCLC [4, 5]. Moreover, genetic variations are considered as important factors to influence the treatment efficacy and prognosis of NSCLC. Interindividual variability in response to cisplatin for NSCLC patients was associated with genetic variants [6–8].

Nucleotide excision repair (NER) participates in DNA repair pathways which were involved in the repair of chromosomal breakage or rearrangement in the processes of DNA damage, replication errors, and recombination [9]. Xeroderma pigmentosum complementation group D (XPD) and xeroderma pigmentosum complementation group F (XPF) are important components of NER. XPD (also called excision repair cross-complimentary group 2), an ATP-dependent helicase, is an essential member of the basal transcription factor TFIIH complex for normal transcription initiation of NER [10]. XPF, also called excision repair cross-complimentary group 4, involves in the recombination repair, mismatch repair, and identification of damage sites [11]. Saviozzi et al. [12] reported that *XPD* and *XPF* genes were significantly overexpressed in NSCLC tissue compared with normal lung tissue. Previous studies have reported that *XPD* and *XPF* polymorphisms were associated with the susceptibility and response to chemotherapy of cancers, including NSCLC. However, those currently available results have been inconsistent [13, 14].

Qinghai-Tibet Plateau is located in northwest China, at an average altitude of over 3,000 m. In high-altitude areas, perennial hypobaric hypoxia and strong ultraviolet radiation may cause genetic variation, which, in turn, affects the occurrence of diseases including cancers. The occurrence and development of NSCLC in high-altitude areas have been fewly reported. The Han population is the largest ethnic group in China and is also widely distributed in high-altitude areas. Here, our study investigated the correlation between *XPD* and *XPF* variants and NSCLC risk among the Chinese Han population in high-altitude areas and assessed the effect of variants on the sensitivity of NSCLC patients to cisplatin-based chemotherapy.

Materials and Methods

Subjects

This study included 1,016 subjects comprised 506 NSCLC cases (59.80 ± 10.63 years, 350 males and 156 females) and 510 healthy controls (59.80 ± 9.08 years, 353 males and 157 females). All subjects were genetically unrelated ethnic Han Chinese. All patients were diagnosed and histopathologically confirmed primary NSCLC from the Qinghai Province Cancer Hospital. Healthy controls were enrolled from the health checkup center of the same hospital. The patients had no history of cancer. Blood samples of patients were gathered before beginning chemotherapy or radiotherapy. The exclusion criteria of the control group included chronic respiratory disease, tuberculosis, inflammation, and autoimmune disorders. Epidemiological and clinical data were available from medical records and standardized questionnaires, respectively. Data on basic information including age, gender, BMI, smoking, and drinking exposure and clinical information about pathological types, lymph nodes metastasis, and stages were collected.

Evaluation of Cisplatin-Based Chemotherapeutic Response

One hundred and eighty-nine NSCLC patients who received cisplatin-based chemotherapy satisfied the Eastern Cooperative Oncology Group performance status 0 or 1. These patients received cisplatin-based chemotherapy every 3 weeks until 6 cycles or tumor progression. Adverse effects were assessed according to the National Cancer Institute Common Toxicity Criteria, version 3.0 standard [15]. The patients were subdivided into toxicity and nontoxicity group. For response to therapy, patients with complete response (CR) or partial response (PR) were defined as the “CR + PR” group, and patients achieving stable disease (SD) or progressive disease (PD) were considered as the “SD + PD” group according to the Response Evaluation Criteria in Solid Tumor Group (RECIST) guidelines [16].

Single-Nucleotide Polymorphisms Selection and Genotyping

The candidate SNPs in *XPD* and *XPF* were selected based on previously reported genetic variants related to NSCLC susceptibility [17]. Of those, we identified tagged SNPs with >5% minor allele frequency for Chinese in the 1,000 Genomes Project data (<http://www.internationalgenome.org/>), and the linkage disequilibrium of a pairwise tagging $r^2 \geq 0.8$. Finally, 8 SNPs in *XPD* (rs13181, rs1052555, rs238406, and rs1799793) and *XPF* (rs231127, rs8054265, rs6498486, and rs3743538) were selected for further genotyping. Peripheral venous blood (5 mL) was drawn from each subject in the EDTA-coated tubes and stored at -80°C after centrifugation. GoldMag DNA Purification Kit (GoldMag Co., Ltd., Xi'an City, China) was used to extract gDNA, and the concentration and purity of the extracted DNA were determined by NanoDrop 2000. We used the Agena MassARRAY platform for SNPs genotyping in accordance with the manufacturer's protocol in a double-blind fashion by 2 people. 5% of samples were randomly selected for re-genotyping. Call rates of genotyping were >95%, and the concordance rate reached 100%.

Statistical Analysis

SPSS 18.0 (SPSS Inc., Chicago, IL, USA) and PLINK 1.0.7 were performed. To assess the differences of demographic and clinical data between the patients and the controls, χ^2 tests for categorical

variables and independent sample *t* test for continuous variables were carried out. Hardy-Weinberg equilibrium in controls was evaluated by the goodness-of-fit χ^2 tests. The correlation of *XPD* and *XPF* variants with NSCLC risk was analyzed using logistic regression by odds ratios (ORs) and 95% confidence intervals (CIs). Further, we performed stratified analysis by gender, age, BMI, status of smoking and drinking, histology, stage, and lymph nodes metastasis. Linkage disequilibrium and haplotype analyses were calculated by Haploview software (version 4.2) and PLINK software. Logistic regression method was utilized to analyze the correlation between SNPs and the effectiveness of cisplatin-based chemotherapy in NSCLC patients. Two-sided *p* value <0.05 was examined statistically significant.

Results

Study Participants

The characteristics of the subjects were shown in Table 1. There were no significant differences in age (*p* = 0.351) and gender (*p* = 0.987) distribution between NSCLC patients and healthy individuals. Table 1 also gave the proportion of BMI, smoking and drinking exposures of all participants, and histological types, lymph nodes metastasis, and stages of patients. The analysis included 189 NSCLC patients treated with cisplatin-based chemotherapy.

The Correlation of *XPD* and *XPF* Polymorphisms with NSCLC Risk

Eight SNPs within *XPD* and *XPF* were genotyped among NSCLC patients and healthy controls. The minor allele frequency of the selected SNPs was >5% (online suppl. Table 1; for all online suppl. material, see www.karger.com/doi/10.1159/000512641). And the genotype of all SNPs in controls was consistent with Hardy-Weinberg equilibrium (*p* > 0.05), which indicated the subjects had a representative of the population. The genotype and allele frequencies of NSCLC cases and controls were revealed in online suppl. Table 2. However, there was no significant difference in genotype and allele frequencies of any SNPs between cases and controls (*p* > 0.05).

The Effect of Age, Gender, BMI, Smoking, and Drinking on the Correlation of *XPD* and *XPF* Variants with NSCLC Risk

The effects of age, gender, BMI, smoking, and drinking on the correlation of *XPD* and *XPF* variants with NSCLC risk were evaluated (Tables 2, 3). In the stratified analysis by age (Table 2), rs13181-G allele increased NSCLC susceptibility at age >59 years in the allele (OR = 1.63, 95% CI: 1.03–2.57, *p* = 0.035), dominant (OR = 1.62, 95% CI:

Table 1. Characteristics of NSCLC patients and health controls

Variables	Cases (<i>n</i> = 506)	Control (<i>n</i> = 510)	<i>p</i> value
<i>Age, n (%)</i>			
Mean ± SD, years	59.80±10.63	59.80±9.08	
>59 years	271 (53.6)	275 (53.9)	0.351
≤59 years	235 (46.4)	235 (46.1)	
<i>Gender, n (%)</i>			
Male	350 (69.2)	353 (69.2)	0.987
Female	156 (30.8)	157 (30.8)	
<i>BMI, n (%)</i>			
≤24 kg/m ²	133 (26.3)	138 (27.1)	
>24 kg/m ²	81 (16.0)	181 (35.5)	
Unavailable	292 (57.7)	191 (37.5)	
<i>Smoking, n (%)</i>			
Yes	242 (47.8)	108 (21.2)	
No	161 (31.8)	180 (35.3)	
Unavailable	103 (20.4)	222 (43.5)	
<i>Drinking, n (%)</i>			
Yes	109 (21.5)	103 (20.2)	
No	267 (52.8)	156 (30.6)	
Unavailable	130 (25.7)	251 (49.2)	
<i>Pathological type, n (%)</i>			
Squamous carcinoma	174 (34.4)		
Adenocarcinoma	212 (41.9)		
Unavailable	120 (23.7)		
<i>Lymph node metastasis, n (%)</i>			
Yes	269 (53.2)		
No	103 (20.4)		
Unavailable	134 (26.5)		
<i>Stage, n (%)</i>			
I–II	93 (18.4)		
III–IV	286 (56.5)		
Unavailable	127 (25.1)		
<i>Cisplatin-based chemotherapy (n = 189)</i>			
Toxicity	37 (19.6)		
Nontoxicity	152 (80.4)		
CR + PR	42 (22.2)		
SD + PD	100 (52.9)		
Unavailable	47 (24.9)		

NSCLC, non-small cell lung cancer; SD, standard deviation; CR, complete response; PR, partial response; SD, stable disease; PD, progression of disease.

1.00–2.62, *p* = 0.049), and additive models (OR = 1.64, 95% CI: 1.02–2.63, *p* = 0.040). The rs1052555-A allele also conferred a higher NSCLC risk at age >59 years in the allele (OR = 1.99, 95% CI: 1.18–3.35, *p* = 0.008), heterozygote (OR = 1.87, 95% CI: 1.08–3.24, *p* = 0.024), dominant (OR = 1.92, 95% CI: 1.12–3.32, *p* = 0.019), and additive

Table 2. Relationships between *XPD* polymorphisms and NSCLC risk according to the stratification by age and gender

SNP id	Models	OR (95% CI)	<i>p</i> value	OR (95% CI)	<i>p</i> value
Age		>59 years		≤59 years	
rs13181	Allele	1.63 (1.03–2.57)	0.035	0.98 (0.63–1.52)	0.910
	Heterozygote	1.59 (0.98–2.57)	0.060	1.04 (0.64–1.68)	0.880
	Homozygote	–	–	–	–
	Dominant	1.62 (1.00–2.62)	0.049	0.99 (0.61–1.59)	0.956
	Recessive	–	–	–	–
	Log-additive	1.64 (1.02–2.63)	0.040	0.93 (0.59–1.47)	0.766
rs1052555	Allele	1.99 (1.18–3.35)	0.008	0.97 (0.57–1.62)	0.895
	Heterozygote	1.87 (1.08–3.24)	0.024	1.01 (0.58–1.75)	0.978
	Homozygote	–	–	–	–
	Dominant	1.92 (1.12–3.32)	0.019	0.97 (0.56–1.68)	0.916
	Recessive	–	–	–	–
	Log-additive	1.94 (1.14–3.32)	0.015	0.93 (0.55–1.59)	0.800
Gender		Males		Females	
rs238406	Allele	0.81 (0.66–1.01)	0.056	1.12 (0.82–1.54)	0.474
	Heterozygote	0.64 (0.46–0.90)	0.011	1.43 (0.85–2.41)	0.182
	Homozygote	0.72 (0.48–1.09)	0.122	1.21 (0.65–2.26)	0.542
	Dominant	0.67 (0.49–0.92)	0.012	1.36 (0.83–2.21)	0.225
	Recessive	0.93 (0.65–1.34)	0.699	0.97 (0.57–1.65)	0.917
	Log-additive	0.82 (0.67–1.01)	0.065	1.12 (0.82–1.52)	0.479

NSCLC, non-small cell lung cancer; SNP, single-nucleotide polymorphism; OR, odds ratio; CI, confidence interval. *p* values were calculated by logistic regression analysis with adjustments for age and gender. Bold *p* < 0.05 means the data are statistically significant. “–” represents the *p* values were unavailable due to the absence of frequency of genotype.

models (OR = 1.94, 95% CI: 1.14–3.32, *p* = 0.015). Stratified by gender (Table 2), rs238406 was a protective factor for NSCLC occurrence in males (heterozygote: OR = 0.64, 95% CI: 0.46–0.90, *p* = 0.011; and dominant: OR = 0.67, 95% CI: 0.49–0.92, *p* = 0.012). In the BMI stratification (Table 3), rs3743538 (TT vs. GG, OR = 3.81, 95% CI: 1.08–13.45, *p* = 0.038 and TT vs. GG-GT, OR = 3.53, 95% CI: 1.01–12.26, *p* = 0.048) increased NSCLC risk in the subgroup with BMI >24 kg/m². Among the subgroup with BMI ≤24 kg/m², rs231127 (OR = 0.38, 95% CI: 0.15–0.94, *p* = 0.036) and rs6498486 (OR = 1.72, 95% CI: 1.02–2.90, *p* = 0.042) were related to NSCLC susceptibility. In

smokers, the rs238406-T allele (T vs. G, OR = 1.51, 95% CI: 1.09–2.09, *p* = 0.012 and additive, OR = 1.51, 95% CI: 1.09–2.10, *p* = 0.014) and TT genotype (TT vs. GG, OR = 2.15, 95% CI: 1.06–4.37, *p* = 0.035 and TT vs. GG-GT, OR = 2.66, 95% CI: 1.53–4.63, *p* = 0.001) had the increased NSCLC susceptibility (Table 3). Among drinkers, rs13181 (TG vs. TT, OR = 2.25, 95% CI: 1.03–4.94, *p* = 0.043) contributed to the increased risk of NSCLC, while rs238406 (GT vs. GG, OR = 0.33, 95% CI: 0.17–0.62, *p* = 0.001 and GT-TT vs. GG, OR = 0.45, 95% CI: 0.25–0.81, *p* = 0.008) decreased the risk (Table 3).

Table 3. Relationships between *XPD* and *XPF* polymorphisms and NSCLC risk according to the stratification by BMI and the status of smoking and drinking

SNP id	Models	OR (95% CI)	<i>p</i> value	OR (95% CI)	<i>p</i> value
BMI		>24 kg/m ²		≤24 kg/m ²	
rs231127	Allele	1.18 (0.80–1.75)	0.393	0.84 (0.59–1.20)	0.339
	Heterozygote	1.03 (0.59–1.82)	0.909	1.15 (0.69–1.90)	0.602
	Homozygote	1.75 (0.69–4.47)	0.239	0.40 (0.16–1.05)	0.063
	Dominant	1.13 (0.65–1.94)	0.665	0.98 (0.60–1.60)	0.936
	Recessive	1.72 (0.71–4.17)	0.227	0.38 (0.15–0.94)	0.036
	Log-additive	1.21 (0.79–1.84)	0.375	0.82 (0.56–1.19)	0.295
rs6498486	Allele	1.14 (0.73–1.76)	0.569	1.37 (0.90–2.06)	0.139
	Heterozygote	1.24 (0.71–2.16)	0.461	1.72 (1.02–2.90)	0.042
	Homozygote	1.38 (0.39–4.91)	0.617	1.02 (0.32–3.19)	0.976
	Dominant	1.25 (0.73–2.15)	0.419	1.61 (0.98–2.65)	0.062
	Recessive	1.27 (0.37–4.43)	0.705	0.84 (0.27–2.60)	0.766
	Log-additive	1.21 (0.77–1.90)	0.413	1.36 (0.90–2.06)	0.149
rs3743538	Allele	1.46 (0.92–2.31)	0.104	1.34 (0.87–2.07)	0.190
	Heterozygote	1.27 (0.70–2.29)	0.430	1.38 (0.80–2.37)	0.244
	Homozygote	3.81 (1.08–13.45)	0.038	1.46 (0.44–4.82)	0.534
	Dominant	1.47 (0.84–2.56)	0.180	1.39 (0.83–2.33)	0.210
	Recessive	3.53 (1.01–12.26)	0.048	1.33 (0.41–4.35)	0.636
	Log-additive	1.55 (0.97–2.45)	0.065	1.30 (0.85–2.00)	0.228
Smoking		Yes		No	
rs238406	Allele	1.51 (1.09–2.09)	0.012	1.06 (0.78–1.43)	0.709
	Heterozygote	0.74 (0.41–1.36)	0.335	1.02 (0.62–1.70)	0.929
	Homozygote	2.15 (1.06–4.37)	0.035	0.97 (0.52–1.81)	0.918
	Dominant	1.07 (0.60–1.91)	0.811	1.01 (0.63–1.62)	0.981
	Recessive	2.66 (1.53–4.63)	0.001	0.95 (0.55–1.65)	0.868
	Log-additive	1.51 (1.09–2.10)	0.014	0.99 (0.73–1.35)	0.937

(Table continued on next page.)

Relationship of Clinicopathological Features with *XPD* and *XPF* Variants

Further, the correlation between *XPD* and *XPF* SNPs and clinicopathological features was assessed, including histological subgroups, clinical stage (III–IV vs. I–II), and lymphatic metastatic status (metastasis vs. nonmetastasis). The results of stratified analyses by histology types showed in Table 4. In lung adenocarcinoma, the allele and/or gen-

otype frequencies of rs13181 and rs1052555 were significantly different. Rs13181 (G vs. T, OR = 1.53, 95% CI: 1.04–2.24, *p* = 0.029; TG vs. TT, OR = 1.70, 95% CI: 1.13–2.57, *p* = 0.011; and TG-GG vs. TT, OR = 1.65, 95% CI: 1.10–2.49, *p* = 0.016) and rs1052555 (A vs. G, OR = 1.63, 95% CI: 1.05–2.53, *p* = 0.029; GA vs. GG, OR = 1.75, 95% CI: 1.10–2.79, *p* = 0.019; and GA-AA vs. GG, OR = 1.71, 95% CI: 1.07–2.71, *p* = 0.024) were related to the increased risk of

Table 3 (continued)

Drinking		Yes		No	
rs13181	Allele	1.75 (0.86–3.56)	0.118	1.09 (0.66–1.79)	0.745
	Heterozygote	2.25 (1.03–4.94)	0.043	1.07 (0.63–1.82)	0.807
	Homozygote	–	–	–	–
	Dominant	2.07 (0.96–4.46)	0.064	1.09 (0.64–1.86)	0.741
	Recessive	–	–	–	–
	Log-additive	1.82 (0.87–3.78)	0.110	1.12 (0.67–1.89)	0.666
rs238406	Allele	0.82 (0.56–1.21)	0.314	1.00 (0.76–1.33)	0.978
	Heterozygote	0.33 (0.17–0.62)	0.001	0.98 (0.62–1.54)	0.931
	Homozygote	0.88 (0.41–1.93)	0.757	1.04 (0.58–1.85)	0.906
	Dominant	0.45 (0.25–0.81)	0.008	0.99 (0.65–1.53)	0.981
	Recessive	1.69 (0.86–3.33)	0.128	1.05 (0.63–1.74)	0.855
	Log-additive	0.85 (0.58–1.23)	0.391	1.01 (0.76–1.35)	0.930

NSCLC, non-small cell lung cancer; SNP, single-nucleotide polymorphism; OR, odds ratio; CI, confidence interval. *p* values were calculated by logistic regression analysis with adjustments for age and gender. Bold *p* < 0.05 means the data are statistically significant. “–” represents the *p* values were unavailable due to the absence of frequency of genotype.

Table 4. The association of *XPD* polymorphisms and NSCLC susceptibility

SNP id	Genotype	Control	Adenocarcinoma			Squamous cell carcinoma		
			case	OR (95% CI)	<i>p</i> value	case	OR (95% CI)	<i>p</i> value
rs13181	T	943	377	1		323	1	
	G	77	47	1.53 (1.04–2.24)	0.029	25	0.95 (0.59–1.51)	0.823
	TT	435	165	1		149	1	
	TG	73	47	1.70 (1.13–2.57)	0.011	25	1.05 (0.64–1.74)	0.840
	GG	2	0	–	0.999	0	–	0.999
	TG-GG	75	47	1.65 (1.10–2.49)	0.016	25	1.03 (0.63–1.70)	0.901
rs1052555	G	966	385	1		326	1	
	A	54	35	1.63 (1.05–2.53)	0.029	22	1.21 (0.72–2.01)	0.470
	GG	457	175	1		152	1	
	GA	52	35	1.75 (1.10–2.79)	0.019	22	1.28 (0.74–2.20)	0.375
	AA	1	0	–	–	0	–	–
	GA-AA	53	35	1.71 (1.07–2.71)	0.024	22	1.27 (0.74–2.18)	0.391
rs238406	G	550	232	1		209	1	
	T	470	190	0.96 (0.76–1.20)	0.715	139	0.78 (0.61–1.00)	0.047
	GG	152	69	1		69	1	
	GT	246	94	0.82 (0.56–1.19)	0.297	71	0.63 (0.43–0.94)	0.024
	TT	112	48	0.93 (0.60–1.46)	0.763	34	0.66 (0.41–1.08)	0.099
	GT-TT	358	142	0.86 (0.60–1.21)	0.378	105	0.64 (0.45–0.93)	0.018

NSCLC, non-small cell lung cancer; SNP, single-nucleotide polymorphism; OR, odds ratio; CI, confidence interval. *p* values were calculated by logistic regression analysis with adjustments for age and gender. Bold *p* < 0.05 means the data are statistically significant. “–” represents the *p* values were unavailable due to the absence of frequency of genotype.

Table 5. Relationships between *XPD* and *XPF* polymorphisms and lymph nodes metastasis in NSCLC patients

SNP id	Model	Allele/ genotype	Metastasis group	Nonmetastasis group	OR (95% CI)	<i>p</i> value
rs238406	Allele	G	306	126	1	0.289
		T	232	80	1.19 (0.86–1.66)	
		GG	90	45	1	
	Heterozygote	GT	126	36	1.72 (1.03–2.89)	0.040
	Homozygote	TT	53	22	1.19 (0.64–2.20)	0.583
	Dominant	GG	90	45	1	0.080
		GT-TT	179	58	1.52 (0.95–2.42)	
	Recessive	GG-GT	216	81	1	0.707
		TT	53	22	0.90 (0.51–1.57)	
Log-additive					1.16 (0.85–1.59)	0.347
rs6498486	Allele	A	402	154	1	0.992
		C	136	52	1.00 (0.69–1.45)	
		AA	144	62	1	
	Heterozygote	AC	114	30	1.63 (0.99–2.69)	0.057
	Homozygote	CC	11	11	0.44 (0.18–1.06)	0.067
	Dominant	AA	144	62	1	0.254
		AC-CC	125	41	1.31 (0.82–2.08)	
	Recessive	AA-AC	258	92	1	0.022
		CC	11	11	0.36 (0.15–0.86)	
Log-additive					1.00 (0.69–1.46)	0.993

NSCLC, non-small cell lung cancer; SNP, single-nucleotide polymorphism; OR, odds ratio; CI, confidence interval. *p* values were calculated by logistic regression analysis with adjustments for age and gender. Bold *p* < 0.05 means the data are statistically significant.

lung adenocarcinoma. In squamous cell carcinoma, rs238406 had a decreased risk (T vs. G, OR = 0.78, 95% CI: 0.61–1.00, *p* = 0.047; GT vs. GG, OR = 0.63, 95% CI: 0.43–0.94, *p* = 0.024; and GT-TT vs. GG, OR = 0.64, 95% CI: 0.45–0.93, *p* = 0.018). We did not find the significant difference in the *XPD* and *XPF* genotypes at different stages of NSCLC (*p* > 0.05). We found that rs238406 GT genotype (OR = 1.72, 95% CI: 1.03–2.89, *p* = 0.040) was highly presented in patients with metastasis, while rs6498486 CC genotype (OR = 0.36, 95% CI: 0.15–0.86, *p* = 0.022) was highly presented in patients without metastasis (Table 5).

Relationship of XPD and XPF Single-Nucleotide Polymorphisms with Cisplatin-Based Chemotherapy Response

Subsequently, we also evaluated the association between *XPD* and *XPF* SNPs and the toxicity or treatment response of NSCLC patients with cisplatin-based chemo-

therapy (Table 6). Among the 189 patients with cisplatin-based chemotherapy, 37 (19.6%) patients suffered from toxicity and 42 (22.2%) patients were chemotherapy responders (CR + PR). In the cisplatin-related toxicity analysis, rs231127 CC genotype was conferred to an increased risk of toxicity compared with TT-TC genotype (OR = 4.15, 95% CI: 1.44–11.93, *p* = 0.008). In the respond of cisplatin therapy, rs13181-G allele and TG genotype were associated with cisplatin-based chemotherapy response under allele (OR = 2.37, 95% CI: 1.12–5.01, *p* = 0.021), heterozygote (OR = 2.73, 95% CI: 1.11–6.73, *p* = 0.029), dominant (OR = 2.92, 95% CI: 1.21–7.07, *p* = 0.017), and additive (OR = 2.91, 95% CI: 1.23–6.86, *p* = 0.015) models. The rs1052555 variants were closely associated with the effectiveness of cisplatin therapy on NSCLC under allele (OR = 2.67, 95% CI: 1.12–6.36, *p* = 0.022), dominant (OR = 2.89, 95% CI: 1.07–7.86, *p* = 0.037), and additive (OR = 2.88, 95% CI: 1.1–7.54, *p* = 0.031) models.

Table 6. Relationships between *XPD* and *XPF* polymorphisms and cisplatin-based chemotherapy response in NSCLC patients

SNP id	Model	Genotype	OR (95% CI)	<i>p</i> value
<i>Toxicity group versus nontoxicity group</i>				
rs231127	Allele	C	1.24 (0.73–2.12)	0.424
	Heterozygote	TC	0.43 (0.18–1.02)	0.056
	Homozygote	CC	2.79 (0.91–8.55)	0.072
	Dominant	TC-CC	0.72 (0.34–1.51)	0.383
	Recessive	CC	4.15 (1.44–11.93)	0.008
	Log-additive		1.22 (0.71–2.1)	0.470
<i>CR + PR group versus SD + PD group</i>				
rs13181	Allele	G	2.37 (1.12–5.01)	0.021
	Heterozygote	TG	2.73 (1.11–6.73)	0.029
	Homozygote	GG	–	–
	Dominant	TG-GG	2.92 (1.21–7.07)	0.017
	Recessive	GG	–	–
	Log-additive		2.91 (1.23–6.86)	0.015
rs1052555	Allele	A	2.67 (1.12–6.36)	0.022
	Heterozygote	GA	2.65 (0.94–7.42)	0.064
	Homozygote	AA	–	–
	Dominant	GA-AA	2.89 (1.07–7.86)	0.037
		AA	–	–
	Log-additive		2.88 (1.1–7.54)	0.031

NSCLC, non-small cell lung cancer; SNP, single-nucleotide polymorphism; OR, odds ratio; CI, confidence interval; CR, complete response; PR, partial response; SD, stable disease; PD, progression of disease. *p* values were calculated by logistic regression analysis with adjustments for age and gender. Bold *p* < 0.05 means the data are statistically significant. “–” represents the *p* values were unavailable due to the absence of frequency of genotype.

Discussion

Here, we evaluated relationships of 8 SNPs in *XPD*/*XPF* with the susceptibility and cisplatin-based chemotherapeutic response to NSCLC among a Chinese Han population in high-altitude areas. Our study found *XPD* rs13181 and rs1052555 possibly contributed to the increased susceptibility of lung adenocarcinoma, while *XPD* rs238406 was a protective factor for lung squamous cell carcinoma. In addition, we also displayed that age, gender, BMI, smoking, and drinking might affect the correlation between *XPD* and *XPF* variants and NSCLC risk. More importantly, *XPD* rs13181, *XPD* rs1052555, and *XPF* rs231127 were associated with cisplatin-based chemotherapy response of NSCLC patients.

XPD gene, mapped on chromosome 19q13.3, plays an important role in the NER pathway, which is involved in transcription-coupled NER. *XPD* polymorphisms can alter the secondary structure of mRNA [18]. Several studies have found some SNPs of *XPD* may be related to the susceptibility of NSCLC and the toxicity of NSCLC patients receiving chemotherapy [13, 19]. Rs13181 (T>G, Lys-751Gln) is a nonsynonymous SNP in *XPD*, and the G allele has the capability to reduce the efficiency of DNA repair [20]. Therefore, the G allele of rs13181 might be a possible risk factor for NSCLC. Although several studies showed that rs13181 was related to NSCLC risk, there were inconsistencies in the Chinese populations. For example, Liu et al. [13] suggested that the G allele of rs13181 was associated with increased susceptibility of NSCLC,

while Qian et al. [14] observed no significant association between rs13181 and NSCLC risk. Such inconsistencies in these reports might be attributable to different environments or insufficient sample sizes. In our study, we found that rs13181-G allele increased 1.53-fold risk of lung adenocarcinoma. Rs13181 variant was also related to an increased risk of NSCLC in the subgroup at age >59 years or in drinkers. Additionally, G allele of rs13181 presented a better response to cisplatin-based chemotherapy, which was inconsistent with the study in the Chinese Han population by Du et al. [21], but consistent with the previously published meta-analysis studies [22, 23]. There were inconsistencies the inconsistent result was also found in *XPD* rs1052555 polymorphism. *XPD* rs1052555C>T (Asp711Asp) was not associated with response to chemotherapy of patients with NSCLC [24]. However, a meta-analysis study revealed that T allele of rs1052555 was a risk allele and might be significantly associated with unfavorable clinical prognosis including treatment response [19]. Consistently, rs1052555 was also associated with cisplatin-based chemotherapy response in our study. Moreover, rs1052555 conferred to an increased susceptibility of lung adenocarcinoma. Rs1052555 also had a higher NSCLC risk among subjects with age >59 years. Rs238406 (G>T, Arg156Arg) is located in the synonymous coding region, which may have a possible impact on the structure of *XPD* protein or the stability of mRNA [25]. Han et al. [26] revealed that rs238406 could confer increased susceptibility to lung adenocarcinoma among the Chinese population. However, we found that rs238406 might be a protective factor for lung squamous cell carcinoma. This result requires a larger sample to validate. In addition, rs238406 was related to the decreased risk of NSCLC in males and drinkers, while increased the risk in smokers. In addition, rs238406 was also related to lymph nodes metastasis in NSCLC patients.

XPF, located on chromosome 16p13.12, is also another important protein in the NER pathway, which plays a key role in DNA repair and maintenance of chromosome stability [27]. *XPF* polymorphisms can alter the function of *XPF*, leading to tumorigenesis and affecting the outcome of cisplatin-based chemotherapy [28]. Previously, *XPF* variants were reported to be associated with various tumors, including colorectal, ovarian, and lung cancer [29–31]. However, few studies have focused on the association between rs231127, rs8054265, rs6498486, and rs3743538 in *XPF* and NSCLC susceptibility. Here, our results revealed that rs231127 and rs6498486 were associated with NSCLC risk in the subgroup with ≤ 24 kg/m²,

while rs3743538 contributed to NSCLC risk among subjects with >24 kg/m². Our results also showed that rs6498486 might be related to the lower incidence of lymph node metastasis. In addition, *XPF* rs231127 had a significant association with the toxicity of cisplatin-based chemotherapy. These results implied that *XPF* polymorphisms could influence the susceptibility and toxicity of chemotherapy to NSCLC.

Some intrinsic limitations should be considered in our study. First, the possibility of selection biases could not be completely excluded in this hospital-based case-control study. Second, the number of patients with cisplatin-based chemotherapy was relatively small. Our results should be interpreted with caution and require further validation in future studies.

Conclusion

In summary, the present study provided some cumulative evidence that *XPD* and *XPF* variants were related to the risk of NSCLC and modulated the toxicity of cisplatin-based chemotherapy among the Chinese Han population in high-altitude areas.

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Statement of Ethics and Consent to Participate

This study was approved by the Ethics Committee of the Qinghai Province Cancer Hospital (QHWY-LL2017-0005) and was in accordance with the Declaration of Helsinki. All participants were aware of the research protocol and signed informed consent form.

Conflict of Interest Statement

The authors have no actual or potential conflicts of interest related to this manuscript. Appropriate approval was obtained, and appropriate procedures were followed concerning human subjects.

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Author Contributions

The work presented here was carried out in collaboration between all authors. Miao Li carried out the molecular genetic studies and drafted the manuscript. Rong Chen collected clinical information about patients and designed primers. Baoyan Ji and Chunmei Fan performed the SNP genotyping experiments. Guanying Wang and Chenli Yue performed the statistical analyses and interpreted the results. Guoquan Li conceived of the study, worked on associated data collection and their interpretation, participated in

the design and coordination of the study, and funded the study. All authors read and approved the final manuscript.

Availability of Data and Material

All the data regarding the findings are available within the manuscript. Anyone who is interested in the information should contact the corresponding author.

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