Impact of GTF2H1 and RAD54L2 gene polymorphisms on the non-small cell lung cancer with Platinum chemotherapy in high altitude areas

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Research article

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Abstract

Background Repair pathway genes are closely related to the sensitivity of tumor patients to drugs. It is particularly important to study the correlation between non-small cell lung cancer (NSCLC) and DNA repair gene (GTF2H1 and RAD54L2) in high altitude areas.Materials and methods Four SNPs on RAD54L2 and five SNPs on GTF2H1 were genotyped via the Agena MassARRAY in 506 age-and gender-matched patients with NSCLC and 510 healthy controls. The influence of GTF2H1 and RAD54L2 on lung cancer was assessed by logistic regression analysis. The effects of polymorphisms of these two genes on the efficacy and side effects of NSCLC patients with platinum-based chemotherapy were further evaluated.Results RAD54L2 rs9864693 GC heterozygote genotype was increased the risk of NSCLC (OR = 1.33, 95%CI: 1.01 – 1.77, p = 0.045). Stratified analysis found that GTF2H1 rs4150667 promoted the risk of lung cancer in individuals younger than 59 years group (OR = 1.32, 95%CI: 1.00 – 1.75, p = 0.048). However, the individuals with GTF2H1 rs3802967 CT-TT reduced the risk of the lung squamous cell carcinoma by 32% (OR = 0.68, 95%CI: 0.46 – 0.99, p = 0.045). The patients with GTF2H1 rs3802967 TT genotypes showed a significantly higher curative effect (OR = 2.65, 95%CI: 1.14 - 6.15, p = 0.023); patients with GTF2H1 rs3802967 TT genotypes showed a significantly lower risk of side effects (OR = 0.32, 95%CI: 0.10 - 0.98, p = 0.047).Conclusion Our study indicated that RAD54L2 and GTF2H1 gene was associated with NSCLC susceptibility.

Background

Lung cancer is called primary bronchogenic carcinoma and is a malignant tumor derived from the trachea, bronchial mucosa or glands, and is currently the most common malignant tumor in the world[1]. According to statistics, in 2015, the incidence of lung cancer in Chinese men and women was 50.9 per 100,000 person-years and 22.4 per 100,000 person-years, respectively, which is the most important cause of death in cancer patients [2]. At present, surgery is still the treatment of choice for early stage lung cancer, most lung cancer patients have been diagnosed at an advanced stage, lost the best treatment opportunity, and its 5-year survival rate is only 19.7% [1, 3]. Most studies suggested that the occurrence of Lung cancer is related to environmental, such as smoking, occupational exposure, and air pollution [4, 5]. At the same, genetic factors play an important role in the development of lung cancer, including *EGFR*[6], *CHRNA5*[7], *CLPTM1L*[8], *TP63*[9], and so on.

GTF2H1 (general transcription factor IIH subunit 1, GTF2H1, p62) protein plays an important role in the nucleotide excision repair (NER) pathway, participates in the early damage recognition of XPC-HR23B protein, and recruits endonuclease XPG to the injury site to complete the enzymatic cleavage process[10-12]. In addition, the GTF2H1 protein is involved in transcription and regulates transcriptional activation of multiple genes[13]. One research found that the variants of rs3802967 and rs4150606 on *GTF2H1* gene increased the risk of lung cancer, and rs4150667 on *GTF2H1* gene variant reduced the risk of lung cancer [14]. So, the genetic polymorphism of *GTF2H1* gene may be involved in the pathogenesis of lung cancer.

RAD54L2, also known as *ARIP4* (Androgen Receptor-Interacting Protein 4), is a protein-coding gene, which belongs to the RAD54 subfamily of SNF2-type chromatin remodeling factor superfamily [15], and has the double-stranded DNA-dependent ATPase activity. In fact, Rad54 interacts with Rad51 and thereby enhances its ability to form cruciform and D-loops. *RAD51* catalyzes DNA repair by homologous recombination (HR) to ensure the stability of cell genome. In a study of the effects of *RAD51* G135C polymorphism on NSCLC patients treated with platinum-paclitaxel / gemcitabine Wrst line chemotherapy, we found that the G135C allele was associated with a higher survival time and had a better prognosis [16]. However, the effect of *RAD54L2* gene on the occurrence and development of lung cancer is unknown.

The occurrence and development of tumors are closely related to genetic susceptibility and mutation. The genotypes have racial differences. Gene mutation is related to regional environmental factors, perennial hypobaric hypoxia and strong ultraviolet radiation in high altitude areas. The occurrence and development of non-small cell lung cancer at altitude is not known. Lung cancer is not only the most common malignant tumor in China, but also one of the most common malignant tumors in our high altitude areas. Therefore, it is particularly important to study the correlation between lung cancer and DNA repair gene polymorphism in high altitude areas. Therefore, we chose two genes *GTF2H1* and *RAD54L2* related to DNA repair to explore their impact on the risk of non-small cell lung cancer in Chinese Han population of living high altitude areas and the efficacy and side effects of platinum chemotherapy.

Methods

Study participants

In high altitude areas, 506 age-and gender-matched patients with lung cancer and 510 healthy controls were selected from the Qinghai Province Cancer Hospital. The inclusion criteria were lung cancer confirmed by histopathology and no history of malignant tumors in other organs. Record whether patients received platinum chemotherapy, and the treatment effect (complete response, CR; partial response PR; stable disease SD; progressive disease, PD), toxicity, lymph node metastasis, clinical stage, smoking and drinking, Body Mass Index (BMI). The inclusion criteria for the control group included medical or family history without cancer or any lung disease. At the time of recruitment, each subject was interviewed by trained personnel using a structured questionnaire to obtain information about demographic characteristics.

This study was conducted under the approval of the Institutional Review Boards of Qinghai Province Cancer Hospital. All participants were aware of the content of the study and signed an informed consent.

SNP selection and genotyping

We selected the GoldMag-Mini Whole Blood Genomic DNA Purification Kit (GoldMag Co. Ltd. Xi'an City, China) to extract the DNA from the 5 ml peripheral venous blood; and Nanodrop 2000 (Gene Company Limited) was used to detect the concentration and purity of samples, DNA to ensure that the samples

could be used for subsequent experiments. rs11720298, rs4687721, rs4687592, and rs9864693 four SNPs on RAD54L2 gene and rs4150530, rs3802967, rs4150606, rs4150658, and rs4150667 on GTF2H1 were selected in our study based on minor allele frequency data more than 0.05 in the global population. Primer design and SNP typing were performed in the same way as previously published articles [17, 18]. The genotyping primers were designed with the Agena MassARRAY Assay Design 3.0 Software [19]. The Agena MassARRAY RS1000 was used for genotyping, and the related data were managed using Agena Typer 4.0 Software [19-21].

Statistical analysis

Demographic characteristics were counted. The Hardy-Weinberg equilibrium (HWE) was calculated by $\chi 2$ test [22]. Five genetic models were used to evaluate the association between gene polymorphisms and lung cancer risk. Odds ratios (ORs) and its corresponding 95%CI were estimated using an logistic regression model with adjustments for age and gender through the PLINK software [23]. Further analysis to assess the impact of polymorphism on lung cancer based on age, gender, smoking, drinking, lymph node metastasis, clinical stages, toxic and side effects, and curative effect. The threshold of p was set to 0.05.

Results

The information of the astrocytoma patients and healthy participants was shown in table 1. From the table 1, we found that the mean of age in case group and control group were 59.80±10.63 and 59.80±9.08, respectively. Of the 506 patients, 269 had lymph node metastasis and 103 had no metastasis. After treatment with platinum-based chemotherapeutic drugs, the patients with partial response and complete response was 42, stable disease and progressive disease was 100.

The table 2 shows the basic information of the four SNPs on the *RAD54L2* gene, including physical location, chromosome, minor allele frequency, HWE. And all variants meet the HWE. Associations between the *RAD54L2* gene polymorphisms and the risk of NSCLC were evaluated under different genetic models. In allele model, we did not find sites that affect the genetic susceptibility of lung cancer (Table 2). While in genotype model, the risk of the NSCLC patients with *RAD54L2* rs9864693 GC heterozygote genotype was increased, compared the individuals with GG wild type genotype, no matter crude analysis and adjusted analysis (crude analysis: OR = 1.33, 95%CI: 1.01 – 1.76, p = 0.046; adjusted analysis: OR = 1.33, 95%CI: 1.01 – 1.77, p = 0.045) (Table 3).

Stratified analysis was carried out based on age, gender, smoking, drinking, lymph node metastasis, clinical stages, toxic and side effects, and curative effect. We only found that the risk of developing NSCLC with the *RAD54L2* rs9864693 CC-GC genotype and was 1.66 times that of the GG genotype in individuals younger than 59 years group (Genotype model: OR = 1.66, 95%CI: 1.13 - 2.43, p = 0.010) (Table 4). In the additive model, *GTF2H1* rs4150667 also promoted the risk of NSCLC in individuals younger than 59 years group (OR = 1.32, 95%CI: 1.00 – 1.75, p = 0.048) (Table 4). In the dominant model, the individuals with *GTF2H1* rs3802967 CT-TT reduced the risk of the lung squamous cell carcinoma by

32%, when compared with the CC genotype individuals (OR = 0.68, 95%CI: 0.46 – 0.99, p = 0.045) (Table 4). No significant results were found in other stratified analyses.

The relationship between gene polymorphism and the efficacy and side effects of platinum chemotherapy in patients with NSCLC was further analyzed (Table 5). The results found that patients with *GTF2H1* rs3802967 TT genotypes showed a significantly higher curative effect, when compared with the CC-CT genotype (OR = 2.65, 95%CI: 1.14 - 6.15, p = 0.023); patients with *GTF2H1* rs3802967 TT genotypes showed a significantly lower risk of side effects, when compared with the CC-CT genotype (OR = 0.32, 95%CI: 0.10 - 0.98, p = 0.047).

Discussion

In our research, we found that *RAD54L2* rs9864693 and *GTF2H1* rs4150667 increased the risk of NSCLC. *GTF2H1* rs3802967 reduced the risk of the lung squamous cell carcinoma, *GTF2H1* rs3802967 “T” allele showed a significantly higher curative effect and lower risk of side effects.

GTF2H1 interacts with the C-terminus and N-terminus of XPC protein, participates in the recruitment of other protein subunits in TFIIH, and initiates the NER repair process. In our study, it was found that *GTF2H1* rs3802967 CT-TT reduced the risk of the lung squamous cell carcinoma. In the previous study, the variant of *GTF2H1* rs3802967 was also significantly associated with the risk of lung cancer[14], which is consistent with our findings. In addition, in the evaluation of efficacy and side effects after platinum-based chemotherapy, *GTF2H1* rs3802967 "T" allele showed a significant higher curative effect and lower risk of side effects. It is indicated that *GTF2H1* rs3802967 may play a protective role in the development of NSCLC. The study found that the expression of *GTF2H1* was down-regulated in lung cancer tissues[24]. The luciferase activity of the vector carrying the T allele was enhanced by lung adenocarcinoma experiments[14], suggesting that the mutation of rs3802967 may affect the binding of *GTF2H1* gene to transcription factor AP-1. In turn, it affects the expression level of *GTF2H1* gene in lung cancer, and further protects the development of lung cancer.

Stratified analysis found that GTF2H1 rs4150667 promoted the risk of NSCLC in individuals younger than 59 years group. While one research found that rs4150667 on *GTF2H1* gene variant reduced the risk of lung cancer [14]. This is contradictory to our findings. In the research of Gong et al., SNP rs4150667 from *GTF2H1* also decreased the risk of ovarian cancer (OR = 0.64)[25]. Whether the variant at this site increases or decreases the risk of the disease requires further confirmation. Besides, rs4150606 on *GTF2H1* gene increased the risk of lung cancer [14]. However, we found no correlation between the variant of rs4150606 on *GTF2H1* gene and the risk of NSCLC. This may be due to the false negative results of our small sample size, and whether these two sites are associated with the risk of lung cancer need to be further expanded.

RAD54L2 (ARIP4) on chromosomal arm 3p, was initially identified as an ATPase of the Rad54/ATRX subfamily of SNF2-like protein, which contains chromatin remodeling activity, interacts with AR and regulates androgen-mediated transactivation [26]. SNF2-like proteins are thought to modify the structure

of chromatin in a non-covalent manner through the rearrangement of nucleosomes. In our research, we found that *RAD54L2* rs9864693 GC increased the risk of NSCLC. Only RAD54L2 gene has been found to affect gastrointestinal stromal tumors, expression of *RAD54L2* with shorter overall survival [27]. The effect of *RAD54L2* gene on lung cancer is not clear. *Rad54* interacts with *Rad51*, which functions during DNA repair. It has been proved that *Rad51* G135C allele was associated with a higher survival time and had a better prognosis in NSCLC patients treated with platinum-paclitaxel / gemcitabine Wrst line chemotherapy [16]. The role of *RAD54L2* gene in the occurrence and development of lung cancer needs to be further clarified.

Conclusions

The result indicates that *RAD54L2* rs9864693 and *GTF2H1* rs3802967 and rs4150667 play an important role in the susceptibility of NSCLC. *GTF2H1* rs3802967 “T” allele showed a significantly higher curative effect and lower risk of side effects. In the next step, we will focus on exploring the molecular mechanism of mutations in these two genes in the occurrence and development of lung cancer.

Declarations

Ethics approval and consent to participate

This study was conducted under the approval of the Institutional Review Boards of Qinghai Province Cancer Hospital. All participants were aware of the content of the study and signed an informed consent.

Competing interests

The authors have declared that they have no conflict of any interests.

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Author contributions

ML drafted the manuscript. BYL and GYW performed the DNA extraction and genotyping; RC and CMF performed the data analysis; CLY performed the sample collection and information recording; ML and GQJ conceived and supervised the study.

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Data Availability

The data that support the findings in this study are available on request from the first author and correspondent author (ML and GQJ). The data are not publicly available as they contain information that could compromise research participant privacy or consent.

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Tables

Table 1 The information of the participants

Characteristics		Case	Control	*p*
Number		506	510	
Age (mean ± SD)		59.80±10.63	59.80±9.08	0.992
	≤ 59	271(54%)	275(54%)	
	59	235(46%)	235(46%)	
Gender				
	Male	350(69%)	353(69%)	
	Female	156(31%)	157(31%)	
BMI (25kg/m^2)				
	≤ 24	133(26%)	138(27%)	
	24	81(16%)	181(36%)	
Smoking				
	Yes	133(26%)	138(27%)	
	No	81(16%)	181(36%)	
	Drinking			
	Yes	109(22%)	103(20%)	
	No	267(53%)	156(31%)	
Histology				
Lung squamous cell carcinoma		174		
Lung adenocarcinoma		212		
Lymph node metastasis				
	Yes	269(53%)		
	No	103(20%)		
Clinical stages				
	I+II	93		
	III+IV	286		
Side effects				
	Yes	37		
	No	152		
Therapeutic evaluation				
	CR+PR	42		
	SD+PD	100		

Table 2 The information of nine gene polymorphisms on the RAD54L2 and GTF2H1 gene

SNP	Chromosome	Physical location	Alleles	MAF-Case	MAF-Control	Gene	HWE-*p*	OR (95%CI)	*p*
rs11720298	3	51547493	A/G	0.25	0.28	RAD54L2	0.229	0.86 (0.70 - 1.05)	0.127
rs4687721	3	51564238	A/G	0.07	0.07	RAD54L2	0.747	0.99 (0.71 - 1.39)	0.972
rs4687592	3	51621840	C/T	0.34	0.33	RAD54L2	0.159	1.07 (0.89 - 1.28)	0.490
rs9864693	3	51622354	C/G	0.45	0.42	RAD54L2	0.856	1.10 (0.92 - 1.31)	0.293
rs4150530	11	18322147	G/T	0.1	0.12	GTF2H1	0.831	0.84 (0.63 - 1.11)	0.219
rs3802967	11	18322517	A/G	0.46	0.48	GTF2H1	0.479	0.92 (0.77 - 1.09)	0.323
rs4150606	11	18342022	A/C	0.13	0.14	GTF2H1	0.591	0.91 (0.71 - 1.18)	0.485
rs4150658	11	18357336	A/G	0.1	0.12	GTF2H1	1.000	0.85 (0.64 - 1.12)	0.253
rs4150667	11	18361364	C/T	0.33	0.32	GTF2H1	0.919	1.05 (0.87 - 1.27)	0.583

Table 3 Risk analysis of RAD54L2rs9864693 and NSCLC in different genetic models by logistic regression analysis

SNP	Model	Genotype	control	case	crude analysis		adjusted analysis	
					OR (95% CI)	*p*-value	OR (95% CI)	*p*-value
RAD54L2rs9864693	Genotype	GG	171	143	1		1	
		GC	247	275	1.33 (1.01 - 1.76)	0.046	1.33 (1.01 - 1.77)	0.045
		CC	92	88	1.14 (0.79 - 1.65)	0.473	1.14 (0.79 - 1.65)	0.472
	Dominant	GG	171	143	1		1	
		GC-CC	339	363	1.28 (0.98 - 1.67)	0.069	1.28 (0.98 - 1.67)	0.069
	Recessive	GG-GC	418	418	1		1	
		CC	92	88	0.96 (0.69 - 1.32)	0.787	0.96 (0.69 - 1.32)	0.787
	Additive	-	-	-	1.1 (0.92 - 1.32)	0.282	1.1 (0.92 - 1.32)	0.282

$p < 0.05$ indicates statistical significance

Table 4 Stratified analysis of clinical variables for associations between gene polymorphism on the RAD54L2 and GTF2H1 gene and the risk of NSCLC.

Group	SNP	Model	Genotype	control	case	adjusted analysis	
						OR (95% CI)	*p*-value
≤59	RAD54L2 rs9864693	Genotype	GG	97	70	1	
			GC	101	119	1.63 (1.09 - 2.45)	0.018
			CC	37	46	1.72 (1.01 - 2.93)	0.045
		Dominant	GG	97	70	1	
			GC-CC	138	165	1.66 (1.13 - 2.43)	0.010
		Recessive	GG-GC	198	189	1	
			CC	37	46	1.30 (0.81 - 2.1)	0.277
		Additive	-	-	-	1.36 (1.05 - 1.76)	0.019
≤59	GTF2H1 rs4150667	Genotype	CC	118	98	1	
			CT	97	109	1.38 (0.94 - 2.03)	0.100
			TT	20	28	1.67 (0.88 - 3.15)	0.115
		Dominant	CC	118	98	1	
			CT-TT	117	137	1.43 (0.99 - 2.07)	0.055
		Recessive	CC-CT	215	207	1	
			TT	20	28	1.42 (0.78 - 2.61)	0.254
		Additive	-	-	-	1.32 (1.00 - 1.75)	0.048
>60	RAD54L2 rs9864693	Genotype	GG	74	73	1	
			GC	146	156	1.09 (0.73 - 1.61)	0.688
			CC	55	42	0.80 (0.47 - 1.34)	0.391
		Dominant	GG	74	73	1	
			GC-CC	201	198	1.01 (0.69 - 1.47)	0.972
		Recessive	GG-GC	220	229	1	
			CC	55	42	0.75 (0.48 - 1.18)	0.215
		Additive	-	-	-	0.91 (0.71 - 1.18)	0.488
>60	GTF2H1 rs4150667	Genotype	CC	120	127	1	
			CT	125	122	0.92 (0.64 - 1.31)	0.626
			TT	30	22	0.67 (0.36 -	0.194

					1.23)	
		Dominant	CC	120	127	1	
			CT-TT	155	144	0.87 (0.62 - 1.22)	0.411
		Recessive	CC-CT	245	249	1	
			TT	30	22	0.70 (0.39 - 1.25)	0.227
		Additive	-	-	-	0.85 (0.66 - 1.11)	0.238
Lung squamous cell carcinoma	GTF2H1 rs3802967	Genotype	CC	133	59	1	
			CT	263	79	0.67 (0.45 - 1)	0.051
			TT	114	36	0.7 (0.43 - 1.15)	0.158
		Dominant	CC	133	59	1	
			CT-TT	337	115	0.68 (0.46 - 0.99)	0.045
		Recessive	CC-CT	396	138	1	
			TT	114	36	0.9 (0.59 - 1.38)	0.629
		Additive	-	-	-	0.82 (0.64 - 1.05)	0.118

$p < 0.05$ indicates statistical significance

Table 5 Association of GTF2H1 rs3802967 polymorphisms and curative effect and side effects in NSCLC patients with Platinum chemotherapy

Group	SNP	Model	Genotype	control	case	OR (95% CI)	*p*-value
curative effect	GTF2H1 rs3802967	Genotype	CC	29	13	1	
			CT	55	15	0.62 (0.25 - 1.49)	0.283
			TT	16	14	1.98 (0.74 - 5.3)	0.171
		Dominant	CC	29	13	1	
			CT-TT	71	29	0.93 (0.42 - 2.08)	0.866
		Recessive	CC-CT	84	28	1	
			TT	16	14	2.65 (1.14 - 6.15)	0.023
		Additive	-	-	-	1.38 (0.82 - 2.32)	0.22
side effects	GTF2H1 rs3802967	Genotype	CC	50	12	1	
			CT	64	21	1.66 (0.71 - 3.86)	0.238
			TT	38	4	0.42 (0.12 - 1.46)	0.172
		Dominant	CC	50	12	1	
			CT-TT	102	25	1.13 (0.51 - 2.49)	0.764
		Recessive	CC-CT	114	33	1	
			TT	38	4	0.32 (0.10 - 0.98)	0.047
		Additive	-	-	-	0.78 (0.47 - 1.29)	0.333

$p < 0.05$ indicates statistical significance