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Correlations of UGT1A1 gene polymorphisms with onset and prognosis of non-small cell lung cancer

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Abstract. – OBJECTIVE: The aim of this study was to investigate the correlations of UDP glucuronosyltransferase family 1 member A1 (UGT1A1) gene polymorphisms with the onset and prognosis of non-small cell lung cancer.

PATIENTS AND METHODS: A total of 400 patients with non-small cell lung cancer (disease group) and healthy controls (control group) in our hospital were selected as research subjects. Genomic DNA was extracted from the peripheral blood. UGT1A1 gene polymorphisms rs8330, rs4148323 and rs35003977 were detected after Polymerase Chain Reaction (PCR) amplification. RT-qPCR was performed to measure the expression level of UGT1A1. The survival of patients was analyzed combined with their prognosis. Moreover, the expression of UGT1A1 gene in lung cancer patients from The Cancer Genome Atlas (TCGA) database was analyzed by bioinformatics, and the prognosis was analyzed.

RESULTS: According to the expression level of UGT1A1 gene from TCGA and GTEx databases, UGT1A1 gene was highly expressed in lung cancer tissues but lowly expressed in normal lung tissues, and the difference was statistically significant ($p<0.05$). Combined with the expression level of UGT1A1 and the prognostic information of lung cancer patients from TCGA database, patients with higher expression level of UGT1A1 gene exhibited significantly better prognosis than those with lower level ($p=0.0013$), suggesting that UGT1A1 gene is an anti-oncogene. There were statistically differences in allele distribution of UGT1A1 gene polymorphism rs8330 between the disease group and control group ($p=0.003$), and the frequency of allele G was higher in disease group. Moreover, the distribution of genotypes of UGT1A1 gene polymorphisms rs8330 ($p=0.006$) and rs4148323 ($p=0.003$) in the disease group was significantly different from that in the control group, and the frequencies of GG genotype of polymorphisms rs8330 and rs4148323 were higher in the disease group. Statistically significant differences in the distribution of recessive models of UGT1A1 gene polymorphism rs8330 were observed between the disease group and control group ($p=0.047$), and the disease group exhibited a lower frequency of recessive model GC + CC than control group. There were evident differences in the distribution of haplotype GGT of UGT1A1 gene polymorphisms rs8330, rs4148323 and rs35003977 between the disease group and control group ($p=0.004$), and the frequencies of haplotype GGT were higher in the disease group than those in the control group. UGT1A1 gene polymorphism rs8330 was remarkably associated with gene expression ($p<0.05$). Meanwhile, the expression of UGT1A1 gene in patients carrying genotype CC declined notably compared with that in patients carrying genotypes GG and GC ($p<0.05$). Furthermore, the polymorphism rs8330 had a significant correlation with the survival of patients in disease group ($p=0.0001$), and patients with genotype CC had the worst prognosis.

CONCLUSIONS: UGT1A1 gene polymorphisms are prominently correlated with the onset and prognosis of non-small cell lung cancer.

Key Words:
UGT1A1, Gene polymorphism, Non-small cell lung cancer.

Introduction

Lung cancer refers to the malignant tumor on the bronchial mucosa or gland of the respiratory system. The morbidity rate of lung cancer ranks top three among all malignant tumors, whose mortality rate is only next to breast cancer, showing a rising trend year by year around the world[1,2]. According to histopathological types, lung cancer can be classified into non-small cell lung cancer and small cell lung cancer. The latter has been found closely related to smoking, with a small proportion[3]. Non-small cell lung cancer accounts for the majority of lung cancer, which mainly

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leads to respiratory symptoms and local compression symptoms. The efficacy of surgical treatment for non-small cell lung cancer is relatively good[4,5]. The specific pathogeny of non-small cell lung cancer remains unclear. Existing studies have demonstrated that the disease is associated with various factors, such as smoking, family heredity, air quality, and working environment[6]. Therefore, exploring the etiology and predisposing factors of non-small cell lung cancer is of great significance for its prevention and treatment.

Gene polymorphism is considered as one of the leading causes of disease development. Meanwhile, it has been found to be associated with the susceptibility to multiple diseases[7,8]. Gene polymorphism may alter gene expressions to affect the activity and content of vital pathway molecules, thereby influencing the occurrence and development of diseases[9]. The onset of non-small cell lung cancer is correlated with the polymorphisms of multiple genes, including Caspase-9[10] and ABCG2[11]. The polymorphisms of UDP glucuronosyltransferase family 1 member A1 (UGT1A1), a gene encoding UDP-glucuronosyltransferase, probably affects the metabolic processes of lung cancer cells. This may eventually change tumor progression and the prognosis of patients.

In this research, therefore, the polymorphisms rs8330, rs4148323 and rs35003977 of UGT1A1 gene in peripheral blood were compared between patients with non-small cell lung cancer and normal subjects. The expression of UGT1A1 gene was compared among subjects as well. In addition, the survival and prognosis analysis were combined with bioinformatics analysis of UGT1A1 expression in lung cancer patients from The Cancer Genome Atlas (TCGA) database. All our findings might help to elucidate the correlations of UGT1A1 gene polymorphisms with the onset and prognosis of non-small cell lung cancer.

Patients and Methods

General Data

Patients diagnosed with non-small cell lung cancer (disease group, n=200) and healthy people receiving physical examination (control group, n=200) in our hospital were selected as research subjects. General and clinical information, including name, gender, age, past history and family history, were collected from the disease group and control group. Patients with non-small cell lung cancer were followed up by professional staff by inquiring their survival conditions, medications and general conditions *via* telephone every month. Inclusion criteria in the disease group were as follows: middle-aged and elderly patients with long-term smoking and exposure to harmful substances, those with chronic cough, blood in the sputum, dyspnea and other respiratory symptoms, those with space-occupying lesion in the lung indicated by X-ray or CT, and those with non-small cell lung cancer confirmed by biopsy. This study was approved by the Ethics Committee of China-Japan Union Hospital of Jilin University. Signed written informed consents were obtained from all participants before the study.

Sample Collection and Preprocessing

Peripheral blood samples were collected from the disease group and control group using purple anticoagulant tubes (36-37 mL/tube). The blood was drawn from patient's elbow vein after disinfection. Next, peripheral blood samples were centrifuged at 3000 rpm/min for 5 min and temporarily stored in a refrigerator at 4°C for deoxyribonucleic acid (DNA) extraction.

DNA Extraction

Genomic DNA was extracted from peripheral blood in the disease group and control group strictly according to the instructions of peripheral blood genomic DNA extraction kit (Invitrogen, Carlsbad, CA, USA). In short, peripheral blood was taken out from the refrigerator at 4°C and centrifuged at 3000 rpm/min. After that, nucleated cells in the middle layer of peripheral blood were mixed with 20 mg/mL proteinase K by Vortexing and with buffer solution by inverting the tube, followed by storage at 65°C. Next, absolute alcohol was added and mixed by shaking for 30 s, and the flocculation was added into an adsorption column for 30 min of centrifugation at 12000 rpm/min. After that, the waste liquid was poured, and the adsorption column was put back to collection tubes. Subsequently, the samples were added with deproteinizing solution, centrifuged and washed with rinsing liquid twice, followed by centrifugation again. Finally, preheated elution buffer was added into the adsorption column, placed for 2 min and centrifuged. The resulting solution was genomic DNA.

Polymerase Chain Reaction (PCR) Amplification and Analysis of Gene Polymorphisms

Primers for UGT1A1 gene polymorphisms rs8330, rs4148323 and rs35003977 were designed by Primer Premier 5 and used for PCR

amplification. Specific sequences were shown in Table I. The PCR products obtained after denaturation, annealing and extension were sent to Tianjin Biotechnology Co., Ltd. (Tianjin, China) for sequencing and polymorphism analysis.

Detection of UGT1A1 Gene

Real-Time quantitative Polymerase Chain Reaction (RT-qPCR) was performed to detect the expression level of UGT1A1 gene. Total RNA in peripheral blood nucleated cells was extracted through TRIzol method (Invitrogen, Carlsbad, CA, USA). Subsequently, extracted RNA was reversely transcribed into complementary deoxyribose nucleic acid (cDNA). RT-qPCR was then performed under the following conditions: 95°C for 5 min, (95°C for 30 s, 55°C for 40 s and 72°C for 40 s) × 45 cycles, and 72°C for 5 min. The primers for UGT1A1 gene and internal reference glyceraldehyde 3-phosphate dehydrogenase (GAPDH) gene were shown in Table I.

Bioinformatics Analysis

The expression of UGT1A gene in lung cancer tissues from TCGA database and that in normal lung tissues from Genotype-Tissue Expression (GTEx) database were analyzed using GEPIA2 tool (http://gepia2.cancer-pku.cn/#index). Meanwhile, the influences of UGT1A gene expression on the survival and prognosis of lung cancer patients were determined *via* web page tool (http://kmplot.com/analysis/).

Statistical Analysis

Statistical Product and Service Solutions (SPSS) 22.0 software (IBM Corp., Armonk, NY, USA) was used for all statistical analysis. Measurement data were compared by *t*-test. Polymorphisms were analyzed online using SHEsis website (http://analysis.bio-x.cn/myAnalysis.php), and log rank test for Kaplan-Meier curves was used for survival analysis. In order to test the population homogeneity of the study subjects, the allele frequencies were tested against Hardy-Weinberg equilibrium by the χ^2 test. $p<0.05$ was considered statistically significant.

Results

Expression of UGT1A1 Gene in Lung Cancer Tissues and Normal Lung Tissues

The expression of UGT1A1 gene in lung cancer tissues and normal lung tissues was shown in Figure 1. According to the expression level of UGT1A1 gene from TCGA and GTEx databases, UGT1A1 gene was highly expressed in lung cancer tissues but lowly expressed in normal lung tissues, and the difference was statistically significant ($p<0.05$).

Influences of UGT1A Gene Expression on the Survival and Prognosis of Lung Cancer Patients

The influences of UGT1A1 gene expression on the survival and prognosis of lung cancer patients were displayed in Figure 2. Combined with the expression level of UGT1A1 and the prognostic information of lung cancer patients from TCGA database, patients with higher expression level of UGT1A1 gene exhibited significantly better prognosis than those with lower expression ($p=0.0013$), suggesting that UGT1A1 gene is an anti-oncogene.

Table I. Primer sequences of the genes for RT-PCR.

	Forward/reverse primer	Primer sequence
Polymorphism rs8330	Forward primer	CATGCTGGGAAGATACTGTTGAT
	Reverse primer	GCCCGAGACTAACAAAAGACTCT
Polymorphism rs8330	Forward primer	TTGTCTGGCTGTTCCCACTTA
	Reverse primer	GGTCCGTCAGCATGACATCA
Polymorphism rs8330	Forward primer	CTGTCTCTGCCCACTGTATTCT
	Reverse primer	TCTGTGAAAAGGCAATGAGCAT
UGT1A1	Forward primer	TCTGCTTCTTCCGTACCTTCT
	Reverse primer	GCTTCAGGTGCTATGACCACAA
GAPDH	Forward primer	CACCTGAAGCCTCAATACACAT
	Reverse primer	CAGTCCGTCCAAGTTCCACC

RT-PCR, quantitative reverse-transcription polymerase chain reaction.

Table II. Allele distribution of UGT1A1 gene polymorphisms rs8330, rs4148323 and rs35003977 in disease group and control group.

Polymorphism	Allele	Control group	Disease group	Odds ratio (OR)	95% confidence interval (95% CI)	χ^2	*p*
rs8330	G	204 (0.510)	245 (0.613)	0.65	0.49-0.87	8.53	0.003
	C	196 (0.490)	155 (0.388)				
rs4148323	G	198 (0.495)	207 (0.517)	0.91	0.69-1.21	0.42	0.524
	A	202 (0.505)	193 (0.482)				
rs35003977	T	182 (0.455)	204 (0.510)	0.82	0.60-1.05	2.42	0.119
	G	218 (0.545)	196 (0.490)				

Allele Distribution of UGT1A1 Gene Polymorphisms rs8330, rs4148323 and rs35003977 in Disease Group and Control Group

All allele frequencies did not deviate from Hardy-Weinberg equilibrium. Based on the distribution of alleles of UGT1A1 gene polymorphisms rs8330, rs4148323 and rs35003977 (Table II), there were statistically significant differences in allele distribution of UGT1A1 gene polymorphism rs8330 between the disease group and control group (p=0.003), and the frequency of allele G was higher in disease group.

Genotype Distribution of UGT1A1 Gene Polymorphisms rs8330, rs4148323 and rs35003977 in Disease Group and Control Group

As for the distribution of genotypes of UGT1A1 gene polymorphisms rs8330, rs4148323 and rs35003977 (Table III), the distribution of genotypes of UGT1A1 gene polymorphisms rs8330 (p=0.006) and rs4148323 (p=0.003) in disease group was remarkably different from that in the control group, and the frequencies of GG genotype of polymorphisms rs8330 and rs4148323 were higher in disease group.

Analysis of UGT1A1 Gene Polymorphisms rs8330, rs4148323 and rs35003977 in Disease Group and Control Group

According to the analysis of UGT1A1 gene polymorphisms rs8330, rs4148323 and rs35003977 (Table IV), statistically significant difference was observed in the distribution of recessive models of UGT1A1 gene polymorphism rs8330 between disease group and control group (p=0.047), and the disease group exhibited a lower frequency of recessive model GC + CC than the control group.

Haplotype Distribution of UGT1A1 Gene Polymorphisms rs8330, rs4148323 and rs35003977 in Disease Group and Control Group

The distribution of haplotypes of UGT1A1 gene polymorphisms rs8330, rs4148323 and rs35003977 in the disease group and control group was shown in Table V. The results showed that there were remarkable differences in the distribution of haplotype GGT of UGT1A1 gene polymorphisms rs8330, rs4148323 and rs35003977 between the disease group and control group (p=0.004), and the frequencies of haplotype GGT were higher in the disease group than those in control group.

Table III. Genotype distribution of UGT1A1 gene polymorphisms rs8330, rs4148323 and rs35003977 in disease group and control group.

Polymorphism	Genotype	Control group	Disease group	χ^2	*p*
rs8330	GG	54 (0.270)	84 (0.420)	9.96	0.006
	GC	96 (0.480)	77 (0.385)		
	CC	50 (0.250)	39 (0.195)		
rs4148323	GG	41 (0.205)	62 (0.310)	11.22	0.003
	GA	116 (0.580)	83 (0.415)		
	AA	43 (0.215)	55 (0.275)		
rs35003977	TT	43 (0.215)	46 (0.230)	4.83	0.089
	TG	96 (0.480)	112 (0.560)		
	GG	61 (0.305)	42 (0.210)		

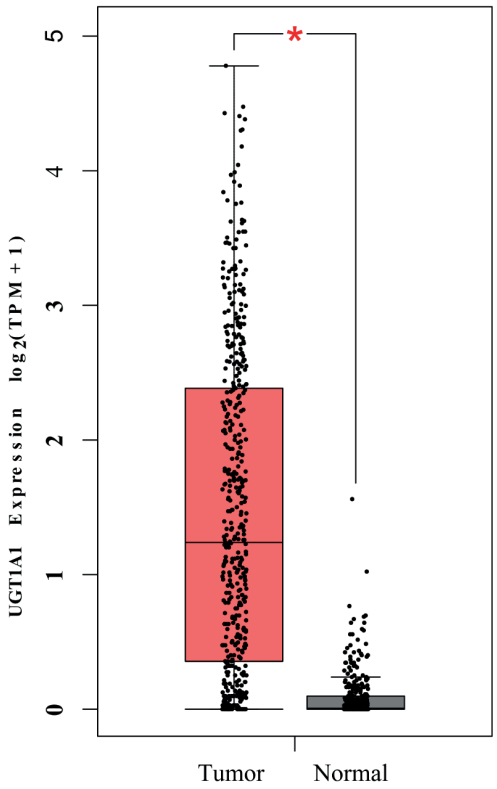

Figure 1. Expression of UGT1A1 gene in lung cancer tissues and normal lung tissues (*p<0.05).

Correlations of UGT1A1 Gene Polymorphisms rs8330, rs4148323 and rs35003977 with Gene Expression in Disease Group and Control Group

The correlations of UGT1A1 gene polymorphisms rs8330, rs4148323 and rs35003977 with gene expression were analyzed (Figure 3). The results demonstrated that UGT1A1 gene polymorphism rs8330 was remarkably associated with gene expression (p<0.05). Meanwhile, the expression of UGT1A1 gene in patients carrying genotype CC declined notably compared with that in patients carrying genotypes GG and GC (p<0.05).

Impacts of UGT1A1 Gene Polymorphism rs8330 on Survival and Prognosis in Disease Group

The impacts of UGT1A1 gene polymorphism rs8330 on the survival and prognosis of patients in disease group were displayed in Figure 4. Since UGT1A1 gene polymorphism rs8330 was evidently related to gene expression, the correlation between this polymorphism and patient's prognosis was determined. The results illustrated that the polymorphism rs8330 had a significant correlation with the survival of patients in disease group (p=0.0001), and patients with genotype CC had the worst prognosis. Moreover, these patients had a higher expression level of UGT1A1 gene (Figure 3). Therefore, the results were consistent with those in Figure 2.

Discussion

With the increasing incidence and death number of lung cancer in China and other countries in the world, scientific researchers have paid more and more attention to the pathogeny and predisposing factors of lung cancer[12]. Non-small cell lung cancer is a pathological type, accounting for the vast majority of lung cancer cases. More than half of these patients have already been diagnosed in the advanced stage, usually accompanied with lymph node infiltration and distant

Table IV. Analysis of UGT1A1 gene polymorphisms rs8330, rs4148323 and rs35003977 in disease group and control group.

	Polymorphism	Genotype	Control group	Disease group	χ^2	p
Dominant model	rs8330	GG + GC	150 (0.750)	161 (0.805)	3.69	0.297
		CC	50 (0.250)	39 (0.195)		
	rs4148323	GG + GA	157 (0.785)	145 (0.725)	5.33	0.149
		AA	43 (0.215)	55 (0.275)		
	rs35003977	TT + TG	139 (0.695)	158 (0.790)	2.23	0.526
		GG	61 (0.305)	42 (0.210)		
Recessive model	rs8330	GG	54 (0.270)	84 (0.420)	7.96	0.047
		GC + CC	146 (0.730)	116 (0.580)		
	rs4148323	GG	41 (0.205)	62 (0.310)	1.82	0.611
		GA + AA	159 (0.795)	138 (0.690)		
	rs35003977	TT	43 (0.215)	46 (0.230)	2.15	0.542
		TG + GG	157 (0.785)	154 (0.770)		

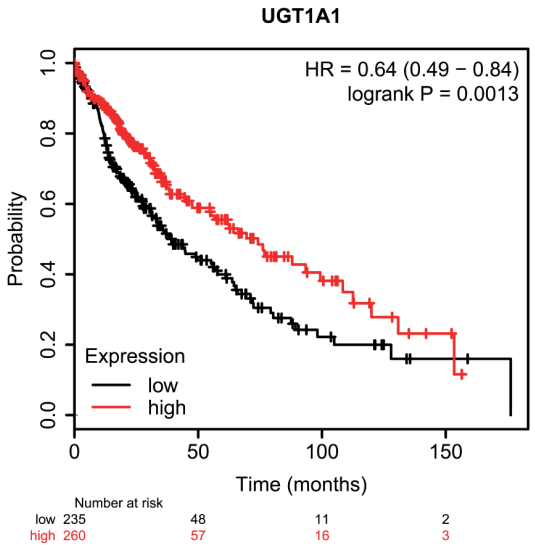

Figure 2. Influences of UGT1A gene expression on the survival and prognosis of lung cancer patients.

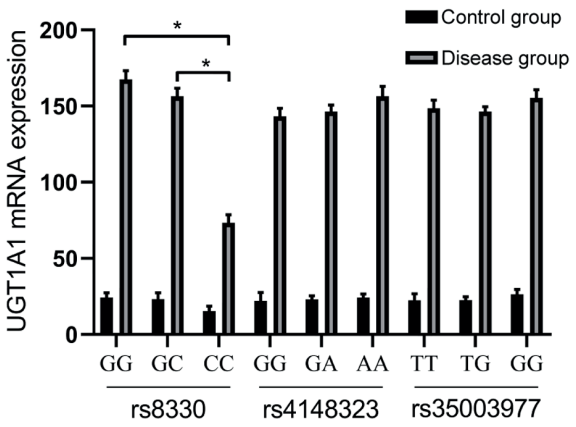

Figure 3. Correlations of UGT1A1 gene polymorphisms rs8330, rs4148323 and rs35003977 with gene expression (*p<0.05).

metastasis. Statistics have shown that these patients are difficult to be treated and are prone to recurrence[13]. Hence, finding highly predisposing factors and preventing non-small cell lung cancer are of important significance for decreasing its morbidity and mortality rates. Moreover, this may be even more significant than studying the treatment strategies for the disease. Existing studies have manifested that non-small cell lung cancer is related to the exposure to harmful substances, such as oil fume, industrial waste gas, asbestos and inorganic arsenic. Meanwhile, it is associated with the decreased intake of vitamins and other cancerocidal substances[14]. Persistent pulmonary inflammation induced by such chronic diseases as pulmonary tuberculosis and chronic viral infections is the cause of non-small cell lung cancer as well[15]. In addition, non-small cell lung cancer has been confirmed closely associated with heredity,

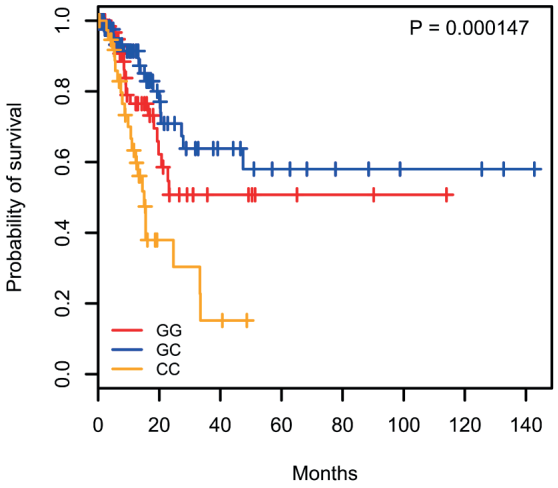

Figure 4. Impacts of UGT1A1 gene polymorphism rs8330 on survival and prognosis in disease group.

Table V. Haplotype distribution of UGT1A1 gene polymorphisms rs8330, rs4148323 and rs35003977 in disease group and control group.

Haplotype	Control group	Disease group	OR	95% CI	χ^2	p
CAG	52.97 (0.132)	37.06 (0.093)	0.669	0.429-1.044	3.167	0.075
CAT	43.97 (0.110)	35.08 (0.088)	0.778	0.488-1.242	1.11	0.292
CGG	52.36 (0.131)	43.82 (0.110)	0.817	0.533-1.253	0.863	0.353
CGT	46.69 (0.117)	39.04 (0.098)	0.818	0.522-1.283	0.765	0.382
GAG	55.23 (0.138)	60.32 (0.151)	1.109	0.747-1.645	0.262	0.609
GAT	49.82 (0.125)	60.53 (0.151)	1.253	0.837-1.876	1.205	0.272
GGG	57.43 (0.144)	54.79 (0.137)	0.947	0.635-1.411	0.072	0.788
GGT	41.51 (0.104)	69.35 (0.173)	1.811	1.199-2.737	8.116	0.004

and the incidence of patients with a family history is higher. Previous studies[16,17] have shown that the causes of non-small cell lung cancer include proto-oncogene mutation and anti-oncogene inactivation, among which gene polymorphism is a crucial player in genetic process. Therefore, researching the relationship between gene polymorphism and the occurrence of non-small cell lung cancer can help to seek for and screen predisposing factors.

As a member of the UGT gene family, UGT1A1 gene is located on chromosome 2q37. It is composed of 5 exons and distributed in various tissues[18]. UGT1A1 gene encodes the enzymes of a kind of glucuronidation pathway, and it can convert small lipophilic molecules (e.g., steroids and drugs) into water-soluble and dischargeable metabolites[19]. It has been discovered that UGT1A1 is correlated with the progression of multiple tumors, including rectal cancer[20]. UGT1A1 gene manifests great differences in sequences among populations in forms of insertion, translocation and polymorphism. Therein, UGT1A1 gene polymorphism has been proved to have correlations with the occurrence and development of a variety of diseases, such as breast cancer[21]. In this study, UGT1A1 gene polymorphisms rs8330, rs4148323 and rs35003977 in peripheral blood nucleated cells were compared between non-small cell lung cancer patients and normal people. It was indicated that the distribution of alleles of UGT1A1 gene polymorphism rs7224199 was significant different between the disease group and control group (p=0.003), and the frequency of allele G was higher in the disease group. Statistically significant differences were observed in the distribution of genotypes of UGT1A1 gene polymorphisms rs8330 (p=0.006) and rs4148323 (p=0.003) between disease group and control group, and disease group had higher frequencies of GG genotype of polymorphisms rs8330 and rs4148323. All these results illustrate that UGT1A1 gene polymorphisms has prominent effects on the susceptibility to non-small cell lung cancer, which may serve as an important factor for early screening and prevention of this disease.

The analysis of two genotypes of a single polymorphism revealed that there was a significant difference in the distribution of recessive models of UGT1A1 gene polymorphism rs8330 between the disease group and control group (p=0.047). The frequency of recessive model GC + CC was lower in the disease group than that in the control group. Haplotype analysis also demonstrated that the distribution of haplotype GGT of UGT1A1 gene polymorphisms rs8330, rs4148323 and rs35003977 displayed significant differences between the disease group and control group (p=0.004), and disease group had increased frequencies of haplotype GGT in comparison with control group. These findings verify the above viewpoints that UGT1A1 gene polymorphisms affect the incidence of non-small cell lung cancer. This further suggests that such influences probably result from the joint action of multiple complex polymorphisms.

In the meantime, the expression level of UGT1A1 gene from TCGA and GTEx databases was analyzed *via* bioinformatics methods. It was indicated that UGT1A1 gene was highly expressed in lung cancer tissues but lowly expressed in normal lung tissues, showing a statistically significant difference (p<0.05). Based on the expression level of UGT1A1 and the prognostic information of lung cancer patients from TCGA database, patients with higher expression level of UGT1A1 gene had significantly better prognosis than those with lower expression (p=0.0013). Our results demonstrated that UGT1A1 gene polymorphism rs8330 had a significant relationship with gene expression. Meanwhile, the expression of UGT1A1 gene in patients with genotype CC was distinctly lower than that in patients with genotypes GG and GC (p<0.05). Additionally, there was a close relationship between polymorphism rs8330 and survival in disease group (p=0.0001), and patients carrying genotype CC had the worst prognosis.

Conclusions

The novelty of this study was that UGT1A1 gene polymorphisms are prominently correlated with the onset and prognosis of non-small cell lung cancer.

Conflict of Interest

The Authors declare that they have no conflict of interests.

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