Technology in Cancer Research & Treatment
Volume 19: 1-5

DOI: 10.1177/1533033820943244
journals.sagepub.com/home/tct
SAGE

Association of ERCC5 Genetic Polymorphisms With Cirrhosis and Liver Cancer

Gang Yang, MM[1], Yuxia Yang, BD[1], Xin Ma, BD[1], Lijun Huang, MM[1], Wenbin Li, MM[1], Xuejuan Song, BD[1], Huiqin Zhang, MM[1], Wenwen Liu, BD[1], and Juanjuan Lu, MM[1]

Abstract

Introduction: To explore association of excision repair cross-complementing 5 (*ERCC5*) genetic polymorphisms with cirrhosis and liver cancer. **Methods:** A total of 365 patients were enrolled, including control group (n = 133), cirrhosis group (n = 122), and liver cancer group (n = 110). The genotyping of *ERCC5* rs2016073, rs751402, rs2094258, rs2296147, and rs2296148 was measured by using MassARRAY iPLEX technology. **Results:** There were no significant differences in gender and drinking among the 3 groups ($P > .05$). There were significant differences among the 3 groups in both age-group $\leq$60 and >60 subgroup patients. Locus rs2016073 was significantly different among 3 groups, and genotype GG (n = 0) was not observed in liver cancer group. As for locus rs751402, there were significant differences among 3 groups, and genotype AA (n = 0) was not observed in liver cancer group. As for locus rs2094258, there were no significant differences among 3 groups. Locus rs2296147 showed no significant differences among 3 groups ($P > .05$), but genotype CC was not observed in liver cancer group (n = 0). As for locus rs2296148, there were significant differences among 3 groups, and genotype TC (n = 0) was not observed in cirrhosis group. Regression analysis found locus rs751402 had significant difference between control group and cirrhosis group, patients with genotype AA and genotype GG were more likely to have cirrhosis than those with genotype GA. **Conclusion:** Our study suggested that genotype AA, genotype GG of *ERCC5* locus rs751402, and genotype TC of locus rs2296148 may be important targets for cirrhosis, while *ERCC5* polymorphisms (rs2016073 and *ERCC5* polymorphisms, rs2016073 with genotype GG, and rs751402 with genotype AA) may be potential markers for liver cancer.

Keywords

ERCC5, genetic polymorphism, cirrhosis, liver cancer

Abbreviations

OR, odds ratio; SNP, single nucleotide polymorphisms.

Received: December 19, 2019; Revised: June 21, 2020; Accepted: June 24, 2020.

Introduction

Liver cancer ranks the sixth in cancer incidence and the second in tumor-related mortality worldwide, with over half of the new cases and deaths occur in China.[1] Cirrhosis is a chronic liver disease and it can advance to liver cancer.[2] Liver cancer is an often fatal malignant tumor with a high recurrence rate and chemoresistance.[3] The relationship between time interval from diagnosis to treatment and survival status of patients with early-stage liver cancer was explored.[4] However, further mechanisms of cirrhosis and liver cancer were still ambiguous.

Excision repair cross-complementing (*ERCC*) genes, key components of the nucleotide excision repair pathway, are regarded as crucial factors for DNA repair capacity.[5] *Excision repair cross-complementing 5* shows an effect on regulating

[1] Digestive Department, Gansu Provincial Hospital, Lanzhou, China

Corresponding Author:
Juanjuan Lu, Gansu Provincial Hospital, 204 Donggang West Road, Lanzhou 730000, China.
Email: juan_lu19@sina.com

Table 1. The PCR Primers.

Genotyping	Primers
rs2016073	ACGTTGGATGCTCCTTTGGAAAGGCTTATC(2nd-PCRP)
	ACGTTGGATGAAGCAGGAAGGGCTTCTAGG(1st-PCRP)
rs751402	ACGTTGGATGGTATTAGACGGAAACCGAGC(2nd-PCRP)
	ACGTTGGATGAAACAGCCAGAAGATGTCCC(1st-PCRP)
rs2094258	ACGTTGGATGCAATTTCCCGTATACTTCTG(2nd-PCRP)
	ACGTTGGATGAACTCAGTGAAAAGGCTGAC(1st-PCRP)
rs2296147	ACGTTGGATGCAGACGTTTGGGCCTAAGC(2nd-PCRP)
	ACGTTGGATGAACACGTCTCAGCAGCTGTC(1st-PCRP)
rs2296148	ACGTTGGATGATTCTTCTACGACGGACTGC(2nd-PCRP)
	ACGTTGGATGCTTTGTTGTGTAGGAGCAGG(1st-PCRP)

DNA excision repair, and DNA repair capacity may be changed by its functional single nucleotide polymorphisms (SNPs), which may contribute to cancer risk.[6] Many early studies have found *ERCC5* polymorphisms to be a potential marker for a variety of cancers.[7-9] Individuals with the inherited ERCC rs751402 CC genotype may experience significant protection against hepatocellular carcinoma, whereas individuals with T alleles appear to be exposed to higher risk.[10] The expression of *ERCC5* protein was significantly increased in tumor tissues compared with paracancerous tissues, and high expression of *ERCC5* predicted a poor prognosis in hepatocellular carcinoma.[11] However, there are very few reports about association of *ERCC5* gene polymorphisms with cirrhosis and liver cancer. Whether *ERCC5* polymorphisms could be used as potential marker for liver cancer was still unknown.

Therefore, this study was designed to explore association of *ERCC5* genetic polymorphisms with cirrhosis and liver cancer. The association of *ERCC5* gene polymorphisms (rs2016073, rs751402, rs2094258, rs2296147, and rs2296148) with cirrhosis and liver cancer was explored by MassARRAY iPLEX technology in this study.

Material and Methods

Patients

This is a prospective, single center, observational study. In this study, 365 patients were enrolled from the Gansu Provincial Hospital between October 2015 and December 2018. All patients were classified into 3 groups: control group (n = 133), cirrhosis group (n = 122), and liver cancer group (n = 110). The basic medical data of patients were obtained from medical records. A standardized questionnaire including social-demographic characteristics was implemented in patients and control. Our study was approved by The Mercy Health Research Ethics Committee of Gansu Provincial Hospital (approval no. 003017). All patients provided written informed consent prior to enrollment in the study.

DNA Extraction and SNPs Genotyping

TIANamp Blood DNA Kit (DP348-03, Tiangen) was used to extract DNA from peripheral blood samples according to instructions. The genotyping of *ERCC5* rs2016073, rs751402, rs2094258, rs2296147, and rs2296148 was analyzed by MassARRAY iPLEX technology (Shanghai Genechem Co, Ltd). The PCR fragments of the investigated polymorphisms were subsequently digested with their specific restriction enzyme. The PCR reaction conditions were shown as follows: 95 °C for 2 minutes, 45 cycles at 95 °C for 30 seconds, annealing at 56 °C for 30 seconds, extension at 72 °C for 60 seconds, and final extension at 72 °C for 5 minutes. After desalted with resin, the Typer software automatically interprets the molecular weight peaks detected by the mass spectrometry, and the transformation shows the molecular mass spectrum peak map corresponding to the SNP site. The PCR primers are listed in Table 1.

Statistical Analysis

Statistical analysis was performed by using SPSS 17.0 software (SPSS Inc). The differences of social-demographic characteristics among patients in 3 groups were compared using χ^2 test. The odds ratio (OR) values in cirrhosis group and liver cancer group were analyzed by regression analysis. P value <.05 was considered as significant.

Results

Basic Information of the Control Group and Liver Cirrhosis, Liver Cancer Group

The study included 133 controls, 122 patients with cirrhosis and 110 patients with liver cancer. The number of male patients in the control group, the cirrhosis group, and liver cancer group were 80, 74, and 72, respectively, and the female patients were 53, 48, and 38. There was no significant difference in gender between the 3 groups ($P > .05$). In addition, the number of people drinking alcohol in the control group, the cirrhosis group, and liver cancer group were 57, 48, and 36, respectively. The number of people who did not drink alcohol was 76, 74, and 74. There were no significant differences in drinking between the 3 groups ($P > .05$). There were significant differences between the 3 groups in the age-group ≤60 and >60 subgroups, the patients in the liver cancer group were older

Table 2. Basic Characteristics Among 3 Groups.

Characteristics	Control	Cirrhosis	Liver cancer	χ^2	*P* value
Gender					
Male, n (%)	80 (35.4)	74 (32.7)	72 (31.9)	0.8421	.6563
Female, n (%)	53 (38.1)	48 (34.5)	38 (27.4)		
Drinking					
Yes, n (%)	57 (40.4)	48 (34.1)	36 (25.5)	2.645	.2664
No, n (%)	76 (34.0)	74 (33.0)	74 (33.0)		
Age (years)	65.3 ± 14.2	61.3 ± 16.4			.0379
≤60, n (%)	106 (48.0)	74 (33.6)	41 (18.4)	45.37	<.0001
>60, n (%)	27 (18.8)	48 (33.3)	69 (47.9)		

Table 3. Comparison of Genetic Loci Among Control Group, Cirrhosis Group, and Liver Cancer Group.

Loci	Genotypes	Control	Cirrhosis	Liver cancer	χ^2	*P* value
rs2016073	AA	67	72	54	27.577	<.0001
	GG	20	18	0		
	AG	46	32	56		
rs751402	AA	20	26	0	39.497	<.0001
	GG	67	72	54		
	GA	48	24	56		
rs2094258	CC	47	49	13	9.332	.053
	TT	16	24	7		
	CT	70	49	33		
rs2296148	CC	128	122	101	9.636	.008
	TC	7	0	9		
rs2296147	CC	4	8	0	7.93	.094
	TT	76	66	64		
	CT	55	48	46		
rs2296148	CC	128	122	101	9.636	.008
	TC	7	0	9		

and the difference was significantly different ($P < .0001$; Table 2).

Comparison of Genetic Loci Among Control Group, Cirrhosis Group, and Liver Cancer Group

In this study, *ERCC5* rs2016073, rs751402, rs2094258, rs2296147, and rs2296148 polymorphisms were analyzed. Our results found that locus rs2016073 was significant difference among 3 groups ($P < .0001$), and genotype GG was not observed in liver cancer group due to there was no genotype GG found in liver cancer group. As for locus rs751402, there were significant differences among 3 groups ($P < .0001$), and genotype AA was not observed in liver cancer group due to there was no genotype AA found in liver cancer group. As for locus rs2094258, there were no significant differences among 3 groups ($P > .05$). Locus rs2296147 showed no significant differences among 3 groups ($P > .05$), but genotype CC was not observed in liver cancer group due to there was no genotype CC found in liver cancer group. As for locus rs2296148, there were significant differences among 3 groups ($P < .05$), and genotype TC was not observed in cirrhosis group due to there was no genotype TC found in cirrhosis group (Table 3).

Regression Analysis of Genetic Loci Among 3 Groups

Regression analysis was performed for *ERCC5* rs2016073, rs751402, rs2094258, rs2296147, and rs2296148 polymorphisms between control group and cirrhosis group, as well as between control group and liver group. However, only locus rs751402 had significant difference between control group and cirrhosis group. The OR value of genotype AA in locus rs751402 was 2.600 (1.214-5.568), indicating that patients with genotype AA were more likely to have cirrhosis than those with genotype GA. And the OR value of genotype GG in locus rs751402 was 2.149 (1.189-3.886), indicating that patients with genotype GG were more likely to have cirrhosis than those with genotype GA (Table 4).

Discussion

As for DNA repair genes, there are many SNPs that may play an important role in impairing protein function and attenuating DNA repair capability, in which may cause genomic instability and individual predisposition to malignancies.[12] *Excision repair cross-complementing 5* can regulate DNA excision repair, and removal of bulky lesions caused by environmental chemicals or UV light.[13] *Excision repair cross-complementing 5* is a novel biomarker of ovarian cancer prognosis and a potential therapeutic target of ovarian cancer response to platinum chemotherapy.[7] In this study, our results found that *ERCC5* gene polymorphisms (rs2016073, rs751402, rs2094258, rs2296147, and rs2296148) were related to cirrhosis and liver cancer, indicating that *ERCC5* gene polymorphisms may serve as new biomarkers for liver diseases.

Only one report found that *ERCC5* promoter polymorphism (rs2016073) was showed a relationship with chemosensitivity of oxaliplatin-based chemotherapy in patients with advanced colorectal cancer.[14] In our study, locus rs2016073 showed significant difference among 3 groups, genotypes AA and AG were found in 3 groups, but genotype GG was only found in liver cancer group, suggesting that genotype GG may be an import genotype to distinguish liver cancer from control and cirrhosis.

The association between SNPs in the *ERCC5* promoter (rs751402) and development of gastric cancer in a Chinese population was found.[15] Stratification by cancer type indicated that rs751402 polymorphism may increase the risk of gastric cancer and hepatocellular carcinoma, which was further confirmed by a false-positive report probability analysis.[16] In addition, *ERCC5* rs751402 polymorphism may be associated with risk of salivary gland tumors.[17] In our study, locus rs751402 showed significant difference among 3 groups, and genotypes GG and GA were found in 3 groups, but genotype AA was only found in liver cancer group, suggesting that genotype AA may be an import genotype to distinguish liver cancer from control

Table 4. Regression Analysis of Genetic Loci Among 3 Groups.

		Control and cirrhosis		Control and liver cancer	
Loci	Genotypes	OR (95% CI)	*P* value	OR (95% CI)	*P* value
rs2016073	AG	1		1	
	AA	1.545 (0.882-2.706)	1.545	0.662 (0.390-1.124)	.127
	GG	1.294 (0.593-2.823)	1.294	0	.998
rs751402	GA	1		1	
	AA	2.600 (1.214-5.568)	.014	0	.998
	GG	2.149 (1.189-3.886)	.011	0.691 (0.408-1.169)	.168
rs2094258	CT	1		1	
	CC	1.596 (0.930-2.739)	.157	0.660 (0.371-1.174)	.157
	TT	2.250 (1.084-4.671)	.675	1.177 (0.550-2.518)	.675
rs2296147	CT	1		1	
	CC	2.292 (0.649-8.088)	.197	0	.999
	TT	0.995 (0.598-1.655)	.985	1.007 (0.602-1.683)	.979
rs2296148	CC			0.614 (0.221-1.705)	.349

Abbreviation: OR, odds ratio.

and cirrhosis. Patients with genotype AA or GG were more likely to have cirrhosis than those with genotype GA.

The rs2094258 polymorphism may be related to the increased risk of GC in Southern China.[18] A case–control study found that *ERCC5* rs2094258 polymorphism may relate to the risk of breast cancer.[19] Previous study found that *ERCC5* rs2094258 showed no association with gastric cancer susceptibility.[8] The same results were found in our study that rs2094258 was no significant difference among 3 groups, suggesting that rs2094258 was not associated with cirrhosis and liver cancer.

Excision repair cross-complementing 5 variant rs2296147 T-allele creates a predicted TP53 binding site and upregulates transcript abundance in normal bronchial epithelial cells.[20] *Excision repair cross-complementing 5* rs2296147 reduced the risk of esophageal cancer, and the results of stratified analysis showed that rs2296147 could reduce the susceptibility to esophageal cancer in women, nonsmokers, drinkers, and nondrinkers.[21] *Excision repair cross-complementing 5* rs2296147 C variant genotypes were associated with a significantly lower ESCC risk.[6] In our study, locus rs2296147 was no significant differences among 3 groups ($P > .05$), indicating that locus rs2296147 may be not related to cirrhosis and liver cancer.

The last locus explored in our study was locus rs2296148. Only one study showed that 372C > T (rs2296148) was not associated with Clinical outcome of oxaliplatin-based chemotherapy in Chinese patients with advanced colorectal cancer.[22] As for locus rs2296148, there were significant differences among 3 groups ($P < .05$), and genotype TC was not observed in cirrhosis group due to there was no genotype TC found in cirrhosis group. Our study provided a reference for rs2296148 to become a marker of liver cancer.

In conclusion, 5 *ERCC5* gene polymorphisms (rs2016073, rs751402, rs2094258, rs2296147, and rs2296148) were explored in our study, and our results found that loci (rs2016073, rs751402, and rs2296148) significant differences among control, cirrhosis, and liver cancer groups, especially genotype AA and genotype GG of rs751402 had significant higher OR value, indicating that they may be important targets for cirrhosis. *Excision repair cross-complementing 5* gene polymorphisms may exert important functions on cirrhosis and liver cancer. Due to small sample size and basic research, further validation by case–control studies with large samples is still needed.

Authors' Note

G.Y. and Y.Y. are cofirst authors. Our study was approved by The Mercy Health Research Ethics Committee of Gansu Provincial Hospital (approval no. 003017). All patients provided written informed consent prior to enrollment in the study.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This study was supported by the Scientific Research Plan Project of Health Industry of Gansu Province (GSWSKY2018-22).

ORCID iD

Juanjuan Lu https://orcid.org/0000-0001-8446-6382

References

1. Fu J, Wang H. Precision diagnosis and treatment of liver cancer in China. *Cancer Lett*. 2017;412:283-288.
2. Roehlen N, Crouchet E, Baumert TF. Liver fibrosis: mechanistic concepts and therapeutic perspectives. *Cells*. 2020;9(4):875.
3. Nio K, Yamashita T, Kaneko S. The evolving concept of liver cancer stem cells. *Mol Cancer*. 2017;16(1):4.
4. Tsai WC, Kung PT, Wang YH, Kuo WY, Li YH. Influence of the time interval from diagnosis to treatment on survival for early-stage liver cancer. *PLoS One*. 2018;13(6):e0199532.

5. Zhao M, Li S, Zhou L, Shen Q, Zhu H, Zhu X. Prognostic values of excision repair cross-complementing genes mRNA expression in ovarian cancer patients. *Life Sci*. 2018;194:34-39.
6. Zhu ML, Shi TY, Hu HC, et al. Polymorphisms in the ERCC5 gene and risk of esophageal squamous cell carcinoma (ESCC) in Eastern Chinese populations. *PLoS One*. 2012;7(7):e41500.
7. Walsh CS, Seishi O, Hisae K, et al. ERCC5 is a novel biomarker of ovarian cancer prognosis. *J Clin Oncol*. 2008;26(18): 2952-2958.
8. Namazi A, Foratyazdi M, Jafari MA, et al. Association between polymorphisms of ERCC5 gene and susceptibility to gastric cancer: a systematic review and meta-analysis. *Asian Pac J Cancer Prev*. 2017;18(10):2611-2618.
9. Schrama D, Scherer D, Schneider M, et al. ERCC5 p.Asp1104His and ERCC2 p.Lys751Gln polymorphisms are independent prognostic factors for the clinical course of melanoma. *J Invest Dermatol*. 2011;131(6):1280-1290.
10. Yoon AJ, Kuo WH, Lin CW, Yang SF. Role of ERCC5 polymorphism in risk of hepatocellular carcinoma. *Oncol Lett*. 2011; 2(5):911-914.
11. Zheng X, Chen K, Liu X, Jiang G, Liu H. High expression of ERCC5 predicts a poor prognosis in hepatocellular carcinoma. *Int J Clin Exp Pathol*. 2018;11(7):3664-3670.
12. Geng P, Ou J, Li J, et al. A comprehensive analysis of influence ERCC polymorphisms confer on the development of brain tumors. *Mol Neurobiol*. 2016;53(4):2705-2714.
13. Mei-Ling Z, Mengyun W, Zhi-Gang C, et al. Association between the ERCC5 Asp1104His polymorphism and cancer risk: a meta-analysis. *PLoS One*. 2012;7(7):e36293.
14. Chen JF, Liang HJ, Wang D, Tong JT, Liao LCC, Hospital S. Relationship between ERCC5 promoter polymorphism and chemosensitivity of oxaliplatin-based chemotherapy in patients with advanced colorectal cancer. *Chin Clin Oncol*. 2009; 14(10):870-874.
15. Lu JJ, Zhang HQ, Mai P, et al. Lack of association between ERCC5 gene polymorphisms and gastric cancer risk in a Chinese population. *Genet Mol Res*. 2016;15(2).
16. Zhou H, Shi TY, Zhang W, et al. XPG gene rs751402 C>T polymorphism and cancer risk: evidence from 22 publications. *Oncotarget*. 2017;8(32):53613-53622.
17. Meng X, Wang QX, Chen MY, Qin G, Wang YP, Liu WX. DNA repair gene polymorphisms in ERCC4 rs6498486 and ERCC5 rs751402 and risk of salivary gland tumors [in Chinese]. *Shanghai Kou Qiang Yi Xue*. 2013;22(4):438-442.
18. Zhang Z, Yin J, Xu Q, Shi J. Association between the XPG gene rs2094258 polymorphism and risk of gastric cancer. *J Clin Lab Anal*. 2018;32(8):e22564.
19. Nari N, Eer D, Lidong R, Guoxin L. Association between ERCC5 gene polymorphisms and breast cancer risk. *Int J Clin Exp Pathol*. 2015;8(3):3192-3197.
20. Zhang X, Crawford EL, Blomquist TM, et al. Abstract 2890: ERCC5 variant rs2296147 T-allele creates a predicted TP53 binding site and up-regulates transcript abundance in normal bronchial epithelial cells, while rs17655 C-allele is linked to miRNA binding site variant and down regulates. *Mol Cell Biol*. 2016;76(14): 2890-2890.
21. Zhang C, Liao Z, Yu G, Huang W, Song X. Study on association between ERCC5 single nucleotide polymorphism and susceptibility to esophageal cancer. *J BUON*. 2017;22(4):979-984.
22. Chen JF, Liang HJ, Zou L, et al. Relationship between ERCC5+25A>G polymorphism and clinical outcome of patients with advanced colorectal cancer treated with platinum-based chemotherapy. *Chin Clin Oncol*. 2011;16(1):9-13.