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The association between rs2910164 in miR-146a and hepatocellular carcinoma risk: a case-control study.

Lei Duan, Wei-xing Wang*

Department of Hepatobillary and Laparoscopic Surgery, Renmin Hospital of Wuhan University, Wuhan, Hubei Province, PR China

Abstract

Several studies reported the association between the miR-146a rs2910164 polymorphism and Hepatocellular Carcinoma (HCC) risk, but the results were controversial. Thus, we did a case-control study to determine the association between miR-146a rs2910164 polymorphism and HCC risk. This study included 188 HCC cases and 186 controls. HCC was diagnosed by liver biopsy. Healthy individuals undergoing routine medical examination without any medical illness. CG genotype in HCC patients with miR-146a rs2910164 polymorphism increased the risk of HCC (OR=1.99, 95% CI 1.27-3.11, P=0.003). CC genotype in HCC patients with miR-146a rs2910164 polymorphism also showed an increased risk of HCC (OR=3.30, 95% CI 1.72-6.32, P=0.0003). In addition, patients with CG and CC had significant increased risk of HCC (OR=2.24, 95% CI 1.47-3.42, P=0.0002) in dominant model. Further, patients with CC genotype also had increased risk of HCC (OR=2.29, 95% CI 1.25-4.19, P=0.0002) in recessive model. The C allele seemed to be a risk factor of HCC (OR=1.88, 95% CI 1.39-2.54, P<0.0001). In conclusion, the study suggested that miR-146a rs2910164 polymorphism was significantly associated with HCC risk.

Keywords: Hepatocellular carcinoma, MicroRNA, Polymorphism, Association.

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Introduction

Hepatocellular Carcinoma (HCC) is known as a major cancer killer in China. Previous study suggested 782,500 new HCC cases and 745,500 deaths occurred worldwide, and China alone accounted for about 50% of these cases and deaths [1]. In recent years there has been a significant progress in clarifying risk factors for hepatocarcinogenesis. However, the etiology of HCC still remains elusive. Genetic factors may contribute to hepatocarcinogenesis mechanism.

MicroRNAs (miRNAs and miRs) are endogenous single-stranded fragments composed by 18-24 nucleotides. Several studies have shown that miRNAs play important roles in the etiology of HCC [2,3]. Zu et al. suggested that miR-146a suppresses HCC by down-regulating TRAF6 [4]. Sun et al. indicated that miR-146a expression was regulated by aberrantly activated STAT3 in HCC cells and exerted negative effects on anti-tumor immune response [5]. Tomokuni et al. indicated that miR-146a regulated the sensitivity of HCC cells to the cytotoxic effects of IFN-α through SMAD4 [6]. Several studies reported the association between the miR-146a rs2910164 polymorphism and HCC risk, but the results were controversial [7,8]. Thus, we did a case-control study to determine the association between miR-146a rs2910164 polymorphism and HCC risk.

Methods

Study subjects

This study included 188 HCC cases and 186 controls. HCC was diagnosed by liver biopsy. Healthy individuals undergoing routine medical examination without any medical illness. Informed consent for sample collection and subsequent analysis was obtained from each subject at recruitment. This study was approved by Renmin Hospital of Wuhan University.

Genotyping assay of miR-146a rs2910164 polymorphism

DNA was extracted from buffy-coat fractions with a TIANamp blood DNA kit provided by Tiangen Biotech (Beijing, China). Duplex polymerase-chain-reaction with the confronting-two-pair primer (PCR-RFLP) analysis was performed to determine the genotype of miR-146a rs2910164 polymorphism.

Statistical analysis

Categorical variables were presented as n of subjects (%) and analysed using χ^2-test. The Hardy-Weinberg equilibrium was analysed using χ^2-test. Odds Ratios (OR) and their corresponding 95% Confidence Intervals (CI) were used to assess the association of polymorphism of miR-146a

rs2910164 polymorphism with the risk of HCC. All statistical analyses were performed by SPSS software (19.0; SPSS, Inc., Chicago, IL, USA).

Results

The HCC group included 132 males and 56 females. The healthy group had 129 males and 57 females. There were no significant differences in age, gender, and smoking status between the two groups (Table 1). However, more HCC patients with drinking status, family history of cancer and HBsAg (Table 1). The distribution of miR-146a rs2910164 polymorphism in controls was in HWE (P>0.05).

As shown in Table 2, CG genotype in HCC patients with miR-146a rs2910164 polymorphism increased the risk of HCC (OR=1.99, 95% CI 1.27-3.11, P=0.003). CC genotype in HCC patients with miR-146a rs2910164 polymorphism also showed an increased risk of HCC (OR=3.30, 95% CI 1.72-6.32, P=0.0003). In addition, patients with CG and CC had significant increased risk of HCC (OR=2.24, 95% CI 1.47-3.42, P=0.0002) in dominant model. Further, patients with CC genotype also had increased risk of HCC (OR=2.29, 95% CI 1.25-4.19, P=0.0002) in recessive model. The C allele seemed to be a risk factor of HCC (OR=1.88, 95% CI 1.39-2.54, P<0.0001).

Table 1. *Baseline characteristics of the included cases and controls.*

Baseline characteristics	Cases (n)	Controls (n)	p
Age (years)			
≤ 60	93	90	0.83
>60	95	96	
Gender			
Male	132	129	0.77
Female	56	57	
Smoking status			
Yes	90	101	0.21
No	98	85	
Drinking status			
Yes	121	96	0.01
No	67	90	
Family history of tumor			
Yes	117	79	0.0001
No	71	87	
HBsAg			
Yes	109	88	0.04
No	79	98	

Table 2. *Results of this case-control study.*

Genetic model	Case (n)	Control (n)	OR	95% CI	p
Genotype model					
GG	58	93			
CG	93	75	1.99	1.27-3.11	0.003
CC	37	18	3.3	1.72-6.32	0.0003
Dominant model					
GG	58	93			
CC+GC	130	93	2.24	1.47-3.42	0.0002
Recessive model					
GG+CG	151	168			
CC	37	18	2.29	1.25-4.19	0.0002
Allele model					
G	209	261			
C	167	111	1.88	1.39-2.54	<0.0001

Discussion

To date, surgical resection and liver transplantation are the best curative options to treat HCC. However, HCC is often diagnosed at an advanced stage and has a poor prognosis. Genetic factors may contribute to the carcinogenic mechanism. Therefore, finding genetic risk factors is very important. In the present study, we found that HCC patients with miR-146a rs2910164 polymorphism increased the risk of HCC in dominant model and recessive model. This result suggested that miR-146a rs2910164 polymorphism may be a genetic risk factor for HCC.

Cui et al. showed that miR-146a down-regulated the expression of SOD2 and enhances ROS generation, leading to increased apoptosis, inhibition of proliferation, and enhanced sensitivity to chemotherapy [9]. Huang et al. validated the combination of YY1 and its interaction with EZH2 at the miR-146a promoter binding site, thereby prohibiting the transcriptional activity of miR-146a in PCa cells [10]. Lu et al. demonstrated that both miR-146a-5p and carboxypeptidase M regulated Src and FAK expression, while the Src-FAK signaling pathway is widely known to be associated with the migration and invasion of multiple tumor cells [11]. Xiang et al. indicated a significant association between miR-146a rs2910164 polymorphism and HNC risk [12]. Xie et al. showed that miR-146a rs2910164 polymorphism was associated with increased gastric cancer risk [13]. Zhang et al. indicated that miR-146a rs2910164 polymorphism is associated with increased risk for cervical and skin squamous cell carcinoma [14].

Several limitations of this meta-analysis should be acknowledged. First, this meta-analysis included only case-control studies. Thus, causal relationship could not to be determined. Second, only one polymorphism was evaluated in this study, which might not be sufficient to address the

complex genetic architecture of HCC. Third, only published articles were included. Publication bias cannot be excluded.

In conclusion, the study suggested that miR-146a rs2910164 polymorphism was significantly associated with HCC risk.

Conflicts of Interest

None

References

1. Torre LA, Bray F, Siegel RL, Ferlay J, Lortet-Tieulent J. Global cancer statistics, 2012. CA Cancer J Clin 2015; 65: 87-108.
2. Huan L, Liang LH, He XH. Role of microRNAs in inflammation-associated liver cancer. Cancer Biol Med 2016; 13: 407-425.
3. Ji J, Zheng X, Forgues M, Yamashita T, Wauthier EL, Reid LM, Wen X, Song Y, Wei JS, Khan J, Thorgeirsson SS, Wang XW. Identification of microRNAs specific for epithelial cell adhesion molecule-positive tumor cells in hepatocellular carcinoma. Hepatology 2015; 62: 829-840.
4. Zu Y, Yang Y, Zhu J, Bo X, Hou S, Zhang B, Qiu J, Zheng J. MiR-146a suppresses hepatocellular carcinoma by downregulating TRAF6. Am J Cancer Res 2016 ; 6: 2502-2513.
5. Sun X, Zhang J, Hou Z, Han Q, Zhang C, Tian Z. miR-146a is directly regulated by STAT3 in human hepatocellular carcinoma cells and involved in anti-tumor immune suppression. Cell Cycle 2015; 14: 243-252.
6. Tomokuni A, Eguchi H, Tomimaru Y, Wada H, Kawamoto K, Kobayashi S, Marubashi S, Tanemura M, Nagano H, Mori M, Doki Y. miR-146a suppresses the sensitivity to interferon-a in hepatocellular carcinoma cells. Biochem Biophys Res Commun 2011; 414: 675-680.
7. Akkiz H, Bayram S, Bekar A, Akgollu E, Uskudar O, Sandikci M. No association of pre-microRNA-146a rs2910164 polymorphism and risk of hepatocellular carcinoma development in Turkish population: a case-control study. Gene 2011; 486: 104-109.
8. Hu M, Zhao L, Hu S, Yang J. The association between two common polymorphisms in MicroRNAs and hepatocellular carcinoma risk in Asian population. PLoS One 2013; 8: e57012.
9. Cui Y, She K, Tian D, Zhang P, Xin X. miR-146a inhibits proliferation and enhances chemosensitivity in epithelial ovarian cancer via reduction of SOD2. Oncol Res 2016; 23: 275-282.
10. Huang Y, Tao T, Liu C, Guan H, Zhang G. Upregulation of miR-146a by YY1 depletion correlates with delayed progression of prostate cancer. Int J Oncol 2017; 50: 421-431.
11. Lu D, Yao Q, Zhan C, Le-Meng Z, Liu H. MicroRNA-146a promote cell migration and invasion in human colorectal cancer via carboxypeptidase M/src-FAK pathway. Oncotarget 2017.
12. Xiang Z, Song J, Zhuo X, Li Q, Zhang X. MiR-146a rs2910164 polymorphism and head and neck carcinoma risk: a meta-analysis based on 10 case-control studies. Oncotarget 2017; 8: 1226-1233.
13. Xie WQ, Tan SY, Wang XF. MiR-146a rs2910164 polymorphism increases risk of gastric cancer: a meta-analysis. World J Gastroenterol 2014; 20: 15440-15447.
14. Zhang X, He R, Ren F, Tang R, Chen G. Association of miR-146a rs2910164 polymorphism with squamous cell carcinoma risk: a meta-analysis. J Buon 2015; 20: 829-841.

*Correspondence to

Wei-xing Wang

Department of Hepatobillary and Laparoscopic Surgery

Renmin Hospital of Wuhan University

PR China