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ORIGINAL ARTICLE

Case Control Study

Effects of interactions between environmental factors and *KIF1B* genetic variants on the risk of hepatocellular carcinoma in a Chinese cohort

Jun-Hu Chen, Yan-Yan Wang, Wei-Biao Lv, Yu Gan, Wei Chang, Na-Na Tian, Xiao-Hui Huang, Li Liu, Xin-Fa Yu, Si-Dong Chen

Jun-Hu Chen, Wei Chang, Si-Dong Chen, Department of Epidemiology, School of Public Health and Tropical Medicine, Southern Medical University, Guangzhou 510515, Guangdong Province, China

Jun-Hu Chen, Li Liu, Yu Gan, Wei Chang, Na-Na Tian, Xiao-Hui Huang, Si-Dong Chen, Department of Epidemiology and Biostatistics, School of Public Health, Guangdong Pharmaceutical University, Guangzhou 510310, Guangdong Province, China

Yan-Yan Wang, Department of Obstetrics and Gynecology, Affiliated HouJie Hospital of Guangdong Medical College, Dongguan 523945, Guangdong Province, China

Wei-Biao Lv, Xin-Fa Yu, Department of Oncology, The First People's Hospital of Shunde, Foshan 528300, Guangdong Province, China

Author contributions: Chen JH and Liu L analyzed the data and wrote the manuscript; Chang W, Tian NN, and Lv WB collected materials and clinical data; Wang YY, Gan Y, and Huang XH performed the experiments; Yu XF and Chen SD conceived and designed the study.

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Data sharing statement: Technical appendix, statistical code, and dataset are available from the corresponding author at chensidong1@126.com.

Correspondence to: Dr. Si-Dong Chen, Professor, Department of Epidemiology, School of Public Health and Tropical Medicine, Southern Medical University, No. 1838, North Guangzhou Avenue, Guangzhou 510515, Guangdong Province, China. chensidong1@126.com
Telephone: +86-20-34055180
Fax: +86-20-34055355

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Abstract

AIM: To examine the effect of the potential interaction between *KIF1B* variants (rs17401966 and rs3748578) and environmental factors on the risk of hepatocellular carcinoma (HCC) in a high-risk region in China.

METHODS: Three hundred and six patients with HCC and 306 hospital-based control participants residing in the Shunde region of Guangdong Province, China were enrolled. Clinical characteristics were collected by reviewing the complete medical histories from the patient archives, and epidemiological data were collected using a questionnaire and clinical examination. Two single nucleotide polymorphisms (SNPs) of *KIF1B* (rs17401966 and rs3748578) were chosen for the current study. All subjects were genotyped

using a TaqMan real-time polymerase chain reaction. Multiplicative and additive logistic regression models were used to evaluate various gene-environment interactions.

RESULTS: Smoking, frequent consumption of raw freshwater fish, hepatitis B virus (HBV) infection, and a family history of HCC were important risk factors for HCC in this population. Chronic infection with HBV was the most important environmental risk factor for HCC [odds ratio (OR) = 12.02; 95% confidence interval (95%CI): 6.02-24.00]. No significant association was found between the *KIF1B* variants alone and the risk of HCC. Nevertheless, a significant additive effect modification was observed between rs17401966 and alcohol consumption (*P* for additive interaction = 0.0382). Compared with non-drinkers carrying either the AG or GG genotype of rs17401966, individuals classified as alcohol consumers with the AA genotype of rs17401966 had a significantly increased risk of HCC (OR = 2.36; 95%CI: 1.49-3.74).

CONCLUSION: The gene-environment interaction between the *KIF1B* rs17401966 variant and alcohol consumption may contribute to the development of HCC in Chinese individuals.

Key words: Hepatocellular carcinoma; Kinesin family member 1B; Environmental factors; Alcohol drinking; Gene-environment interaction

Core tip: *KIF1B* has been proposed as a promising susceptibility gene for hepatocellular carcinoma (HCC) by a recent genome-wide association study (GWAS) in Chinese populations. However, the most significant variant (rs17401966) in this GWAS yielded inconsistent results in subsequent replication studies. In this work, we evaluated the role of rs17401966 in genetic susceptibility to HCC and gene-environment interactions. Our study demonstrates that the gene-environment interaction between the *KIF1B* rs17401966 variant and drinking alcohol significantly contributed to the development of HCC in the Chinese population.

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INTRODUCTION

Hepatocellular carcinoma (HCC) is one of the most common malignancies worldwide. HCC ranks as the fifth most common cancer in men and seventh most common cancer in women[1]. Eastern Asia experiences a large burden of the geographical distribution of HCC; China alone accounts for approximately 55% of all HCC cases worldwide[2]. Prognosis of HCC patients is poor, with an average 3-year survival rate of 13%-21%[3,4]. Due to the high disease burden worldwide, it is important to identify individuals who are at a higher risk of HCC and to identify risk factors that may be modifiable. Several environmental factors that increase the risk of HCC have been found, including chronic infection with hepatitis B virus (HBV) or hepatitis C virus (HCV), exposure to aflatoxin, and consumption of alcohol[5-7].

However, only a small percentage of individuals who are exposed to these risk factors will eventually develop HCC, highlighting that genetic susceptibility is another factor for the development of HCC. HCC involves a complex interplay of multiple genetic and environmental factors[8]. However, underlying genetic mechanisms of hepatocellular carcinogenesis have not yet been fully elucidated.

Kinesin superfamily proteins (*KIFs*) make up a large gene family of microtubule motor proteins[9]. *KIF1B*, a member of the *KIF* family, maps to a gene locus at 1p36.22 and encodes two alternatively spliced isoforms, *KIF1B*α and *KIF1B*β; both isoforms form homodimers and transport mitochondria and synaptic vesicle precursors, respectively. It has been postulated that *KIF1B* acts as a tumor suppressor. Downregulation of *KIFs* has been shown to contribute to tumorigenesis of certain cancers, including brain, colon and breast cancers[10]. Recently, Zhang *et al*[11] performed a genome-wide association study (GWAS) and found that *KIF1B* is a promising susceptibility gene for HCC in five independent Chinese populations. In this GWAS, the most significant variant of *KIF1B* (rs17401966), located in the intron of the gene, was associated with a decreased risk of HCC [joint odds ratio (OR) = 0.61, $P = 1.7 \times 10^{-18}$]. However, more recent studies have not drawn the same conclusion. Al-Qahtani *et al*[12] reported no significant association between the rs17401966 variant of *KIF1B* and HBV-related HCC. Sawai *et al*[13] also showed no association between rs17401966 and HBV-related HCC in a Japanese cohort. These inconsistent results may partly be due to the distinct genetic architecture among the different study populations. Additionally, the significant findings obtained by Zhang *et al*[11] may have resulted from a phenomenon known as the "winner's curse," where the odds ratio of the candidate variant is overestimated in the population, leading to reporting a positive result[14]. Another reason for the discrepancy among studies could be the complex gene-environment interactions involved in the development of HCC that have been neglected. Hence, we conducted a case-control study with HCC patients and hospital-based controls to clarify the effect of rs17401966 in *KIF1B* on HCC. In addition, one single nucleotide polymorphism (SNP),

rs3748578, was in strong linkage disequilibrium (LD) with rs17401966[15], which was also associated with HBV-induced HCC. We also investigated the potential functional role of this variant rs3748578. We applied both additive and multiplicative models using a logistic regression analysis framework to assess the potential interactions between the variants and environmental factors in development of HCC in a Chinese cohort.

MATERIALS AND METHODS

Study population

Three hundred and six patients with HCC and 306 control patients were recruited from Shunde First People's Hospital (Foshan, China) from October 2010 to October 2012. A diagnosis of HCC was made through a combination of liver function tests, serum immunological markers, liver ultrasonography (US) or computed tomography (CT), and pathological confirmation. Patients were excluded if they were diagnosed with cancer other than HCC after the workup. Age and sex-matched control participants with no history of cancer were enrolled from the hospital at the same time as case enrollment. Clinical characteristics were collected by reviewing the complete medical histories from the patient archives, including age, gender, serum α-fetoprotein (AFP) levels, hepatitis B surface antigen (HBsAg) status, HBV-DNA titer, alanine aminotransferase (ALT) levels, aspartate aminotransferase (AST) levels, and total bilirubin levels. Chronic infection with hepatitis B virus (CHB) was diagnosed based on HBsAg seropositivity, positive serum HBV-DNA levels, and continuously elevated ALT over a period of 6 mo.

Epidemiological data were collected using a questionnaire and clinical examination. The main definitions of risk categories were as follows: (1) a cigarette smoker is a person who smokes one or more cigarettes per day for at least 6 mo; (2) an alcohol drinker is a person who consumes beer, wine, or hard liquor at least once weekly for at least 6 mo during their lifetime; and (3) a family history of cancer in the first degree relatives (parents, siblings, and children). Written informed consent was obtained from all subjects. The study was approved by the Ethics Committee of the First People's Hospital of Shunde.

Genetic variant genotyping

As previously described, rs1740966 variant was found to be the most significant HCC-associated variant with another candidate variant, rs3748578, in high-linkage to rs1740966. Zhang *et al*[15] predicted that both rs1740966 and rs3748578 may function in HCC tumor suppression. Therefore, we chose two SNPs (rs17401966 and rs3748578) of *KIF1B* for the current study.

DNA was extracted using the TIANamp Blood DNA Kit (Tiangen, Beijing, China) according to the manufacturer's protocol. Genomic DNA was extracted from peripheral whole blood. All subjects were genotyped using TaqMan real-time polymerase chain reaction (Applied Biosystems, Foster City, CA, United States) without knowledge of subjects' infection status. Samples were heated to 95 ℃ for 10 min followed by 45 cycles of 95 ℃ for 15 s and 60 ℃ for 1 min. The ABI Prism 7900HT Sequence Detection System (Applied Biosystems, Carlsbad, CA, United States) was used to analyze the endpoint fluorescence. To ensure the accuracy of genotyping, > 5% of the samples were randomly selected and repeated, yielding a 100% concordance.

Statistical analysis

Differences in the distribution of demographic characteristics, lifestyles, and HBV infection status between cases and controls were evaluated using χ^2 test and *t* test, where appropriate. Hardy-Weinberg equilibrium (HWE) was tested for the genetic variants in controls. Logistic regressions were used to estimate the associations of environmental factors with HCC and ORs and corresponding 95% confidence intervals (CIs) were calculated. Logistic regressions were also fit to explore associations of genetic variants and HCC, taking into account both dominant and recessive inheritance patterns. Potential gene-environment interactions were studied using a logistic regression framework that employed both multiplicative and additive interaction models with a bootstrapping procedure. All statistical analyses were conducted using Stata software, version 14.0 (College Station, TX, United States). All probability analyses were two-sided tests where a P value < 0.05 was considered statistically significant.

RESULTS

A total of 306 patients with HCC (264 males and 42 females) and 306 controls (264 males and 42 females) were enrolled in the study with a mean age (± standard deviation) of 55.84 (± 11.49) and 55.83 (± 11.67) years, respectively. The general characteristics of the subjects are presented in Table 1. No significant differences were found between healthy controls and patients with HCC with regard to age and gender (P = 0.992 and P = 0.998, respectively). Logistic regression analysis suggested that smoking, frequent consumption of raw freshwater fish, HBV infection, and family history of HCC were important risk factors for HCC in the Shunde region of China (Table 1).

The genotypic distributions of rs3748578 and rs17401966 did not differ significantly between the cases and controls (Table 2). Logistic regression analysis failed to show a significant association between HCC with either rs3748578 or rs17401966 for all genetic models (Table 3).

Tables 4 and 5 show the results of additive and multiplicative interaction analysis between the two

Table 1 Distribution of selected characteristics and environmental factors in hepatocellular carcinoma cases and controls *n* (%)

Variable	Case (*n* = 306)	Control (*n* = 306)	*P* value	OR[3]	95%CI
Age, yr (mean ± SD)	55.84 ± 11.49	55.83 ± 11.67	0.992[1]		
Sex					
Male	264 (86.27)	264 (86.27)			
Female	42 (13.73)	42 (13.73)	0.998[2]		
Tobacco smoking					
No	95 (31.05)	139 (45.42)			
Yes	211 (68.95)	167 (54.58)	< 0.014[2]		
Alcohol drinking					
No	133 (43.46)	188 (38.56)		1.00	-
Yes	173 (56.54)	118 (61.44)	0.012[2]	2.45	1.24-4.82
History of raw freshwater fish eating					
No	111 (36.27)	171 (55.88)		1.00	-
Yes	195 (63.73)	135 (44.12)	0.030[2]	1.99	1.06-3.75
Status of HBV infection					
No	77 (25.16)	252 (82.35)		1.00	-
Yes	229 (74.84)	54 (17.65)	< 0.013[2]	12.02	6.02-24.00
Family history of HCC					
No	256 (83.66)	294 (96.08)		1.00	-
Yes	50 (16.34)	12 (3.92)	< 0.011[2]	6.90	2.10-22.73

[1]*P* value was calculated by the *t* test; [2]*P* value was calculated by the χ^2 test; [3]ORs were adjusted for age. HBV: Hepatitis B virus; HCC: Hepatocellular carcinoma; OR: Odds ratio.

Table 2 Distribution of rs3748578 and rs17401966 in hepatocellular carcinoma cases and controls *n* (%)

Variants	Genotypes	Case (*n* = 306)	Control (*n* = 306)	χ^2	*P* value	HWE
rs3748578	GG	169 (55.22)	150 (49.02)			
	AG	122 (39.87)	138 (45.10)			
	AA	15 (4.91)	18 (5.88)	2.39	0.303	0.058
rs17401966	AA	159 (51.96)	150 (49.02)			
	AG	126 (41.18)	138 (45.10)			
	GG	21 (6.86)	18 (5.88)	1.04	0.595	0.058

HWE: Hardy-Weinberg equilibrium.

Table 3 Association analysis between *KIF1B* variants and risk of hepatocellular carcinoma development *n* (%)

Variants	Crude OR (95%CI)	*P* value	Adjusted OR[1] (95%CI)	*P* value[1]
rs3748578				
GG	1.00		1.00	
AG	0.74 (0.36-1.52)	0.411	0.71 (0.33-1.53)	0.380
AA	0.79 (0.57-1.09)	0.148	0.82 (0.58-1.62)	0.260
Dominant model	0.78 (0.57-1.07)	0.124	0.80 (0.57-1.13)	0.209
Recessive model	0.83 (0.41-1.67)	0.592	0.77 (0.36-1.65)	0.507
Additive model	0.82 (0.63-1.07)	0.137	0.83 (0.62-1.10)	0.193
rs17401966				
AA	1.00		1.00	
AG	0.86 (0.62-1.20)	0.374	0.86 (0.62-1.20)	0.379
GG	1.10 (0.56-2.15)	0.778	1.12 (0.57-2.21)	0.746
Dominant model	0.89 (0.65-1.22)	0.467	0.91 (0.64-1.27)	0.566
Recessive model	1.18 (0.62-2.26)	0.620	1.06 (0.52-2.15)	0.871
Additive model	0.95 (0.73-1.23)	0.692	0.94 (0.71-1.25)	0.685

[1]The adjusted ORs, 95% confidence intervals (CIs) and their corresponding *P* values were calculated in a logistic regression model by adjusting for age, alcohol drinking, history of raw freshwater fish eating, history of chronic hepatitis B virus infection, family history of HBV infection, and family history of hepatoma.

variants and the main environmental risk factors for HCC. A significant additive interaction was seen between rs17401966 and alcohol consumption (P = 0.0382). Compared with non-drinkers carrying the rs17401966 AG or GG genotype, individuals who consumed alcohol and carried the AA genotype had a significantly increased risk of HCC, with an adjusted OR of 2.36 (95%CI: 1.49-3.74, P = 0.0382). No

Table 4 Interaction analysis between rs3748578 and environmental factors in hepatocellular carcinoma development

Variant and environmental factors		Cases	Controls	OR	95%CI	*P* value[1]	P value[2]
rs3748578 and alcohol drinking						0.945	0.228
AG + AA	No	63	92	1.00			
GG	No	70	96	1.06	0.68-1.66		
AG + AA	Yes	74	64	1.69	1.06-2.68		
GG	Yes	99	54	2.68	1.69-4.25		
rs3748578 and history of raw freshwater fish eating						0.557	0.681
AG + AA	No	49	89	1.00			
GG	No	62	82	1.37	0.85-2.22		
AG + AA	Yes	88	67	2.39	1.49-3.82		
GG	Yes	107	68	2.86	1.80-4.54		
rs3748578 and history of chronic hepatitis B virus infection						0.850	0.815
AG + AA	No	30	126	1.00			
GG	No	47	126	1.57	0.93-2.64		
AG + AA	Yes	107	30	14.98	8.49-26.43		
GG	Yes	122	24	21.35	11.82-38.58		
rs3748578 and family history of HCC						0.372	0.555
AG + AA	No	117	152	1.00			
GG	No	136	142	1.24	0.89-1.74		
AG + AA	Yes	20	4	6.50	2.16-19.52		
GG	Yes	33	8	5.36	2.39-12.04		

[1]*P* values were calculated by the test for additive interaction; [2]*P* values were calculated by the test for multiplicative interaction.

Table 5 Interaction analysis between rs17401966 and major environmental factors in hepatocellular carcinoma development

Variant and environmental factors		Cases	Controls	OR	95%CI	*P* value[1]	*P* value[2]
rs17401966 and alcohol drinking						0.038	0.102
AG + GG	No	69	91	1.00			
AA	No	64	97	0.87	0.56-1.36		
AG + GG	Yes	78	65	1.58	1.00-2.49		
AA	Yes	95	53	2.36	1.49-3.74		
rs17401966 and history of raw freshwater fish eating						0.470	0.852
AG + GG	No	53	88	1.00			
AA	No	58	83	1.16	0.72-1.87		
AG + GG	Yes	94	68	2.30	1.45-3.64		
AA	Yes	101	67	2.50	1.58-3.96		
rs17401966 and history of chronic hepatitis B virus infection						0.269	0.753
AG + GG	No	32	126	1.00			
AA	No	45	126	1.41	0.84-2.36		
AG + GG	Yes	115	30	15.09	8.63-26.39		
AA	Yes	114	24	18.7	10.40-33.63		
rs17401966 and family history of hepatoma						0.697	0.524
AG + GG	No	125	152	1.00			
AA	No	128	142	1.10	0.78-1.53		
AG + GG	Yes	22	4	6.69	2.25-19.92		
AA	Yes	31	8	4.71	2.09-10.62		

[1]*P* values were calculated by test for additive interaction; [2]*P* values were calculated by test for multiplicative interaction.

significant interactions were observed between the rs3748578 variant and environmental factors.

DISCUSSION

The current study aimed to investigate whether two variants of *KIF1B* (rs17401966 and rs3748578) interacted with environmental risk factors of HCC to influence the risk of HCC. A significant additive interaction was observed between rs17401966 and alcohol consumption.

HCC is a complex disease associated with many risk factors and cofactors[16]. The major risk factor for HCC in China is clearly chronic HBV infection[17], with an 8%-20% prevalence of HBV[18] and approximately 93 million chronic HBV carriers[19]. The proportion of HBV-positive HCC has significantly increased, with 76% of HCC cases being HBV positive[20], which was consistent with 74.84% in our research. However, compared to China, the proportion of HCV-positive HCC was high in the United States, Italy, Japan, Brazil, Taiwan, Egypt, and other countries[20]. As we know, HCV prevalence

in China is low (< 1.5%)[21], which is transmitted primarily through intravenous drug use and invasive medical treatment, particularly hemodialysis[22]. The overall prevalence of anti-HCV antibody (anti-HCV) in Guangdong Province was about 0.50%[23-25], after the implementation of strict blood screening and other procedural measures, and we did not describe the relationship between HCV and HCC in the research.

In this study, we did not find a significant association between rs17401966 and HCC. This result is not consistent with the results reported in the GWAS study by Zhang *et al*[11]. One possible explanation for this discrepancy is the fact that the study samples were made up of individuals with different genetic architectures, who were from south China and Japan. Additionally, according to evolutionary theory, individual common variants often exert modest effects on common diseases[26]. In other words, sufficient statistical power to detect a disease with low penetrance due to a specific variant would require enrollment of thousands of subjects in the study. A recent meta-analysis of rs17401966 and HCC summarized data from 7596 HCC cases and 9614 controls; this meta-analysis supported Zhang *et al*'s[15] findings, indicating a significant association between rs17401966 and HCC. Nevertheless, according to the common disease-common variant (CDCV) hypothesis, cumulative effects of multiple common variants or their interactions with environment factors underlie common diseases. The finding in the present study on the interaction between rs17401966 and alcohol consumption fits the CDCV hypothesis. Zhang *et al*[11] suggested a significant association between rs17401966 genotypes and expression of *KIF1B* in liver tissues, with carriers of the G allele having a greater *KIF1B* level than individuals without G allele (AA carriers). However, several studies have found that the G allele of rs17401966 demonstrated a protective effect on the susceptibility to HCC[27-29]. This inconsistency might be attributed to the fact that there were heterogeneous population structures. It is necessary to investigate the exact effect of ethnicity on the association between *KIF1B* polymorphisms and HCC risk in future. It has been hypothesized that *KIF1B* can act as a tumor suppressor. The mechanism by which this occurs is still unclear, but *KIF1B* may induce apoptosis by acting downstream of *EglN3* prolyl hydroxylase[30], ultimately leading to inhibition of malignant transformation and progression.

Alcohol consumption is common in Guangdong Province, where the total drinking rate is 33.3%[31], with the region of Shunde having an even higher rate, especially in residents who habitually drink brewed Chinese rice wine[32]. Ethanol, the active compound in alcoholic beverages, is metabolized to acetaldehyde, which has been found to be mutagenic and carcinogenic[33,34], and other studies reported that alcohol was involved in hepatocarcinogenesis[35,36]. Therefore, a significant joint effect and interaction between rs17401966 and alcohol consumption was observed, suggesting that gene-environment interactions may provide further insights for comprehensive understanding of HCC in the Shunde area.

Our study is not without limitations. Hospital-based samples may lead to a selection bias of participants. Secondly, the sample size was limited and statistical power was insufficient for detection of a modest effect size of individual common variants. Thirdly, only two variants in the *KIF1B* gene were assessed in this study, which may fail to reflect the genetic mechanism of other *KIF1B* variants in the development of HCC.

In conclusion, we identified a statistically significant interaction between the rs17401966 variant of *KIF1B* and alcohol consumption that contributes to the development of HCC in the Shunde region of China. This study further supports the hypothesis that *KIF1B* is an important susceptibility gene for HCC in the Chinese population. Comprehensive studies with larger sample sizes and more diverse independent populations are warranted to better understand the underlying mechanisms of *KIF1B* genetic variants in the development of HCC.

COMMENTS

Background

Several environmental factors have been identified that increase the risk of hepatocellular carcinoma (HCC). However, only a small percentage of individuals who are exposed to these risk factors will eventually develop HCC, highlighting genetic susceptibility as another factor at play in the development of HCC. HCC involves a complex interplay of multiple genetic and environmental factors.

Research frontiers

According to a recent genome-wide association study, *KIF1B* has been identified as a promising susceptibility gene for HCC in Chinese adults. However, one of the significant variants (rs17401966) in this study yielded inconsistent results in the subsequent replication studies. Indeed, it is important to evaluate the role of rs17401966 in genetic susceptibility to HCC and gene-environment interactions.

Innovations and breakthroughs

The authors confirm the gene-environment interaction between the *KIF1B* rs17401966 variant and alcohol consumption in the development of HCC in Chinese individuals.

Applications

KIF1B SNPs and gene-environment interaction should be added as valuable knowledge in the field of hepatology.

Peer-review

The authors conducted a case-control study with HCC patients and hospital-based controls to clarify the effect of rs17401966 in *KIF1B* on HCC and further examined the potential interaction between variants in *KIF1B* and environmental factors on the risk of HCC in a high-risk region of China. They found a gene-environment interaction between the *KIF1B* rs17401966 variant and alcohol consumption influenced the development of HCC in Chinese individuals. Their findings add valuable knowledge in the field of hepatology.

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