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The role of *IL22* polymorphisms on liver cirrhosis in patients with hepatitis B virus

A case control study

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Abstract

Glycogen storage disease (GSD) type IX, characterized by liver enlargement and elevated aminotransferase levels, is the most frequent type of GSD. The global incidence of GSD type IXa is only about 1/100,000 individuals. Case reports of GSD type IX are rare in China. We present the first case report of GSD type IXa in Northeast China caused by mutation of PHKA2.

An 11-year-old boy was referred to our hospital because of liver enlargement with consistently elevated transaminase levels over 6 months.

Histopathological results following an ultrasound-guided liver biopsy confirmed a diagnosis of GSD. Further genetic testing showed that the patient had GSD type IXa caused by the c.133C>T mutation in PHAK2.

We placed the patient on a high-protein and high-starch diet and provided hepatoprotective and supportive therapy.

The patient's transaminase levels decreased significantly and were nearly normal at 10-month follow-up.

This is the first reported case of GSD type IXa in Northeast China. We hope that the detailed and complete report of this case will provide a reference for the diagnosis of liver enlargement of unknown etiology in future clinical practice.

Abbreviations: CHB = chronic hepatitis B, CI = confidence interval, HBV = hepatitis B virus, HCC = hepatocellular carcinoma, IL-22 = interleukin-22, LC = liver cirrhosis, MDR = multifactor dimensionality reduction, OR = odds ratio, SNP = single nucleotide polymorphisms.

Keywords: hepatitis B virus, hepatocellular carcinoma, interleukin-22, liver cirrhosis, single nucleotide polymorphisms

1. Introduction

Hepatitis B virus (HBV) infection is one of the most common infectious diseases of global public health concern, with more than 240 million chronic HBV carriers today.[1] These patients are at high risk of developing HBV-related diseases, such as liver cirrhosis (LC) and hepatocellular carcinoma (HCC), which account for 600,000 deaths annually.[2] Infection with HBV and the development of LC or HCC are responsible for a heavy disease burden worldwide.[3–5] Although HBV infection is a significant risk factor for liver disease, clinical outcomes after exposure to HBV are highly variable, as both genetic and environmental factors critically modulate susceptibility to and progression of liver disease.[6,7]

Interleukin (IL)-22 is a recently identified cytokine that is mainly secreted by lymphocytes.[8] Several studies show that IL-22 plays an important role in protecting against inflammation, inducing anti-oxidative activity, and promoting liver regeneration in most acute inflammatory diseases.[4,9,10] However, some studies report that IL-22 may play a pathological role in certain pathophysiological conditions such as chronic inflammation.[11,12]

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Many studies have evaluated the role of IL-22 in liver disease. IL-22 aggravates inflammation in a mouse model of HBV infection[13,14] and stimulates tissue regeneration[15] in experimental models of liver disease but protects against acute hepatitis.[16] Kong et al found that IL-22 induces hepatic stellate cell senescence and restricts liver fibrosis in mice.[17] Furthermore, Alain et al provide strong evidence that IL-22 protects against and IL-22 binding protein aggravates liver fibrosis and cirrhosis in humans with chronic hepatitis C virus infection.[18] However, Kronenberger et al reported that the elevation of systemic IL–22 may be used to predict reduced survival in patients with advanced LC.[19] Considering these findings, the role of IL-22 in chronic liver diseases remains unclear.[20–22] Therefore, the goal of this study was to evaluate associations between eight *IL22* single nucleotide polymorphisms (SNPs) and the development of chronic HBV cirrhosis and HBV-related HCC within a Chinese Han population.

2. Patients and methods

2.1. Study participants

This retrospective study included 103 patients with chronic hepatitis B (CHB), 264 patients with HBV-related LC, and 282 patients with HBV-related HCC. All patients were ethnic Han Chinese who were recruited between Jan 2012 and Dec 2014 at The First Hospital of Jilin University in Changchun. Frequency matching by age and sex was performed for each group. CHB was defined as persistent or intermittent elevations in alanine transaminase levels (≥2 times the upper limit of normal) and elevated HBV DNA levels for at least 6 months. HBV-related HCC was diagnosed based on

(1) positive results on computed tomography, magnetic resonance imaging, or ultrasonography and
(2) combined positive findings upon cytological or pathological examination.

HBV-related LC was characterized by active necro-inflammatory liver disease with fibrosis on imaging examination without evidence of HCC according to guidelines for the prevention and treatment of CHB (2010 version) and diagnostic criteria (10th National Conference on Viral Hepatitis and Hepatology 2000, China). All patients were positive for HBV but negative for hepatitis C virus and human immunodeficiency virus according to serology tests and infection history. Exclusion criteria included the presence of autoimmune alcoholic liver disease, hemorrhagic liver disease, or intra- and extra-hepatic bile duct stones and other liver diseases. We also collected demographic data from each patient, including smoking and drinking status. Individuals who smoked daily for at least 1 year were defined as smokers, and those who consumed alcoholic drinks more than once per week for 6 months were considered drinkers. Written informed consent was obtained from all patients, and the study was approved by The First Hospital Ethical Committee of Jilin University.

2.2. Statistical analysis

The χ^2 test was used to evaluate differences in demographic and clinical data among groups. Distributions of allele and genotype frequencies were analyzed using χ^2 or Fisher exact tests. Haploview software was used for haplotype analysis of polymorphisms. Multifactor dimensionality reduction (MDR) was used to identify the best interaction combination of SNPs, smoking, and drinking. Two-sided P values $<.05$ were considered statistically significant. All data were analyzed using SPSS18.0 statistical software.

3. Results

3.1. Patient characteristics

The study included a total of 649 participants consisting of 103 CHB patients (83 males and 20females), 264 LC patients (210 males and 54 females), and 282 HCC patients (241 males and 41 females). All groups contained a higher proportion of males, with no significant difference in gender distribution among groups ($P > .0.05$). The mean age of patients in the CHB, LC, and HCC groups was 47.8 ± 6.7, 48.3 ± 10.3, and 49.7 ± 7.8 years, respectively. The proportion of smokers and alcohol user were not significantly different between CHB and LC, while the rate of smokers and alcohol user were higher in HCC than CHB. Detailed patient characteristics for all groups, including sex, age, and smoking and drinking status, are provided in Table 1.

3.2. Genotype distribution and allele frequency of IL22 SNPs

Genotype distribution and allele frequencies of the SNPs in *IL22* are shown in Table 2. Genotype and allele distributions of rs1179249 and rs2227472 were significantly different between CHB and LC groups (both $P < .05$). Compared with the ancestral allele (C) and genotype (CC), the mutation allele(A) and genotype (AA) of rs1179249 were significantly associated with a decreased

Table 1

Basic information of 649 cases with HBV infection.

Groups	CHB n = 103	LC n = 264	HCC n = 282	P^*	P^{**}	$P^{\#}$
Gender (M/F)	83/20	210/54	241/41	.824	.246	.068
Age (yrs)	47.95 ± 6.69	48.28 ± 10.34	49.70 ± 7.76	.342	.049	.094
Smoking (n, %)				.931	.007	<.001
Yes	36 (35.0)	91 (34.5)	142 (50.2)			
No	67 (65.0)	173 (65.5)	140 (49.8)			
Drinking (n, %)				.108	.006	.158
Yes	27 (26.2)	94 (35.6)	118 (41.8)			
No	76 (73.8)	170 (64.4)	164 (58.2)			

CHB = Chronic Hepatitis B, HCC = Hepatocellular Carcinoma, LC = Liver Cirrhosis.
$P^{\#}$ = HCC vs LC, P^{**} = HCC vs CHB, P^{*} = LC vs CHB.

Table 2

Genotype and allele frequencies for SNPs of IL-22 gene.

			HBV-related LC			HBV-related HCC			LC vs HCC	
Groups		CHB (n=103)	LC (n=264)	OR (95%CI)	P^*	HCC (n=282)	OR (95%CI)	P^{**}	OR (95%CI)	$P^{\#}$
rs1026788		n=103	n=262			n=280				
Genotype	AA	32 (31.1)	66 (25.2)	Reference	.063	87 (31.1)	Reference	.359	Reference	.208
	AG	59 (57.3)	138 (52.7)	1.13 (0.67,1.91)		144 (51.4)	0.90 (0.54,1.49)		0.79 (0.53,1.18)	
	GG	12 (11.7)	58 (22.1)	2.34 (1.11,4.97)		49 (17.5)	1.50 (0.71,3.18)		0.64 (0.39,1.05)	
Allele	A	123 (59.7)	270 (51.5)	Reference	.046	320 (56.9)	Reference	.491	Reference	.074
	G	83 (40.3)	254 (48.5)	1.41 (1.02,1.97)		242 (43.1)	1.12 (0.81,1.55)		0.80 (0.63,1.02)	
rs1179249		n=103	n=264			n=282				
Genotype	CC	37 (35.9)	129 (48.9)	Reference	.031	123 (43.6)	Reference	.383	Reference	.066
	AC	53 (51.5)	118 (44.7)	0.64 (0.39,1.04)		125 (44.3)	0.71 (0.44,1.16)		1.11 (0.78,1.58)	
	AA	13 (12.6)	17 (6.4)	0.38 (0.17,0.84)		34 (12.1)	0.79 (0.38,1.64)		2.10 (1.11,3.95)	
Allele	C	127 (61.7)	376 (71.2)	Reference	.012	371 (65.8)	Reference	.289	Reference	.054
	A	79 (38.3)	152 (28.8)	0.65 (0.46,0.91)		193 (34.2)	0.84 (0.60,1.16)		1.29 (0.99,1.66)	
rs2046068		n=102	n=264			n=280				
Genotype	AA	63 (61.8)	154 (58.3)	Reference	.857	172 (61.4)	Reference	.552	Reference	.201
	AC	35 (34.3)	99 (37.5)	1.16 (0.73,1.88)		89 (31.8)	0.93 (0.57,1.51)		0.81 (0.56,1.15)	
	CC	4 (3.9)	11 (4.2)	1.13 (0.35,3.67)		19 (6.8)	1.74 (0.57,5.31)		1.55 (0.71 (3.35)	
Allele	A	161 (78.9)	407 (77.1)	Reference	.593	433 (77.3)	Reference	.638	Reference	.925
	C	43 (21.1)	121 (22.9)	1.11 (0.75,1.65)		127 (22.7)	0.10 (0.74,1.62)		0.99 (0.74,1.31)	
rs2227472		n=102	n=260			n=282				
Genotype	AA	35 (34.3)	68 (26.2)	Reference	.038	86 (31.0)	Reference	.278	Reference	.318
	AG	55 (53.9)	132 (50.8)	1.24 (0.74,2.07)		139 (50.2)	1.03 (0.62,1.70)		0.83 (0.56,1.24)	
	GG	12 (11.8)	60 (23.1)	2.57 (1.23,5.40)		52 (18.8)	1.76 (0.84,3.70)		0.69 (0.42,1.12)	
Allele	A	125 (61.3)	268 (51.5)	Reference	.018	311 (56.1)	Reference	.204	Reference	.131
	G	79 (38.7)	252 (48.5)	1.49 (1.07,2.07)		243 (43.9)	1.24 (0.89,1.72)		0.83 (0.65,1.06)	
rs2227473		n=103	n=261			n=276				
Genotype	AA	1 (1.0)	5 (1.9)	Reference	.66	5 (1.80)	Reference	.834	Reference	.805
	AG	24 (23.3)	69 (26.4)	0.58 (0.06,5.17)		66 (23.9)	0.55 (0.06,4.95)		0.96 (0.27,3.46)	
	GG	78 (75.7)	187 (71.6)	0.48 (0.06,4.17)		205 (74.3)	0.53 (0.06,4.57)		1.10 (0.31,3.85)	
Allele	A	26 (12.6)	79 (15.1)	Reference	.385	76 (13.8)	Reference	.681	Reference	.524
	G	180 (87.4)	443 (84.9)	0.81 (0.50,1.30)		476 (86.2)	0.91 (0.56,1.46)		1.12 (0.80,1.57)	
rs2227485		n=103	n=262			n=281				
Genotype	CC	32 (31.1)	69 (26.3)	Reference	.061	91 (32.4)	Reference	.301	Reference	.184
	CT	58 (56.3)	131 (50.0)	1.05 (0.62,1.76)		138 (49.1)	0.84 (0.50,1.39)		0.80 (0.54,1.18)	
	TT	13 (12.6)	62 (23.7)	2.21 (1.07,4.59)		52 (18.5)	1.41 (0.68,2.92)		0.64 (0.39,1.03)	
Allele	C	122 (59.2)	269 (51.3)	Reference	.054	320 (56.9)	Reference	.571	Reference	.064
	T	84 (40.8)	255 (48.7)	1.38 (0.99,1.91)		242 (43.1)	1.10 (0.79,1.52)		0.80 (0.63,1.01)	
rs2227491		n=103	n=264			n=278				
Genotype	AA	32 (31.1)	67 (25.5)	Reference	.051	88 (31.7)	Reference	.29	Reference	.183
	AG	59 (57.3)	136 (51.7)	1.1 (0.65,1.85)		140 (50.4)	0.86 (0.52,1.43)		0.78 (0.53,1.16)	
	GG	12 (11.7)	60 (22.8)	2.39 (1.13,5.05)		50 (18.0)	1.52 (0.72,3.20)		0.63 (0.39,1.04)	
Allele	A	123 (59.7)	270 (51.3)	Reference	.041	316 (56.8)	Reference	.476	Reference	.069
	G	83 (40.3)	256 (48.7)	1.41 (1.01,1.95)		240 (43.2)	1.13 (0.81,1.56)		0.80 (0.63,1.02)	
rs7314777		n=103	n=263			n=271				
Genotype	TT	78 (75.7)	189 (71.9)	Reference	.695	206 (73.3)	Reference	.881	Reference	.937
	TC	24 (23.3)	70 (26.6)	1.2 (0.71,2.05)		71 (25.3)	1.12 (0.66,1.91)		0.93 (0.63,1.37)	
	CC	1 (1.0)	4 (1.5)	1.65 (0.18,15.0)		4 (1.4)	1.52 (0.17,13.77)		0.92 (0.23,3.72)	
Allele	T	180 (87.4)	448 (85.2)	Reference	.442	483 (85.9)	Reference	.608	Reference	.731
	C	26 (12.6)	78 (14.8)	1.21 (0.75,1.94)		79 (14.1)	1.13 (0.70,1.82)		0.94 (0.67,1.32)	

CHB = Chronic Hepatitis B, HCC = Hepatocellular Carcinoma, LC = Liver Cirrhosis.
$P^{\#}$ = HCC vs LC, P^{**} = HCC vs CHB, P^* = LC vs CHB.

risk of LC, with odds ratios (ORs) of 0.38 (95% confidence interval (CI): 0.17, 0.84) and 0.65(95%CI: 0.46, 0.91), respectively. The genotype GG of rs2227472 was significantly more frequent in the LC group (23.1%) than in the CHB group (11.8%; $P=.018$). The G allele of rs1026788 was significantly more frequent in the LC group (48.5%) than in the CHB group (40.3%; $P=.046$). Also, the G allele of and rs2227491 was significantly more frequent in the LC group (48.7%) than in the CHB group (40.3%; $P=.041$). No significant differences in allele frequencies of rs2046068, rs2227473, rs2227485, rs2227491, orrs7314777 were observed between LC, HCC, and CHB patients ($P>.05$).

3.3. Haplotype analysis

To assess the combined effects of SNPs in *IL22*on LC and HCC, we performed haplotype analysis as shown in Table 3. We found that an *IL22* haplotype consisting of the minor alleles of rs1179249 and the major alleles of rs2046068, rs2227491, rs2227485, rs2227473, rs2227472, rs7314777, and rs1026788

Table 3

Haplotyping analysis of IL22 SNPs in HBV infection diseases.

	Frequency (%)			LC vs CHB		HCC vs CHB		HCC vs LC	
	CHB	LC	HCC	*P*	OR	*P*	OR	*P*	OR
CAGTGGTG	38.83	47.71	43.25		1.0 (Ref)		1.0 (Ref)		1.0 (Ref)
AAACGATA	37.86	28.20	33.94	.008	0.61 (0.42,0.88)	.245	0.81 (0.56,1.16)	.047	1.33 (1.004,1.755)
CCACAACA	12.14	14.75	13.80	.971	0.99 (0.59,1.66)	.922	1.03 (0.61,1.72)	.848	1.036 (0.721,1.488)
CCACGATA	8.25	7.22	9.01	.28	0.71 (0.38,1.33)	.929	0.97 (0.53,1.79)	.177	1.371 (0.517,2.170)

CHB = Chronic Hepatitis B, HCC = Hepatocellular Carcinoma, LC = Liver Cirrhosis.
SNPs are as follows: rs1179249 rs2046068 rs2227491 rs2227485 rs2227473 rs2227472 rs7314777 rs1026788.

occurred less frequently in the LC and HCC groups than in the CHB group (28.2%, 33.94%, and 37.86%, respectively). The difference was significant between the LC and CHB groups (OR: 0.61; 95%CI: 0.42, 0.88; $P = .008$) and between the HCC and LC groups (OR: 1.33; 95%CI: 1.00, 1.76; $P = .047$) but not between the HCC and CHB groups (OR:0.81; 95%CI: 0.56, 1.16; $P = .245$). Haplotypes CCACAACA and CCACGATA were not significantly associated with LC or HCC.

3.4. Gene-environment interaction

We also investigated interactions between eight SNPs in *IL22* and cigarette smoking or alcohol consumption on HCC risk using MDR models as summarized in Table 4. We found no significant models ($P > .05$) involving an interaction between SNPs and smoking or drinking.

4. Discussion

The clinical outcome of HBV infection is dependent on the complex interplay between HBV replication and host immune response.[23,24] Recent years, several studies have reported that cytokines and regulatory molecules should be regarded as fundamental mediators in determining the host's innate and adaptive immune responses to HBV and viral clearance, and, therefore, the level of cytokine expression may play a key role in disease outcome and effective antiviral immunity.[25,26] Tian et al reported that IL-17 expression and promoter methylation were associated with chronic HBV infection progression, especially in the HBV-HCC group.[27] Other studies have also suggested that IL-4, IL-6, IL-10 et al involved in hepatitis virus replication and further disease progression.[28,29] In addition to protein expression levels, the genetic levels of various cytokines have also been reported to be associated with HBV/HCV infection outcomes. HBV-related LC and HCC are related to several genetic variations including *NTCP*,[30] *STAT4*,[31] *HIF-2a*,[32] and *GSTO*.[33] AA genotype of IL 12B gene presented more frequently in late stages of HCV chronically ill patients.[34] In the present study, we investigated relationships between eight SNPs of the *IL22* gene and HBV-related LC and HCC with in a Han Chinese population. Ancestral C allele of rs1179249 was associated with LC susceptibility, whereas the ancestral A allele of rs2227491, rs2227472, and rs1026788 were associated with LC non-susceptibility. According to our knowledge, SNPs in gene *IL22* affect the IL22 excretion and secretion, which is located at promoter, 5'UTR, intron, and 3'UTR, consequentially influencing the activity of RNA transcription (initiation, elongation, enhancer, and termination) and RNA translation. These results were consistent with previous studies which showed that *IL22* is associated with liver fibrosis.[17,18]

Haplotype analysis indicated a combined effect of SNPs in *IL22* on the risk of LC and HCC. The rs1179249 A allele alone or in combination with other SNPs' alleles significantly decreases the risk of development of LC in Chinese CHB population. The relationship of *IL22* alleles and haplotype polymorphism with LC were obtained and unique in north Chinese Han population. Further studies of haplotype composition in subjects with the rs1179249 genotype are necessary to assess the risk of LC and HCC. CHB patients in north east Han People carry particular unsusceptible haplotypes (AAACGATA) might correlated with liver disease progression. The mechanisms by which the differential effects of these haplotype affect the susceptibility to LC and HCC are not clear and requires further study. As IL-22 regulates multiple inflammatory diseases,[35] we speculate that polymorphisms in the *IL22* gene may contribute to the persistence and progression of CHB inflammation.

No associations between HCC and SNPs (rs1179249 rs2046068 rs2227491 rs2227485 rs2227473 rs2227472 rs7314777 rs1026788) were observed. As we know that HCC susceptibility is influenced by both genetic and environmental factors. Several environmental factors, including cigarette smoking and alcohol consumption, have been suggested to increase the risk of HCC.[36–38] In the present study, rates of smoking and drinking were higher in HCC patients than in CHB patients. Therefore, we not only investigated the effect of gene-gene interactions on HCC but also the effect of gene-environment interactions involving smoking and drinking. However, we found no significant interactions between SNPs and smoking or drinking on HCC susceptibility. According to Internet journal searching, there was no study that mentioned illness progression in chronic liver disease based on *IL22* gene polymorphism studies. One explanation of the inconsistency between the results

Table 4

MDR analysis on the best gene-smoking-drinking interaction models.

Locus No	Best Combination	Cross-validation consistency	Testing accuracy	*P* value
1	Smoking	6/10	0.5451	.6152
2	Smoking, rs2227472	4/10	0.5630	.4885
3	Smoking, Drinking, rs2227472	8/10	0.5689	.4438

of LC and HCC may be the different mechanisms in the progression from CHB to LC or HCC.

As we know, disease progression of CH to LC or HCC needs a long time period (10–30 years), and there were many factors may affect the progression of CHB. Multivariate and regression models using more variables (Living habits and clinical information) were needed to design a better model for prediction of illness progression. Secondly, Liver biopsy was not done because approvals for invasive procedures and liver surgeries (liver resection or transplantation) were only rarely given, so we cannot examine all the LC patients with liver biopsy. Moreover, the statistical power of our study is limited by the sample size, particularly for statistical analyses of gene–environment interactions; Further studies based on a larger number of subjects are required to confirm this issue. In summary, our results provide evidence that *IL22* SNPs differ between LC and CHB patients, which is the first evidence that IL-22 plays a role in the development and progression of LC in patients with CHB in Han Chinese Population.

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