Polymorphisms of Killer Cell Immunoglobulin-like Receptor Gene: Possible Association with Susceptibility to or Clearance of Hepatitis B Virus Infection in Chinese Han Population

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Aim To explore whether killer cell immunoglobulin-like receptors (KIR) gene polymorphisms are associated with susceptibility to persistent hepatitis B virus (HBV) infection or HBV clearance.

Methods Fifteen known KIR genes were determined in 150 chronic hepatitis B patients, 251 spontaneously recovered controls, and 412 healthy controls by the sequence specific primer polymerase chain reaction (SSP-PCR) method. KIR genotype frequency (gf) differences were tested for significance by two-tailed Fisher exact test or χ^2 test. Multifactorial analysis was also performed by logistic analysis (the SAS system).

Results Framework genes *KIR2DL4*, *KIR3DL2*, *KIR3DL3*, and *KIRZ* were present in all individuals. The frequencies of *KIR2DS2* and KIR2DS3 were higher in chronic hepatitis B patients, than in both healthy and spontaneously recovered controls. The frequencies of activating *KIR2DS1*, *KIR3DS1*, and the inhibitory *KIR2DL5* were higher in spontaneously recovered controls than in chronic hepatitis B patients and healthy controls.

Conclusion KIR polymorphisms may be associated with susceptibility to HBV infection or HBV clearance. It could be suggested that *KIR2DS2* and *KIR2DS3* were HBV-susceptive genes, which induced a persistent yet weak inflammatory reaction that resulted in continuous injury of live tissues and chronic hepatitis. *KIR2DS1*, *KIR3DS1*, and *KIR2DL5*, on the other hand, may be protective genes that facilitated the clearance of HBV.

Hepatitis B virus (HBV) infection, one of the major viral diseases in the word, especially in China, causes a broad spectrum of liver diseases (1). It has been documented that there are currently about 350 million people with persistent HBV infection worldwide. Persistent HBV infection has been regarded as a multifactorial disorder relevant to virus, host age, sex, environment, and concurrent infections with the hepatitis C and D virus, and human immunodeficiency virus (HIV) (2). Segregation analysis and twin studies strongly support the role of host genetic background in determining the course of HBV infection (3-5). Actually, the susceptibility to infectious diseases is governed by a number of different factors, such as cytokine production, antigen presentation, and receptor recognition. Of note, genetic susceptibility to persistent HBV infection or HBV clearance are likely polygenic, pertaining to genes such as the genes of human leukocyte antigen (HLA) and class cytokine receptor.

It has been reported that killer cell immunoglobulin-like receptor (KIR) genes present diversity in the Chinese population (6,7). However, it is unknown whether KIR genes participate in the regulation of HBV infectious process. KIR gene family, located on human chromosome 19q13.4, encodes HLA class I receptors expressed by natural killer (NK) cells and subsets of T-cells. KIR genes are organized in a highly polymorphic, multi-gene family with considerable allelic polymorphism. The genes have been divided into distinct groups, depending on the number of external immunoglobulin domains (2D or 3D). The presence of a long cytoplasmatic tail with two immune tyrosine-based inhibitory motifs (ITIM) allows the transduction of inhibitory signals and characterizes the inhibitory KIRs (2DL, 3DL), whereas the presence of short cytoplasmatic tails corresponds to the activating KIR receptors (2DS, 3DS) (8-11). Theoretically, NK cells and T cells activation may be regulated by one of the two following mechanisms: the presence of and signaling through activating receptors on a large proportion of effector cells (ie, KIR haplotypes containing many activating receptors) or the presence of inhibitory receptor-ligand combinations that send relatively poor inhibitory signals. Upon interaction with HLA class I molecules expressed on the surface of target cells, KIR genes provide activating or suppressing signals to regulate the activation of NK cells and T cells, thereby playing an important role in antiviral and anti-tumor immunity (12).

Previous studies have demonstrated that KIR genes are involved in the pathogenesis of a variety of diseases, including rheumatoid arthritis, vasculitis (13,14), psoriatic arthritis (15), type 1 diabetes mellitus (16), and hepatitis C virus (17). However up to now, the role of KIR polymorphisms in patients with HBV infection has not been investigated. Therefore, the present study was designed to investigate the KIR gene polymorphisms in a large cohort of 150 chronic hepatitis B patients, 251 spontaneously recovered cases, and 412 healthy controls by means of sequence specific primer polymerase chain reaction (SSP-PCR), with special attention given to the relationship between KIRs and the HBV infection or HBV clearance.

Methods

Study subjects

The 813 samples analyzed for this study comprised 150 samples from patients with chronic hepatitis B (CHB), 251 spontaneously recovered (SR) controls, and 412 healthy unrelated adult Chinese recruited from Shandong Provincial Hospital and Jinan Infectious Disease Hospital, both in Jinan, between October 2004 and August 2006. CHB patients were required to have a history of hepatitis B viral

infection for more than one year and elevated levels of alanine aminotransferase/aspartate aminotransferase or total bilirubin when recruited. Those who were negative for hepatitis B surface antigen (HBsAg) and positive for both hepatitis B surface antibody (HBsAb) and hepatitis B core antibody (HBcAb) were defined as SR controls. All the recruited subjects had no serological evidence of hepatitis C virus, hepatitis D virus, and HIV coinfection; they had no diabetes, malignant tumor, or any autoimmune diseases (18). All studies were performed after informed consent was obtained from the subjects.

Research approach

Genome DNA extraction. Genomic DNA sample was extracted from 5mL EDTA (EDTA) anticoagulated peripheral blood with a standard salting-out procedure and stored at -20°C before use.

Genotyping with SSP-PCR method. KIR genotyping was performed by the sequence-specific primer polymerase chain reaction (SSP-PCR) method in all the recruited subjects. KIR locus typing was performed to detect the presence or absence of a total of 14 KIR loci and one pseudogene KIRZ. Among them, 8 KIR genes (*2DLI*, *2DL2*, *2DL3*, *2DL4*, *2DL5*, 3DL1,*3DL2*, and *3DL3*) were responsible for inhibitory functions and 6 KIR genes (*2DS1*, *2DS2*, *2DS3*, *2DS4*, *2DS5*, and *3DS1*) for conveying activating signals. The SSP-PCR primers used for the detection of KIR loci were based on primer sites that have been previously described (15). Among the 29 formatted couple primers (Shanghai BoYa biotechnology Co.Ltd, Shangai, China), *2DS5* gene uses one couple primer and each of the 14 surplus genes uses two couple primers, so as to ensure a detectable rate of positive gene (KIR genes primer in Table

Table 1. Sequence specific polymerase chain reaction (PCR) primers of killer cell immunoglobulin-like receptors (KIR) genes

	Primer		
KIR gene	forward (5'-3')	reverse (5'- 3')	Base pair
2DL1	GTT GGT CAG ATG TCA TGT TTG AA	GGT CCC TGC CAG GTC TTG CG	127
	TGG ACC AAG AGT CTG CAG GA	TGT TGT CTC CCT AGA AGA CG	330
2DL2	CTG GCC CAC CCA GGT CG	GGA CCG ATG GAG AAG TTG GCT	173
	GAG GGG GAG GCC CAT GAA T	TCG AGT TTG ACC ACT CGT AT	150
2DL3	CTT CAT CGC TGG TGC TG	AGG CTC TTG GTC CAT TAC AA	550
	TCC TTC ATC GCT GGT GCT G	GGC AGG AGA CAA CTT TGG ATC A	800
2DL4	CAG GAC AAG CCC TTC TGC	CTG GGT GCC GAC CAC T	254
	ACC TTC GCT TAC AGC CCG	GGG TTT CCT GTG ACA GAA ACA G	288
2DL5	GCG CTG TGG TGC CTC G	GAC CAC TCA ATG GGG GAG C	214
	TGC AGC TCC AGG AGC TCA	GGG TCT GAC CAC TCA TAG GGT	194
3DL1	CGC TGT GGT GCC TCG A	GGT GTG AAC CCC GAC ATG	197
	CCC TGG TGA AAT CAG GAG AGA G	TGT AGG TCC CTG CAA GGG CAA	181
3DL2	CAA ACC CTT CCT GTC TGC CC	GTG CCG ACC ACC CAG TGA	245
	CCC ATG AAC GTA GGC TCC G	CAC ACG CAG GGC AGG G	130
3DL3	GTC AGA TGT CAG GTT TGA GCG	CAT GGA ATA GTT GAC CTG GGA AC	112
	GCA GCT CCC GGA GCT TG	GGG TCT GAC CAC GCG TG	190
2DS1	CTTCTCCATCAGTCGCATGAA	CTTCTCCATCAGTCGCATGAG	102
	CTTCTCCATCAGTCGCATGAA	AGAGGGTCACTGGGAGCTGAC	102
2DS2	TTC TGC ACA GAG AGG GGA AGT A	AGG TCA CTG GGA GCT GAC AA	173
	CGG GCC CCA CGG TTT	GGT CAC TCG AGT TTG ACC ACT CA	240
2DS3	TGG CCC ACC CAG GTC G	TGA AAA CTG ATA GGG GGA GTG AGG	242
	CTA TGA CAT GTA CCA TCT ATC CAC	AAG CAG TGG GTC ACT TGA C	190
2DS4	CTG GCC CTC CCA GGT CA	TCT GTA GGT TCC TGC AAG GAC AG	204
	CTG GCC CTC CCA GGT CA	GGA ATG TTC CGT TGA TGC	2000
2DS5	TGA TGG GGT CTC CAA GGG	TCC AGA GGG TCA CTG GGC	125
3DS1	AGC CTG CAG GGA ACA GAA G	GCC TGA CTG TGG TGC TCG	300
	CCT GGT GAA ATC AGG AGA GAG	GTC CCT GCA AGG GCA C	177
2DP1	GTC TGC CTG GCC CAG CT	GTG TGA ACC CCG ACA TCT GTA C	205
	CCA TCG GTC CCA TGA TGG	CAC TGG GAG CTG ACA ACT GAT G	90

1). The framework genes (*2DL4*, *3DL2*, and *3DL3*) served as a positive marker of PCR. PCR was conducted by the Gene Amp PCR system 9700-R (Applied Biosystems, Foster City, CA, USA). Briefly, 1μL of genomic DNA was amplified in a volume of approximately 20 μL system including 6μL primers, 2 μL 10 × PCR buffer,1.6 μL $MgCL_2$ (25 000 μM), 0.4 μL dNTP (10 000 μM), 0.125 μL Taq polymerase (5 U/ μL), and 8.875 μL dH_2O. After the initial denaturation for 1 minute at 96°C, the samples were amplified in the following way: 5 cycles of 25 seconds at 96°C, 45 seconds at 65°C, and 30 seconds at 72°C; 21 cycles of 25 seconds at 96°C, 45 seconds at 60°C, and 30 seconds at 72°C; 5 cycles of 25 seconds at 96°C, 1 minute at 55°C, 2 minutes at 72°C; and a prolongation of 10-minute at 72°C.

Agarose gel electrophoreses and image scanning. The PCR products, together with approximately 3μL 100 base pairs (bp) DNA ladder as molecular weight marker (MBI, San Francisco, CA, USA), were electrophoresed on 1.5% agarose gels with bromophenol blue, keeping voltage at 160 V for 30 minutes. After electrophoresis, the agarose gel was scanned and imaged by Alphaimager TM 2200 instrument (Alpha Innotech Corporation, San Leandro, CA, USA) and each sample was genotyped. A result of electrophoresis of the KIR genes PCR products is shown in Figure 1. All primers were validated to be gene-specific by PCR product sequencing.

Statistical analysis

The phenotype frequency (pf, %) of each KIR was calculated as the percentage of positive numbers among all specimens. Genotype frequency (gf) was calculated with the formula $gf = 1 - \sqrt{(1 - pf)}$. KIR genotype frequency (gf) differences were tested for significance by two-tailed Fisher exact test or χ^2 test. Analyses were performed by the SAS 9.0 statistical package (SAS, Cary, NC, USA).

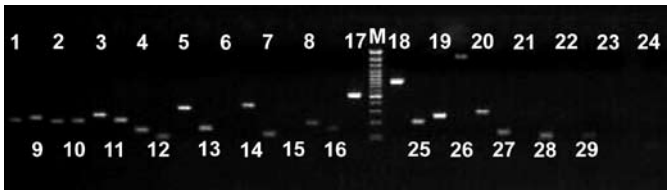

Figure 1. Amplification production electrophoresis picture of a chronic hepatitis B patient. The corresponding digits represent: 1,2 – KIR3DL1; 3,4 – KIR3DL2; 5,6 – KIR3DS1; 7,8 – KIR3DL3; 9,10 – KIR2DL5; 11,12 – KIRZ; 13,14 – KIR2DL1; 15,16 – KIR2DL2; 17,18 – KIR2DL3; 19,20 – KIR2DL4; 21,22 – KIR2DS2; 23,24 – KIR2DS3; 25,26 – KIR2DS4; 27 – KIR2DS5; 28,29 – KIR2DS1; M – M-DNA marker. All KIR phenotypes were positive except KIR2DS3 (23,24).

Results

In this study, all the tested KIR genes were present in both patient groups and control group in different frequencies. Framework genes *KIR2DL4*, *KIR3DL2*, *KIR3DL3*, and *KIRZ* were present in all individuals (Table 2).

KIR phenotype and genotype frequency in patients and control subjects

The total carriage frequency of *KIR2DL5*, *KIR2DS2*, *KIR2DS3*, and *KIR2DS5* was higher in CHB patients than in health control subjects ($P = 0.001$, $P = 0.001$, $P = 0.011$, and $P = 0.028$, respectively).

The total carriage frequency of *KIR2DS2* and *KIR2DS3* was higher ($P = 0.001$,

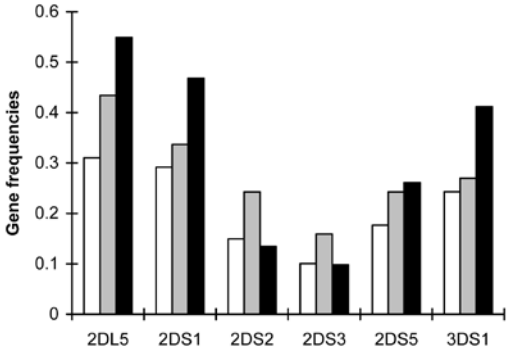

Figure 2. Comparison of killer cell immunoglobulin-like receptors gene frequencies. Closed bars – healthy controls; open bars – chronic hepatitis B group; gray bars – spontaneously recovered controls.

Table 2. Killer cell immunoglobulin-like receptors (KIR) phenotype frequency (pf) and genotype frequencies (gf) in patients and control subjects*

	Group										
	healthy controls (N = 412)			chronic hepatitis B (N = 150)				spontaneously recovered controls (N = 251)				
KIR	+	pf (%)	gf (%)	+	pf (%)	gf	P_C	+	pf (%)	gf (%)	P_S	P
Inhibitory												
2DL1	407	98.79	89.00	150	100	100	1	248	98.80	89.05	1	1
2DL2	79	19.17	10.10	21	11.00	7.26	0.172	39	15.54	0.08	0.251	0.773
2DL3	407	98.79	89.00	150	100	100	1	237	94.42	76.38	0.045	0.062
2DL4	412	100	100	150	100	100	1	251	100	100	1	1
2DL5	216	52.43	31.03	102	68.00	43.43	0.001	200	79.68	54.92	0	0.001
3DL1	407	98.79	89.00	150	100	100	1	247	98.41	87.39	0.736	0.654
3DL2	412	100	100	150	100	100	1	251	100	100	1	1
3DL3	412	100	100	150	100	100	1	251	100	100	1	1
Activating												
2DS1	205	49.76	29.16	84	56.00	33.67	0.215	180	71.71	46.81	0	0.001
2DS2	114	27.67	14.95	64	42.67	24.28	0.001	63	25.10	13.46	0.526	0.001
2DS3	79	19.17	10.09	44	29.33	15.93	0.011	47	18.73	9.85	0.919	0.014
2DS4	399	96.84	82.22	148	98.67	88.47	0.375	251	100	100	0.022	0.059
2DS5	133	32.20	17.66	64	42.67	24.28	0.028	114	45.42	26.12	0.001	0.605
3DS1	176	42.72	24.32	70	46.67	26.97	0.442	164	65.34	41.13	0	0.001
Pseudogene												
KIRZ	412	100	100	150	100	100	NS	251	100	1	1	1

*Abbreviations: + – positive case numbers; PC – P value for the comparison between chronic hepatitis group and healthy control group; PS – P value for the comparison between spontaneously recovered group and healthy control group; P – P-value for the comparison between spontaneously recovered group and chronic hepatitis group.

$P = 0.014$, respectively), while the frequency of *KIR2DL5*, *KIR2DS1*, and *KIR3DS1* was lower ($P = 0.001$, $P = 0.001$, and $P = 0.001$, respectively) in CHB patients than in SR controls. As for KIR2DS5, there was no significant difference between these two groups ($P = 0.605$).

The total carriage frequency of *KIR2DL5*, *KIR2DS1*, *KIR2DS5*, and *KIR3DS1* in SR controls was significantly higher than in healthy controls ($P<0.001$, $P<0.001$, $P<0.001$, and $P<0.001$, respectively). There was no significant difference in the frequency of *KIR2DS2* and *KIR2DS3* between the two groups ($P = 0.526$, $P = 0.919$, respectively) (Table 2, Figure 2).

Activating KIRs in healthy controls and SR controls

We divided SR and healthy controls into 2 groups as follows: group one with a single activating KIR gene and group two with 2 or more activating KIR genes. Out of 251 SR controls, only 56 were in the group one and 195 in the group two (22.31% and 77.69%, respectively). On the contrary, the percentage in healthy controls was 66.26% and 33.74%, respectively.

Discussion

Our data clearly showed that there was a difference in the frequencies of these KIR genes in three different sets of subjects. To date, most of the studies on human genes relevant to HBV infection have focused on HLA genetic alteration. For example, genetic association analyses based on Gambian, European, and Asian cohorts have implicated the role of HLA allele DRB1*1302 in the clearance of HBV infection (21-23). As KIR molecules modulate cell function upon the recognition of HLA class I, it can be inferred that KIR gene may also exert a crucial role in the pathogenesis of HBV infection. In the present study, we analyzed 15 known KIR genes in CHB, SR control, and healthy control group. We found that the frequencies of *KIR2DS2* and *KIR2DS3* in CHB patients were significantly higher than in normal controls, but not in SR controls, indicating that the two genes may serve as HBV infectious susceptibility genes.

Recent evidence has suggested that a subset of T cells expressing *KIR2DS2* can mediate vascular damage in patients with rheumatoid arthritis, implicating a role of activating KIR in rheumatoid arthritis (16) and other autoimmune diseases (14). Although the samples used in this study were different, our results were, at least in part, in agreement with these findings. This suggests that *KIR2DS2* is involved in inflammatory reaction and also that the excessive inflammatory reaction leads to liver tissue damage.

Clinically, HBV infection does not invariably result in chronic hepatitis since the host possesses the ability to eliminate the virus spontaneously in most cases. It is believed that the antibody response to viral envelope antigens contributes to clearance of the virus and that cytotoxic T cells mediate viral clearance by killing the infected cells. In addition, one study has shown that cytotoxic T lymphocytes inhibit HBV gene expression through the secretion of antiviral cytokines and that the expression of these cytokines may be the principal mechanism of viral clearance during HBV infection (24). It is hypothesized that chronic infection is related to a weak T-cell response to viral antigens. Recent research has demonstrated that KIRs expressed on the cell surface of NK and T cells play a role in the regulation of innate and acquired anti-virus immune responses through the transduction of inhibitory or activating signals (11,19,20). In CHB, the excessive expression of *KIR2DS2* and *KIR2DS3* may weakly activate NK or T cells' cytotoxicity and regulate it, leading to deferrable and persistent destruction of the hepatocytes. *KIR2DS2* and *KIR2DS3* are observed in high positive linkage disequilibrium (25), which might be a reason for the simultaneous increase of both of them.

To further analyze our data according to the number of activating KIRs and inhibitory KIRs, we found that there was a significant difference in the two kinds of KIRs between SR controls and healthy control group (Table 2, Figure 2). This may mean that, in SR patients, more activating KIRs send more activating signals to NK cells or to T cells, resulting in HBV clearance or recruitment of other cells of the immune system.

In this study, both the activating *KIR2DS1*, *KIR3DS1* and the inhibitory KIR2DL5 were higher in SR patients than in healthy controls and CHB patients. So, we suggested that these KIR genes may play a role in the clearance of HBV.

In conclusion, our results implicate that *KIR2DS2* and *KIR2DS3* may act as HBV susceptive genes to induce a persistent weak inflammatory reaction that results in continuous injury of live tissues and chronic hepatitis; whereas, *KIR2DS1*, *KIR3DS1*, and *KIR2DL5* may be protective genes that facilitate the clearance of HBV.

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