PO Box 2345, Beijing 100023, China
www.wjgnet.com
wjg@wjgnet.com

World J Gastroenterol 2006 August 14; 12(30): 4788-4793
World Journal of Gastroenterology ISSN 1007-9327

REVIEW

Host susceptibility to persistent hepatitis B virus infection

Ying-Li He, Ying-Ren Zhao, Shu-Lin Zhang, Shu-Mei Lin

Ying-Li He, Ying-Ren Zhao, Shu-Lin Zhang, Shu-Mei Lin, Department of Infectious Diseases, the First Hospital of Xi'an Jiaotong University, Xi'an 710061, Shaanxi Province, China
Supported by The National Natural Science Foundation of China, No. 30230210
Correspondence to: Ying-Ren Zhao, PhD, Department of Infectious Diseases, the First Hospital of Xi'an Jiaotong University, Xi'an 710061, Shaanxi Province, China. zhaoyingren@sohu.com
Telephone: +86-29-81023957 Fax: +86-29-85323634
Received: 2006-04-03 Accepted: 2006-04-24

Abstract

Genetic epidemiology researches such as twin studies, family-clustering of hepatitis B virus (HBV) infection studies and ethnic difference studies have provided the evidence that host genetic factors play an important role in determining the outcome of HBV infection. The opening questions include which human genes are important in infection and how to find them. Though a number of studies have sought genetic associations between HBV infection/persistence and gene polymorphisms, the candidate gene-based approach is clearly inadequate to fully explain the genetic basis of the disease. With the advent of new genetic markers and automated genotyping, genetic mapping can be conducted extremely rapid. This approach has been successful in some infectious diseases. Linkage analysis can find host genes susceptible to HBV and is of great clinical importance.

Key words: Hepatitis B virus; Susceptibility; Association study; Linkage study

He YL, Zhao YR, Zhang SL, Lin SM. Host susceptibility to persistent hepatitis B virus infection. *World J Gastroenterol* 2006; 12(30): 4788-4793

http://www.wjgnet.com/1007-9327/12/4788.asp

INTRODUCTION

Hepatitis B virus (HBV) infection is a serious global health problem, with 2 billion people infected worldwide, and 350 million suffering from chronic HBV infection. HBV infection results in 500 000 to 1.2 million deaths per year caused by chronic hepatitis, cirrhosis, and hepatocellular carcinoma and is the 10th leading cause of death worldwide[1]. The mechanisms of persistent HBV infection are not fully understood, but they seem to involve several aspects and the genetic component, in particular, is still controversial[2]. Early studies by Blumberg *et al*[3] have also suggested a recessive mode of inheritance for HBV viral persistence, but this is perhaps an oversimplification giving the more recent advances in knowledge of the effect of maternal viral infection and the transmissibility of the virus[4].

Generally, exposure to HBV can cause a broad spectrum of infection[5]. Ninety to ninety-five percent of adults infected with HBV can eliminate the virus and only 5%-10% of them become chronic HBV carriers, 20%-30% of chronic HBV carriers develop chronic hepatitis B (CHB) and 5% of them develop liver cirrhosis and hepatocellular carcinoma in a long term of disease course. Some rare cases result in a fulminant infection in which the liver is rapidly overwhelmed and ultimately fails. What factors determine why one develops a life-threatening infection, whereas another carries HBV as a harmless commensal or limits the infection to a clinical trivial episode? There is evidence that host genetic factors play an important role in determining the outcome of HBV infection[6,7].

EPIDEMIOLOGY EVIDENCE FOR HUMAN GENETIC SUSCEPTIBILITY TO PERSISTENT HBV INFECTION: TWINS, FAMILY-CLUSTERING OF HBV INFECTION AND ETHNIC DIFFERENCES

Twin studies

Studies of susceptibility to diseases in identical and non-identical twins are extremely useful in evaluating the importance of inherited *vs* environmental factors in disease susceptibility[8]. If the concordance rates for infection and clearance of HBV are significantly higher in monozygotic (MZ) than in dizygotic (DZ) twins, the process of HBV infection and persistence is more genetically decisive. Lin *et al*[9] studied 289 pairs of MZ twins, 102 pairs of DZ twins and 375 pairs of age-sex-matched singleton controls and found that there is a significant difference in the concordance of HBV infection between MZ and DZ twins and controls, suggesting that the genetic influence occurs in response to HBV infection. Xu *et al*[10] also found that not only the concordance rate of infection, but the concordance of clinical phenotype and serological

patterns between MZ and control groups is significantly different, indicating that genetic factors influence not only susceptibility to infection but also clinical outcome.

Genetic factors not only influence host response to HBV infection, but also affect the response to HB vaccine. Hohler *et al*[11] prospectively studied and vaccinated 202 twin pairs with a combined recombinant HBsAg vaccine and found that the heritability of anti-HBs immune response is 0.61, which means that 60% of the phenotypic variance of responsiveness to HB vaccine can be explained by genetic effect and 40% by environmental effect.

Family-clustering of HBV infection

Most of us do not inherit single-gene diseases. We all, however, inherit slightly different variants of each of our pairs of 30 000 genes. These differences may determine whether we are more or less likely to develop particular health problems or diseases than other people. Genes are shared within families. Because we inherit genes from our parents, a parent who has inherited a particular gene mutation generally means that each child has a fifty-fifty chance of having the same mutation. In fact, many cases of diseases not showing the clear inherited patterns of single-gene diseases, show family clustering patterns that are due, at least in part, to genetics. Substantial genetic epidemiology studies indicate that HBV spreads in families. The familial occurrence of HBV infection has been well established in some ethnic groups. Ohbayashi *et al*[12] have reported 3 Japanese families in which 36 of the 54 members are HBsAg positive. Of these, some are healthy carriers while others have liver cirrhosis and hepatocellular carcinoma. Similar observations have been reported in American[13], European[14] and Asian[15,16] continents.

This observed familial clustering may stem from inherited defects in specific genes, from shared environmental exposures among family members or from interaction between specific genetic and environmental factors. If a trait has a genetic basis, the relatives of affected individuals will be affected more frequently than the relatives of unaffected people, and the prevalence of disease decreases from monozygotic (MZ) twin to the first-, second- and third-degree relatives. If the disorder has an environmental basis only, the possibility of infection in each family member is equal[17]. Tong *et al*[18] reported that HBV markers are detected more frequently in blood relatives than in non-blood relatives of the index cases in family. Wang *et al*[19] also showed that HBsAg carrier rate decreases in the order of the first, second and third degree relatives, indicating that it is the defect gene shared by family members that produces the epidemiological characteristics of family-clustering HBV infection.

Ethnic differences

Another method used to investigate the role of host genetics in infectious diseases is to look for differences in clinical disease and immune response between different ethnic groups having equal exposure to the same pathogen. Carrilho *et al*[20] determined the frequency of HBV markers of genetically related (consanguineous) and non-genetically related (non-consanguineous) Brazilian families of Asian origin and Western origin and found that the occurrence of HBsAg is significantly higher ($P < 0.0001$) in family members of Asian origin (81.8%) than in those of Western origin (36.5%), which is in line with the high HBsAg prevalence in Asian countries and the relatively low HBsAg prevalence in Western countries[21]. Though the Asians live in Brazilia, a country with a low HBsAg prevalence, and the environment has changed, disease-related genes remain shared within the ethnic group, indicating that Asians possess the HBV susceptible gene(s). This is why they are more susceptible to HBV.

Tong *et al*[18] tested family members of Asian and non-Asian patients for HBV markers, and found that Asian family members have a significant increase in HBsAg (34% higher) and antibodies to HBsAg or to hepatitis B core antigen (50% higher) compared with the non-Asian family members. Moreover, birthplace, either in Asia or in United States, does not influence the frequency of antigenemia. In China, the prevalence of HBsAg is 19.1% in Mongoloid populations[22], and 10% in Chinese Han populations in the same area. These studies have provided important insights into the fact that different ethnics in the same region have different HBV epidemiological characteristics and the same races in the different region share the same prevalence of HBV markers, indicating that genetic factors may play a role in maintaining the frequency of HBV infection and persistence. Moreover, molecular epidemiology study has identified several genetically determined differences between races.

Taken together these epidemiological data provide strong evidence for a genetic predisposition to HBV infection and raise the questions of which human genes are important in infection and how to find them.

TWO METHODS USED TO IDENTIFY HBV SUSCEPTIBLE GENES

Analysis of the human genome has focused primarily on variations that occur between people in their DNA sequence[23]. Because these differences contribute to the differences in our susceptibility to developing specific diseases, naturally occurring genetic variations in the human genome are frequently found (about every 3 to 500 bp) most often in the form of a change from one base to another, namely a single nucleotide polymorphism (SNP)[24]. Other common forms of variation include microsatellite where a short sequence, usually a dinucleotide repeat is bound, so that one person might have 10 and 12 copies of the repeating motif and others have 9 and 11 copies. If the repeating sequence is longer, the motif is known as a minisatellite[25]. They are widely used to determine similarities and differences of human and hunter disease-related genes. Because this kind of genetic variations often varies between individuals (i.e., it is highly polymorphic), microsatellites are particularly informative in the genetic sense[26]. Analysis of genetic susceptibility to HBV infection aims to link these DNA variations (the genotype) with a particular HBV infection (the phenotype). HBV infection and clearance are complex traits[27], meaning that the genetic contribution to them is not inherited in a

Table 1 Gene polymorphisms associated with clearance of HBV infection

Gene/loci	Population	Sample size	*P* value	Reference
HLA A 0301	Caucasian	563	0.0005	[30]
HLA -DRB1 1302	Caucasian	563	0.03	[30]
HLA-DRB1 1302	Gambian	638	0.012	[31]
HLA-DRB1 1101/1104	Chinese	190	0.0145	[32]
HLA-DQA1 0301	Chinese	190	0.0167	[32]
HLA-DR13	Korean	1272	< 0.001	[33]
TNF-alpha-238 GG genotype	Chinese	895	0.041	[34]
TNF-alpha-308 A	Korean	1400	< 0.001	[35]
TNF-alpha-857 TT genotype	Chinese	355	0.02	[36]
CTLA-4-1722 C			0.06	[37]
CTLA-4+49 G			0.02	[37]
CCR5 59029 G allele	Chinese	377	0.001	[38]

Table 2 Gene polymorphisms associated with susceptibility to chronic hepatitis B

Gene/loci	Population	Sample size	*P* value	Reference
HLA B 08	Caucasian	563	0.03	[30]
HLA B 44-Cw 1601	Caucasian	563	0.02	[30]
HLA B 44-Cw 0501	Caucasian	563	0.006	[30]
HLA-DRB1 0301	Chinese	190	0.0074	[32]
HLA-DRB1 1301/2				[39]
HLA-DR6	Korean	1272	< 0.001	[33]
HLA-DQA1 0501	Chinese	190	0.0157	[32]
HLA -DQA1 0501	African American	91	0.05	[40]
HLA -DQB1 0301	African American	91	0.01	[40]
HLA-DQB1 0301	Chinese	190	0.0075	[32]
TNF-alpha-863 A	Korean	1400		[35]
TNF-alpha-238 GG genotype	Chinese	355	0.02	[36]
TNF-alpha-238 GG genotype	Chinese	455	0.02	[41]
TNF-alpha-857 CC genotype	Chinese	895	< 0.001	[34]
IFN-gamma A/A genotype		77		[42]
CTLA-4+6230 A			0.04	[37]
CCR5 59029 A allelic genotype	Chinese	377	0.002	[38]
ESR1 29 T/T genotype	Chinese	2318	< 0.001	[43]

simple Mendelian manner and several polymorphic genes exert effects on the outcome[28]. Many possible approaches to mapping the genes underlying complex traits fall broadly into two categories: candidate gene- based association studies and genome-wide linkage studies[29].

Association studies

Association studies compare the frequency of alleles or genotypes of a particular variant between disease cases and controls to link the genotype with the particular phenotype. Such studies are widely used to investigate inflammatory and infectious diseases. Repeat sequences, such as those of microsatellites, lend themselves less well to association studies because they are intrinsically unstable and may undergo considerable mutations over successive generations and disease-modifying polymorphisms may have arisen many hundreds of generations previously. SNPs, on the other hand, are stable, common and increasingly amenable to high throughput automated genotyping. A number of studies have sought genetic associations between HBV infection/persistence and gene polymorphisms (Tables 1 and 2).

The huge variation in clinical response to identical infecting pathogens is due to the combined effects of genetic variation both in the infecting pathogen and in the infected host[44]. Its ability to mount an effective immune response to infection is a powerful evolutionary selection pressure, contributing to human genetic diversity. The advantage of a flexible immune response, allowing an efficient response to diverse pathogens without damage to the host, is reflected in marked genetic variability of immune-related genes among (both in DNA sequence and in protein structure) in the entire human genome[45].

The prototype region for genetic association studies is the human leukocyte antigen (HLA) loci involved in antigen processing and presentation. HLA associated with infections such as AIDS[46], tuberculosis[47], leprosy[48], malaria[49] and persistence of hepatitis-C virus[50] has been well-described. This is most obvious within the HLA region, where functional variation has arisen as a strategy to combat pathogen antigenic diversity. Indeed in HBV infection, maximal HLA variation appears to have a direct protective effect, individuals with the most different alleles at class Ⅱ HLA loci have the slowest HBV disease progression and the lowest mortality (a "heterozygous advantage")[51]. Conversely, lack of HLA diversity (a "homozygous disadvantage") may increase the susceptibility to HBV infection among isolated communities[52]. The extensive linkage disequilibrium across some HLA regions makes it difficult to localize specific disease-associated polymorphisms, although the HLA allelic association has allowed identification of critically pathogenic epitopes in some diseases[39], which might act as potential vaccine candidates.

Disease associations involving loci outside the HLA region are also valuable in identifying the functional molecular basis underlying infectious disease resistance. For example, HIV uses various chemokine receptors as cofactors for CD4 binding to gain entry into human leukocytes. A functional polymorphism of the chemokine receptor CCR5, which is essential for HIV entry into macrophages, results in a truncated nonfunctional protein that confers highly significant protection against HIV susceptibility in the homozygous state and slows disease progression in heterozygotes[53,54]. Chang *et al*[38] have developed the association between CCR5 and HBV infection, though the biological process and significance in HBV infection need to be further studied.

Shortcoming of association studies in susceptible gene hunting

The number of studies seeking to identify genes that influence susceptibility to persistent HBV infection has greatly increased since we entered the "post-genomic" era. These studies are fuelled by the unlimited availability of

Table 3 Successful linkage analysis in infectious diseases

Diseases	Location of predisposing genes	Reference
H pylori	IFNGR1	[60]
Plasmodium falciparum	5q31-q33, MHC	[61-64]
Kala-azar	22q12, Imr2, Imr1	[65]
Tuberculosis	15q and Xq	[66]
Schistosoma mansoni	5q31-q33	[67]
Leprosy	10p13, 6q25	[68, 69]

SNPs, the relative ease of performing genotyping assays based on PCR technology, and the desire to identify major disease susceptibility gene(s). Literature is now littered with unreproducible genetic association studies that confuse the readers and have an understandable impact on the willingness of editors to accept further manuscripts for publication[27]. *Nature Genetics* published an editorial in 1999 that set out a list of criteria for genetic association studies[55]: plausible biological context, rigorous phenotypic selection (case selection), independent replication, rigorous genotyping, low *P* values, appropriate statistical analysis, and transmission disequilibrium test. Up to now, few candidate genes can fully meet the criteria.

Candidate gene-based association studies rely on having predicted the identity of the correct gene or genes, usually on the basis of biological hypotheses or the location of the candidate within a previously determined region of linkage[56]. Even if these hypotheses are broad (for example, involving the testing of all genes in the insulin-signaling pathway), they will, at best, identify only a fraction of genetic risk factors for diseases in which the pathophysiology is relatively well understood. When the fundamental physiological defects of a disease are unknown, the candidate-gene approach is clearly inadequate to fully explain the genetic basis of the disease[29]. In 2004, *Hepatology* editor appealed for less hypothesis-driven association studies that result in a negative or weak correlation[27].

Linkage studies

Linkage is the tendency for genes and other genetic markers to be inherited together because of their location near one another on the same chromosome. Linkage studies classically seek to identify microsatellite markers that are inherited more commonly than expected by siblings who have the disease of interest ("affected sibling pairs")[57]. Genetic linkage analysis is a powerful tool to detect the chromosomal location of disease genes[58]. A linkage study is to use a large number of families to look for regions of linkage to a disease, which suggest the presence of loci containing genes that may predispose to this disease. Linkage studies have the advantage of making no supposition about which genes might be involved in a disease, in that they merely identify stretches of chromosome around the microsatellite markers and can be used to examine the entire genome (a "whole genome screen")[58].

With the advent of new genetic markers and automated genotyping, genetic mapping can be conducted extremely rapid[28,59]. This approach has been successful in some infectious diseases (Table 3), but no report on such similar scans for HBV viral persistence is available. Recently a research team of Xi'an Jiaotong University has collected 327 HBV-infected subjects of 32 family pedigrees from a remote village (data not published), which makes it possible to find chromosome regions containing determinant(s) of persistent HBV infection. Their results will be reported soon.

CLINICAL IMPLICATION OF GENETIC STUDIES OF HBV INFECTION

Studies of the genetic determinants for HBV susceptibility can reveal fundamental data concerning the human immune system. The ultimate goal of such studies is the identification of critical immunologic mechanisms in the disease process to develop specific therapeutic interventions. As the precise immune deficiency is identified, it may be possible to "bypass" the identified immune deficiency with a specific therapy.

A specific genetic defect has been identified in rarer single gene defects, which may offer preconception genetic counseling to affected families. In complex diseases it might ultimately be possible to identify patients whose risk factors make them candidates for targeted therapies. Once the genotypic markers for a poor outcome of HBV infections are found, they in combination with rapid genotyping technology may allow more intensive therapies for those patients who are at the greatest risk of poor outcome and death[70,71]. The potential to target drug treatment, both in terms of identifying patients most likely to benefit clinically and in terms of predicting those who are susceptible to either favorable or adverse pharmacologic outcome, is of great importance. It is conceivable that in the future our understanding of host genetics will largely influence our therapeutic response to HBV-infected patients and determine our choice of both preventive and curative interventions.

REFERENCES

1 **Rehermann B**, Nascimbeni M. Immunology of hepatitis B virus and hepatitis C virus infection. *Nat Rev Immunol* 2005; **5**: 215-229
2 **Owada T**, Matsubayashi K, Sakata H, Ihara H, Sato S, Ikebuchi K, Kato T, Azuma H, Ikeda H. Interaction between desialylated hepatitis B virus and asialoglycoprotein receptor on hepatocytes may be indispensable for viral binding and entry. *J Viral Hepat* 2006; **13**: 11-18
3 **Blumberg BS**, Friedlaender JS, Woodside A, Sutnick AI, London WT. Hepatitis and Australia antigen: autosomal recessive inheritance of susceptibility to infection in humans. *Proc Natl Acad Sci U S A* 1969; **62**: 1108-1115
4 **Hann HW**, Kim CY, London WT, Whitford P, Blumberg BS. Hepatitis B virus and primary hepatocellular carcinoma: family studies in Korea. *Int J Cancer* 1982; **30**: 47-51
5 **Ganem D**, Prince AM. Hepatitis B virus infection--natural history and clinical consequences. *N Engl J Med* 2004; **350**: 1118-1129
6 **Frodsham AJ**. Host genetics and the outcome of hepatitis B viral infection. *Transpl Immunol* 2005; **14**: 183-186
7 **Schaefer S**. Hepatitis B virus: significance of genotypes. *J Viral Hepat* 2005; **12**: 111-124

8 **vB Hjelmborg J**, Iachine I, Skytthe A, Vaupel JW, McGue M, Koskenvuo M, Kaprio J, Pedersen NL, Christensen K. Genetic influence on human lifespan and longevity. *Hum Genet* 2006; **119**: 312-321

9 **Lin TM**, Chen CJ, Wu MM, Yang CS, Chen JS, Lin CC, Kwang TY, Hsu ST, Lin SY, Hsu LC. Hepatitis B virus markers in Chinese twins. *Anticancer Res* 1989; **9**: 737-741

10 **Xu BY**, Wang YM, Deng GH, Huang YP, Zhong LH, Liu GD, Tan ZX, Fan Y, Ding ST. [The primary comparative analysis between the host genetic factors and their relationships with clinical phenotype of HBV infected twins]. *Zhonghua Yi Xue Za Zhi* 2004; **84**: 189-193

11 **Höhler T**, Reuss E, Evers N, Dietrich E, Rittner C, Freitag CM, Vollmar J, Schneider PM, Fimmers R. Differential genetic determination of immune responsiveness to hepatitis B surface antigen and to hepatitis A virus: a vaccination study in twins. *Lancet* 2002; **360**: 991-995

12 **Obayashi A**, Okochi K, Mayumi M. Familial clustering of asymptomatic carriers of Australia antigen and patients with chronic liver disease or primary liver cancer. *Gastroenterology* 1972; **62**: 618-625

13 **Motta-Castro AR**, Martins RM, Yoshida CF, Teles SA, Paniago AM, Lima KM, Gomes SA. Hepatitis B virus infection in isolated Afro-Brazilian communities. *J Med Virol* 2005; **77**: 188-193

14 **Bosch J**, Brugera M, Rodes J. Familial spread of type-B hepatitis. *Lancet* 1973; **2**: 457

15 **Beasley RP**, Hwang LY, Stevens CE, Lin CC, Hsieh FJ, Wang KY, Sun TS, Szmuness W. Efficacy of hepatitis B immune globulin for prevention of perinatal transmission of the hepatitis B virus carrier state: final report of a randomized double-blind, placebo-controlled trial. *Hepatology* 1983; **3**: 135-141

16 **Lin JB**, Lin DB, Chen SC, Chen PS, Chen WK. Seroepidemiology of hepatitis A, B, C, and E viruses infection among preschool children in Taiwan. *J Med Virol* 2006; **78**: 18-23

17 **Amundadottir LT**, Thorvaldsson S, Gudbjartsson DF, Sulem P, Kristjansson K, Arnason S, Gulcher JR, Bjornsson J, Kong A, Thorsteinsdottir U, Stefansson K. Cancer as a complex phenotype: pattern of cancer distribution within and beyond the nuclear family. *PLoS Med* 2004; **1**: e65

18 **Tong MJ**, Weiner JM, Ashcavai MW, Redeker AG, Comparini S, Vyas GN. A comparative study of hepatitis B viral markers in the family members of Asian and non-Asian patients with hepatitis B surface antigen-positive hepatocellular carcinoma and with chronic hepatitis B infection. *J Infect Dis* 1979; **140**: 506-512

19 **Wang WJ**, Xu HW, Men BY. [A genetic epidemiologic study on HBsAg chronic carriers]. *Zhonghua Liu Xing Bing Xue Za Zhi* 1996; **17**: 148-151

20 **Carrilho FJ**, Ono-Nita SK, Cardoso RA, Cancado EL, Pinho JR, Alves VA, Da Silva LC. A prospective study of hepatitis B virus markers in patients with chronic HBV infection from Brazilian families of Western and Asian origin. *Braz J Med Biol Res* 2005; **38**: 1399-1408

21 **Custer B**, Sullivan SD, Hazlet TK, Iloeje U, Veenstra DL, Kowdley KV. Global epidemiology of hepatitis B virus. *J Clin Gastroenterol* 2004; **38**: S158-S168

22 **Zhao SM**, Li HC, Lou H, Lu XX, Yu XF, Gao DH, Hu J, Chiba H, Takezaki T, Takeshita H, Yashiki S, Fujiyoshi T, Sonoda S, Tajima K. High Prevalence of HBV in Tibet, China. *Asian Pac J Cancer Prev* 2001; **2**: 299-304

23 **Cavalli-Sforza LL**. The Human Genome Diversity Project: past, present and future. *Nat Rev Genet* 2005; **6**: 333-340

24 **Smith C**. Genomics: SNPs and human disease. *Nature* 2005; **435**: 993

25 **Lin J**, Liu KY. Linkage and association analyses of microsatellites and single-nucleotide polymorphisms in nuclear families. *BMC Genet* 2005; **6** Suppl 1: S25

26 **Badzioch MD**, Goode EL, Jarvik GP. The role of parametric linkage methods in complex trait analyses using microsatellites. *BMC Genet* 2005; **6** Suppl 1: S48

27 **Thursz M**. Pros and cons of genetic association studies in hepatitis B. *Hepatology* 2004; **40**: 284-286

28 **Newton-Cheh C**, Hirschhorn JN. Genetic association studies of complex traits: design and analysis issues. *Mutat Res* 2005; **573**: 54-69

29 **Hirschhorn JN**, Daly MJ. Genome-wide association studies for common diseases and complex traits. *Nat Rev Genet* 2005; **6**: 95-108

30 **Thio CL**, Thomas DL, Karacki P, Gao X, Marti D, Kaslow RA, Goedert JJ, Hilgartner M, Strathdee SA, Duggal P, O'Brien SJ, Astemborski J, Carrington M. Comprehensive analysis of class I and class II HLA antigens and chronic hepatitis B virus infection. *J Virol* 2003; **77**: 12083-12087

31 **Thursz MR**, Kwiatkowski D, Allsopp CE, Greenwood BM, Thomas HC, Hill AV. Association between an MHC class II allele and clearance of hepatitis B virus in the Gambia. *N Engl J Med* 1995; **332**: 1065-1069

32 **Jiang YG**, Wang YM, Liu TH, Liu J. Association between HLA class II gene and susceptibility or resistance to chronic hepatitis B. *World J Gastroenterol* 2003; **9**: 2221-2225

33 **Ahn SH**, Han KH, Park JY, Lee CK, Kang SW, Chon CY, Kim YS, Park K, Kim DK, Moon YM. Association between hepatitis B virus infection and HLA-DR type in Korea. *Hepatology* 2000; **31**: 1371-1373

34 **Li HQ**, Li Z, Liu Y, Li JH, Dong JQ, Gao JR, Gou CY, Li H. Association of polymorphism of tumor necrosis factor-alpha gene promoter region with outcome of hepatitis B virus infection. *World J Gastroenterol* 2005; **11**: 5213-5217

35 **Kim YJ**, Lee HS, Yoon JH, Kim CY, Park MH, Kim LH, Park BL, Shin HD. Association of TNF-alpha promoter polymorphisms with the clearance of hepatitis B virus infection. *Hum Mol Genet* 2003; **12**: 2541-2546

36 **Liu Y**, Guo XH, Du T, Li JH, Zhu XL, Gao JR, Lu LP, Gou CY, Li Z, Li H. [Association of TNFA polymorphisms with the outcomes of HBV infection]. *Zhonghua Yi Xue Yi Chuan Xue Za Zhi* 2005; **22**: 406-410

37 **Thio CL**, Mosbruger TL, Kaslow RA, Karp CL, Strathdee SA, Vlahov D, O'Brien SJ, Astemborski J, Thomas DL. Cytotoxic T-lymphocyte antigen 4 gene and recovery from hepatitis B virus infection. *J Virol* 2004; **78**: 11258-11262

38 **Chang HY**, Ahn SH, Kim DY, Shin JS, Kim YS, Hong SP, Chung HJ, Kim SO, Yoo WD, Han KH. [Association between CCR5 promoter polymorphisms and hepatitis B virus infection]. *Korean J Hepatol* 2005; **11**: 116-124

39 **Godkin A**, Davenport M, Hill AV. Molecular analysis of HLA class II associations with hepatitis B virus clearance and vaccine nonresponsiveness. *Hepatology* 2005; **41**: 1383-1390

40 **Thio CL**, Carrington M, Marti D, O'Brien SJ, Vlahov D, Nelson KE, Astemborski J, Thomas DL. Class II HLA alleles and hepatitis B virus persistence in African Americans. *J Infect Dis* 1999; **179**: 1004-1006

41 **Lu LP**, Li XW, Liu Y, Sun GC, Wang XP, Zhu XL, Hu QY, Li H. Association of -238G/A polymorphism of tumor necrosis factor-alpha gene promoter region with outcomes of hepatitis B virus infection in Chinese Han population. *World J Gastroenterol* 2004; **10**: 1810-1814

42 **Ben-Ari Z**, Mor E, Papo O, Kfir B, Sulkes J, Tambur AR, Tur-Kaspa R, Klein T. Cytokine gene polymorphisms in patients infected with hepatitis B virus. *Am J Gastroenterol* 2003; **98**: 144-150

43 **Deng G**, Zhou G, Zhai Y, Li S, Li X, Li Y, Zhang R, Yao Z, Shen Y, Qiang B, Wang Y, He F. Association of estrogen receptor alpha polymorphisms with susceptibility to chronic hepatitis B virus infection. *Hepatology* 2004; **40**: 318-326

44 **Liu W**, Kaiser MG, Lamont SJ. Natural resistance-associated macrophage protein 1 gene polymorphisms and response to vaccine against or challenge with Salmonella enteritidis in young chicks. *Poult Sci* 2003; **82**: 259-266

45 **Prugnolle F**, Manica A, Charpentier M, Guégan JF, Guernier V, Balloux F. Pathogen-driven selection and worldwide HLA class I diversity. *Curr Biol* 2005; **15**: 1022-1027

46 **Stephens HA**. HIV-1 diversity versus HLA class I polymorphism. *Trends Immunol* 2005; **26**: 41-47

47 **Delgado JC**, Baena A, Thim S, Goldfeld AE. Aspartic acid homozygosity at codon 57 of HLA-DQ beta is associated with susceptibility to pulmonary tuberculosis in Cambodia. *J Immu-*

nol 2006; **176**: 1090-1097
48 **Shankarkumar U**. HLA associations in leprosy patients from Mumbai, India. *Lepr Rev* 2004; **75**: 79-85
49 **Lyke KE**, Burges RB, Cissoko Y, Sangare L, Kone A, Dao M, Diarra I, Fernández-Vina MA, Plowe CV, Doumbo OK, Sztein MB. HLA-A2 supertype-restricted cell-mediated immunity by peripheral blood mononuclear cells derived from Malian children with severe or uncomplicated Plasmodium falciparum malaria and healthy controls. *Infect Immun* 2005; **73**: 5799-5808
50 **Yang M**, Zhu F, Sønderstrup G, Eckels DD. Recognition of endogenously synthesized HLA-DR4 restricted HCV epitopes presented by autologous EBV transformed B-lymphoblastoid cell line. *Vaccine* 2005; **23**: 951-962
51 **Kiepiela P**, Leslie AJ, Honeyborne I, Ramduth D, Thobakgale C, Chetty S, Rathnavalu P, Moore C, Pfafferott KJ, Hilton L, Zimbwa P, Moore S, Allen T, Brander C, Addo MM, Altfeld M, James I, Mallal S, Bunce M, Barber LD, Szinger J, Day C, Klenerman P, Mullins J, Korber B, Coovadia HM, Walker BD, Goulder PJ. Dominant influence of HLA-B in mediating the potential co-evolution of HIV and HLA. *Nature* 2004; **432**: 769-775
52 **Stear MJ**, Innocent GT, Buitkamp J. The evolution and maintenance of polymorphism in the major histocompatibility complex. *Vet Immunol Immunopathol* 2005; **108**: 53-57
53 **Mack M**, Pfirstinger J, Haas J, Nelson PJ, Kufer P, Riethmüller G, Schlöndorff D. Preferential targeting of CD4-CCR5 complexes with bifunctional inhibitors: a novel approach to block HIV-1 infection. *J Immunol* 2005; **175**: 7586-7593
54 **Pakarasang M**, Wasi C, Suwanagool S, Chalermchockcharoenkit A, Auewarakul P. Increased HIV-DNA load in CCR5-negative lymphocytes without viral phenotypic change. *Virology* 2006; **347**: 372-378
55 Freely associating. *Nat Genet* 1999; **22**: 1-2
56 **Daly AK**, Day CP. Candidate gene case-control association studies: advantages and potential pitfalls. *Br J Clin Pharmacol* 2001; **52**: 489-499
57 **Morton NE**. Linkage disequilibrium maps and association mapping. *J Clin Invest* 2005; **115**: 1425-1430
58 **Dawn Teare M**, Barrett JH. Genetic linkage studies. *Lancet* 2005; **366**: 1036-1044
59 **Hirschhorn JN**. Genetic approaches to studying common diseases and complex traits. *Pediatr Res* 2005; **57**: 74R-77R
60 **Thye T**, Burchard GD, Nilius M, Müller-Myhsok B, Horstmann RD. Genomewide linkage analysis identifies polymorphism in the human interferon-gamma receptor affecting Helicobacter pylori infection. *Am J Hum Genet* 2003; **72**: 448-453
61 **Flori L**, Kumulungui B, Aucan C, Esnault C, Traoré AS, Fumoux F, Rihet P. Linkage and association between Plasmodium falciparum blood infection levels and chromosome 5q31-q33. *Genes Immun* 2003; **4**: 265-268
62 **Rihet P**, Traoré Y, Abel L, Aucan C, Traoré-Leroux T, Fumoux F. Malaria in humans: Plasmodium falciparum blood infection levels are linked to chromosome 5q31-q33. *Am J Hum Genet* 1998; **63**: 498-505
63 **Garcia A**, Marquet S, Bucheton B, Hillaire D, Cot M, Fievet N, Dessein AJ, Abel L. Linkage analysis of blood Plasmodium falciparum levels: interest of the 5q31-q33 chromosome region. *Am J Trop Med Hyg* 1998; **58**: 705-709
64 **Jepson A**, Sisay-Joof F, Banya W, Hassan-King M, Frodsham A, Bennett S, Hill AV, Whittle H. Genetic linkage of mild malaria to the major histocompatibility complex in Gambian children: study of affected sibling pairs. *BMJ* 1997; **315**: 96-97
65 **Bucheton B**, Abel L, El-Safi S, Kheir MM, Pavek S, Lemainque A, Dessein AJ. A major susceptibility locus on chromosome 22q12 plays a critical role in the control of kala-azar. *Am J Hum Genet* 2003; **73**: 1052-1060
66 **Bellamy R**, Beyers N, McAdam KP, Ruwende C, Gie R, Samaai P, Bester D, Meyer M, Corrah T, Collin M, Camidge DR, Wilkinson D, Hoal-Van Helden E, Whittle HC, Amos W, van Helden P, Hill AV. Genetic susceptibility to tuberculosis in Africans: a genome-wide scan. *Proc Natl Acad Sci U S A* 2000; **97**: 8005-8009
67 **Marquet S**, Abel L, Hillaire D, Dessein A. Full results of the genome-wide scan which localises a locus controlling the intensity of infection by Schistosoma mansoni on chromosome 5q31-q33. *Eur J Hum Genet* 1999; **7**: 88-97
68 **Siddiqui MR**, Meisner S, Tosh K, Balakrishnan K, Ghei S, Fisher SE, Golding M, Shanker Narayan NP, Sitaraman T, Sengupta U, Pitchappan R, Hill AV. A major susceptibility locus for leprosy in India maps to chromosome 10p13. *Nat Genet* 2001; **27**: 439-441
69 **Mira MT**, Alcaïs A, Van Thuc N, Thai VH, Huong NT, Ba NN, Verner A, Hudson TJ, Abel L, Schurr E. Chromosome 6q25 is linked to susceptibility to leprosy in a Vietnamese population. *Nat Genet* 2003; **33**: 412-415
70 **Kacprzak-Bergman I**, Nowakowska B. Influence of genetic factors on the susceptibility to HBV infection, its clinical pictures, and responsiveness to HBV vaccination. *Arch Immunol Ther Exp (Warsz)* 2005; **53**: 139-142
71 **Feitelson MA**, Pan J, Lian Z. Early molecular and genetic determinants of primary liver malignancy. *Surg Clin North Am* 2004; **84**: 339-354

S- Editor Wang J **L- Editor** Wang XL **E- Editor** Bai SH