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• REVIEW •

Current status and prospects of studies on human genetic alleles associated with hepatitis B virus infection

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Abstract

Chronic hepatitis B virus (HBV) infection can cause a broad spectrum diseases, including from asymptomatic HBV carriers or cryptic hepatitis, to acute hepatitis, chronic hepatitis, Liver cirrhosis and primary hepatocellular carcinoma. The variable pattern and clinical outcome of the infection were mainly determined by virological itself factors, host immunological factors and genetic factors as well as the experimental factors. Among the human genetic factors, major candidate or identified genes involved in the process of HBV infection fall into the following categories: (1) genes that mediate the processes of viral entry into hepatocytes, including genes involved in viral binding, fusion with cellular membrane and transportation in target cells; (2) genes that modulate or control the immune response to HBV infection; (3) genes that participate in the pathological alterations in liver tissue; (4) genes involved in the development of liver cirrhosis and hepatocellular carcinoma associated with chronic HBV infection, including genes related to mother-to-infant transmission of HBV infection; and (5) those that contribute to resistance to antiviral therapies. Most of the reports of human genes associated with HBV infection have currently focused on HLA associations. For example, some investigators reported the association of the HLA class II alleles such as DRB1*1302 or HLA-DR13 or DQA1*0501-DQB1*0301-DQB1*1102 haplotypes with acute and/or chronic hepatitis B virus infection, respectively. Several pro-inflammatory cytokines such as Th1 cytokines (including IL-2 and IFN-γ) and TNF-α have been identified to participate the process of viral clearance and host immune response to HBV. In contrast, the Th2 cytokine IL-10 serves as a potent inhibitor of Th1 effector cells in HBV diseases. The MBP polymorphisms in its encoding region were found to be involved in chronic infection. Thus, reports from various laboratories have shown some inconsistencies with regard to the effects of host genetic factors on HBV clearance and persistence. Since genetic interactions are complex, it is unlikely that a single allelic variant is responsible for HBV resistance or susceptibility. However, the collective influence of several single nucleotide polymorphisms (SNPs) or haplotype (s) may underlie the natural combinational or synergistic protection against HBV. The future study including the multi-cohort collaboration will be needed to clarify these preliminary associations and identify other potential candidate genes. The ongoing study of the distributions and functions of the implicated allele polymorphisms will not only provide insight into the pathogenesis of HBV infection, but may also provide a novel rationale for new methods of diagnosis and therapeutic strategies.

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INTRODUCTION

Chronic hepatitis B virus (HBV) infection is one of the most common infectious diseases and leads to high morbidity and mortality due to the development of liver cirrhosis (LC) and hepatocellular carcinomas (HCC). It is estimated that HBV is present in a reservoir of more than 130 million chronic carriers, representing more than 10 % of Chinese population[1]. In particular, more than 23 million of Chinese HBV-infected subjects clinically manifest liver damage with abnormally elevated ALT levels and HBV active replication. Generally, exposure to HBV can cause a broad spectrum ranging from no infection to different clinical conditions[2]. What produces the individual or ethnic differences in infection, severity, and outcome? The reasons for this variation in the natural history of HBV infection are not fully understood, but are environmental factors and the following: (1) *Virological factors* such as viral load, genotype, and genetic divergence due to viral gene mutations. HBV mutates very rapidly and uses high genetic variability as an effective mechanism for escaping the host immune response[3]. (2) *Immunological factors* including the innate and adaptive immune responses against viral infection, which play important roles in modulating both the antiviral immune response and host susceptibility to HBV. The rapid mutations in HBV epitopes recognized by HBV-specific CTLs may cause both humoral and cell-mediated virus-specific immune responses to quickly lose their ability to efficiently control the virus[4,5]. (3) The *host genetic factors* are believed to be responsible for clinical outcomes of many infectious diseases[6-9].

In the last decade, the virological and immunological factors of HBV have been extensively studied, but the examination of the relationship between host genetics and HBV resistance is still in its infancy[10-12]. Therefore, this review focuses on the recent progress in study of human genetic alleles associated with chronic HBV infection, and discuss the unanswered questions and future directions in this field.

HOST GENETIC FACTORS INVOLVED IN HBV INFECTION

HBV-infected subjects generally fall into one of the following clinical types: (1) asymptomatic HBV carriers and cryptic hepatitis; (2) acute hepatitis; (3) chronic hepatitis; (4) liver cirrhosis with or without decompensated liver failure; and (5) primary hepatocellular carcinoma associated with HBV infection[2,13]. However, the pattern and clinical outcome of the infection are highly variable. Why is this? Previous epidemiological investigation in humans suggests that there is

a strong genetic component to affect the individual susceptibility to infectious pathogens[14-16], although to date, no single allele has not been clearly associated with HBV persistence or disease severity. However, the following reflects individual and ethnic differences in response to HBV infection.

(1) Infection with the same HBV virus has been found to cause various clinical outcomes in patients. In adults suffering from primary HBV infection, 90-95 % of the subjects can successfully clarify the virus through self-limiting hepatitis and only 5-10 % of adults become chronic HBV carriers[17]. Among the chronically infected subjects, 20-30 % lead to liver cirrhosis and -5 % develop hepatocellular carcinoma through a long-term disease progression. Of teen-ager subjects that acquire HBV infection from either perinatal or horizontal transmission, more than 90 % develop chronic infection. In China, mother-to-child transmission of HBV was once a common source of chronic infection.

(2) The long-term follow-up studies indicate that some individuals in high-risk groups (e.g. spouses in HBV-infected families) never develop the disease. This suggest the existence of an individual-specific resistance to HBV infection[1,3].

(3) There is a different incidence and infection rate among global ethnic groups. HBV infection is significantly endemic in Asia and Africa, and there is a significantly higher incidence of chronic HBV infection in Chinese compared to Caucasians[18].

(4) In clinic, HBV-infected individuals may display complete, partial or no response to interferon-a or Lamivudine antiviral therapy alone or in combination.

(5) Around 85 % of healthy subjects can produce the efficient protective anti-HBsAg antibody upon the HBV vaccination, while remaining fail.

The above-mentioned data suggests that the knowledge of understanding human genetic factors may provide critical clues not only to the ethnic diversity of HBV infection, but also to the issue of disparity in therapeutic response[19]. The human genome project has indicated that there are approximately thirty-five thousand genes in the human genome. Many of these alleles contain polymorphisms such as single nucleotide polymorphisms (SNPs) within the encoding or flanking regions. It is estimated that there are 3.5 million SNPs within human genome and there are likely to explain much of the genetic diversity of individuals and ethnic groups[13]. If a specific SNP version is associated with a favorable outcome and low risk of progression of HBV infection and liver disease, the allele may be considered an ' HBV resistant' allele. Conversely, a version of the SNP that confers an unwanted HBV phenotype (quick disease progression or high risk of severe infection) may be called a ' HBV susceptible' allele. Current research is focusing on the hunt and identification for these alleles.

SELECTION OF CANDIDATE ALLELES

Two strategies are currently used in the study involving genetic markers associated with disease phenotypes. The *candidate gene method* is the typing of markers located near genes that could be chemically related to the disease in question[20]. Conversely, a genome-wide search scans markers throughout the whole genome in search of chromosomal regions that could be associated with disease susceptibility or resistance. The choice of candidate genes for the first method is strongly determined by the function (or putative function) of the gene and its possible role in the host response to HBV infection and disease progression. Major genes involved in the process of HBV infection can be identified by characterizing host response to HBV exposure such as clinical response, biological response (intensity of infection), and immunological response (levels of antibodies, cytokines or cell-mediated response against HBV)[10]. These biological processes may then suggest genes of interest for screening. Many of the candidate genes fall into the following categories: (1) genes that mediate the processes of viral entry into hepatocytes, including genes involved in viral binding, fusion with cellular membrane and transportation in target cells; (2) genes that modulate or control the immune response to HBV infection; (3) genes that participate in the pathological alterations in liver tissue; (4) genes involved in the development of liver cirrhosis and hepatocellular carcinoma associated with chronic HBV infection, including genes related to mother-to-infant transmission of HBV infection; and (5) those that contribute to resistance to antiviral therapies[19,20]. This study is still in its early stages, and much more remains to be done on candidate genes, including the clarification of sequence, identification of mutant SNPs, functional evaluation of SNPs, and evaluation of their association with diseases.

ADVANCES ASSOCIATED WITH INDIVIDUAL GENETIC SUSCEPTIBILITY TO HBV INFECTION

Some candidate gene work has been completed at this time. Since both chemokine receptor and HLA genes play critical roles in host immune response to viral infection, they are among the first HBV candidate genes screened.

HLA class I and II alleles

The genes for HLA class I (HLA-A, -B, and -C) and class II (HLA-DRB1, -DQA1, -DQB1, -DPA1, and -DPB1) are located on the short arm of chromosome 6. As the primary modulator of host immune response, the HLA molecules present foreign antigens to both the CD4+ T lymphocytes and the CD8+ cytolytic T cells, leading to both humoral and cell-mediated immune response. The majority of the human genetic studies associated with HBV infection has focused on HLA associations[21]. Thursz et alinvestigated a large cohort of pediatric patients from Gambia and identified the association of the HLA class II allele DRB1*1302 with a self-limiting course of acute hepatitis B[23,24]. Hohler *et al*[17]. confirmed the effect of DBR1*1302 in Gambian adults that seemed to clear the HBV infection *in vivo*. Thio *et al*[25] examined the DQA1*0501, DQB1*0301 and DQA1-DQB1 haplotypes and found the haplotype cluster of DQA1*0501-DQB1*0301-DQB1*1102 had a significant association with viral persistence. However, Zavaglia *et al* reported that no correlation could be observed between the clearance of HBV or HCV virus and HLA phenotypes[22]. Recently, Diepolder *et al* reported that HLA-DR13 allele is less frequent in patients with chronic hepatitis B than in healthy controls or subjects with a self-limiting hepatitis B[26]. Additional study has confirmed a strong association between the HLA class II allele DR13 and a self-limiting course of acute HBV infection. Rapid progression to chronic hepatitis B is rare in these patients, suggesting that patients with HLA-DR13 can mount a more vigorous CD+ T cell response to HBV core antigen during acute HBV infection. The beneficial effect of HLA-DR13 allele on the outcome of HBV infection may either be the result of more proficient antigen presentation by the HLA-DR13 molecules themselves or of a linked polymorphism in a neighboring immunoregulatory gene. To date, no associations between HLA class I alleles and the viral persistence or disease progression in HBV-infected patients was found, though class I molecule mediates the cytotoxic T lymphocyte (CTL) response through the cytolytic and noncytolytic mechanisms[13]. Future studies have to investigate whether one of these polymorphisms or a yet unidentified immunoregulatory gene is possibly associated with a more successful immune response against HBV[27].

Cytokine and chemokines

Since individual variation in cytokine release is predominantly caused by polymorphisms near or within the genes[28,29], heterogeneity of the candidate gene in HBV-infected patients serves as a probable biomarker for influence the disease phenotypes. Several pro-inflammatory cytokines such as Th1 cytokines (including IL-2 and IFN-γ) and tumor necrosis factor-alpha (TNF-α) have been identified as participating in the viral clearance and the host immune response to HBV. In contrast, the Th2 cytokine IL-10 serves as a potent inhibitor of Th1 effector cells[30].

Tumor necrosis factor (TNF)-α is an important cytokine involved in noncytotoxic antiviral mechanisms[31]. This gene is located within the class III region of the MHC complex and has five polymorphisms in its promoter region, located at positions -1031(T/C), -863(C/A), -857(C/T), -308(G/A) and -238(G/A) respectively [negative numbers represent number of bases upstream from the transcription initiation site][32,33]. Miyazoe *et al* reported the TNF-α gene promoter polymorphisms were not linked to disease progression in HBV carriers in Japan[34], however both Hohler[35,36] found that the two polymorphisms such as -308(G/A) and -238(G/A) were significantly associated with HBV or HCV persistence in patients. It is thought that the polymorphism influences the expression of TNF-α, which may block HBV gene expression. Similar to TNF-α, IFN-γ clears HBV *in vivo* by a noncytolytic effect. Hoffmann *et al*[18]. showed that the Asian population contains more IFN-γ genotypes that result in low expression than do Caucasian populations, which suggests the possibility of an association between low IFN-γ expression in the highly HBV-susceptible Asian population.

The promoter region of IL-10 gene contains three SNPs at position -1082 (A/G), -819 (T/C), and -592 (A/C), which may assort into three different haplotypes[37]. Miyazoe *et al* analyzed the distributions of TNF-α and IL-10 promoter SNPs in Japanese HBV-infected petitents and found that the -819T and -592A wild-type alleles in the IL-10 gene promoter were significantly more common in asymptomatic carriers than in patients with chronic progressive liver diseases[32], suggesting that inheritance of the IL-10 gene promoter polymorphisms is relevant to progression in chronic HBV infection, perhapse due to decreased IL-10 production induced by -819T and -592A haplotype allele.

Mannose binding protein (MBP)

MBP is a calcium-dependent opsonin that plays an important role in innate immunity by activating the classical complement pathway and phagocytosis. There are three identified polymorphisms in the MBP gene encoding region (in codons 54, 57 and 52), leading to low serum concentrations and thus abolishing its ability to affect host immunity because of an opsonic defect. The middle surface protein of HBV viral envelope contains a mannose-rich oligosaccharide to which MBP could potentially bind. Thomas *et al* showed that 27 % of Caucasian patients chronically infected with HBV were homozygous or heterozygous for the codon 52 mutant allele whereas only 11 % of patients with acute infection and 4 % of controls carried the wild type allele, which suggests that the codon 52 mutant gene has been associated with persistence of HBV infection[38]. The higher frequency of the codon 52 mutation among the HBV patients than among controls is probably consistent with the fact that the mutation leads to the failure of opsonisation and phagocytosis of HBV. Yuen *et al*[39]. reported that the codon 54 mutation was associated with symptomatic persistent viral infection in Chinese patients. In German Caucasians and Gambians, these MBP polymorphisms were not associated with chronic infection[40].

Vitamin D receptor, cytochrome P450 and Complement four associated with HBV infection

The active form of vitamin D is an immunomodulatory hormone that inhibits the Th1 response and activates the Th2 immune reaction. Bellamy *et al*. studied two known Vitamin D receptor gene polymorphisms in Gambian HBV-infected patients and found that the tt genotype of one polymorphism was associated with viral clearance[41].

Thus far, reports from various laboratories have shown some inconsistencies with regard to the effects of host genetic factors on HBV clearance and persistence. This ambiguity may be attributable to one or more of the following reasons: (1) a complex interaction between the virus and host multiple alleles; (2) the ethnic differences in the studied groups; (3) an association with a gene in linkage disequilibrium with an HLA allele. Therefore, a global multicort studies may be needed to integrate the genetic data and the clinical data for fully clarification of underlying immunogenetic pathogenesis of HBV infection. In addition, further candidate genes must be identified and screened for associated polymorphisms.

PROSPECT FOR STUDY OF HBV RESISTANCE ALLELES

A growing body of evidence related to the genetic effects on infectious diseases has shown only a fraction of the total picture. The most successful example is the identification of CCR5 delta32 allele in HIV-1 infection[8,42]. Since genetic interactions are complex, it is unlikely that a single allelic variant is responsible for HBV resistance or susceptibility[43]. However, the collective influence of several SNPs or haplotype(s) may exert the natural combinational or synergistic protection against HBV. Recently developed genetic epidemiology strategies and dense genome-wide search, together with the growing availability of candidate alleles and suquence information supply a basic platform for identifying genes associated in HBV infection. These investigations will depend on the interactions of many different factors including the viral phenotypes, population traits, accurate measurement of environmental factors, and previous knowledge. Genetic resistance to HBV-induced persistent hepatitis is likely to involve a complex array of host genetic effects involving multiple variants and haplotypes. Because of this, future study including the multicohort collaboration will be needed to clarify these preliminary associations and identify other potential candidate genes[20]. In addition, it will be necessary to functionally characterize the identified associated genes, such as versions of HLA molecules and MBP, and see whether the mutations have functional significance in terms of individual susceptibility to HBV infection. The ongoing study of the distributions and functions of the implicated allele polymorphisms will not only provide insight into the pathogenesis of HBV infection, but may also provide a novel rationale for new methods of diagnosis and therapeutic strategies[44].

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