HLA-DPB1 alleles in hepatitis B vaccine response
A meta-analysis
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Abstract

Background: The role of the HLA-DRB1 and HLA-DQB1 genes in the antibody response to hepatitis B (HB) vaccine has been well established; however, the involvement of the HLA-DPB1 allele in the HB vaccine immune response remained to be clarified by a systematic review.

Methods: A meta-analysis was performed in which databases were searched for relevant studies published in English or Chinese up until June 1, 2020. Six studies were identified and a total of 10 alleles were processed into statistical processing in this meta-analysis.

Results: Three thousand one hundred forty four subjects (including 2477 responders and 667 non-responders) were included in this research. Alleles HLA-DPB1∗02:02, DPB1∗03:01, DPB1∗04:01, DPB1∗04:02, and DPB1∗14:01 were found to be associated with a significant increase in the antibody response to HB vaccine, and their pooled odds ratios (ORs) were 4.53, 1.57, 3.33, 4.20, and 1.79, respectively; whereas DPB1∗05:01 (OR=0.73) showed the opposite correlation.

Conclusions: These findings suggested that specific HLA-DPB1 alleles are associated with the antibody response to HB vaccine.

Abbreviations: CI = confidence interval, HB = hepatitis B, HBV = hepatitis B virus, HLA = human leukocyte antigen, OR = odds ratio, SNP = single nucleotide polymorphism.

Keywords: alleles, hepatitis B virus, human leukocyte antigens, vaccine response

1. Introduction

Hepatitis B virus (HBV) infection is a major global health problem. The prevalence of HBV infection in China was approximately 5.49% of the population in 2015,[28] with around 93 million people infected with HBV and approximately 30 million people suffering from HBV-related diseases,[15] making this virus a significant public health burden in China.[31] Hepatitis B (HB) vaccination is an effective measure to reduce the risk of HBV infection. In China, a HBV vaccination program was introduced in 1992 that required all newborns to be vaccinated against HB; however, the cost of vaccination was met by parents and this may have prevented some children from being vaccinated. The China GAVI Project was initiated in 2002 to provide HB vaccine to infants free of charge in the areas of China worst affected by the virus. On March 24, 2005, the State Council promulgated the no. 434 order of “vaccine circulation and prevention inoculation management regulations” to the whole country. Consequently, all newborns were inoculated with HB vaccine free of charge, after which, a significant decline in the HBsAg-positive rate to 0.94% was recorded in China.[10] However, individuals who failed to respond to HB vaccination during infancy may not be fully protected against HBV infection in adolescence. Furthermore, breakthrough and chronic HBV infections were repeatedly reported in individuals who had received complete doses of HB vaccine. It is therefore important to research the mechanism of non-response to HB vaccine to better protect this portion of the population from HB infection.

It had been estimated that the heritability of post-vaccination antibody titers is higher than 70%.[18] A genome wide association study has been proven to be an efficient technique to evaluate the effect of host genetic factors on common traits. Genome wide association studies[7,22,34] revealed that some of the DRB1 and DQB1 genes and related single nucleotide polymorphisms (SNPs) play key roles in the HB vaccine response in different populations. It was reported[22] that 5 HLA-DRB1-DQB1 haplotypes, 2 HLA-DPB1 alleles and BTNL2 genes were associated with the immune response to HB vaccine in a large cohort Japanese population. Another systematic review revealed[17] that 3 HLA-DRB1 and 2 HLA-DQB1 variants were associated with a significant increase in the antibody response to HB vaccine, while 4 DRB1 alleles and 1 DQB1 allele showed the opposite trend. With the exception of the HLA-II alleles, some HLA-II-related SNPs have been found to

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be related to the HB vaccination response, such as rs9277535,[31] rs3077,[13] rs7770370[34] and rs9271768.[20] Recently, variants of the HLA-DPB1 locus were found to have strong genome-wide associations with the outcomes of HBV infection in several Asian populations.[12,15,16] HLA-DPB1, a HLA class II molecule expressed as a cell-surface glycoprotein, not only binds to exogenous antigens and some DPB1 alleles but also binds to endogenous antigens and presents them to CD4+ T cells. Research[15] found that DPB1 04:02 had a significant association with both the vaccine response and a high-tier response, whereas DPB1 05:01 was significantly correlated with non-responders. Other research demonstrated[35] that the HLA-DPB1 05:01 and 09:01 alleles significantly correlated with HB low responders, and the 02:01, 02:02, 03:01, 04:01 and 14:01 alleles strongly correlated with HB high responders. To confirm these previous findings and to explore the association of HLA-DPB1 with the response to booster HB vaccination, we performed a meta-analysis to clarify the relationship between HLA-DPB1 polymorphism and the degree of HB vaccination response.

2. Materials and methods

2.1. Selection of studies

We searched the PubMed, EMBASE, Cochrane library, Chinese CNKI, and Wanfang databases using the MeSH terms “Hepatitis B Vaccines”, “HLA Antigens” or “Histocompatibility Antigens”, and the individual corresponding free terms. Furthermore, we performed manual searches by scanning the reference lists of the included articles to locate additional papers related to the topic. The following inclusive criteria were set and reviewed by 2 independent investigators:

1. recombinant vaccine;
2. study’s method based on a cohort study design;
3. studies showing interest in the association between HLA alleles and the response to HB (the vaccines were classified into responders (anti-HB ≥10IU/L) and non-responders (anti-HB < 10IU/L) after the whole vaccine schedule); and
4. study followed the standard vaccination protocol using the currently licensed HB recombinant vaccines (immunized at 0, 1 and 6 months, with or without 1 additional dose).

The exclusion criteria were as follows:

1. not published as a full text;
2. cohort studies without defined groups of non-responders and responders, or the responder anti-HB threshold was no higher than 10IU/L;
3. HLA-DPB1 typing had not been obtained for the different groups, or the HLA-DPB1 distribution was not in accordance with Hardy–Weinberg equilibrium.

If data were duplicated between studies, only the study most recently published with the larger number of participants was included.

2.2. Data extraction and synthesis

Two investigators (Guojin Ou and Xiaojuan Liu) carefully examined and extracted the published data independently based on our inclusion and exclusion criteria. Disagreements were resolved by discussion and consensus; with a third reviewer (YongMei Jiang) making the ultimate decision if a consensus was not achieved. We extracted the following information from each study: first author, year of publication, ethnicity, the number of cases and controls for each group, the HLA-DPB1 typing method and the references. The quality of each study was assessed independently by 2 authors using the Newcastle–Ottawa Scale system,[23] which includes 3 aspects: selection (0–4 points), comparability (0–2 points), and exposure (0–3 points). The Newcastle–Ottawa Scale scores ranged from 0 (low quality) to 9 (high quality). Studies scoring more than 7 were considered to be of high quality. This study was approved by the ethics committee of the West China Second University Hospital.

2.3. Statistical analysis

The Hardy–Weinberg equilibrium of the genotype distributions of the HLA-DPB1 alleles were examined using Arlequin 3.5.1.2 software. Review Manager 5.2 software was used to perform meta-analysis. Odd ratios (ORs) with 95% confidence intervals (CIs) were used to assess the strength of associations between HLA-DPB1 polymorphisms and the HBV immune response. The I² test was performed to assess heterogeneity between studies. If the heterogeneity was not significant (I² > 1, I² < 50.0%), the fixed-effects model was used to pool the ORs; otherwise, the random-effects model was used. Two-sided P values <.05 were considered statistically significant.

3. Results

3.1. Flow diagrams detailing the selection process of eligible studies

The selection process employed to identify eligible studies is displayed in Figure 1. A total of 206 studies were acquired from the PubMed, EMBASE, and China National Knowledge Infrastructure (CNKI) databases. After reviewing the titles, abstracts and full text, we excluded 199 irrelevant studies. Finally, a total of 6 articles were included in the meta-analysis.[5,7,19,22,27,32,35] The main characteristics of all of the eligible studies are shown in Tables 1 and 2. Furthermore, all these studies assessed the association between HLA-DPB1 and the immune response to HB vaccine. The 6 articles included 3144 HB vaccine responders and 667 HB vaccine non-responders used as controls to assess the risk of HLA-DPB1.

3.2. Association between HLA-DPB1 and the HB vaccine response

The results of the meta-analysis are presented in Table 3 and Figures 2–7. A total of 10 alleles were subjected to statistical processing. The pooled risk estimates indicated that DPB1 02:02 (OR = 4.53, 95% CI: 1.64–12.55), DPB1 03:01 (OR = 1.57, 95% CI: 1.33–2.08), DPB1 04:01 (OR = 3.67, 95% CI: 1.26–10.48), DPB1 04:02 (OR = 4.20, 95% CI: 2.70–6.52) and DPB1 14:01 (OR = 1.79, 95% CI: 1.03–3.12) were associated with a significant increase in the antibody response to HB vaccine. Whereas DPB1 05:01 (OR = 0.73, 95% CI: 0.69–0.78) showed the opposite trend. These findings suggested that inheriting certain HLA-DPB1 alleles could either strengthen or diminish the HB vaccine response.

3.3. Publication bias

Publication bias of the included articles was assessed using Begg funnel plot. The shape of the funnel plot appeared symmetrical...
Records identified through database searching (n =686)

Records excluded duplicates (n =384)

Records after duplicates removed (n=302)

Records excluded non cohort study or not associated with DPB1 gene (n=286)

Records screened (n=16)

No full-text articles and not given DPB1 alleles were excluded (n =9)

Full-text articles assessed for eligibility (n=7)

1 article!with special population and the number of cases is too small was excluded (n=1)

Studies included in qualitative synthesis (n=6)

Studies included in quantitative synthesis (meta-analysis) (n=6)

Figure 1. Flow chart of articles election.

Table 1
Characteristics of the studies regarding hepatitis B vaccine response in different populations.

| First author | Year | Ethnicity | R  | NR  | Genotype method | NOS | Refs |
|--------------|------|-----------|----|-----|-----------------|-----|------|
| Desombere I  | 1998 | Caucasians| 100| 46  | PCR-SSO         | 8   | [7]  |
| Wu TW        | 2013 | Taiwanese | 510| 171 | PCR-SBT         | 9   | [35] |
| Sakai A      | 2016 | Japanese  | 418| 156 | PCR-SSO         | 9   | [27] |
| Nishida N    | 2018 | Japanese  | 1009|94  | Array assay     | 9   | [22] |
| Wang LY      | 2019 | Taiwanese | 207| 152 | PCR-SBT         | 9   | [32] |
| Chung S      | 2019 | Korean    | 233| 48  | PCR-SBT         | 8   | [5]  |
and showed no obvious publication bias for HLA-DPB1 metamorphism (Fig. 8).

4. Discussion

The World Health Organization recommends universal vaccination against HB to ultimately eliminate HBV. This recommendation had been progressively implemented across 168 countries of the world via a universal program by the end of 2006. The China GAVI Project was initiated in 2002 to provide HB vaccine to infants to prevent the consequences of HBV infection in specifically-selected areas. By 2009, coverage of the three-dose HB vaccine regimen had been increased in these areas and inoculation at birth had been increased to almost 90%. This initiative reduced HBV prevalence to <1% among children in these areas, prevented 24 million chronic HBV infections and 4.3 million future deaths due to cirrhosis, hepatocellular carcinoma and acute hepatitis. Active and passive immunizations (HBIG

**Table 2**

| Distribution of HLA-DPB1 alleles in different studies. |
|--------------------------------------------------------|
| First author (year) | 02:01 | 02:02 | 03:01 | 04:01 | 04:02 | 05:01 | 09:01 | 13:01 | 14:01 | 17:01 | Refs |
|---------------------|-------|-------|-------|-------|-------|-------|-------|-------|-------|-------|------|
| Desombere I (1998)  | R, n  | 22    | –     | 20    | 67    | 21    | 5     | 0     | 2     | 2     | 4    |
| Wu TW (2013)        | NR, n | 20    | –     | 7     | 12    | 4     | 0     | 4     | 6     | 1     | 1    |
| Sakai A (2016)      | R, n  | 195   | 26    | 41    | 44    | 100   | 295   | 93    | 16    | 13    | –    |
| Nishida N (2018)    | NR, n | 62    | 6     | 15    | 5     | 14    | 157   | 35    | 3     | 5     | 1    |
| Wang LY (2019)      | R, n  | 469   | -     | 107   | -     | 194   | 833   | 204   | -25   | -     | -    |
| NR, n               | 43    | –     | 7     | –     | 2     | 108   | 20    | -     | -     | -     | -    |
| Chung S (2019)      | R, n  | 123   | 25    | 13    | 45    | 51    | 145   | 13    | 25    | 5     | 9    |
| NR, n               | 27    | 1     | 3     | 6     | 1     | 47    | 1     | 7     | –     | 7     | -    |

**Table 3**

| Overall results regarding HLA-DPB1 polymorphisms in hepatitis B response patients. |
|------------------------------------------|--------|----------------|---------|-------|---------|---------|----------------|-------------|
| HLA-DPB1*                                | N      | P, %           | P       | Model | OR (95% CI) | P value |
| 02:01                                   | 5      | 55             | .05     | R     | 1.05 (0.85–1.30) | .06     |
| 02:02                                   | 4      | 54             | .09     | R     | 4.53 (1.64–12.55) | .004    |
| 03:01                                   | 6      | 22             | .27     | F     | 1.57 (1.13–2.19)  | .008    |
| 04:01                                   | 5      | 2              | .40     | F     | 3.33 (2.26–4.90)  | <.00001 |
| 04:02                                   | 6      | 0              | .43     | F     | 4.20 (2.70–6.52)  | <.00001 |
| 05:01                                   | 5      | 0              | .61     | F     | 0.73 (0.69–0.78)  | <.00001 |
| 09:01                                   | 5      | 51             | .08     | R     | 0.76 (0.47–1.25)  | .28     |
| 13:01                                   | 5      | 44             | .13     | F     | 0.77 (0.56–1.06)  | .11     |
| 14:01                                   | 4      | 0              | .52     | F     | 1.79 (1.03–3.12)  | .04     |
| 17:01                                   | 3      | 37             | .21     | F     | 0.47 (0.21–1.09)  | .07     |

and showed no obvious publication bias for HLA-DPB1 metamorphism (Fig. 8).

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**Figure 2.** Meta-analysis of correlation of the HLA-DPB1 02:02 allele polymorphism in HB vaccine response.
Figure 3. Meta-analysis of correlation of the HLA-DPB1*03:01 allele polymorphism in HB vaccine response.

Figure 4. Meta-analysis of correlation of the HLA-DPB1*04:01 allele polymorphism in HB vaccine response.

Figure 5. Meta-analysis of correlation of the HLA-DPB1*04:02 allele polymorphism in HB vaccine response.

Figure 6. Meta-analysis of correlation of the HLA-DPB1*05:01 allele polymorphism in HB vaccine response.
Figure 7. Meta-analysis of correlation of the HLA-DPB1*14:01 allele polymorphism in HB vaccine response.

Figure 8. Egger funnel plot for the assessment of HLA-DPB1*02:02, DPB1*03:01, DPB1*04:01, DPB1*04:02, DPB1*14:01, and DPB1*05:01.
and HB vaccines) are the most cost-effective means of preventing chronic HB infection in infants and have the potential to have a sustained impact on global HBV incidence. However, it has been reported that 58.2% of adolescents who received a primary series of HB vaccinations as infants with GMC had anti-HB levels of <10 mIU/mL. Another study found that 60.0% of such adolescents had anti-HB concentrations <10 mIU/mL on baseline testing. A booster higher vaccine dose should be sufficient to achieve adequate protection by raising the anti-HB level. Even with the additional dose of HB vaccine, 5% to 10% of individuals still failed to respond to the vaccine, and the precise mechanisms determining responsiveness to the HB vaccine are poorly understood. Some factors associated with vaccine nonresponsiveness include obesity, age at first vaccination, sex, immune status and genetic factors.

A number of cohort studies have assessed the associations between HLA-II gene polymorphisms and the progression of HBV infection, including HBV infection susceptibility, HBV spontaneous clearance, HBV-related HCC development and the HB vaccination response. It has been suggested that an anti-HB titer of 10 mIU/mL is necessary for the prevention of HBV infection. HLA-II genes, including the HLA-DR, HLA-DQ, HLA-DP and DR-DQ-DP haplotypes, were reported to be associated with the immunological response to HB vaccine in healthy people. A meta-analysis of 2308 subjects (including 1215 responders, 873 non-responders and 220 controls) found that DRB1*01, DRB1*13, DQB1*05 (DQB1*0501), DQB1*06 and DQB1*0602 were associated with a significant increase in the antibody response to HB vaccine, whereas DRB1*03 (DRB1*0301), DRB1*04, DRB1*07, DRB1*13, and DQB1*02 showed the opposite trend. The DRB1*01:01, DRB1*01:01, DRB1*01:01 and DRB1*05:01 and DRB1*06:01 were associated with a significant increase in the antibody response to HB vaccine, whereas DRB1*04:05:01 and DRB1*04:05:01 and DRB1*04:05:01 and DRB1*05:01 and DRB1*06:01 were associated with a significant increase in the antibody response to HB vaccine. While DRB1*04:05:01 and DRB1*05:01 and DRB1*06:01 showed the opposite trend.

The association between HLA-DPB1 polymorphisms and the immunological response to HB vaccine have been investigated in different populations, but these findings remain controversial or inconclusive. Martinetti and colleagues found that a statistically significant increase in DPB1*02:01 and DPB1*03:01 alleles related to a non- or hypo-immune response to HB vaccine, whereas DPB1*04:01 was related to a positive response to HB vaccine. DPB1*04:01 was also more abundant in good vaccine responders in the Caucasian population and the Japanese population. DPB1*04:02 was also related to a high HB vaccine response, whereas DPB1*05:01 was related to a lower HB vaccine response in the Asian population. With the exception of DPB1 alleles, DPA1 and DP-related SNPs were also reported to correlate with the HB vaccine response, with DPA1*01:03 and rs3077715 being significantly more prevalent in HB vaccine responders, and DPA1*02:02, rs307773 and rs3277535G being significantly less prevalent in HB vaccine responders.

A previous study found that low expression levels of DP mRNA correlated with non-susceptibility to HBV. Whether DP expression is associated with the HB vaccine response remains to be determined. The amino acids at position 84 to 87 of the second exon of the antigen presentation sequence of DPB1, including GGPA (with linkage to DPB1*04:01, 04:02 and 02:02) and DENA (with linkage to DPB1*05:01, 1401 and 03:01), located at the groove contacting the peptide residues of pocket-1, may be responsible for the different antigen-presenting functions that may lead to the different levels of immune response to HB vaccine. The latest research found that HLA-DPB1 molecules encoding DP84Gly (including DPB1*04:01, DPB1*04:02, DPB1*02:01 and DPB1*02:02) do not bind to the invariant chain (II) via the class II-associated invariant chain peptide region to constitutively present endogenous peptides. This means that DP84Gly-related alleles can use both class I and II antigen processing pathways to present peptides derived from intracellular and extracellular sources; however, DP84Asp (including DPB1*05:01) does not possess such endogenous antigen presentation function. Therefore, these polymorphisms have different functions in autoimmune, antiviral and antitumor mechanisms through the different functions of antigen presentation in the CD4+ T cell immune response. The DP84Gly genotype not only plays a unique antiviral function in adaptive immunity, but also acts as a ligand of NKp44 to activate natural killer (NK) T cells to play an antiviral role in the immune response. Further studies should reveal whether the DP84Gly genotype can promote the immune response to HB vaccine by binding to NKp44 and activating NK cells.

In this meta-analysis, we found that DPB1*02:02, DPB1*03:01, DPB1*04:01, DPB1*04:02 and DPB1*14:01 were associated with a significant increase in the antibody response to HB vaccine, with pooled OR values of 4.53, 1.57, 3.33, 4.20, and 1.79, respectively. From the ORs, we found that alleles DPB1*02:02, DPB1*04:01 and DPB1*04:02 were associated with a hyper HB vaccine response, whereas DPB1*05:01 (OR = 0.73) was related to a hypo HB vaccine response; these results were in accordance with previous reports. However, the correlation between DPB1*03:01 and DPB1*14:01 carriers and an increased response to HB vaccine is controversial. In an Italian study involved a small group of infants, DPB1*03:01 was demonstrated to be related to a non- or hypo-immune response to HB vaccine, whereas the opposite results were found in a group of Taiwanese adolescents, and other studies failed to find an association between DPB1*03:01 and DPB1*14:01 and the HB vaccine response. Similar to DPB1*05:01, DPB1*03:01 and DPB1*14:01 were shown to display linkage with DP84Asp and were associated with a lower response to HBV antigens, resulting in susceptibility to HBV, a higher likelihood of chronic HBV infections or susceptibility to hepatocellular carcinoma. As the ORs of DPB1*03:01 and DPB1*14:01 in the HB vaccine response were low (1.57 and 1.79), whether these alleles are linked to a lower response to HB vaccine should be the subject of future research in larger and more diverse study populations.

To the best of our knowledge, this is the first meta-analysis providing comprehensive insights into the effects of DPB1 on the HB vaccine response. This meta-analysis had several limitations. More precise analysis was not able to be performed because we were unable to obtain the original data for all of the studies, and the subgroup analysis, for example, for age, sex, body mass index and lifestyle, could not be adjusted. Furthermore, our analysis did not consider the possible effects of gene-environment interactions. Therefore, more studies are needed to confirm our findings.

In conclusion, our meta-analysis revealed that HLA-DPB1*02:02, DPB1*03:01, DPB1*04:01, DPB1*04:02, and DPB1*14:01 are related to a strengthened HB vaccination response, and HLA-DPB1*05:01 serves as a low HB vaccination response marker. However, more large-scale studies are warranted to support our findings.
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