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Host Genetics of Response to Hepatitis B Vaccine: A Systematic Review

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Summary

Background. Hepatitis B virus (HBV) is an important cause of chronic viral disease worldwide and can be life threatening. While a safe and effective vaccine is widely available, 5 to 10% of healthy vaccinees fail to achieve a protective anti-hepatitis B surface antigen antibody (anti-HBs) titer (>10mIU/ml). A limited number of studies investigated host genetics of the response to HBV vaccine. To our knowledge, no comprehensive overview of genetic polymorphisms both within and outside the HLA system has been done so far.

Aim. The aim of this study was to perform a systematic review of the literature of human genetics influencing immune response after hepatitis B vaccination.

Methods. Literature searches using keywords were conducted in the electronic databases Medline, Embase and ISI Web of Science the cut-off date being March 2014. After selection of papers according to stringent inclusion criteria, relevant information was systematically collected from the remaining articles, including demographic data, number of patients, schedule and type of vaccine, phenotypes, genes and single nucleotide polymorphisms (SNPs) genotyping results and their association with immune response to hepatitis B vaccine.

Results. The literature search produced a total of 1968 articles from which 46 studies were kept for further analyses. From these studies, data was extracted for 19 alleles from the human leukocyte antigen (HLA) region that were reported as significant at least twice. Among those alleles, 9 were firmly associated with vaccine response outcome (DQ2 [DQB1*02 and DQB1*0201], DR3 [DRB1*03 and DRB1*0301], DR7 [DRB1*07 and DRB1*0701], C4AQ0, DPB1*0401, DQ3, DQB1*06, DRB1*01 and DRB1*13 [DRB1*1301]). In addition, data was extracted for 55 different genes from which 13 extra-HLA genes had polymorphisms that were studied by different group of investigators or by the same group with a replication study. Among the 13 genes allowing comparison, 4 genes (IL-1B, IL-2, IL-4R and IL-6) revealed no significant data, 6 genes (IL-4, IL-10, IL-12B, IL-13, TNFA, IFNG and TLR2) were explored with inconsistent results and 2 genes (CD3Z and ITGAL) yielded promising results as their association with vaccine response was confirmed by a replication approach. Furthermore, this review produced a list of 46 SNPs from 26 genes that were associated with immune response to vaccine only once, providing novel candidates to be tested in datasets from existing genome-wide association studies (GWAS).

Conclusion. To the best of our knowledge, this is the first systematic review of immunogenetic studies of response to hepatitis B vaccine. While this work reassesses the role of several HLA alleles on vaccine response outcome, the associations with polymorphisms in genes outside the HLA region were rather inconsistent. Moreover, this work produced a list of 46 significant SNPs that were reported by a single group of investigators, opening up some interesting possibilities for further research.

Keywords. Hepatitis B vaccine. Anti-HBs antigen antibody. Immunogenetics. Human leukocyte antigen. Single nucleotide polymorphism.

Introduction

Hepatitis B virus (HBV) infection represents an important public health problem around the world. It is estimated that 2 billion people have been infected and that more that 350 million are chronic carriers of the virus (1). The outcome of acute HBV infection, which ranges from asymptomatic to fulminant hepatitis, is variable and age dependent: roughly 95% of neonates, 20-30% of children and less than 5% of adults develop chronic infection (2). Chronic infection may lead to liver cirrhosis and hepatocellular carcinoma (HCC). More than 780'000 people die every year due to the consequences of HBV infection (1). Nevertheless, the differential outcome of HBV infection is still not fully understood and may be explained by host, viral and environmental factors. Host genetics of HBV chronic infection was investigated and produced interesting results, mainly amongst the Human Leukocyte Antigen (HLA) region and the cytokine genes, which are reviewed in some papers (3-10) or meta-analysis (11-15).

Safe and effective hepatitis B vaccines have been commercially available since 1982. Most of the vaccines that are used nowadays are derived from recombinant DNA technologies while the first vaccines available were obtained by gathering hepatitis B surface antigen (HBsAg) from the plasma of chronic HBV carriers (16). The World Health Organization (WHO) recommended national childhood immunization programs since 1992, and as of today, about 180 countries have introduced children and/or adolescent vaccination (17). The vaccine has been demonstrated to minimize the incidence of HBV infection, especially when given early in life, and to lower the incidence of HCC (18-20), making hepatitis B vaccination a precious tool to reduce HBV burden of disease.

An anti-hepatitis B surface antigen (anti-HBs) antibody titer ≥10 mIU/ml measured 1 to 3 months after administration of the last dose of the primer vaccination is considered to be protective (21). Even if the efficacy of the vaccine has been proven to be very high, it is estimated that 5-10% of healthy vaccinees fail to reach the protective threshold of anti-HBs antibody (17, 22, 23). Apart from the obvious immunosuppressive causes of non-response (such as HIV infection, immunosuppressive drugs), it has been shown that smoking, high body mass index (BMI), male sex, age (more than 30 years old), alcoholism and chronic renal or liver failure had a negative impact on hepatitis B vaccine response (23-25). Besides, genetic factors seem to have an important role for non-response among healthy individuals. The recent advances in genotyping technologies allow investigating the heterogeneity in immune vaccine response with a growing interest in predicting vaccine response and will possibly permit developing newer effective individualized vaccines (26).

The first studies investigating genetics of non-response to hepatitis B vaccine started in the 1980's with the analysis of HLA polymorphisms (27). To our knowledge, only two meta-analysis have been conducted to date. The first one by Li et al. assessed the potential role of HLA class II DRB1 and DQB1 alleles in immune response to hepatitis B vaccine by including 15 studies, mainly from Asian populations, and highlighted seven DRB1 and three DQB1 alleles that were associated either with non-response or with response to hepatitis B vaccine (28). The second one by Cui et al. investigated IL4 gene polymorphisms and included a total of eight studies, from which five covered response to vaccine (29). However, both meta-analysis highlighted several limitations including small sample sized studies, single allele analysis in the HLA system, lack of access to the original data of the studies and difficulty to assess ethnic subgroups. Yet, no comprehensive overview of genetic polymorphisms both within and outside the HLA system has been done to our knowledge so far.

In this study, we performed a systematic analysis and review of the available literature focusing on the association of genetic polymorphisms with the immune response to hepatitis B vaccine. The aim of this work was to establish a comprehensive list of genes and SNPs that have an effect or not on the response variability to vaccine.

Material and methods

Literature searches using keywords were conducted in the electronic databases Medline (Pubmed), Embase and ISI Web of Science through the program EndNoteX7, the cut-off date being March 2014. The keyword searches carried out were done with using the combination of "hepatitis B", "hepatitis B virus", "hepatitis B vaccine", "HBsAg" and "HBV" with the statement "OR", the statement "AND" combined with the following keywords "immunogenetics", "genetic susceptibility", "human genetics" and "genetic polymorphism" with the statement "OR". In addition, we performed manual searches according to the reference lists of the included articles to identify additional papers related to the topic.

The titles and corresponding abstracts of the articles, as well as other baseline information such as author names, date of publishing, the International Standard Serial Number (ISSN) were exported into the program EndNoteX7. The list of items thus generated was screened by a 3-fold process, first by title, second by abstract and third by full-text article reading, in order to get the most relevant material for the review, after applying stringent selection criteria as described below.

Articles were excluded from this review when they focused on, (A) HBV-related topics other than response to vaccine or susceptibility to chronic hepatitis B (such as liver cirrhosis and steatosis, hepatocellular carcinoma, response to treatment,

epidemiologic data, pathophysiology of HBV and immunity studies), (B) functional susceptibility (such as cellular susceptibility), (C) viral (but not host) genetics, (D) other hepatitis viruses (such as HCV, HDV and HAV), (E) pathogen other than HBV, diseases other than hepatitis B disease, studies performed in transplanted population, animal study, studies focusing on genotyping techniques. Articles in a language other than English were not considered. Duplicates were removed. Finally, reviews and meta-analysis were also excluded. Studies representing a special population such as neonates, HIV co-infected individuals and hemodialysis patients were still included.

Because of the unexpected amount of results after the first screening step, we decided in a second time to focus on studies concerning response to hepatitis B vaccine. The data concerning chronic hepatitis B were set aside and will be analyzed in a separate review.

For papers that were selected according to the aforementioned criteria, additional information was extracted in order to permit a comparison of one with another. Additional data included phenotype tested (non-response, response, mean or median anti-HBs titer), response criteria (anti-HBs antibody cut-off levels), type of vaccine and vaccine schedules, country of origin of the article, cohort population characteristics such as size, ethnicity, age, gender, co-infections and co-morbidities, type of analysis (univariate or multivariate), genes and single nucleotide polymorphisms (SNPs), major and minor alleles, dominant, recessive or additive mode of inheritance, odds ratios or relative risks, 95% confidence interval, p-values, and information on multiple testing correction. Family, twin or genome-wide association studies (GWAS) were analyzed separately.

For the sake of clarity and to allow a comparison between studies, we admitted that all the different schedules and types of vaccine had the same immunogenicity (efficacy of plasma-derived and recombinant vaccines are equivalent but routes of administration, schedule and dosages may cause variable response in healthy individuals (30)). All studies were then grouped together according to gene/SNPs or HLA class tested. This produced three lists. The first one was a list of the HLA alleles tested at least two times by different papers. The second one was a list of SNPs that were studied at least twice by several papers (or within the same paper including a replication study) thus permitting comparisons between studies. The third one was a list of SNPs analyzed only once by one paper, therefore no comparison was achievable.

In order to allow a maximal number of comparisons between studies, we have chosen to present the data analyzed with the dominant mode of inheritance (i.e. comparison of patients carrying either one or two copies of the minor [mutant], rare allele to those carrying two copies of the major [ancestral], most common allele) as a baseline in the summary tables. Whenever feasible the statistical analysis presented

by each article was redone using Stata/IC 13.1 so as to verify and validate the quality of the data presented. Pertinent data resulting from comparisons using the recessive or additive mode of inheritance were indicated separately.

Results

After removal of duplicates, the literature search returned a library of 1968 articles (Figure 1). The manual research added 24 papers. From those, 1596 were eliminated for non-relevance, based on their title (N=1259), abstract (N=16) or full text (N=7). Articles considering chronic versus acute HBV infection were also removed (n=314). Forty-six studies were finally selected for further analyses.

Studies' characteristics

Among the 46 included studies, 3 were twin studies, two were family studies and one was a GWAS (31-36). Studies included in the final analysis had a variable number of patients. Eight had more than 1000 participants, four had between 999 and 500 participants, 27 had between 499 and 100 participants and finally seven studies included less than 100 participants. Most of the studies were made among Caucasians individuals (N=26, Table 1). Thirteen studies were performed among Asian individuals, especially the ones studying the genes out of the HLA system. Three studies were done among Africans and four studies included mixed ethnicities as the cohort contained both Caucasians and African Americans patients.

The majority of the studies were performed among adults (N=32) and 17 studies reported a pediatric population (age <20 years old). Three studies included individuals showing past or chronic HBV infection (37-39). One analyzed genetic factors associated with both response to vaccine and seroconversion to anti-HBc (anti-hepatitis B core antigen antibody), indicating infection despite vaccination (38). Only results on response to vaccine are reported. Another one compared vaccine induced immunity to natural HBV infection induced immunity as a second outcome (the first outcome was immunogenetics of response in non-infected vaccinees and only those results are considered) (39). A last one had a mixed population of either HBV vaccinees or HBV exposed individuals that were stratified based on their anti-HBs titer and compared as non-responders versus responders to HBsAg (37). Several studies included patients co-infected with HIV-1 (2 studies, (40, 41)) or with HCV (2 studies, (37, 39)). Four studies included hemodialysis patients (37, 39, 42, 43).

Type of vaccines and vaccine schedules varied widely. Thirty-nine papers were performed with the recombinant vaccine while 10 studies used the non-recombinant plasma-derived hepatitis B vaccine (3 studies included patients vaccinated with either the one or the other). Twenty-nine studies used a 3 doses schedule, from which 5 repeated doses administration in case of non-response, while 9 directly administrated

4 initial doses. Six studies included patients who received different schedules (either 3 or >3 doses). Two studies evaluated response to a booster dose of hepatitis B vaccine: the first one consisted in a booster vaccine (1x10ug of HBsAg) about 2 years after a standard immunization (pre-booster anti-HBs level was not described) (44) and the second one in a booster vaccine (1x20ug of HBsAg) about 15 years after primary infantile immunization (in individuals with pre-booster anti-HBs titer less than 10 mIU/ml) (45). The span of doses ranged from 2 to 40ug of HBsAg. The route of administration was predominantly intra-muscular (N=23), but 5 studies reported sub-cutaneous or intra-dermal injections (46-50), which are known to be less immunogenic routes (30). Two studies reported either intra-muscular or intra-dermal injections (38, 51). Sixteen studies did not describe the route of administration. The anti-HBs titer was assessed within one month after the last dose administration in the majority of the studies (N=28), while in 16 other papers, the time of measurement was not specified.

There were different ways to determine the phenotype of vaccine response depending on the studies (Table 2). The qualitative way was the most operated, especially througha dichotomized way by the comparisons between non-responders and responders to hepatitis B vaccine. In another hand, 11 studies considered response to vaccine as a continuous trait. Eight studies (31, 32, 38, 47, 51-54) have chosen to log-transformed anti-HBsAg antibody titers from which seven reported a log normal distribution. One study (44) used percentiles (with a dichotomized analysis with a cut-off at percentile 50), one study reported geometric mean titers for the whole group of vaccinees (55) and finally one paper described anti-HBs mean titers (56).

In 9 papers, HLA allele frequencies in non-responders was compared with the frequencies in a non-vaccinated control population and were therefore described as unmatched studies (39, 46, 48, 57-62).

HLA alleles associated with non-response to hepatitis B vaccination

HLA system represents the most investigated field in term of immunogenetics of the response to HBsAg vaccine. The oldest studies included in this review are from 1988 (48, 59, 62). Among the 46 included studies, 33 analyzed the impact of HLA alleles on the antibody response to hepatitis B vaccination and 28 of them could be compared (1 family study (34), 1 twin study (32), 2 SNPs studies reported below (53, 63) and 1 GWAS (36) were not considered in this part of the review). Out of these 28 studies, 18 analyzed HLA class I, 28 HLA class II and 5 HLA class III (complement system). HLA-DR locus was the most studied locus in term of vaccine response, quickly followed by HLA-DQ locus. In contrast to the extra-HLA studies previously exposed, the majority of the present studies were performed among Caucasians (or a mix population comprising Caucasian individuals) (N=22). According to the large number of allele tested and for the purpose of conciseness, we aimed to present in this review the alleles that were reported as significant by at least 2 papers (Table 3).

HLA-A2. This allele was studied in 5 Caucasian papers (39, 41, 43, 61, 64). This allele was significantly associated with non-response to vaccine in two different studies both performed on hemodialysis patients (and HCV co-infected individuals in (39)). Those results were not confirmed by the other more recent studies, although they had a small number of patients.

HLA-B8. This allele was the most studied allele of the HLA-class I region among Caucasians with at least two significant data. A total of six studies (43, 49, 61, 62, 64, 65) reported this allele but only 2 of them, published before 2000, found out a significant association with response to vaccine (43, 62). Those observations need to be confirmed in further studies.

HLA-DPB1*0301. Out of the 3 studies that investigated this allele, 2 showed significant but divergent data (45, 60, 66). Despite a comparable size, one was performed in Caucasians infants with childhood immunization (60) whereas the other one on Asian adults who were booster vaccinated (45). Further studies have to demonstrate the role of this allele depending on the ethnicity.

HLA-DPB1*0401. Three different studies presented similar significant results among Caucasians and Asians, with an association of this allele with the responder phenotype (45, 60, 66). The study design of those papers was heterogeneous and so this association have to be replicated in other well designed studies.

HLA-DQ2. Amongst 5 studies (39, 43, 58, 64, 65), two reported a significant association of this allele with non-response to vaccine but were realized in hemodialysis patients (39, 43).

HLA-DQB1*02. Amongst the 6 studies that investigated this allele (35, 40, 41, 50, 61, 67), 5 described a similar trend than those assessing DQ2 allele and only two of them reached the significant statistical threshold (41, 61). Among the 4 studies which analyzed DQB1*0201 (44, 60, 66, 68), three reached significance (60, 66, 68). Those observations let us expect that DQB1*02 is a good risk factor candidate for non-response in Caucasians.

HLA-DQ3. One study among Asian individuals and 2 among Caucasian observed a significant association between this allele and the responder phenotype (43, 58, 66). Another unmatched Asian study failed to demonstrate such an association (48).

HLA-DQB1*03. Three of the five studies that covered this allele found out a significant association with response to HBsAg vaccine (41, 44, 61, 66, 67). One of them (44), designed with 79 participants whose response to vaccine was considered as a continuous trait, reported an association of HLA-DQB1*03 with a titer above the

50th percentile. According to those observations, DQB1*03 seems to play a role in vaccine response. This role has to be validated in further studies.

HLA-DQB1*06. One study realized among individuals with mixed ethnicities and HIV co-infected individuals reported a significant association of DQB1*06 with the responder phenotype (the p-value was adjusted for age, gender, ethnicity, vaccine schedule and HIV status) (41). Two other studies of Caucasian individuals out of 5 investigating **DQB1*0602** allele reported a significant association with the responder phenotype (50, 61). Altogether, those results make HLA-DQB1*06 allele an interesting candidate factor for response to vaccine among Caucasians.

HLA-DR1. Of the six studies that covered this allele (43, 46, 50, 59, 64, 66), three reported a significant association with response to vaccine (43, 46, 64).

HLA-DRB1*01. Two recent studies with an important number of participants out of 6 that covered this allele tended to confirm a protective role of DRB1*01 (31, 42). Additional studies would be required to confirm this observation.

HLA-DR2. Regarding the other alleles of the HLA-DR locus, only few studies investigated DR2 allele. A total of four studies (42, 43, 59, 66) analyzed this allele (including one analyzing **HLA-DRB1*02** allele) with consistent data for responder phenotype even if one of the study didn't reach significance (66).

HLA-DR3. HLA-DR3, with **DRB1*03** and **DRB1*0301**, was one of the most reported allele among the HLA system in this review, mostly among Caucasians (19 papers, including one with two cohorts both adult and pediatric (69). A number of studies observed significant associations with the non-responder phenotype (35, 39, 40, 42, 43, 49, 52, 57, 67, 69). Two American studies were performed among HIV co-infected adolescents (including HIV co-infected individuals) from mix ethnicities (Caucasians [including Hispanic individuals] and Afro-Americans) and only one reported significant data (40). In this study, the association remained significant when tested among 308 HIV negative individuals according to a multivariable model comparing non-responders to responders. Through this review, HLA-DR3 seems to be one of the most validated risk factor for non-response amongst HBsAg vaccinees.

HLA-DR4. Nine studies covered this allele and only three of them, including 2 unmatched studies among Asian individuals, reported significant associations with divergent effect depending on the ethnicity (43, 46, 48). The seven more recent studies among Caucasians that included HLA-DRB1*04 in their analysis didn't find out any significant association (31, 41, 42, 44, 61, 68, 69). HLA-DR4 might have a role in the host genetics of Asian individuals and this possible association has to be validated by new well-designed studies.

HLA-DR5. A total of three articles, published before 2000, related significant but divergent data (43, 59, 66). The role of this allele is unclear and has to be determined by other modern studies.

HLA-DR6. Two out of the four studies that analyzed this allele reported significant results (43, 46). As for HLA-DR5, the role of HLA-DR6 remains unclear in this review, reason why this allele has to be assessed in modern studies.

HLA-DR7. HLA-DR7, with DRB1*07 and DRB1*0701, was covered by a total of nineteen studies making this allele one of the most reported in the HLA system (together with DR3). Ten of these studies demonstrated a significant association with non-response (39-41, 43, 52, 57, 61, 62, 66, 69), while only one suggested association with the responder phenotype (35). According to the more recent and more powerful studies, HLA-DRB1*07 seems to have a negative impact on response to hepatitis B vaccine.

HLA-DRB1*11. The association with the responder phenotype was significant in two out of the 8 studies that included this allele (31, 67). The more recent studies, but with less than 170 participants and with potential confounding factors, didn't reach the statistical significant threshold for this association (41, 68). The role of this allele in the Caucasian population has to be clarified in larger studies. No significant associations were reported for HLA-DR11 (46, 50, 64).

HLA-DR13. Ten studies investigated the role of either DR13, **DRB1*13** or **DRB1*1301** alleles in response to HBV vaccine, from which 3 reported a significant association with the responder phenotype (50, 52, 69). One of them demonstrated such association both in an adult and in a children cohort of vaccines (69). A more recent study performed on the same cohort of healthy Caucasian adults confirmed an association of DRB1*1301 with the responder phenotype (52). Those findings would need further validation.

HLA-DR14. Only two studies among the 9 which investigated the implication of either DR14 or **DRB1*14** or **DRB1*1401** on response to vaccine showed significant associations (42, 58). The potential association with the non-responder phenotype cannot be confirmed by this review.

HLA-DR15. Out of the ten studies that covered DR15 and **DRB1*15** alleles (31, 40, 42, 44, 50, 58, 61, 64, 68, 69), only two related an association with responder phenotype with statistical significance (31, 50). The most recent study by Li et al. observed a similar trend in a univariate analysis confined to 255 HIV positive individuals but without reaching significance (40). Overall, the role of DR-15 allele in vaccine response remains unclear.

C4AQ0. The only allele of the HLA-class III region to be reported as significant at least in two studies was C4AQ0 allele. The six Caucasian studies that included this allele demonstrated a marked significant association with the non-responder phenotype (35, 43, 52, 57, 60, 67). These data make C4AQ0 one of the best candidate allele for vaccine response prediction among Caucasians (see also family studies below).

Polymorphisms associated with non-response to hepatitis B vaccination

Among the 46 included studies, 14 involved gene polymorphisms analysis other than HLA alleles and two studies reported SNPs within HLA-B, -DQA1, -DQA2 and -DR genes, making a total of 15 papers. Overall, these studies analyzed the role of polymorphisms from 55 genes on response to vaccine. Out of the 16 genes that were studied in at least two papers, 13 genes contained SNPs that were analyzed at least two times and could therefore be compared in term of statistical results (N=19). This list of 13 genes included IL10 (6 papers), IL12B (5 papers), TNFA (5 papers), IL4 (5 papers), IL1B, IL2, IL4R, IL6, IL13, IFNG, TLR2 (2 papers, respectively), CD3Z (1 paper with replication study) and ITGAL (1 paper with replication study). Details on the statistical results of the SNPs that were analyzed in more than one study are described in Table 4.

IL10. The most studied gene was IL10, which was analyzed in 7 different papers (from which one set forth data regarding haplotypes analysis and so could not be used), mainly among Asians. These studies comprised 3 different SNPs. The only significant results were reported for rs1800872 (in strong linkage disequilibrium with rs1800871) by Lin et al. (70) thru the recessive mode among 278 long term non-responders (anti-HBs ≤12 mIU/ml) compared to 176 long term responders, with an increasing risk for non-response. This observation cannot be confirmed regarding the other studies. It is noteworthy that these studies were performed among different populations (one with HIV co-infected individuals (41)) and with variable phenotypes.

IL12B. Two IL12B SNPs (rs3212227 and rs17860508) in five different papers were available for comparison (37, 41, 54, 71, 72). One study, which analyzed the effect of rs3212227 on the median anti-HBs titer among 139 healthy children of 1 year old, reported a significantly lower titer regarding the dominant mode (54). Other larger studies failed to show a significant association for this polymorphism according to a qualitative model. One study showed an association of rs17860508 with non-response (41). This study was performed among healthy and HIV positive adolescents from mix ethnicities and even if the results were adjusted for age, gender, ethnicity and HIV status, they have to be treated with caution. The other study (71) with more cases and controls reported a similar trend (recessive mode), even if the analyzed phenotypes of response were different.

IL4. Five different papers studied three polymorphisms of IL4 gene (41, 55, 71-73). The most reported was rs2243250, for which 2 studies realized among Asians found

significant but divergent data (55, 72). 2 studies reported a second SNP (rs2070874), and only the Asian study observed a significant association of this polymorphism with poor response to vaccine (72). The third SNP (rs2243248), studied in two papers, didn't show significant results. The two polymorphisms rs2243250 and rs2070874 might play a role in immune response to HBsAg in Asian individuals.

TNFA. One SNP (rs1800629) in TNFA gene was analyzed in five papers (41, 54, 55, 72, 74). Only one of them reported a significant positive effect on median anti-HBs titer (54). Another more recent study, with a similar number of participants but from a different ethnicity (Asians), didn't confirm the effect of this SNP among anti-HBs titer (continuous trait) (55).

IFNG. Two studies covered the same SNP in this gene (38, 71). Hennig et al. performed their study among a cohort of 662 Africans from the Gambia and observed a significant positive effect of rs2069727 on the Geometric Mean peak anti-HBs Titer (GMT). Due to a small number of non-responders, the authors didn't carry out a case-control study. No significant effect was reported by the other study.

IL1B. Two studies that measured rs16944 in IL1B didn't observe any significant impact of this polymorphism (55, 72).

IL2. Two studies failed to detect any association between response to vaccine and rs2069762 (41, 72).

IL4R. One polymorphism within IL4R gene (rs1801275) was analyzed by two papers with different ethnicities and different phenotypes but didn't show significant data (41, 55).

TLR2. One SNP in TLR2 gene, rs3804100, was assessed in two Asian studies (41, 73). The significant association with non-response observed in the first, small powered study (73) failed to be confirmed in a larger one (72).

CD3Z. A group investigated a SNP in CD3Z (rs12133337), in a two-step replication study performed among a large Asian population (75). The authors found out a positive association with poor response to hepatitis B vaccination. Further studies are needed to confirm the potential role of this SNP.

ITGAL. Two SNPs in this gene (rs4243232 and rs2230433) were explored in a two-fold analysis in an African population, first among 662 vaccinees and in a second time among 393 vaccinees (38). Even if the two polymorphisms showed a significant positive association with a higher anti-HBs titer (continuous trait), only data concerning rs2230433 returned significant in the second fold phase. This observation would require validation in other large population studies.

A total of 46 SNPs from 26 genes (3 genes that were cited previously and 23 other) were significantly associated only once with response to hepatitis B vaccine (14 of them were reported as haplotypes). A total of 41 SNPs in 29 genes (7 genes previously cited and 22 other) were not associated with the outcome of HBsAg vaccination (Table 5).

Family, twin studies and GWAS.

We identified three twin studies among our literature review. Höhler et al. investigated heritability of HBsAg vaccine response in 382 Caucasians twins (192 monozygotic and 190 dizygotic) vaccinated with a 3 fold 20ug recombinant HBsAg vaccine and found out that 60% of the phenotypic variance could be explained by additive genetic and 40% by non-shared environmental effects (31). The authors suggested that 40% of this genetic contribution is affected by MHC-genes (mainly HLA-DRB1* locus) and 60% by non MHC-genes. Another study in the same cohort of twins related that approximately 25% of heritability of vaccine response is determined by variability in the IL-10 promoter (rs1800896, rs1800871 and rs1800872) (33). However, we previously reported that data from studies that analyzed those three SNPs were rather inconclusive (see above and Table 4). Newport et al. observed a heritability reaching 77% for hepatitis B vaccine response among 207 twin pairs from the Gambia (32). This heritability was higher than the other studied vaccines (oral polio (60%), tetanus (44%) and diphtheria (49%)).

Two family studies were recorded (34, 35). Kruskall et al. reported the association of homozygous individuals for the extended HLA-B8-SC01-DR3 haplotype with the non-response phenotype by analyzing 43 members of ten Caucasians families immunized with plasma-derived HBsAg and suggested that response was inherited in a dominant mode. De Silvestri et al. showed through the analysis of families of 27 non-responders that C4AQ0 allele, previously associated with the non-responder phenotype (see above), was almost always transmitted to non-responders, but 13 of the 27 families with a non-responder baby were not carriers of C4AQ0 allele. Although not statistically significant, this data tends to further support the implication of C4AQ0 in response to HBV vaccine.

Only one GWAS appeared in this literature review (36). This 2-stage GWAS was performed among Indonesians from Batam and the surrounding islands near Singapore. In the first stage, 1638 vaccinees were genotyped for a total of 455508 SNPs and in the second stage 1931 individuals were genotyped for a total of 1706 SNPs leading to the identification of three SNPs within the HLA complex. These are rs3135363 in HLA-DR locus (which appeared to be the most significant contributor to antibody response, even after adjusting for the effects of other independent loci) and rs9267665 in the HLA-class III region, both associated with poor response to vaccine and rs9277535 in the HLA-DP locus (HLA-DPB1) associated with good response. Those three SNPs were not reported in the other studies included in this literature research, but the HLA loci corresponding to these polymorphisms (HLA-DR, HLA-

DPB1 and HLA-class III) have been associated with variation in vaccine responsiveness by the HLA studies included in this systematic review. The same association with good response was observed for HLA-DPB1 alleles (see above).

Finally, this literature research disclosed one study that investigated haptoglobin gene phenotype with the immune response after hepatitis B vaccine (56). Haptoglobin is coded by 2 different genes and could therefore be described by three polymorphisms: Hp 1-1, Hp 2-1, Hp 2-2. This study performed among 100 healthy Caucasians vaccinated with a recombinant hepatitis B vaccine reported that subjects with a 2-2 haptoglobin phenotype produced significantly lower anti-HBs titer compared to the other phenotypes. To our knowledge, this is the only study relating this gene in the immune response to hepatitis B vaccine.

Discussion

This review focused on the human genetics of the immune response to hepatitis B vaccination and included a total of 46 studies disclosing a list of 55 candidate genes and another list of 19 alleles in the Major Histocompatibility Complex (MHC) that may influence the outcome after HBsAg vaccination. To our knowledge, this is the first systematic review covering genetic factors both outside and within the HLA system and limited to hepatitis B vaccine since others reviewed them separately or for several vaccines at the same time (76-78).

Firstly, our systematic review shows that the most studied genetic region regarding the response to hepatitis B vaccine is the HLA region. A total of 33 studies among the 46 included in our work focused on MHC complex. Data presented are consistent (Table 4) and reflects the crucial role of this complex in antigen processing. Among the HLA alleles, this review found out 9 alleles that were firmly associated with immune response after hepatitis B vaccination (validated by at least three different studies and with coherent association): DQ2 (DQB1*02 and DQB1*0201), DR3 (DRB1*03 and DRB1*0301), DR7 (DRB1*07 and DRB1*0701) and C4AQ0 associated with non-responder phenotype; DPB1*0401, DQ3, DQB1*06, DRB1*01 and DRB1*13 (DRB1*1301) associated with responder phenotype. Furthermore, two studies reported significant polymorphisms located in HLA-DQA1, -DQB1 and -DRA genes. One GWAS reported three significant polymorphisms in HLA-DR locus, HLA-DPB1 gene and HLA-class III region, and those results tend to further confirm the previously reported associations. None of these SNPs were analyzed twice. Our results are in accordance with those previously reported in other reviews (4, 76, 77, 79). The present work has the advantage of collecting an important number of HLA studies (not gathered in previous reviews) and thus presenting a better comprehensive overview of the different alleles in terms of association with the responsiveness to hepatitis B vaccine.

Secondly, this work shows that polymorphisms studied at least by two papers demonstrate inconsistent data while many interesting candidate genes are reported but not validated (Table 2 and 3). Our work summarizes an extensive list of SNPs associated with response to HBsAg vaccination from individual studies. These polymorphisms can now be systematically tested in datasets such as the one built in our institution (more than 700 healthcare workers vaccinees), thereby opening some interesting possibilities for further research.

Among the 55 genes covered by the included studies, 19 polymorphisms from 13 genes have been analyzed more than once. Those genes could be classified in three categories. 4 genes including IL1B, IL2, IL4R and IL6 revealed no significant data; 6 genes including IL4, IL10, IL12B, IL13, TNFA, IFNG and TLR2 were explored with inconsistent results, as significant and non-significant associations were observed and sometimes even reverse associations; 2 studies identified interesting genes including CD3Z and ITGAL which were confirmed by a replication approach (38, 75), but both investigations were conducted by the same research group. One meta-analysis found that three SNPs among IL4 gene, rs2243250, rs2070874 and rs2227284, were associated with a good response to hepatitis B vaccine among Asian individuals but not among Caucasians (29). In our review, data concerning rs2243250 and rs2070874 polymorphisms were inconsistent and rs2227284 SNP was studied only once in (72), thus not permitting statistical comparisons.

Finally, this literary search shows that a great majority of the HLA studies were performed among Caucasians population while the majority of the papers reporting genes outside the MHC region were realized in Asians individuals. There are relatively few studies analyzing African populations although Africa is one of the important prevalent regions for HBV endemicity (Table 1). Hennig et al. reviewed host genetic factors influencing HBV infection, liver cancer and vaccine response with a focus on Africa, and these studies are included in our review (80).

This literary search was firstly designed to highlight papers covering either HBV infection or vaccine response, thereby making this research less specific to the vaccine response. This bias was partially corrected with manual searches through the pertinent papers collected. Like most systematic reviews, this work has other important limitations. These are linked to the heterogeneity of the studies in term of population (age, gender, ethnicity, co-morbidities), control population (vaccinated or not), vaccine types and schedules, phenotypes compared and definitions (non-responders, high-responders, etc.), genotyping (inconsistencies in polymorphisms denomination, quality check for sequencing, etc.), statistical analysis (absence of reporting for Bonferroni's correction for example) and quality. Three of the included studies screened more than 100 genes, using an approach similar to that of GWAS (38, 51, 63). One of them did not mention Bonferroni's correction (38). Despite the fact that HBsAg vaccination represents an easier and reproducible way to study immunogenetics of HBV infection, we found only a few papers using a properly

comparable way of vaccine administration and outcome analysis. A standardized way of vaccination against HBV would allow more pertinent and more robust studies and meta-analysis. Nevertheless, we tried to be as strict as possible regarding the inclusion criteria of the articles in order to end up with a list of studies that would be as comparable as possible.

Altogether, this master thesis is the first systematic review of immunogenetic studies of response to hepatitis B vaccine within and out the HLA system. Despite the fact that HLA alleles seems to be well-known influencing factors, this work shows that only little is known about the role of polymorphisms in other genes, including cytokine genes and surface receptors genes. While polymorphisms studied more than once are rather inconsistent, many polymorphisms still not validated may have an interesting role in immune response after hepatitis B vaccination.

Table 1. Patients' ethnicity and country of origin.

	Number of articles per Ethnicity				
Country	Caucasian	Asian	African	Mix	Total
Germany	6	–	–	–	6
Italy	4	–	–	–	4
USA	2	–	–	4[1]	6
UK	2	–	–	–	2
Belgium	2	–	–	–	2
Brazil	1	–	–	–	1
France	1	–	–	–	1
Greece	1	–	–	–	1
Hungary	1	–	–	–	1
India	1	–	–	–	1
Iran	1	–	–	–	1
Poland	1	–	–	–	1
Spain	1	–	–	–	1
Sweden	1	–	–	–	1
Turkey	1	–	–	–	1
China	–	4	–	–	4
Taiwan	–	4	–	–	4
Japan	–	3	–	–	3
Indonesia	–	1	–	–	1
Singapore	–	1	–	–	1
Gambia	–	–	3	–	3
Total	26	13	3	4	46

[1] This study contained mixed population of Caucasians and African Americans.

Table 2. Phenotypes of response to vaccine according to studies.

	Number of groups	Phenotypes	Anti-HBs cut-off level(s)	Study
Qualitative	2	NR vs R	10 mIU/ml	(37, 39, 41-43, 49, 52, 65, 69)
			1 mIU/ml[1]	(45)
			2000 RIA units	(34)
			<10 and >100 mIU/ml	(50, 63, 64, 68, 73)
		NR vs HR	<10 and >1000 mIU/ml	(66)
		LTLR vs LTR[2]	10 mIU/ml	(70, 72)
		LR vs HR	10-99 and >1000 mIU/ml	(71, 75)
		R vs HR	10-1000 and >1000 mIU/ml	(55, 74)
		NR vs controls[3]	NR: <3 mIU/ml	(59)
			NR: <10 mIU/ml	(60, 61)
			NR: <10 RIA units	(57)
			ULR: <20 mIU/ml[4]	(58)
			NR: S/N <2 RIA units	(46)
			NR: S/N <9.9 SRU	(62)
			NR: ?	(48)
	3	NR, MR and HR	<10, 10-1000 and >1000 mIU/ml	(40)
		hR, R and HR	<100; 100-1000 and >1000 mIU/ml	(36)
	4	tNR, SR, LR and R	<10[4], >100[4], 11-40 and >100 mIU/ml	(35, 67)
Qantitative (continuous trait)	–	standardized anti-HBs log titer	–	(31-33, 38, 47, 51, 53, 54)
	–	anti-HBs mean titer	–	(55)
	–	geometric mean titer	–	(56)
	2	percentiles	≤50% vs >50%[1]	(44)

Abbreviations: aNR: absolute non-responder, anti-HBs: anti-hepatitis B surface antigen antibody, HR: high responder, hR: hypo-responder, IU: international units, LTNR: long term non-responder, LTR: long term responder, LR: low responder, NR: non-responder, R: responder, RIA: radioimmuno assay, S/N: sample counts per minute divided by mean of negative controls, SR: slow responders, SRU: sample ratio units, tNR: true non-responder, ULR: ultimate low responder. MR: moderate responder,

[1] Anti-HBs titer after booster dose

[2] Anti-HBs titer was measured ca 6 years (72) and ca 17 years (70) after neonatal immunization

[3] Controls are unvaccinated individuals

[4] Anti-HBs titer after revaccination

Table 3. Genetic studies of immune response to hepatitis B vaccine for HLA alleles reported as significant at least twice.

								Non-response to vaccine		
HLA type	HLA subtype	First author	Year	N	Cases/controls[1]		Ethnicity	OR	95% CI	P
HLA class I										
HLA-A	A2	Stachowski (43)	1995	153	34/119	matched	C	_	_	<0.01
		Peces (39)	1997	333	13NRs/43Rs/277	matched and unmatched	C	7.10[2]	_	<0.05
		McDermott (61)	1997	217	86/131	unmatched	C	_	_	NS
		Wang (41)	2004	164	79/85	matched	mix	_	_	NS
		Albayrak (64)	2011	68	25/43	matched	C	_	_	NS
HLA-B	B8	Weissman (62)	1988	1051	22/1029	unmatched	C	_	_	<0.02
		Varla-Leftherioti (49)	1990	169	68/101	matched	C	_	_	NS
		Stachowski (43)	1995	153	34/119	matched	C	_	_	<10E-15
		McDermott (61)	1997	217	86/131	unmatched	C	_	_	NS
		Das (65)	2004	30	15/15	matched	C	_	_	NS
		Albayrak (64)	2011	68	25/43	matched	C	_	_	NS
HLA class II										
HLA-DP	DPB1*0301	Martinetti (60)	1995	638	26/612	unmatched	C	2.90	_	0.03
		Desombere (66)	1998	146	46/100	matched	C	0.75[2]	_	NS
		Wu (45)	2013	681	171/510	matched	A	0.29	0.12-0.67	0.004
	DPB1*0401	Martinetti (60)	1995	638	26/612	unmatched	C	0.24	_	0.009
		Desombere (66)	1998	146	46/100	matched	C	0.18[2]	_	<0.01
		Wu (45)	2013	681	171/510	matched	A	0.28	0.11-0.70	0.009
HLA-DQ	DQ2	Hsu (58)	1993	700	23/677	unmatched	A	1.90[2]	_	NS
		Stachowski (43)	1995	153	34/119	matched	C	_	_	<10E-13

								Non-response to vaccine		
HLA type	HLA subtype	First author	Year	N	Cases/controls[1]		Ethnicity	OR	95% CI	P
		Peces (39)	1997	333	13NRs/43Rs/277	matched and unmatched	C	4.20[2]	_	<0.05
		Das (65)	2004	30	15/15	matched	C	_	_	NS
		Albayrak (64)	2011	68	25/43	matched	C	_	_	NS
	DQB1*02	McDermott (61)	1997	203	86/117	matched	C	5.65[2]	_	<0.001
		Langö-Warensjö (50)	1998	122	53/69	matched	C	_	_	NS
		Martinetti (67)	2000	92	16/76	matched	C	3.03	1.24-7.39	NS
		De Silvestri (35)	2001	71	31/40	matched	C	2.20	_	NS
		Wang (41)	2004	164	79/85	matched	mix	2.55	_	0.002[3]
		Li (40)	2009	335	97HRs/160MRs/78NRs	matched	mix	1.45[4]	0.93-2.22	0.1[5]
	DQB1*0201	Martinetti (60)	1995	558	34/524	unmatched	C	2.80	_	0.02
		Desombere (66)	1998	146	46/100	matched	C	4.78[2]	_	0.001
		Lindemann (44)	2002	79	_	_	C	_	_	NS
		Amirzargar (68)	2008	58	12/46	matched	C	2.94	1.04-8.33	0.04
	DQ3	Hsu (58)	1993	700	23/677	unmatched	A	0.20[2]	_	0.001
		Stachowski (43)	1995	153	34/119	matched	C	_	_	<10E-6
		Desombere (66)	1998	146	46/100	matched	C	0.37	_	<0.01
	DQw3	Watanabe (48)	1988	2073	19/1988	unmatched	A	_	_	NS
	DQB1*03	Wang (41)	2004	164	79/85	matched	mix	_	_	NS
	DQB1*0301	McDermott (61)	1997	203	86/117	matched	C	_	_	NS
		Desombere (66)	1998	146	46/100	matched	C	0.07[2]	_	<0.005
		Martinetti (67)	2000	92	16/76	matched	C	0.00	0.00-0.33	0.02
		Lindemann (44)	2002	79	_	_	C	_	_	0.03
	DQB1*0301/0304	Langö-Warensjö (50)	1998	122	53/69	matched	C	_	_	NS
	DQB1*03011	Amirzargar (68)	2008	58	12/46	matched	C	0.85	0.17-3.57	1

								Non-response to vaccine		
HLA type	HLA subtype	First author	Year	N	Cases/controls[1]		Ethnicity	OR	95% CI	P
	DQB1*06	Wang (41)	2004	164	79/85	matched	mix	0.72[6]	_	0.02[3]
	DQB1*0602	McDermott (61)	1997	217	86/131	unmatched	C	0.25[2]	_	<0.001
		Desombere (66)	1998	146	46/100	matched	C	0.44	_	NS
		Langö-Warensjö (50)	1998	122	53/69	matched	C	_	_	0.01
		Lindenmann (44)	2002	79	_	_	C	_	_	NS
		Amirzargar (68)	2008	58	12/46	matched	C	0.31	0.01-2.56	0.45
HLA-DR	DR1	Krämer (59)	1988	2524	25/2499	unmatched	C	1.30	_	NS
		Hatae (46)	1992	153	33/120	unmatched	A	0.00[2]	_	0.02
		Stachowski (43)	1995	153	34/119	matched	C	_	_	0.02
		Desombere (66)	1998	146	46/100	matched	C	0.09[2]	_	NS
		Langö-Warensjö (50)	1998	121	53/68	matched	C	_	_	NS
		Albayrak (64)	2011	68	25/43	matched	C	NC	NC	<0.05
	DRB1*01	McDermott (61)	1997	203	86/117	matched	C	_	_	NS
		Caillat-Zucman (42)	1998	415	114/301	matched	C	0.47	0.25-0.87	0.02
		Höhler (69)	1998	126	73/53	matched	C	_	_	NS
		Lindemann (44)	2002	79	_	_	C	_	_	NS
		Höhler (31)	2002	382	_	_	C	_	_	0.02
		Wang (41)	2004	164	79/85	matched	mix	_	_	NS
	DRB1*0101	Amirzargar (68)	2008	58	12/46	matched	C	0.40	0.02-3.45	0.7
	DR2	Krämer (59)	1988	2524	25/2499	unmatched	C	0.27	_	NS
		Stachowski (43)	1995	153	34/119	matched	C	_	_	<0.01
		Desombere (66)	1998	146	46/100	matched	C	0.65[2]	_	NS
	DRB1*02	Caillat-Zucman (42)	1998	415	114/301	matched	C	0.55	0.30-0.99	0.05

								Non-response to vaccine		
HLA type	HLA subtype	First author	Year	N	Cases/controls[1]		Ethnicity	OR	95% CI	P
	DR3	Krämer (59)	1988	2524	25/2499	unmatched	C	2.80	_	NS
		Weissman (62)	1988	1167	22/1145	unmatched	C	_	_	NS
		Varla-Leftherioti (49)	1990	169	68/101	matched	C	_	_	0.02
		Hsu (58)	1993	700	23/677	unmatched	A	1.50[2]	_	NS
		Stachowski (43)	1995	153	34/119	matched	C	_	_	<10E-10
		Dondi (57)	1996	400	30/370	unmatched	C	3.48[2]	_	0.002
		Peces (39)	1997	333	13NRs/43Rs/277	matched and unmarched	C	3.40[2]	_	<0.05
		Desombere (66)	1998	146	46/100	matched	C	2.55[2]	_	NS
		Langö-Warensjö (50)	1998	121	53/68	matched	C	_	_	NS
	DRB1*03	McDermott (61)	1997	203	86/117	matched	C	_	_	NS
		Caillat-Zucman (42)	1998	415	114/301	matched	C	2.42	1.46-3.96	0.001
		Höhler (69)	1998	126	73/53	matched	C	_	_	0.03
		Höhler (69)	1998	118	62/56[7]	matched	C	_	_	0.002
		De Silvestri (35)	2001	71	31/40	matched	C	4.10	_	0.007
		Lindemann (44)	2002	79	_	_	C	_	_	NS
		Wang (41)	2004	164	79/85	matched	mix	_	_	0.1[3]
		Li (40)	2009	335	97HRs/160MRs/78NRs	matched	mix	1.72[4]	1.02-2.94	0.04[5, 8]
	DRB1*0301	Martinetti (67)	2000	92	16/76	matched	C	8.18	2.55-26.3	0.003
		Höhler (52)	2002	126	73/53	matched	C	_	_	0.04
		Amirzargar (68)	2008	58	12/46	matched	C	2.08	0.47-9.09	0.26
	DR4	Watanabe (48)	1988	2073	19/1988	unmatched	A	2.57[2]	_	<0.05
		Weissman (62)	1988	1167	22/1145	unmatched	C	_	_	NS
		Krämer (59)	1988	2524	25/2499	unmatched	C	1.49	_	NS
		Hatae (46)	1992	153	33/120	unmatched	A	3.02[2]	_	0.05

								Non-response to vaccine		
HLA type	HLA subtype	First author	Year	N	Cases/controls[1]		Ethnicity	OR	95% CI	P
		Hsu (58)	1993	700	23/677	unmatched	A	1.50[2]	_	NS
		Stachowski (43)	1995	153	34/119	matched	C	_	_	<0.01
		Desombere (66)	1998	146	46/100	matched	C	0.77[2]	_	NS
		Langö-Warensjö (50)	1998	121	53/68	matched	C	_	_	NS
		Albayrak (64)	2011	68	25/43	matched	C	_	_	NS
	DRB1*04	McDermott (61)	1997	203	86/117	matched	C	_	_	NS
		Caillat-Zucman (42)	1998	415	114/301	matched	C	_	_	NS
		Höhler (69)	1998	244	135/109	matched	C	_	_	NS
		Lindemann (44)	2002	79	_	_	C	_	_	NS
		Höhler (31)	2002	382	_	_	C	_	_	0.2
		Wang (41)	2004	164	79/85	matched	mix	_	_	NS
		Amirzargar (68)	2008	58	12/46	matched	C	2.08	0.47-9.09	0.3
	DR5	Krämer (59)	1988	2524	25/2499	unmatched	C	2.95	_	NS
		Stachowski (43)	1995	153	34/119	matched	C	_	_	<0.001
		Desombere (66)	1998	146	46/100	matched	C	0.08[2]	_	<0.05
	DR(w)6	Krämer (59)	1988	2524	25/2499	unmatched	C	0.97	_	NS
		Hatae (46)	1992	153	33/120	unmatched	A	0.10[2]	_	0.048
		Stachowski (43)	1995	153	34/119	matched	C	_	_	<0.01
		Desombere (66)	1998	146	46/100	matched	C	1.04[2]	_	NS
	DR7	Weissman (62)	1988	1167	22/1145	unmatched	C	_	_	<0.02
		Krämer (59)	1988	2524	25/2499	unmatched	C	0.86	_	NS
		Hsu (58)	1993	700	23/677	unmatched	A	1.60[2]	_	NS
		Stachowski (43)	1995	153	34/119	matched	C	_	_	<0.001
		Dondi (57)	1996	400	30/370	unmatched	C	2.24[2]	_	0.03
		Peces (39)	1997	333	13NRs/43Rs/277	matched and	C	5.10[2]	_	<0.05

								Non-response to vaccine		
HLA type	HLA subtype	First author	Year	N	Cases/controls[1]		Ethnicity	OR	95% CI	P
						unmarched				
		Desombere (66)	1998	146	46/100	matched	C	4.39[2]	_	<0.005
		Langö-Warensjö (50)	1998	121	53/68	matched	C	_	_	NS
		Albayrak (64)	2011	68	25/43	matched	C	_	_	NS
	DRB1*07	McDermott (61)	1997	217	86/131	unmatched	C	3.01[2]	_	<0.001
		Caillat-Zucman (42)	1998	415	114/301	matched	C	_	_	NS
		Höhler (69)	1998	126	73/53	matched	C	_	_	0.002
		De Silvestri (35)	2001	71	31/40	matched	C	0.90	_	<0.05
		Lindemann (44)	2002	79	_	_	C	_	_	NS
		Höhler (31)	2002	382	_	_	C	_	_	0.5
		Wang (41)	2004	164	79/85	matched	mix	5.18[6]	_	2.0E-4[3, 9]
		Amirzargar (68)	2008	58	12/46	matched	C	1.47	0.44-4.76	0.6
	DRB1*0701	Höhler (52)	2002	126	73/53	matched	C	7.49	2.51-22.3	3.0E-4[10]
		Li (40)	2009	335	97HRs/160MRs/78NRs	matched	mix	1.79[4]	1.07-2.94	0.025[5, 11]
	DR(w)11	Hatae (46)	1992	153	33/120	unmatched	A	11.9[2]	_	0.4
		Langö-Warensjö (50)	1998	121	53/68	matched	C	_	_	NS
		Albayrak (64)	2011	68	25/43	matched	C	_	_	NS
	DRB1*11	McDermott (61)	1997	203	86/117	matched	C	_	_	NS
		Caillat-Zucman (42)	1998	415	114/301	matched	C	_	_	NS
		Höhler (69)	1998	244	135/109	matched	C	_	_	NS
		Martinetti (67)	2000	92	16/76	matched	C	0.00	0.00-0.41	0.047
		Lindemann (44)	2002	79	_	_	C	_	_	NS
		Höhler (31)	2002	382	_	_	C	_	_	0.01
		Wang (41)	2004	164	79/85	matched	mix	_	_	0.08[3]

								Non-response to vaccine		
HLA type	HLA subtype	First author	Year	N	Cases/controls[1]		Ethnicity	OR	95% CI	P
		Amirzargar (68)	2008	58	12/46	matched	C	0.32	0.01-2.63	0.45
	DR13	Albayrak (64)	2011	68	25/43	matched	C	_	_	NS
	DRB1*13	McDermott (61)	1997	203	86/117	matched	C	_	_	NS
		Höhler (69)	1998	126	73/53	matched	C	0.10[2]	_	1.0E-4
		Höhler (69)	1998	118	62/56[7]	matched	C	_	_	0.04
		Caillat-Zucman (42)	1998	415	114/301	matched	C	_	_	NS
		Höhler (31)	2002	382	_	_	C	_	_	0.7
		Wang (41)	2004	164	79/85	matched	mix	_	_	NS
	DRB1*1301	Langö-Warensjö (50)	1998	121	53/68	matched	C	_	_	<0.05
		Höhler (52)	2002	126	73/53	matched	C	0.14	0.04-0.51	0.003[10]
		Lindemann (44)	2002	79	_	_	C	_	_	NS
		Amirzargar (68)	2008	58	12/46	matched	C	0.46	0.02-4.00	0.7
	DR14	Hsu (58)	1993	700	23/677	unmatched	A	4.40[2]	_	0.01
		Langö-Warensjö (50)	1998	121	53/68	matched	C	_	_	NS
		Albayrak (64)	2011	68	25/43	matched	C	_	_	NS
	DRB1*14	McDermott (61)	1997	203	86/117	matched	C	_	_	NS
		Caillat-Zucman (42)	1998	415	114/301	matched	C	3.46	1.39-8.60	0.008
		Höhler (69)	1998	244	135/109	matched	C	_	_	NS
		Lindemann (44)	2002	79	_	_	C	_	_	NS
		Höhler (31)	2002	382	_	_	C	_	_	0.7
	DRB1*1401	Amirzargar (68)	2008	58	12/46	matched	C	0.95	0.04-10.0	1
	DR15	Hsu (58)	1993	700	23/677	unmatched	A	0.70[2]	_	NS
		Langö-Warensjö (50)	1998	121	53/68	matched	C	_	_	<0.01

								Non-response to vaccine		
HLA type	HLA subtype	First author	Year	N	Cases/controls[1]		Ethnicity	OR	95% CI	P
	DRB1*15	Albayrak (64)	2011	68	25/43	matched	C	_	_	NS
		McDermott (61)	1997	203	86/117	matched	C	_	_	NS
		Caillat-Zucman (42)	1998	415	114/301	matched	C	_	_	NS
		Höhler (69)	1998	244	135/109	matched	C	_	_	NS
		Lindemann (44)	2002	79	_	_	C	_	_	NS
		Höhler (31)	2002	382	_	_	C	_	_	0.03
		Amirzargar (68)	2008	58	12/46	matched	C	0.29	0.01-2.38	0.3
		Li (40)	2009	335	97HRs/160MRs/78NRs	matched	mix	0.62	0.35-1.07	0.09[12]
HLA class III										
C4	C4AQ0	Martinetti (60)	1995	224	34/190	unmatched	C	6.51	_	1.0E-4
		Stachowski (43)	1995	153	34/119	matched	C	_	_	<0.001
		Dondi (57)	1996	400	30/370	unmatched	C	3.25[2]	_	0.001
		Martinetti (67)	2000	49	9/40	matched	C	18.0	2.44-145	0.02
		De Silvestri (35)	2001	71	31/40	matched	C	9.10	_	2.0 E-5
		Höhler (52)	2002	126	73/53	matched	C	3.60	1.44-9.00	0.05[10]

Abbreviations: HLA: human leukocyte antigen, HR: high responder, MR: moderate responder, N: total number of patients included in the study, NR: non-responder, OR: odds ratio, CI: confidence interval, P: p-value, R: responder.
The studies that were comparing the frequency of a HLA allele in a non-responders group to an unvaccinated control group were considered as unmatched studies.
When required, OR, RO or RR were reversed for the sake of comparison.
[1] Unless otherwise indicated and when studies are matched, cases are non-responders and controls are responders to HBV vaccine
[2] Relative risk (RR)
[3] Adjusted for ethnicity, gender, age, HBV vaccine product group, and HIV-1 serostatus
[4] Proportional odds ratio (pOR)
[5] Adjusted for age, ethnicity, gender and HIV serostatus
[6] Relative odds (RO)
[7] Cohort of children that were immunized at 3, 4 and 5 months of age
[8] Multivariable model without individuals being HIV positive (308 patients, NR vs. HR+MR): OR=2.38, 95% CI 1.20-4.76, P=0.013.

[9] Multivariable logistic regression analysis RO=4.89, 95% CI 1.50-15.93, P=0.008
[10] Logistic regression analysis
[11] Multivariable model without HIV positive individuals (308 patients, NR vs. HR+MR): OR=2.78, 95% CI 1.37-5.56, P=0.005
[12] Univariate analysis, confined to HIV positive individuals (N=255)

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