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Host genetic polymorphisms and chronic hepatitis B: a systematic review and meta-analysis

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Summary

Introduction. Hepatitis B virus (HBV) infection is major health problem around the world. Chronic HBV infection is a life-threatening condition when the disease progresses to liver cirrhosis or hepatocellular carcinoma. Yet it is not well understood why some individuals are chronically infected whereas the others can spontaneously resolve the infection. Recent studies analyzed the association between genetic polymorphisms and the chronicity of HBV infection with conflicting results.

Aim. The objective of this study was to summarize from existing literature the association between genetic polymorphisms and the predisposition to chronic HBV infection comparing chronic carriers with spontaneous resolvers.

Methods. Review of the literature on the subject was performed by using three online databases: PubMed, Embase and ISI Web Of Knowledge. Keywords composed of free terms and/or thesaurus were selected with stringent criteria to build search equations. Pertinent materials were further selected by using a three-step process. The first articles were screened by title, the second by abstract and the third by full-text. Study characteristics, allelic counts and genotype distribution were collected from the articles. To make the results uniform and thus comparable, the univariate unconditional dominant model was chosen as reference for genetic associations. A meta-analysis was performed to assess the strength of the association.

Results. In total 126 articles out of 4901 passed selection and were included in the systematic review. After removing duplicates, articles with other language than English and other articles than original papers, 3314 articles were remaining. 2452 of them were removed based on their title, then 360 based on their abstract and finally 376 based on their full text. Most studies included individuals of Asian ethnicity. The median date of publication was 2010. A total number of 396 polymorphisms were analyzed in 117 genes, with 47 polymorphisms analyzed more than once and 349 of them analyzed only once. Among polymorphisms analyzed once, 45 showed significant p-values ($p<0.05$), with rs2071543 in LMP7 and rs1799988 in CCR5 presenting P values <1E-05. Among polymorphisms analyzed more than once, 15 polymorphisms among 13 genes showed significant association considering the whole population: TNF, a locus near HLA-C, UBE2L3, MCP1, STAT4, CCR5, IL18, TAP1, GNLY, IFNL, IL10, IFNG, and CTLA4. Among them, rs1800630 in TNF (OR=1.38, 95% CI 1.15-1.65), rs3130542 in a locus near the HLA-C gene (OR=1.42, 95% CI 1.23-1.64) and rs482116 in UBE2L3 (OR=0.77, 95% CI 0.66-0.89) showed the most consistent association. Other associations are less robust.

Conclusion. To our knowledge, this is the first such exhaustive systematic review and meta-analysis that has been performed on the subject. Although large number of polymorphisms in immune genes were studied, most of the significant associations were either reported only once without further replication or not equally validated. This may be due to the limitations of the studies, such as different ethnicity of study population, the choice of study subgroups, study design. Further genetic studies are needed to verify those findings.

Keywords. Hepatitis B virus. HBV. Chronicity. Polymorphism. SNP.

Background

The hepatitis B infection is a liver disease caused by hepatitis B virus (HBV). It is a population health concern with approximately 250 million chronically infected persons worldwide (1). The West Pacific region and the African region are the most endemic (1).

HBV infection has a variable disease course. The acute infection has a large range of clinical features: in most cases asymptomatic infection occurs, but rarely life-threatening fulminant hepatitis requiring urgent transplantation can happen. HBV chronic infection has mostly a subclinical course and the prognosis depends on the progression of the disease to liver cirrhosis and HBV-related hepatocarcinoma. The persistent infection is still associated with high mortality risk (2). Effective and safe vaccine has been developed to protect from getting infected with HBV virus, develop chronic disease and HBV related liver cancer. The current used drugs to treat chronic infection are pegylated interferon-alpha (subcutaneous injections) or oral agents as lamivudine, adefovir, telbivudine and tenofovir. Pegylated interferon alpha treatment has multiple side effects but no viral resistance. Oral agents are well tolerated but present high viral resistance. Unfortunately, the HBsAg seroconversion rate is globally weak (3).

The diagnosis of acute HBV infection as well as those for chronic HBV infection is based on the viral serological markers. The HBV acute infection is defined by the presence of HBV surface antigens (HBsAg), antibodies IgM against viral core (HBcAb IgM) and the absence of antibodies against HBsAg (HBsAb). The HBV chronic infection is defined by presence of HBsAg for at least 6 months with negative HBsAb and positive IgG against viral core (HBcAb IgG)(4). The spontaneous recovery is defined by the presence of HBsAb and IgG HBcAg without HBsAg positivity and antiviral treatment.

It is well established that the risk of transition between acute to chronic infections depends on the age of the infected subject. Neonates are at highest risk for developing chronic infection (about 95% individuals), whereas in adults risk of chronic infection is relatively low (less than 5% individuals) (4).

Liver damage and control of viral replication are immunomediated with no cytopathogenic effect of HBV. Both the innate immunity and the adaptive immunity are implicated in the pathogenesis of HBV infection (4, 5). It has been shown that adaptive immunity is crucial for resolution of acute HBV infection with strong T-cell mediated responses to HBV epitopes, whereas in chronic infection, those T-cell-mediated responses are subsequently weaken. Polymorphisms in genes involved in the immunity system could confer a protection against or a susceptibility to HBV infection. To date few meta-analysis studies explored the association between HBV persistent infection and polymorphisms, comparing chronic carrier and spontaneous resolvers, in seven immune genes, including tumor necrosis factor alpha (TNF-alpha)(6-8), Signal Transducers and Activators of Transcription 4 (STATA4)(9), cytotoxic T-lymphocyte associated protein 4 (CTLA-4)(10), Interferon lambda 3/4 (IFN 3/4)(11, 12), Interleukin-10 (IL-10)(13-15), interferon-gamma (IFN-gamma)(11, 16), and mannose binding lectin (MBL)(17). Although some of those studies reported potentially significant associations, the role of these polymorphisms in chronic HBV infection remains unclear.

In this study, a systematic review and meta-analysis of the literature was performed focusing on the polymorphisms associated with the chronicity of HBV infection. The aim of this research was to assess the strength of the reported associations coming from case-control candidate genes and Genome-Wide Association studies (GWAS).

Materials and Methods

Search strategy. Pertinent articles were obtained from 3 publicly-available datasets (PubMed, Embase and Web of Science) which were searched up to April 2016. A population-intervention-comparison-outcome (PICO) method was then used to develop the best search strategy to fit to the study question. It resulted in 3 complex "search equations", each composed of a combination of free terms and thesaurus terms (MESH for Pubmed, EMTREE for Embase) or just free terms (ISI Web of Science, Annex 1).

Data selection. Bibliographic data such as title, abstract text, author names, publication date, International Standard Serial Number (ISSN) and the Digital Object Identifier (DOI) were exported into EndNoteX7© (developed by Clarivate Analytics©). Articles recorded in duplicates, those written in a language other than English and those reporting non-original data, such as reviews or meta-analyses, were excluded. Remaining entries were further selected according to the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) flow diagram, which proposes a 3-step exclusion process based on articles (1) title, (2) abstract and (3) full text reading.

Data extraction. The information extracted from the studies included bibliographic data (as described above), main characteristics of cases and controls (ethnicity, country, family relatedness, history of chronic liver diseases, HIV or/and HCV co-infection, HBV vaccine status and history of antiviral therapy), relevant information on genetic testing (gene and polymorphism identification [NCBI SNP ID and alternatively the position], genotypic and allelic counts) as well as summary statistics for the genetic association with phenotypes (e.g. odds ratio, OR, 95% confidence interval, 95% CI, p-value, mode of inheritance as well as univariate versus multivariate type of models). When studies analyzed separate cohorts, each cohort was considered a separate group of meta-analyses (see comments below).

Statistical analysis. To compare the results from different studies, a dominant model was chosen. The minor allele of each SNP was considered the risk allele. Statistics (OR, the 95%CI and p-values) were calculated for each association from genotype counts by using the STATA13© software (College Station Texas, USA). When genotype data were missing, they were calculated from allelic data assuming Hardy-Weinberg equilibrium. Those statistics were performed for each ethnic group as well as for the whole population. All associations identified more than once were meta-analyzed by using the program metan implemented in Stata. Heterogeneity between studies was assessed using an I-square test, with Chi^2 test $P < 0.10$ or $I^2 > 50\%$ indicating a substantial heterogeneity. Results were calculated considering either a Mantel-Haenszel (MH) fixed-effects or a Der Simonian and Laird (DSL) random-effects model (18). For the sake of simplicity, the random effect statistics are presented by default in this study. The most relevant results are presented in the text, while complete statistics are shown in supplementary figures. Forest plots for each meta-analysis are presented in supplementary Figures 1-26.

Results

The search strategy identified 3314 articles, among which 2452 were removed based on their title, 360 based on their abstract and 376 based on their full text (Figure 1). The remaining 126 articles analyzed a total of 396 polymorphisms from 117 different genes among ethnicity (Table 1). Out of those, 47 polymorphisms from 26 different genes were analyzed more than once and meta-analyzed. A total of 349 other polymorphisms from 107 different genes were studied only once.

Studies' characteristics.

Most studies were based on a candidate gene approach and one was a genome-wide association study (GWAS). Studies analyzed from 1 to 35 polymorphisms from 1 to 10 genes. The median study size was of 607 individuals, with sizes ranges from 52 to 2688. Publication years ranged from 1996 to 2016, with a median in 2010. Most studies included Asians (N=100), followed by Caucasians (N=18) and Africans (N=2). Six studies did not include information about ethnicity and two included both Caucasian and African participants.

There was an important heterogeneity in the definitions used for cases and controls. Patients with chronic hepatitis B were defined according to standard serological criteria (positive HBs antigen and negative anti-HBs) in some studies, while the other did not refer to any serological definitions. Chronic HBV carriers included different types of patients according studies, ranging from asymptomatic carriers to patients with documented HBV-induced cirrhosis or hepatocarcinoma (Table 2). Similarly, controls were defined as individuals with a resolved hepatitis B based on serological criteria (negative HBs antigen, positive anti-HBs and anti-HBc) in some studies, while other used clinical definitions, such as a "past history" or "resolved" hepatitis B with/without documented positive HBs-AG at the time of infection.

Studies also differed in their way to account for potential biases (Table 2), such as ensuring that controls did not have a previous antiviral treatment and/or co-infection with HCV or HIV. One study was performed among hemophilic patients.

Meta-analyses of polymorphisms studied more than once.

When considering the total population, significant associations were observed for 15 SNPs from 13 genes/loci (TNF, a locus near HLA-C, UBE2L3, MCP1, STAT4, CCR5, IL18, TAP1, GNLY, IFNL, IL10, IFNG, and CTLA4) (Figure 2). While most association were significant when using both a random and fixed effect model (TNF, locus near HLAC, UBE2L3, MCP1, STAT4, CCR5, IL18. TAP1, GNLY, CTLA4), other were significant only in meta-analyses using a fixed model effect (IFNL, IL10, IFNG, CCR5). In addition, some associations were significant only in meta-analyses from studies of Caucasian patients (IFNL, CTLA4, CCR5 and TNF) and disappeared when the meta-analyses included additional studies from Asian patients (Table 3)

Among the most striking associations between a SNP and chronic hepatitis B was found for the SNP *rs1800630* in TNF gene (OR=1.38, 95% CI 1.15-1.65), which resulted from 9 studies including 4705 patients (Figure 2 and supplementary figure S24), most performed among Asian patients (19-27).

Two significant associations come from a single GWAS study using a discovery cohort and two validation cohorts, which altogether included >7000 patients. One was found for a locus near the HLA-C gene (*rs3130542*, OR=1.42, 95% CI 1.23-1.64, Figure S15) and the other for *rs482116* in UBE2L3 (OR=0.77, 95% CI 0.66-0.89, Figure S25).

Two other relevant associations were observed in meta-analyses from 3 different studies or cohorts of Asian individuals. The MCP1 *rs1024611* SNP was associated with an increased risk of developing chronic hepatitis B (OR=1.27, 95% CI 1.02-1.57, Figure S17) (24, 28, 29). The STAT4 *rs7574865* SNP was associated with protection against the disease (OR=0.81, 95% CI 0.67-0.97, Figure S20) (30, 31).

Several other associations were observed in meta-analyses from only 2 studies or cohorts, including *rs333* in CCR5 (OR=0.51, 95% CI 0.38-0.70, Figure S2) (32, 33), *rs1946518* in IL18 (OR=1.99, 95% CI 1.16-3.44, Figure S14) (34, 35), *rs1135216* in TAP1 (OR=1.76, 95% 1.34-2.32, Figure S21) (36, 37) and borderline association for *rs11127* in GNLY (OR=0.75, 95% CI 0.57-1.00, Figure S6) (38, 39) and *rs8105790* in IFNL (OR=0.51, 95% CI 0.24-1.10) (40, 41).

Some other associations were significant considering the whole population only when the meta-analyses used a fixed effect model, including *rs2430561* in IFNG (OR=0.75, 95% CI 0.59-0.94)(42-47), *rs1799987* in CCR5 (OR=0.83, 95% CI 0.70-0.98)(24, 29, 32, 48), *rs12980275* (OR=0.84, 95%CI=0.73-0.97)(31, 40, 41, 49-52) and *rs8105790* in IFNL (OR=0.59, 95% CI 0.47-0.75) (40, 41). Borderline results were observed in *rs1800872* in IL10 (OR=0.84, 95% CI 0.71-1.00)(24, 45, 46, 53-56) and *rs3087243* (OR=1.18, 95%CI=1.00-1.40) and *rs231775* in CTLA4 (OR=0.84, 95%CI=0.71-1.00)(24, 57, 58).

Four other associations were detected in meta-analyses from Caucasian patients, including *rs361525* in TNF gene (OR=2.37, 95%CI=0.78-7.20)(20-24, 26, 27, 53, 59-62), *rs231775* (OR=0.66, 95% CI 0.52-0.83), and *rs733618* (OR=0.57, 95% CI 0.38-0.86)(24, 57) in CTLA4 (Figure S3) as well as rs12980275 in IFNL (OR=0.66, 95%CI 0.52-0.83) (31, 40, 41, 49-52). However, these associations were not confirmed after the inclusion of studies of Asian individuals (Table 3).

Polymorphisms studied only once.

Studies that showing a significant association of a SNP not studied elsewhere with chronic hepatitis B are listed in Table 4. Among those, 2 SNPs from 2 genes (CCR5 and LMPT7) had P values <1E-05, 4 SNPs from 4 genes (ESR1, IL17A, IL20 and TRIM22) had P values <1E-04, 16 SNPs from 12 genes (ADAR1, BIM, CCND2, CIITA, COL3A1, ERB4, IFNA1, IFNG, IL10, IL6, MBL2, STAT4) had P values <1E-03, and 23 SNPs from 19 genes (BIRC5, CCND2, CISH, DNMT1, ERBB4, IFNA1, IL2, NFKBIA, IP10, ITGAV, KlRD1, MTP, MXA, SOCS1, SPP1, TAP2, TBX21, TGFA, TGFBR3, TIM3, ZNRD1-AS1) had P values <5E-02.

Discussion

HBV chronic infection is a worldwide preoccupation. A better understanding of the pathogenesis is necessary to have a better approach of the disease management. The genetic factors could help to identify patients which are more susceptible to chronic HBV infection. This review aimed to summarize current literature on polymorphisms associated with chronicity of HBV infection compared to spontaneous resolvers based on a systematic review and meta-analysis.

Important number of case-control studies analyzed the role of immune gene polymorphisms on susceptibility to chronic HBV infection. Most of them were not included in previous reviews. Majority of the studies included in our review involved Asian participants originated from China and used relatively large cohorts of participants. None of the studies included HCV co-infection, but five studies considered HIV positive cohort among participants.

Among polymorphisms analyzed more than once, very promising results were found for *rs1800630* in TNF gene, *rs3130542* in a locus near the HLA-C gene and *rs482116* in UBE2L3 gene. Consistent results were found for *rs1024611* in MCP1 gene, *rs7574865* in STAT4 gene. Less consistent results were found for *rs333* in CCR5 gene, *rs1946518* in IL18, *rs1135216* in TAP1, *rs11127* in GNLY, *rs12980275* and *rs8105790* in IFNL, *rs1800872* in IL10, *rs2430561* in IFNG, *rs231775* and *rs733618* in CTLA4. Many polymorphisms which show significant results were studied only once thus should be treated with caution until further studies confirm these associations.

Very promising association was found for *rs1800630* considering overall or Asian population in TNF-alpha gene in our meta-analysis including nine studies on this polymorphism. Significant results were found for *rs361525* only considering Caucasian population in random model. Four polymorphisms, *rs1799724,* r*s1799964, rs1800629* and *rs361525* did not show interesting results. To date three previous meta-analyses studied the association between polymorphisms in TNF-alpha gene and persistent infection of HBV. Yet, our study did not uniformly replicate findings coming from those meta-analyses. For polymorphism *rs1800630*, no significant association in overall and Asian population was found in a meta-analysis including six studies (6) and no association in overall, Asian and Caucasian population was found in a meta-analysis including eleven studies on this polymorphism (7). For polymorphism *rs1800629*, in a meta-analysis including ten studies, significant association was found among Asian ethnicity cohorts or overall population, but not in Caucasian population (6). No significant association was found in a meta-analysis including two studies analyzing *rs1799964* (6). Significant association was found for *rs361525* considering Caucasian population, but not in overall and Asian population in two meta-analysis including nine and nineteen studies, respectively (6, 7). For *rs1799724,* no significant association was found in a meta-analysis including five studies (6) and significant association was found among Asian population in a meta-analysis of fourteen studies (8). The heterogeneity of results between our study and previously published meta-analyses may be due to the reasons described below. Further validation studies are needed to verify those observations.

The *rs7574865* polymorphism in STAT4 gene showed significant associations among overall and Asian population in our review. Yet, one small size meta-analysis failed to show significant association for STAT4 *rs7574865* (9) polymorphism with chronic HBV infection. These results make this polymorphism suggestive and worth further replication.

Interestingly, two polymorphisms in IFNL3/4 (*rs12980275* and *rs8105790*) were significantly associated with HBV chronic infection. The *rs12980275* polymorphism showed significant association only among Caucasian but not Asian population in random model and overall population in fixed

model. Those findings are correlated to the frequency of this variant among Asian (9%) and Caucasian (30%) based on 1000genomes database (http://www.internationalgenome.org/1000-genomes-browser). The *rs8105790* polymorphism, showed association with overall (in fixed model) and Caucasian population (in random model). Two relevant meta-analyses studied IFNL3/4 *rs12979860* (11, 12)*, rs12980275* (12) and *rs8099917* (12) polymorphisms but no significant association were revealed. The conflicting results about *rs12980275* between previous meta-analyses and ours can be explained by the fact that no ethnical subgroups have been sub-studied in the aforementioned meta-analyses. Unfortunately, none meta-analysis focusing on *rs8105790* was found to compare our results.

The *rs1800872* in IL10 gene presented significant association in our study, but only when considering fixed model in overall population (borderline result). The other two IL10 polymorphisms, including *rs1800871* and *rs1800896*, did not show any association. Three meta-analyses on polymorphisms of IL10 were published. One of them showed significant associations for polymorphism *rs1800872* among Chinese population (15), but two other did not reproduce this association (13, 14). The heterogeneity between results observed for this polymorphism among Asians and Caucasians can be explained by a different allele frequency of *rs1800872* SNP among ethnicities (A is a minor allele in Caucasian and African but major allele in Asian population). Alike in our meta-analysis, no significant results were observed for *rs1800896* in other previous meta-analyses (13-15).

Interesting results were found for one polymorphism in CTLA4 (*rs231775*), among Caucasian population in random model and in overall population in fixed model (borderline result). Only one meta-analysis has been performed so far on the role of CTLA4 *rs231775* polymorphism in HBV chronic infection, and showed significant association among overall population (when using spontaneous clearers as controls) or among overall and Asian population (when using mixed spontaneous resolvers and healthy controls as a control group), yet not among Caucasians (10). The discordance between our study and previous meta-analysis can be, at least in part, explained by differences in study design.

The polymorphism *rs2430561* in IFN-gamma gene showed significant association among overall (in fixed model) and Asian population (random model). Two pertinent meta-analyses tried to assess the role of *rs2430561*, one with no significant results (11) and one with significant association only among Asian, but not in overall population (16). Those results suggest that the role of this polymorphism needs to be verified by additional studies.

None significant results were found for all analyzed polymorphisms of MBL2 gene. Four MBL2 polymorphisms *rs5030737, rs1800450, rs1800451* and *rs7096206* were reviewed in one meta-analysis (17), yet no significant results were found which is in line with results found by this review.

Although in most of the cases this systematic review and meta-analysis shows similar effect of studied polymorphisms on HBV chronic infections to those reported by previous meta-analysis, some were not. In fact, although those previous meta-analysis used dominant model and spontaneous resolvers as control group, they sometimes present a lack of clarity in groups definition. Thus, they could use different case subgroups and ethnic populations, leading to the discrepancy described above. For example, HBV-related cirrhosis or HBV-related carcinoma may be the most current used subgroups among case group (chronic carrier), whereas our study mostly included chronic hepatitis B subgroup among chronic carrier. Therefore, the results coming from those meta-analyses cannot be directly compared with those received in this review.

It needs to be mentioned that this systematic review and meta-analysis has some limitations. Firstly, the search was restricted due to unexpected high amount of original papers resulting from the literature search. It focused on chronicity/persistence instead of spontaneous clearance and treatment-induced clearance of the virus. Only spontaneously recovered subjects/groups from articles were considered as control group instead of both healthy controls and/or spontaneously recovered controls. HLA system, KIR and microRNA studies were removed. Those restrictions may conduce to missing variants and associated information. Secondly, selected studies were often heterogeneous, i.e. they used different type of populations (ethnicity and subgroups). Thirdly, this study is based on retrospective cases-controls studies: the causality is less consistent than those found in prospective studies.

The strength of this study is the precise and transparent methodology and the fact that a meta-analysis was combined to a systematic review through the same study. Thus, the data were systematically re-calculated in the same genetic model to get uniform results and improve comparison among studies, even if they had poor methodology.

In conclusion, to our knowledge this is the first exhaustive systematic review and meta-analysis to assess the role of all previously studied polymorphisms in immunity genes outside HLA region on chronicity of HBV infection. Although most of the polymorphisms were not significantly associated with chronic HBV infection across different studies, some showed robust association, and so they represent good candidates for future replication studies.

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Table 1. Number of polymorphisms and genes by significance and ethnic groups[1]

		SNPs (genes) tested only once			SNPs (genes) tested more than once		
Ethnicity	**SNPs (genes)**	**Total tested**	**No sign. Assoc.**	**Sign. Assoc**	**Total tested**	**No sign. Assoc.**	**Sign. Assoc**
Asian	335 (108)	299 (101)	250 (87)	49 (40)	36 (22)	27 (16)	9 (9)
Caucasian	71 (19)	55 (16)	53 (15)	2 (2)	16 (7)	9 (5)	7 (4)
African	37 (4)	37 (4)	35 (4)	2 (2)	0 (0)	0 (0)	0 (0)
All	**396 (117)**	**349 (107)**	**297 (94)**	**52 (42)**	**47 (26)**	**32 (19)**	**15 (13)**

[1] A SNP can be tested in >1 ethnic group

Table 2. Heterogenic features of studies

Type of chronic HBV carrier	Studies including	Studies not including
Asymptomatic (ASc)	13	113
Inactive (IC)	15	111
Chronic hepatitis B (CHB)	74	52
HBV-related cirrhosis (LC)	37	89
HBV-related hepatocarcinoma (HCC)	20	76
Total chronic carrier (CC)[1]	126	0

Potential bias	Excluded	Not excluded	Not specified
Antiviral treatment (in potential controls)	30	1	95
History of vaccination	28	0	98
HCV co-infection in participants	89	0	37
HIV co-infection in participants	68	5	53
Genetically unrelated subjects	2	35	89

Abbreviation: NS = Not Specified; HIV= Human immunodeficiency virus; HCV: Hepatitis C Virus.

[1] Studies may include more than one type of chronic HBV carrier

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Table 3. Significant associations in meta-analyses by ethnic groups

Gene SNP	Model effect	All ethnic groups				Asians				Caucasians			
		NP	NS	OR (95% CI)	P[1]	NP	NS	OR (95% CI)	P[1]	NP	NS	OR (95% CI)	P[1]
TNF_rs1800630	random	4705	9	**1.38 (1.15-1.65)**	**7.79E-04**	4425	8	**1.41 (1.16-1.71)**	**7.28E-04**	280	1	1.12 (0.66-1.89)	6.76E-01
nearHLAC_rs3130542	random	7130	3	**1.42 (1.23-1.64)**	**3.38E-11**	7130	3	**1.42 (1.23-1.64)**	**3.38E-11**				
UBE2L3_rs4821116	random	7163	3	**0.77 (0.66-0.89)**	**1.16E-07**	7163	3	**0.77 (0.66-0.89)**	**1.16E-07**				
MCP1_rs1024611	random	2653	3	**1.27 (1.02-1.57)**	**2.40E-02**	2653	3	**1.27 (1.02-1.57)**	**2.40E-02**				
STAT4_rs7574865	random	1816	3	**0.81 (0.67-0.97)**	**2.43E-02**	1816	3	**0.81 (0.67-0.97)**	**2.43E-02**				
CCR5_rs333	random	1023	2	**0.51 (0.38-0.70)**	**2.46E-05**					1023	2	**0.51 (0.38-0.70)**	**2.46E-05**
IL18_rs1946518	random	1073	2	**1.99 (1.16-3.44)**	**7.40E-05**	1073	2	**1.99 (1.16-3.44)**	**7.40E-05**				
TAP1_rs1135216	random	1116	2	**1.76 (1.34-2.32)**	**4.70E-03**	1116	2	**1.76 (1.34-2.32)**	**4.70E-03**				
GNLY_rs11127	random	918	2	0.75 (0.57-1.00)	5.58E-02	918	2	0.75 (0.57-1.00)	5.58E-02				
IFNL_rs8105790	fixed[2]	1662	2	**0.51 (0.24-1.10)**	**5.97E-04**					1662	2	**0.51 (0.24-1.10)**	**5.97E-04**
IFNL_rs12980275	random	5648	8	0.85 (0.69-1.05)	6.83E-02	3949	6	1.00 (0.83-1.22)	6.71E-01	1699	2	**0.66 (0.52-0.83)**	**4.76E-03**
CTLA4_rs231775	random	2821	4	0.83 (0.67-1.04)	8.97E-02	1777	2	0.99 (0.79-1.23)	6.97E-01	928	2	**0.68 (0.51-0.89)**	**4.76E-03**
CTLA4_rs3087243	random	2821	4	**1.21 (0.93-1.57)**	**1.74E-02**	1777	2	1.02 (0.82-1.27)	9.71E-01	928	2	**1.45 (1.08-1.94)**	**1.33E-02**
CTLA4_rs733618	random	1709	3	0.79 (0.49-1.27)	3.52E-01	665	1	1.16 (0.85-1.58)	3.51E-01	928	2	**0.57 (0.38-0.86)**	**6.65E-03**
CCR5_rs1799987	random	2740	4	0.82 (0.56-1.20)	3.46E-01	2214	3	0.73 (0.47-1.12)	1.02E-01	526	1	1.20 (0.82-1.77)	3.46E-01
IFNG_rs2430561	fixed[2]	1483	6	**0.71 (0.50-1.00)**	**9.12E-07**	1197	3	**0.71 (0.47-1.08)**	**6.04E-04**	220	2	0.71 (0.23-2.15)	9.60E-01
IL10_rs1800872	fixed[2]	2645	7	0.84 (0.69-1.03)	1.98E-01	1865	4	0.85 (0.60-1.21)	6.46E-02	659	3	0.84 (0.61-1.17)	7.48E-01
TNF_rs361525	random	5702	12	0.85 (0.56-1.28)	9.86E-01	5319	10	0.73 (0.47-1.12)	4.46E-01	383	2	**2.37 (0.78 -7.20)**	**2.47E-02**

SNP stands for single nucleotide polymorphism, NS the number studies included in the meta-analysis, NP the number of patients, OR odds ratio, CI confidence interval. Risk alleles and wild type alleles are described for each SNP as (A>a) with "A" being the wild type allele and "a" the risk allele. ORs were obtained using a DSL random effects model (unless the association was significant only when using the fixed effect), using a dominant mode of inheritance.

[1] Recalculated P values (χ^2) do not necessarily reflect significance (P<0.05) as obtained from the 95% CI (crossing 1) obtained in the meta-analysis (fixed or random effect).

[2] The association in the global population (all ethnic groups) was significant only when using the fixed effect model.

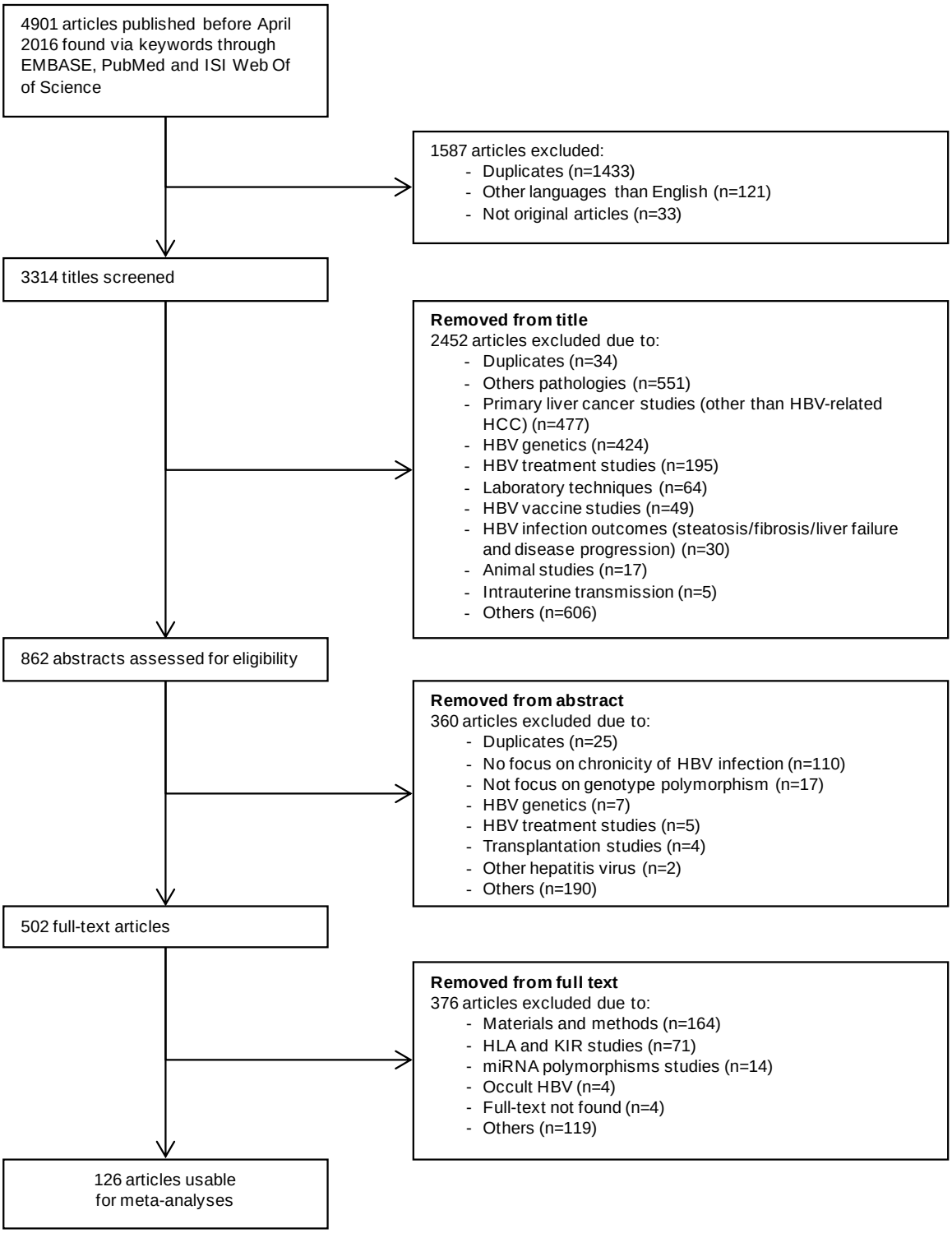
Table 4. Significant associations in single studies.

Author, pub. date	Gene, SNP	Ethnicity	Ncas	Nctr	OR	95% CI	P
Shi, C. et al. 2011 (36)	LMP7_rs2071543	ASI	191	165	2.47	(1.57-3.88)	3.31E-05
Ahn, S. H. et al. 2006 (48)	CCR5_rs1799988	ASI	349	243	0.46	(0.31-0.69)	7.73E-05
Deng, G. et al. 2004 (63)	ESR1_rs2077647	ASI	1271	742	0.70	(0.57-0.85)	2.10E-04
Li, N. et al. 2014 (64)	IL17A_rs8193036	ASI	395	75	0.38	(0.22-0.66)	2.30E-04
Truelove, A. L. et al. 2008 (54)	IL20_rs1518108	AFR	45	76	5.26	(1.88-16.81)	3.25E-04
Zhao, N. et al. 2014 (65)	TRIM22_rs10838543	ASI	765	248	1.80	(1.26-2.60)	6.72E-04
Zhang, X. et al. 2007 (66)	CIITA_−1350c/t	ASI	1108	312	0.63	(0.48-0.84)	1.06E-03
Zhang, T. C. et al. 2014 (67)	IL10_rs3024490	ASI	995	301	1.56	(1.19-2.03)	1.06E-03
Lee, S. K. et al. 2008 (68)	COL3A1_rs3106796	ASI	292	107	2.14	(1.30-3.49)	1.91E-03
Thio, C. L. et al. 2007* (32)	CCRL2_rs6441977	CAU	189	336	0.52	(0.34-0.81)	1.98E-03
Peng, H. et al. 2015 (69)	BIM_rs3827537	ASI	858	428	1.56	(1.17-2.10)	1.99E-03
Abbott, W. et al. 2007 (70)	IFNG_rs2234688	ASI	60	66	0.31	(0.14-0.68)	2.28E-03
Zhou, Jie et al. 2007 (71)	IFNAR1_rs16997869	ASI	320	148	1.88	(1.23-2.91)	2.47E-03
Zhang, X. et al. 2007 (66)	CIITA_−944g/c	ASI	1108	312	1.51	(1.15-1.98)	2.76E-03
Santos, J. C. et al. 2015 (72)	IFNA1_rs202055606	ALL	94	114	0.43	(0.24-0.79)	3.48E-03
Fletcher, G. J. et al. 2010 (73)	MBL2_rs5030737	ASI	134	148	0.21	(0.05-0.66)	3.72E-03
Lu, Y. et al. 2014 (74)	IL6_rs1800796	ASI	219	212	0.57	(0.38-0.85)	3.77E-03
Lu, Y. et al. 2015 (30)	STAT4_rs8179673	ASI	278	279	0.61	(0.43-0.87)	4.89E-03
Park, T. J. et al. 2010* (75)	CCND2_rs1049606	ASI	667	432	0.70	(0.54-0.91)	5.71E-03
Liu, Y. et al. 2016 (76)	ERBB4_rs6147150	ASI	1337	1332	0.81	(0.70-0.95)	8.08E-03
Wu, X. et al. 2014 (77)	ADAR1_rs4845384	ASI	256	229	1.63	(1.12-2.38)	8.16E-03
Lu, Y. et al. 2015 (30)	STAT4_rs7582694	ASI	288	287	0.64	(0.45-0.90)	9.38E-03
Chun, J. Y. et al. 2009* (78)	DNMT1_rs4804490	ASI	668	432	1.39	(1.07-1.79)	1.09E-02
Kim, J. H. et al. 2011* (79)	TGFBR3_rs1805113	ASI	638	427	0.69	(0.51-0.93)	1.21E-02
Chen, S. et al. 2009 (80)	TBX21_rs4794067	ASI	1074	310	1.52	(1.07-2.18)	1.62E-02
Liu, Y. et al. 2016 (76)	ERBB4_rs1836724	ASI	1338	1333	0.83	(0.71-0.97)	1.76E-02
Lee, S. K. et al. 2009 (81)	ITGAV_rs2290083	ASI	197	107	1.86	(1.09-3.19)	1.87E-02
Zhang, Q. et al. 2014 (82)	NFKBIA_rs3138053	ASI	942	312	0.68	(0.50-0.94)	1.88E-02
Kim, Y. J. et al. 2010* (83)	TGFa_+103461t>c	ASI	653	431	1.42	(1.05-1.93)	1.95E-02
Kim, J. H. et al. 2011* (79)	TGFBR3_rs1805117	ASI	636	428	0.71	(0.53-0.95)	1.96E-02
Yang, Z. T. et al. 2008 (84)	MTP_rs1800591	ASI	316	316	0.65	(0.44-0.96)	2.90E-02
Xu, Z. et al. 2013 (85)	IP10_rs1439490	ASI	381	196	1.61	(1.03-2.56)	2.92E-02

Author, pub. date	Gene, SNP	Ethnicity	Ncas	Nctr	OR	95% CI	P
Kimkong, I. et al. 2013 (86)	IFNA1_rs1332190	ASI	180	173	0.61	(0.39-0.96)	3.01E-02
Liao, J. et al. 2014 (87)	TIM3_rs25855	ALL	200	200	1.59	(1.04-2.43)	3.16E-02
Wen, J. et al. 2015 (88)	ZNRD1AS1_rs3757328	ASI	1327	1341	0.83	(0.70-0.99)	3.18E-02
Kim, Y. J. et al. 2010* (83)	TGFa_+106151c>g	ASI	653	431	0.77	(0.60-0.99)	3.50E-02
Gao, Q. J. et al. 2009 (46)	IL2_rs2069762	ASI	69	74	0.46	(0.22-0.97)	3.86E-02
Park, T. J. et al. 2010* (75)	CCND2_rs3217805	ASI	667	434	0.76	(0.58-0.99)	3.89E-02
Peng, X. M. et al. 2007 (44)	MxA_rs2071430	ASI	340	100	0.62	(0.38-0.99)	4.07E-02
Hu, Z. et al. 2014 (89)	CISH_rs414171	ASI	594	425	0.75	(0.57-0.99)	4.09E-02
Lee, Jin Sol et al. 2009* (90)	BIRC5_rs17886532	ASI	632	434	0.77	(0.60-1.00)	4.19E-02
Shin, H. D. et al. 2007 (91)	SPP1_rs2853744	ASI	634	422	1.29	(1.00-1.67)	4.44E-02
Ma, J. et al. 2010 (92)	Klrd1_rs2617160	ASI	285	215	0.68	(0.46-1.01)	4.62E-02
Zhang, P. et al. 2014 (93)	SOCS1_rs243327	ASI	477	93	1.65	(0.99-2.80)	4.66E-02
Shi, C. et al. 2011 (36)	TAP2_rs241447	ASI	191	165	0.64	(0.40-1.00)	4.98E-02

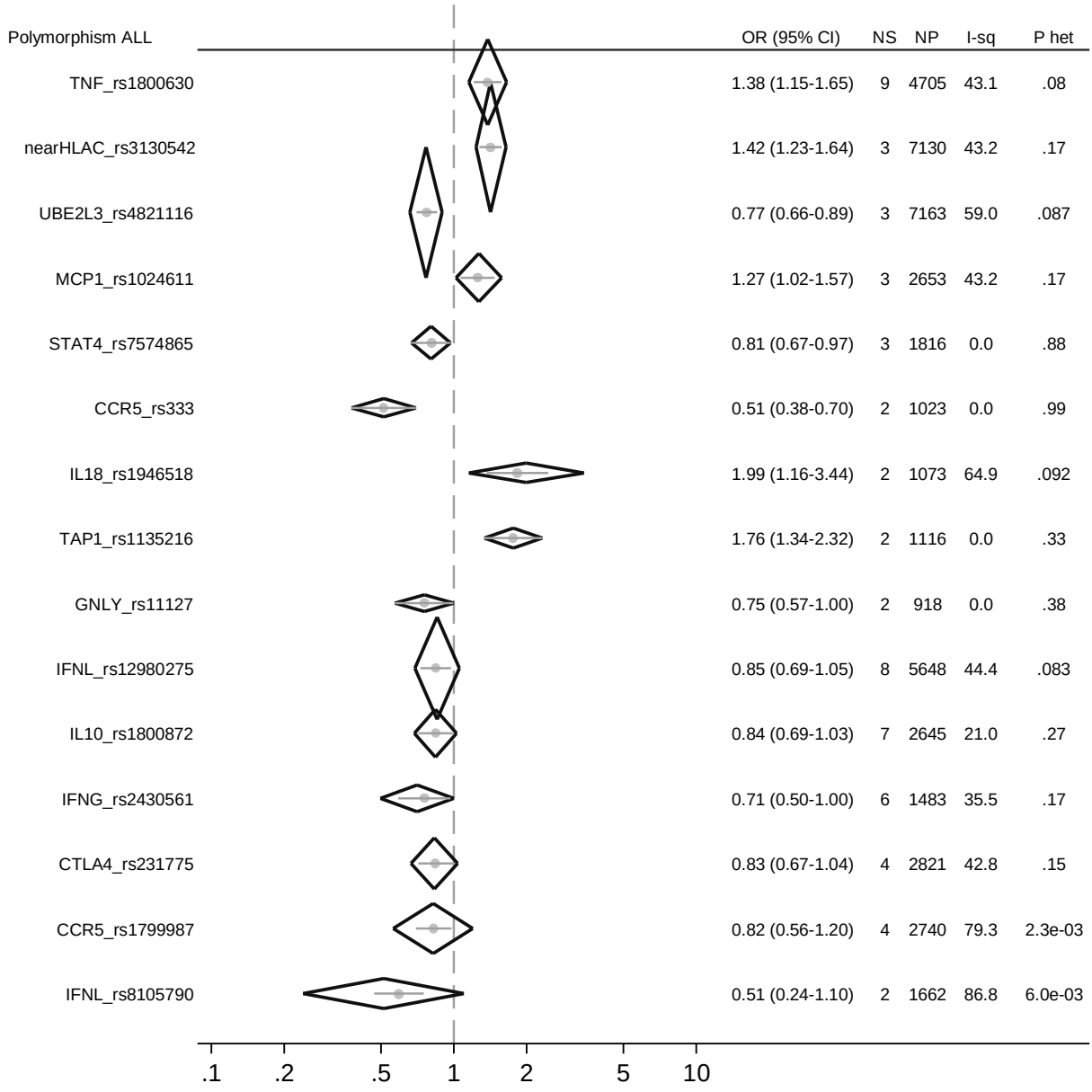
SNP stands for single nucleotide polymorphism, NS the number studies included in the meta-analysis, Nca the number of cases, Nctr number of controls, OR odds ratio, CI confidence interval. Risk alleles and wild type alleles are described for each SNP as (A>a) with “A” being the wild type allele and “a” the risk allele. For studies marked with a *, genotypes were recalculated based on allele frequencies, assuming Hardy-Weinberg equilibrium.

Figure 1. PRISMA flow chart[1]



[1] PRISMA stands for Preferred Reporting Items for Systematic Reviews and Meta-analysis.

Figure 2. Meta-analyses of polymorphisms significantly associated with chronic hepatitis B.



Diamond shapes represent Odds rations (Ors) and 95% confidence intervals (CI) estimated by a DSL random effect model by using a dominant mode of inheritance, with the estimate of heterogeneity (I^2, P het) being taken from the MH model. The height of diamonds is proportional to the number of patients entered in each meta-analysis. NS stands for number of studies, NP for number of patients. Gray dots and lines represent ORs and 95% CI estimated by fixed effect models (MH). These data summarize studies from all ethnic groups and are sorted according to (1) significance in a random (>fixed) effect model, (2) the number of studies and (3) recalculated P value for the association (not shown).

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