Host genetic factors associated with hepatitis B virus infection and progression to chronic disease: A systematic review and Meta analysis

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Abstract

Abstract Background Contradicting results from many laboratories on the role of genetic factors in the susceptibility/resistance to hepatitis B infection have been reported. In this review we examined 27 published full research articles and assessed the role of Th1/Th2 cytokine promoter and vitamin D receptor gene polymorphisms. We summarized the available data on the relationship between the gene polymorphisms and susceptibility/resistance to hepatitis B virus infection together with likely disease evolution to come up with candidate single nucleotide polymorphisms implicated in the disease state with the population. Method The study was done in tandem with the PRISMA standards and the Cochran's Q test, I² statistics for heterogeneity and the Odds ratio were calculated using a commercially available soft ware called MedCalcs (<http://www.medcalc.org>). A random effects model was used to pool the odds ratio for heterogeneities $\geq 50\%$ or else a fixed effects model was used. All analyses were done at 95% Confidence Interval and a $P < 0.05$ was considered statistically significant. Results We found that IL-10-592C/A genotype AA ($P = 0.017$, OR=0.752, 95%CI=0.595 to 0.950) and TNF- α -238G/A genotype AA+ AG ($P < 0.001$, OR=0.407, 95%CI=0.005 to 30.1) were significantly associated with reduced risk of hepatitis B infection by the random effects model. TNF- α -238G/A genotype GG had the risk of chronic infection (OR=3.587, 95% CI= 0.127 to 101.176) under the random effect model. Most of the other SNPs had borderline risk of HBV infection (OR 0.6 to 1.12) with a few cases of high risk, IL-10-1082A/G genotype AA (OR=1.608, 95%CI=0.861 to 3.003) and reduced risk, IL-10-1082A/G genotype AG (OR=0.485, 95% CI=0.232 to 1.014) Conclusion We found that IL-10-592C/A genotype AA and TNF- α -238G/A genotype AA+ AG were significantly associated with reduced risk of hepatitis B infection.

Introduction

The pattern and clinical manifestation of hepatitis B infection is variable and a genetic component is highly implicated in susceptibility and evolution of the disease. However results from many laboratories have reported with contradictions and concordances on which alleles are involved in disease severity and evolution from chronic infection, through acute disease, inactive carrier state, self-limiting to liver cirrhosis and hepatocellular carcinoma (F. Wang, 2003). The available data suggests that understanding human genetic factors will provide constructive clues on the disparity in the evolution of the disease among different populations. The recently completed human genome project (HGP) reported 35,000 genes whose alleles are highly polymorphic with single nucleotide polymorphisms (SNPs) in the gene itself, the flanking regions or the promoter region (F. Wang, 2003). There are an estimated number of 3.5 million SNPs in our genome implicated in the population and individual differences that manifest in HBV susceptibility and evolution (F. Wang, 2003). These polymorphisms in promoter region of a particular gene will affect the expression levels of the genes resulting into protective effect (HBV resistant alleles) or increased prone to infection (HBV susceptibility). Establishing the gene loci that are responsible for the disease outcome in HBV infection requires knowledge of the function of the gene and its role in the host response to HBV infection (Q. Gao et al., 2017). One plausible alternative is assaying the immunological responses by looking at the levels of cytokines during HBV infection. Several Th1 cytokines (TNF- α and

INF- γ) participate in viral clearance while Th2 cytokine like IL-10 are potent inhibitors of Th1 effector cells (Sofian et al., 2013). In addition Vitamin D is involved in the immune modulation between Th1 and Th2 cytokines by inhibiting the Th1 responses and activating Th2 responses (F. Wang, 2003). Thus discussing the effect of SNPs in the Th1/Th2 cytokine promoter genes in the susceptibility to HBV infection and disease profile in isolation without paying attention to the polymorphisms in the VDR gene will give inconclusive arguments.

Tumor Necrosis Factor alpha (TNF- α) gene has five single nucleotide polymorphisms in the promoter region located at the following positions upstream of the transcription initiation site; -238G/A, -308G/A, -857C/T, -863C/A and -1031T/C (Gusatti et al., 2016). However in our meta-analysis and systematic review, we investigated the relationship between -238G/A and -308G/A polymorphisms and the susceptibility to HBV infection as well as the disease profile in chronically infected patients. Interleukin 10 (IL-10) gene has three single nucleotide polymorphisms in the promoter region located at -1082A/G, -819T/C and -592A/C upstream of the transcription initiation site (F. Wang, 2003, Dondeti, El-maadawy, & Talaat, 2016). Polymorphisms in the IL-10 promoter gene will affect its expression and being a potent inhibitor of Th1 cytokines, the expression of Th1 cytokines will be affected.

The aim of this study was to evaluate the role of the polymorphisms in the cytokine promoter genes and vitamin D receptor in the individual and population based differences to infection with hepatitis B virus. Understanding the polymorphisms within the promoter genes of the Th1/Th2 cytokines as well as in the vitamin D receptor genes, a hormone that modulates the activities of Th1 and Th2 cytokines with illuminate on the individual/population based differences in the susceptibility to hepatitis B infection.

Materials And Methods

Journal article search strategy

This study was done in tandem with the PRISMA standards (see details of PRISMA checklist). The effect of host genetic factors particularly Single Nucleotide Polymorphisms (SNPs) in selected Th1/Th2 cytokine genes and Vitamin D Receptor (VDR) polymorphisms on the chronicity of hepatitis B infection and clinical profiles of the diseases were identified by thorough searches in the following data bases; Biomed central, PubMed, and Google scholar up to December, 2017. The following terms were used during the search: "Th1 cytokines", "Th2 cytokines", "promoter gene polymorphisms", "IL-10", "TNF- α " "IFN- γ " "VDR" or "Vitamin D Receptor", "genotype" and "HBV or hepatitis B". The search results yielded over 700 journal articles.

Selection of articles for meta-analysis

The articles obtained were evaluated by three independent reviewers (HMK, HN and DN) for them to be either excluded or included in the study. The papers included in the study were selected after meeting the

following preconditions; must have been a case-control or cohort study, assessing the polymorphisms in the VDR gene, IL-10, TNF- α or INF- γ gene promoter and HBV clinical outcome, and the distribution of the genotypes in the healthy controls within the population were in conformity to Hardy-Weinberg equilibrium

Articles excluded from the study included those with insufficient data, not investigating cytokines, investigating haplotypes or review/meta-analyses.

Extracting data from the journal articles

Two of the authors (HMK and HN) designed a protocol for the selection criteria aforementioned above. Both reviewers extracted data independently and entered the data in the spread sheet pending its analysis. The two authors compared their records after the review of the journal articles and any differences in the records was resolved following a consensus in their meetings. In our meta-analysis, the following characteristics were recorded for each study; first author, year of publication, country/ethnicity, genotyping method, definition of a case/control, gene locus investigated and number of cases/controls.

Quality assessment

The quality of each study was assessed by two independent reviewers (HMK and HN) and the Newcastle-Ottawa scale was used (Stang, 2010). The third and fourth authors (HS and DN) supervised the work of the HMK and HN to ensure consistence in the quality of the work assessed. Three dimensions of comparability, selection and exposure were considered as described in the Newcastle-Ottawa scale. Studies were assigned scores ranging from the worst of zero to the best of 9. Any study with a score ≥ 7 was declared a high quality study.

Data analysis

Cochran's Q test and I^2 statistics were performed using the commercially available software (<http://www.medcalc.org>) to evaluate the extent of heterogeneity of all the eligible studies for meta-analysis (Zintzaras & JP, 2005). For studies with P_{het} Value greater than 0.1, there was no heterogeneity among the pooled studies (Zintzaras & JP, 2005). In effect, the fixed effects model was used in the absence of the heterogeneity. Or else, the random effect model was used (Zintzaras & JP, 2005) The odds ratios for each study and 95% CI were calculated to determine the association of the polymorphisms in the promoter genes of Th1/Th2 cytokines and the VDR with chronicity and clinical outcome of the disease. The pooled odds ratios were determined and a $p < 0.05$ was considered statistically significant and the publication bias was assessed by carrying out a funnel plot. All analyses were performed using the a statistical software called MedCalc available on <http://www.medcalc.org>

Results

Studies included in the meta-analysis and their characteristics

The screening of the eligible studies was done the PRISMA strategy (Figure 1). In total, 27 articles with a total of 6,181 cases and 4,540 controls. The characteristics of each study were presented in Table 1. In our study, 12 eligible studies involved IL–10–1082A/G and IL–10–592C/A polymorphisms (Dondeti, El-maadawy, & Talaat, 2016, Heidari, Moudi, Sagheb, & Moudi, 2016, Gao et al., 2016, Gusatti et al., 2016, Yao et al., 2015, Manjita et al., 2014, Sofian et al., 2013, Ge et al., 2009, Baghi, Alavian, Mehrnoush, & Salimi, 2015, Q. Gao et al., 2017) Sofian et al., 2013), 8 eligible studies involved INF- γ +874 (Heidari et al., 2016, Yao et al., 2015, Migita et al., 2005, Ognjanovic, Yuan, Chaptman, Fan, & Yu, 2009), 9 studies involved TNF- α (Panigrahi et al., 2014, Gusatti et al., 2016, Panigrahi et al., 2014, Migita et al., 2005, Q. Gao et al., 2017, Ognjanovic et al., 2009, Kim et al., 2018, Heidari et al., 2016, Fletcher et al., 2011) and 5 studies involved VDR (Falletti et al., 2010, Suneetha et al., 2006, Peng et al., 2014, Elmer, Tuncbilek, Aydin, & Hizel, 2013, X. Yao et al., 2013). The numbers of quality scores for each study for each study were summarized in Table 1.

Fig.1: Flow chart for study eligibility following PRISMA criterion

In total, 27 full research articles were used in our meta-analysis. The characteristics of the studies are indicated in table 1 below.

Table 1: Characteristics of eligible studies for meta-analysis

Table 2: General results of the meta-analysis on the cytokine/VDR gene polymorphisms and clinical outcome of HBV infection

Figure 2: Dominant models IL–10–592 AA on the risk of HBV –HC. The association was indicated as odds ratio (OR) with corresponding 95% confidence interval. The OR estimate of each study is indicated by the solid black square. The size of the square represents the weight contributed by each study in the meta-analysis. The pooled Odds ratio for both fixed effects and random effects is shown by the diamonds. OR more than 1 indicates increased risk or susceptibility to HBV infection

The results show that IL–10–592AA genotype when compared between CHB infected patients and healthy controls, was significantly associated with decreased risk of HBV infection under the Random effect model ($P = 0.017$, $OR = 0.752$, $95\%CI = 0.595$ to 0.950 , Figure 2, Table 2). On the other hand, the prevalence of the genotype AA+ AC between the health controls and the CHB patients, it was shown to have a decreased risk of CHB though the findings were not statistically significant ($P = 0.303$, $OR = 0.787$, $95\%CI = 0.505$ to 1.228 , Figure 3, Table 2).

Figure 3: Dominant model IL–10–592 AA+AC on the risk of CHB when compared with health controls. The association was indicated as odds ratio (OR) with corresponding 95% confidence interval. The OR estimate of each study is indicated by the solid black square. The size of the square represents the weight

contributed by each study in the meta-analysis. The pooled Odds ratio for both fixed effects and random effects is shown by the diamonds. OR more than 1 indicates increased risk or susceptibility to HBV infection

Additionally, we observed a statistically significant association between the IL-10-592AA genotype with resolving HBV infection in the fixed effects model ($P = 0.039$, $OR = 0.602$, $95\%CI = 0.372$ to 0.974 , Figure 3, Table 2). Further analysis of the IL-10592 AA + AC genotype among the chronically infected patients and the asymptomatic carriers (ASC) was associated with decreased risk under the fixed effects model ($P = 0.103$, $OR = 0.705$, $95\%CI = 0.463$ to 1.073 , Figure 4, Table 2).

Figure 4 Dominant model IL-10-592 AA on the risk of HBV –self resolved. The association was indicated as odds ratio (OR) with corresponding 95% confidence interval. The OR estimate of each study is indicated by the solid black square. The size of the square represents the weight contributed by each study in the meta-analysis. The pooled Odds ratio for both fixed effects and random effects is shown by the diamonds. OR more than 1 indicates increased risk or susceptibility to HBV infection

Figure 5 Dominant model IL-10-592 AA +AC on the risk of HBV –ASC. The association was indicated as odds ratio (OR) with corresponding 95% confidence interval. The OR estimate of each study is indicated by the solid black square. The size of the square represents the weight contributed by each study in the meta-analysis. The pooled Odds ratio for both fixed effects and random effects is shown by the diamonds. OR more than 1 indicates increased risk or susceptibility to HBV infection

Our meta-analysis also investigated the prevalence of single nucleotide polymorphisms at the IL-10-1082 genetic loci among the cases and controls. The IL-10-1082 AA, AG and GA+ GG genotypes in the HBV patients and controls showed that AA genotype was associated with increased chances of developing CHB infection while AG + GG combined and AG were associated with decreased risk of infection ($P = 0.136$, $OR = 1.61$, $95\% CI = 0.861$ to 3.003 , $P = 0.054$, $OR = 0.485$, $95\%CI = 0.232$ to 1.014 , $P = 0.587$, $OR = 0.826$, $95\%CI = 0.415$ to 1.644 respectively, Table 2 and Figure 6)

Figure 6 Dominant model IL-10-1082 AA, AG and AA + AG on the risk of CHB –health controls. The association was indicated as odds ratio (OR) with corresponding 95% confidence interval. The OR estimate of each study is indicated by the solid black square. The size of the square represents the weight contributed by each study in the meta-analysis. The pooled Odds ratio for both fixed effects and random effects is shown by the diamonds. OR more than 1 indicates increased risk or susceptibility to HBV infection

The IL-10-1082 AA, AG and GA+ GG genotypes in the HBV patients and self limited /resolved showed that AA genotype was associated with increased chances of developing CHB infection while AG and GA+ GG combined were associated with increased chances of resolving the disease ($P = 0.788$, $OR = 1.045$, $95\% CI = 0.757$ to 1.442 , $P = 0.782$, $OR = 0.932$, $95\%CI = 0.565$ to 1.538 , $P = 0.788$, $OR = 0.957$, $95\% CI = 0.693$ to 1.320 , Figure 7, Table 2)

Figure 7: Dominant model IL-10-1082 AA, AG and AA + AG on the risk of HBV –self resolved. The association was indicated as odds ratio (OR) with corresponding 95% confidence interval. The OR estimate of each study is indicated by the solid black square. The size of the square represents the weight contributed by each study in the meta-analysis. The pooled Odds ratio for both fixed effects and random effects is shown by the diamonds. OR more than 1 indicates increased risk or susceptibility to HBV infection

Relationship between the polymorphisms in the Tumor necrosis factor alpha (TNF- α -238G/A) and the development of HBV infection

In the present meta-analysis, the results from the random effects model suggested that the genotypes AA+GG and GG were associated with reduced risk of infection when the prevalence of these genotypes were compared in the health controls and chronic sufferers of the disease ($P = 0.733$, $OR = 0.863$, $95\%CI = 0.371$ to 2.008 and $P = 0.101$, $R = 0.409$, $95\%CI = 0.140$ to 1.18) respectively. However the combined genotypes AA+GG had a borderline reduced risk compared to the single genotype GG (Figure 8, Table 2).

Figure 8: Dominant model TNF- α -238 AA+GG and GG on the risk of HBV compared to the Health controls. The association was indicated as odds ratio (OR) with corresponding 95% confidence interval. The OR estimate of each study is indicated by the solid black square. The size of the square represents the weight contributed by each study in the meta-analysis. The pooled Odds ratio for both fixed effects and random effects is shown by the diamonds. OR more than 1 indicates increased risk or susceptibility to HBV infection

For further assessment, we carried group analysis involving resolved and asymptomatic controls and compared them with chronic carriers of HBV (Figure 9, Table 2). GA+GG and AG were associated with borderline reduced risk of HBV chronicity but increasing cases of HBV resolution ($P < 0.001$, $OR = 0.407$, $95\%CI = 0.005$ to 30.1 and, $P = 0.453$, $OR = 3.587$, $95\%CI = 0.127$ to 101.176). The results for the patients with GA+GG who had resolved HBV when compared with the chronically infected patients were statistically significant ($P < 0.001$).

On comparing the patients with chronic HBV infection with the asymptomatic carriers, AA+AG genotypes had borderline reduced risk of chronic infection ($P = 0.0356$, $OR = 0.845$, $95\%CI = 0.591$ to 1.208) under the fixed effects model while GG genotype had increased risk of remaining chronically infected ($P = 0.289$, $OR = 1.4$, $95\%CI = 0.591$ to 1.208) under the random effects model

Figure 9: Dominant model TNF- α -238 AA+GG and GG on the risk of HBV compared to the asymptomatic and self resolved. The association was indicated as odds ratio (OR) with corresponding 95% confidence interval. The OR estimate of each study is indicated by the solid black square. The size of the square represents the weight contributed by each study in the meta-analysis. The pooled Odds ratio for both

fixed effects and random effects is shown by the diamonds. OR more than 1 indicates increased risk or susceptibility to HBV infection

Relationship between the polymorphisms in the Interferon Gamma (INF- γ +874A/T) and the development of HBV infection

In our meta-analysis, we also compared the prevalence of INF- γ +874 AA+ AT and AA among the chronically infected HBV patients with the health controls to establish the association of these genotype to the susceptibility/resistance to HBV infection (Table 2). The pooled odds ratios for genotype AA showed a border line reduced risk of HBV infections by the random model ($P = 0.944$, OR = 0.976, 95%CI = 0.491 to 1.937) while the results for the combined genotypes AA+AT reported a much reduced risk of HBV infection when the chronically infected patients were compared with the health controls by random model ($P = 0.139$, OR = 0.522, 95% CI = 0.220 to 1.235)

Relationship between the polymorphisms in the Vitamin D Receptor (VDR A/a & VDR T/t) genes and the development of HBV infection

We compared the relative risk of two polymorphisms in the genes of the receptors of vitamin D (VDR A/a and T/t) in the homozygous dominant, heterozygous and homozygous recessive. Our study established that in the homozygous state, AA ($P = 0.227$, OR = 0.792, 95%CI = 0.543 to 1.156) & aa, ($P = 0.553$, OR = 0.831, 95% CI = 0.452 to 1.529) there was a reduced risk of infection with HBV. However, in the heterozygous state, Aa ($P = 0.628$, OR = 1.059, 95%CI = 0.840 to 1.33) revealing a borderline increased risk. (Figure 10, Table 2)

Figure 10: Dominant and recessive model of VDR A/a, genotypes AA, Aa and aa on the risk of HBV compared to the self controls. The association was indicated as odds ratio (OR) with corresponding 95% confidence interval. The OR estimate of each study is indicated by the solid black square. The size of the square represents the weight contributed by each study in the meta-analysis. The pooled Odds ratio for both fixed effects and random effects is shown by the diamonds. OR more than 1 indicates increased risk or susceptibility to HBV infection

Regarding the VDR T/t gene polymorphism, our meta-analysis established the homozygous genotype TT ($P = 0.791$, OR = 0.776, 95%CI = 0.813 to 1.171) and tt ($P = 0.832$, OR = 0.976, 95% CI = 0.779 to 1.223) were associated with reduced risk of infection with HBV whereas the heterozygous genotype Tt ($P = 0.496$, OR = 1.06, 95%CI = 0.895 to 1.258) was associated with increased risk of chronic infection with HBV (Figure 11, Table 2)

Figure 11: Dominant and recessive model of VDR T/t, genotypes *TT*, *Tt* and *tt* on the risk of HBV compared to the self controls. The association was indicated as odds ratio (OR) with corresponding 95% confidence interval. The OR estimate of each study is indicated by the solid black square. The size of the square represents the weight contributed by each study in the meta-analysis. The pooled Odds ratio for both fixed effects and random effects is shown by the diamonds. OR more than 1 indicates increased risk or susceptibility to HBV infection

Publication bias

A Begg's funnel plot was used to investigate publication bias in our meta-analysis. the results showed no significant publication bias was detected with the funnel plot.

Fig: 12 Begg's funnel plot for publication bias

Discussion

The differences in the susceptibility to HBV infection, disease evolution and clinical outcome at population and individual levels have been implicated on the differences in host genetic factors (F. Wang, 2003) The cytokine genes and their promoter gene polymorphisms remain pivotal in this subject. Cytokines modulate nearly phases of immune response following an infection with HBV. Polymorphisms in their genes and or their promoter will affect their expression levels which in turn compromise their immune modulator role. In addition, vitamin D has been closely linked to immune modulation of Th1/Th2 cytokines. Consequently, polymorphisms in Vitamin D receptor genes will influence the susceptibility and disease profile following an infection (Peng et al., 2014) Previous studies and meta-analyses have reported contradictions in their findings and few of these studies have integrated cytokine gene promoter polymorphisms and VDR polymorphisms. The aim of this current study is to illuminate on to the role selected host genetic factors in disease evolution and susceptibility to HBV infection. The study focused on seven SNPs; two in the cytokine promoter genes and 2 in the VDR gene polymorphism. The SNPs in the cytokine gene promoter included IL-10-592C/A, IL-10-1082A/G, TNF- α -238G/A, TNF- α -308G/A, and INF- γ +874A/T while the SNPs in the VDR gene included VDR A/a and VDR T/t. genotypes frequencies were compared between the chronic hepatitis B infected (CHB) and health controls (HC), resolved and asymptomatic carriers (ASC).

Interleukin-10 (IL-10) is a key immune regulatory cytokine which is secreted by mainly T-helper 2 (Th2) cells and T-regulatory cells (Treg) as well as macrophages (L. Gao et al., 2016). IL-10 inhibits the secretion of TNF- α ; a Th1 cytokine justifies its immune regulatory role. In our systematic review and meta-analysis, IL-10-592AA was associated with reduced risk of HBV infection as well as increased chances of resolving the infection (Table 2 & Figure 2). This finding is not surprising as it was consistent with an earlier finding by Wang, Huang, Sun, Ma, & Zhen, (2011) who established the frequency of genotype AA was more frequent in patients with viral clearance. Consistent results have also been reported by Turner,

William, Sankaran, Lazarus, & Sinnott, (1997) who established that IL-10-592AA genotype exerts a protective effect against HBV infection. In our study, IL-10-592CC was associated with increased risk of chronic infection (Table 2, Figures, 2-6) reducing the chances of resolving the infection consistent with the findings by Wang et al., (2012). Thus allele C mutated to A provides protection against HBV infection while mutation of allele A to C at the same locus would increase the susceptibility to chronic infection. However, the association of IL-10-592CC genotype in our meta-analysis and in other studies (Cheong et al., 2006) lacked statistical significance and more work still needs to be done to confirm this relationship.

When the frequency of IL-10-1082A/G was evaluated between the CHB patients and health controls/resolved, IL-1082AA was associated with increased risk of HBV infection and progressing to chronic disease while the genotypes IL-10-1082 AG was associated with reduced risk of infection (Figure 6, Table 2). Therefore allele A mutated to G will reduce the risk of HBV infection and progression while allele G mutated to allele A will increase the risk of infection. Our finding from the meta-analysis was consistent with the earlier findings by Gao et al. 2017 who reported that allele G was protective while allele A shown increased susceptibility. Thus A mutated to G will increase protection against HBV infection and progression to liver cirrhosis while allele G mutated to A increases susceptibility. However the findings of the current meta-analysis contradicted with the findings reported by Moudi et al., (2016) who reported an increased susceptibility to HBV infection in subjects with IL-10-1082AG and GG genotypes.

Tumor Necrosis Factor- α (TNF- α) and Interferon gamma (INF- γ) are Th1 cytokines that participate in host immune response during HBV infection and viral clearance (F. Wang, 2003). TNF- α has five polymorphisms in its promoter region located at the following positions upstream of the transcription initiation site; -1030C/T, -863C/A, -857C/T, -308G/A and 238G/A. Of these the most implicated in diseases profile and susceptibility to HBV infection are -308G/A and -238G/A (Kruger, Gerken, Schneider, & Bu, 1998) and have been reviewed in our systematic review and meta-analysis. In the current study, TNF- α -238 AA+AG was associated with reduced risk of HBV infection and showed an increase in asymptomatic as well as resolved subjects. However, genotype GG was associated with increased risk of chronic infection (Table 2, Figure 9). The finding in our meta-analysis is consistent with the finding reported by (Panigrahi et al., 2014) who reported was significantly high TNF- α -238GG genotype in the cases than the controls and a high TNF- α AA in the controls than the cases. This suggests that allele A mutated into G at the above locus would increase the susceptibility to HBV infection. Studies by (Li et al., 2005) have posted similar findings. Other studies by (Kao et al., 2010) however contradicted our findings and those from other earlier reported studies.

In the present study, the frequency of TNF- α -308G/A among the chronically infected HBV subjects and those who had resolved the virus was investigated in order to come up with constructive clues pertaining its role in HBV clearance. The genotype GG was associated with borderline viral clearance (OR = 0.803) while the genotypes AA+ AG were associated with a lower risk of infection to chronicity (OR = 1.124). This finding is consistent with the finding from a meta-analysis by (Zheng et al., 2010) which reported a lower risk associated with -308 variant genotypes AA and GA as well as a moderate decrease in risk among

subjects with TNF- α -308GG (Wei, Liu, & Chen, 2011). However, these findings are contradicted by (Kruger et al., 1998) leaving knowledge gaps justifying the need for more studies.

Interferon gamma has similar effector mechanism as tumour necrosis factor alpha. Polymorphisms in the promoter site of the INF- γ +874A/T gene locus and their association with hepatitis B susceptibility/resistance have been investigated elsewhere and in our meta-analysis. In the current study, the AA + AT were associated with reduced risk of HBV infection (OR = 0.522) while genotype AA was only associated with a borderline protective role (OR = 0.976). The INF- γ +874 T/A genotype TT is associated with high expression of the cytokine which is a potent anti-viral cytokine reducing the susceptibility to HBV infection (Sun et al., 2015). In contrast the AA genotype is associated with low cytokine expression increasing the risk of HBV infection consistent with our findings. However, in the current meta-analysis, the AT + TT genotype suggests a reduced risk of HBV infection. This shows that the T-allele is probably dominant over A allele and has more powers of expression such that only individuals with AA genotype are at a risk of HBV infection

In active form, vitamin D is an immune regulatory hormone that activates Th2 cytokines and inhibits Th1 cytokine mediated reactions. Polymorphisms in the genes for vitamin D receptors will affect the expression levels of both Th1 and Th2 cytokines and this will in turn influence the evolution of the disease as well as the susceptibility/resistance to infection. The VDR gene has four polymorphisms that are implicated in several immune mediated diseases including HBV infection (Suneetha et al., 2006). In this meta-analysis VDR Apa1 (A/a) and Taq1(T/t) and their association with disease susceptibility/resistance as well as disease evolution were investigated. We compared the prevalence of these genotypes in the heterozygous state and homozygous state in the health controls and chronically infected subjects in the same population. Our findings reported reduced risk of infection in both homozygous (dominant and recessive) while the heterozygous were associated with mild risk of infection (Table 2). These findings are similar to findings by (Suneetha et al., 2006) who reported association of aa/AA and tt/TT with more severe disease than the heterozygous Aa or Tt.

In conclusion, our meta-analysis of 27 eligible case-control studies indicated that IL-10-1082AA, and TNF- α AA + GG genotypes significantly associated with reduced risk of hepatitis B infection by the random model. Several other polymorphisms are associated with reduced risk of HBV infection with OR<1 but the results were not statistically significant. It is worth noting that several SNPs were associated with increased risk of HBV infection particularly IL-10-1082AA and TNF- α 238GG with high Odds ratio, though most of the SNPs had borderline risk of HBV infection. Thus more validations are needed to qualify the results of our meta-analysis especially using the African population because there scanty information in literature that has investigated SNPs in the cytokine promoter genes and then VDR gene polymorphisms.

Our meta-analysis could not go without limitations. First, some studies had small sample size hence low statistical power, consequently most of the SNP analyses were indicating association with increased/decreased risk of infection with HBV culminating into chronicity, but lacked statistical

significance. Secondly, most of the studies were from a localized ethnic group and the findings could not be generalized to other population especially the African population

However, despite the above limitations, our meta-analysis pooled a reasonable number of cases and controls to raise the statistical power.

Declaration

The authors declare that they have no conflict of interest

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Tables

Table 1: Characteristics of eligible studies for meta-analysis

First author, Year	Ethnicity	genotyping Method	Case	Control	QS	Loci	Number	
							Case	Control
Baba, M	Egyptian	SSP-PCR	CHB	Healthy	7	IL-10-1082A/G	118	119
Bitar M, 2016	Iranian	RFLP-PCR	CHB	Healthy	7	IL-10-592 C/A	221	200
Catia, S, 2017	Italian	SSP-PCR	CHB	Self limited	8	INF- γ + 874 A/T	30	40
Edmond, 2010	F, Italian	RFLP-PCR	LC	Healthy	7	VDR A/a	240	236
Edmond, 2010	F, Italian	RFLP-PCR	LC	Healthy	7	VDR T/t	240	236
Fletcher, 2011	Turkey	RFLP-PCR	CHB	Resolved	7	TNF- α -238 G/A	137	150
Gao, 2016	Chinese	RFLP-PCR	CHB	Resolved	7	IL-10-592 C/A	180	75
Gao, 2016	Chinese	RFLP-PCR	CHB	Resolved	7	IL-10-1082A/G	190	81
Gusatti, 2016	Brazil	Mini seq	CHB	Resolved	7	IL-10-592 C/A	193	147
Gusatti, 2016	Brazil	Mini seq	CHB	Resolved	7	IL-10-1082A/G	196	149
Gusatti, 2016	Brazil	Mini seq	CHB	Resolved	7	TNF- α -238 G/A	149	196
Hohler, 1997	T, German	Dot Blot	CHB	Healthy	8	TNF- α -238 G/A	71	90
Hong-Quan, 2005	Chinese	RFLP-PCR	CHB	Self limited	7	TNF- α -238 G/A	443	244
Lanjie, 2015	Chinese	RFLP-PCR	CHB	Healthy	7	IL-10-592 C/A	318	318
Lanjie, 2015	Chinese	RFLP-PCR	CHB	Healthy	7	IL-10-1082A/G	318	318
Mangita, 2014	S, India	RFLP-PCR	CHB, LC	Healthy	7	INF- γ + 874 A/T	232	76
Manjita, 2015	India	RFLP-PCR	CHB, LC	Healthy	6	IL-10-592 C/A	232	76

Manjita, 2015	India	SSP-PCR	CHB, LC	Healthy	6	IL-10- 1082A/G	232	76
Masoomah, S, 2013	Iranian	SSP-PCR	CHB	Resolved, Healthy	7	IL-10-592 C/A	66	61
Masoomah, S, 2013	Iranian	SSP-PCR	CHB	Healthy	6	IL-10- 1082A/G	66	61
Migita, 2005	Asian	SSP-PCR	HCC	No HCC	6	TNF- α -238 G/A	52	184
Migita, 2005	Asian	SSP-PCR	HCC	No HCC	6	INF- γ + 874 A/T	188	48
Mita, 2016	Asian	SS-PCR	CHB	Healthy	7	IL-10- 1082A/G	221	200
Nadia, 2016	Iranian	SSP-PCR	CHB	Healthy	7	INF- γ + 874 A/T	282	316
Nadia, 2016	Iranian	SSP-PCR	CHB	Healthy	7	INF- γ + 874 A/T	282	316
Pathokamuri, 2006	India	RFLP-PCR	CHB	Healthy	8	TNF- α -238 G/A	214	408
Pathokamuri, 2006	India	RFLP-PCR	CHB	Healthy	8	VDR A/a	214	408
Pathokamuri, 2006	India	RFLP-PCR	CHB	Healthy	8	VDR T/t	214	408
Peng, Q, 2014	Chinese	RFLP-PCR	CHB, HCC	Healthy	7	VDRC/T	480	180
Peng, Q, 2014	Chinese	RFLP-PCR	CHB, HCC	Healthy	7	VDRC/G	480	180
Qiu, J, 2009	Chinese	RFLP-PCR	CHB	Healthy	7	IL-10-592 C/A	69	74
Qiu, J, 2009	Chinese	RFLP-PCR	CHB	Healthy	8	IL-10- 1082A/G	69	74
Qiu, J, 2009	Chinese	RFLP-PCR	CHB	Healthy	8	INF- γ + 874 A/T	69	74
Qiu, J, 2017	Chinese	RFLP-PCR	CHB	Healthy	8	IL-10- 1082A/G	203	74
Qiu, J, 2017	Chinese	RFLP-PCR	CHB	Healthy	8	INF- γ + 874 A/T	203	74
Rojesh, 2014	P, India	RFLP-PCR	CHB	Healthy	6	TNF- α -238 G/A	110	85
Sahand	G, Iranian		LC,	Inactive	6	IL-10-592	111	55

2015			CHB	carrier			C/A		
Sahand, 2015	Iranian	RFLP-PCR	LC, CHB	Inactive carrier	6		IL-10- 1082A/G	111	55
Semra, T, 2013	Turkey	ARMS-PCR	CHB, IC	Healthy	7		VDR A/a	110	56
Semra, T, 2013	Turkey	ARMS-PCR	CHB, IC	Healthy	7		VDR T/t	110	56
Shaoyang, W, 2011	Chinese	RFLP-PCR	CHB	Healthy	6		IL-10-592 C/A	52	48
Shaoyang, W, 2011	Chinese	RFLP-PCR	CHB	Healthy	6		IL-10- 1082A/G	52	48
Simona, 2009	Hispanic	RT- PCR	CHB	Healthy	8		IL-10- 1082A/G	214	115
Simona, 2009	Hispanic	RT-PCR	CHB	Healthy	8		TNF- α -238 G/A	120	230
Simona, 2009	USA	qPCR	CHB	Healthy	8		INF- γ + 874 A/T	120	230
Xing, Y, 2013	Chinese	RFLP-PCR	HCC	HCC, HBV	No	7	VDR A/a	436	131
Xing, Y, 2013	Chinese	RFLP-PCR	HCC	HCC, HBV	No	7	VDR T/t	436	131
Yoon J, 2003	South Korea	SBE	CHB	Self limited	7		TNF- α -238 G/A	1,109	291
Zahra, H, 2016	Iranian	ARMS-PCR	CHB	Self limited	6		TNF- α -238 G/A	100	40

Table 2: General results of the meta-analysis on the cytokine/VDR gene polymorphisms and clinical outcome of HBV infection

SNPs	case/control	Genotype	No	OR (95%CI)		Heterogeneity				Model
						P	I ²	Q	Phet	
IL-10-592C/A	CHB/HC	AA	8	0.752(0.595 to 0.950)		0.017	64.13	9.0	0.2523	Random
		AC	8	1.149(0.958 to 1.377)		0.135	40.25	11.7	0.1103	Fixed
		CC	8	1.306(0.786 to 2.170)		0.303	66.59	18.0	0.0063	Random
		AA + AC	8	0.787 (0.505 to 1.228)		0.292	64.34	19.6	0.0064	Random
	CHB/Resolved	AA	3	0.602(0.372 to 0.974)		0.039	38.22	3.2	0.1982	Fixed
		AC	3	1.155(0.793 to 1.683)		0.453	39.86	3.3	0.1896	Fixed
		CC	3	1.353(0.850 to 2.154)		0.202	0	0.2	0.9244	Fixed
		AA+ AC	3	1.061(0.566 to 1.990)		0.853	53.96	4.3	0.114	Random
IL-10-1082A/G	CHB/ASC	CC	3	1.419(0.932 to 2.160)		0.103	12.32	2.3	0.3197	Fixed
		AA+ AC	3	0.705(0.463 to 1.073)		0.103	12.32	2.3	0.3197	Fixed
	CHB/HC	AA	8	1.608(0.861 to 3.003)		0.136	84.99	46.6	<0.0001	Random
		AG	8	0.485(0.232 to 1.014)		0.054	91.27	8.2	<0.0001	Random
		GA+GG	8	0.826(0.415 to 1.644)		0.587	87.83	57.5	<0.0001	Random
	CHB/Resolved	GA+GG	4	0.957(0.693 to 1.320)		0.788	0	2.5	0.4769	Fixed
		AA	4	1.045(0.757 to 1.442)		0.788	0	2.5	0.4789	Fixed
		AG	3	0.932(0.565 to 1.538)		0.782	0	1.4	0.4877	Fixed
TNF- α -238G/A	CHB/HC	AA+ AG	5	0.863(0.371 to 2.008)		0.733	85.97	28.5	<0.0001	Random
		GG	5	0.409(0.140 to 1.154)		0.101	93.15	58.4	<0.0001	Random

				1.189)						
TNF- α-238G/A	CHB/Resolved	AA+AG	4	0.407(0.005 30.1)	to	<0.001	98.81	251.3	<0.0001	Random
		GG	4	3.587(0.127 101.176	to	0.453	98.09	157.5	<0.0001	Random
TNF- α-238G/A	CHB/ASC	AA+AG	4	0.845(0.591 1.208)	to	0.356	39.13	4.9	0.1771	Fixed
		GG	4	1.4(0.591 1.208)	to	0.289	52.24	6.3	0.0987	Random
TNF- α-308G/A	CHB/Resolved	AA+AG	6	1.124(0.725 1.743)	to	0.523	55.17	11.2	0.0484	Random
		GG	6	0.803(0.479 1.36)	to	0.405	71.26	17.4	0.038	Random
INF- γ+874A/T	CHB/HC	AT+TT	6	0.522(0.220 1.235)	to	0.139	91.75	60.6	<0.0001	Random
		AA	6	0.976(0.491 1.937)	to	0.944	86.41	36.8	<0.0001	Random
VDR A/a	CHB/HC	AA	3	0.792(0.543 1.156)	to	0.227	53.01	4.3	0.119	Random
		Aa	3	1.059 (0.840 1.33)	to	0.628	8.4	2.2	0.3356	Fixed
		aa	3	0.831(0.452 1.529)	to	0.553	81.76	11.0	0.041	Random
VDR T/t	CHB/HC	TT	4	0.776 (0.813 1.171)	to	0.791	5.13	3.2	0.3673	Fixed
		Tt	4	1.06 (0.895 1.258)	to	0.496	0	1.8	0.6152	Fixed
		tt	3	0.976 (0.779 1.223)	to	0.832	0	1.1	0.5803	Fixed

Figures

Figure 1

Flow chart for study eligibility following PRISMA criterion In total, 27 full research articles were used in our meta-analysis. The characteristics of the studies are indicated in table 1 below.

Figure 2

Dominant models IL-10-592 AA on the risk of HBV –HC. The association was indicated as odds ratio (OR) with corresponding 95% confidence interval. The OR estimate of each study is indicated by the solid black square. The size of the square represents the weight contributed by each study in the meta-analysis. The pooled Odds ratio for both fixed effects and random effects is shown by the diamonds. OR more than 1 indicates increased risk or susceptibility to HBV infection

Figure 3

Dominant model IL-10-592 AA+AC on the risk of CHB when compared with health controls . The association was indicated as odds ratio (OR) with corresponding 95% confidence interval. The OR estimate of each study is indicated by the solid black square. The size of the square represents the weight contributed by each study in the meta-analysis. The pooled Odds ratio for both fixed effects and random effects is shown by the diamonds. OR more than 1 indicates increased risk or susceptibility to HBV infection

Figure 4

Dominant model IL-10-592 AA on the risk of HBV –self resolved. The association was indicated as odds ratio (OR) with corresponding 95% confidence interval. The OR estimate of each study is indicated by the solid black square. The size of the square represents the weight contributed by each study in the meta-analysis. The pooled Odds ratio for both fixed effects and random effects is shown by the diamonds. OR more than 1 indicates increased risk or susceptibility to HBV infection

Figure 5

Dominant model IL-10-592 AA +AC on the risk of HBV –ASC. The association was indicated as odds ratio (OR) with corresponding 95% confidence interval. The OR estimate of each study is indicated by the solid black square. The size of the square represents the weight contributed by each study in the meta-analysis. The pooled Odds ratio for both fixed effects and random effects is shown by the diamonds. OR more than 1 indicates increased risk or susceptibility to HBV infection

Figure 7

Dominant model IL-10-1082 AA, AG and AA + AG on the risk of HBV –self resolved . The association was indicated as odds ratio (OR) with corresponding 95% confidence interval. The OR estimate of each study is indicated by the solid black square. The size of the square represents the weight contributed by each study in the meta-analysis. The pooled Odds ratio for both fixed effects and random effects is shown by the diamonds. OR more than 1 indicates increased risk or susceptibility to HBV infection

Figure 8

Dominant model TNF- α -238 AA+GG and GG on the risk of HBV compared to the Health controls. The association was indicated as odds ratio (OR) with corresponding 95% confidence interval. The OR estimate of each study is indicated by the solid black square. The size of the square represents the weight contributed by each study in the meta-analysis. The pooled Odds ratio for both fixed effects and random effects is shown by the diamonds. OR more than 1 indicates increased risk or susceptibility to HBV infection

Figure 9

Dominant model TNF- α -238 AA+GG and GG on the risk of HBV compared to the asymptomatic and self resolved. The association was indicated as odds ratio (OR) with corresponding 95% confidence interval. The OR estimate of each study is indicated by the solid black square. The size of the square represents the weight contributed by each study in the meta-analysis. The pooled Odds ratio for both fixed effects and random effects is shown by the diamonds. OR more than 1 indicates increased risk or susceptibility to HBV infection

Figure 10

Dominant and recessive model of VDR A/a , genotypes AA, Aa and aa on the risk of HBV compared to the self controls. The association was indicated as odds ratio (OR) with corresponding 95% confidence interval. The OR estimate of each study is indicated by the solid black square. The size of the square represents the weight contributed by each study in the meta-analysis. The pooled Odds ratio for both fixed effects and random effects is shown by the diamonds. OR more than 1 indicates increased risk or susceptibility to HBV infection

Figure 11

Dominant and recessive model of VDR T/t , genotypes TT, Tt and tt on the risk of HBV compared to the self controls. The association was indicated as odds ratio (OR) with corresponding 95% confidence interval. The OR estimate of each study is indicated by the solid black square. The size of the square represents the weight contributed by each study in the meta-analysis. The pooled Odds ratio for both fixed effects and random effects is shown by the diamonds. OR more than 1 indicates increased risk or susceptibility to HBV infection

Figure 12

Begg's funnel plot for publication bias

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