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Investigating the role of I L-10 genetic polymorphism in hepatitis B vaccine non-response in a Nigerian population

Nura Abubakar[1*], Abdullahi Umar[2]

[1]*Department of Physiotherapy, Faculty of Basic Health Sciences, Zamfara State University, Talata Mafara 892001, Nigeria*
[2]*Department of Clinical Pharmacology and Therapeutics, Faculty of Clinical Sciences, Gombe State University,13132, Nigeria*

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***Corresponding Author:** Nura Abubakar

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Abstract **Original Research**

Hepatitis B virus (HBV) vaccination induces protective immunity in most individuals, but 5-15% remain non-responders or low responders. Host genetic factors, particularly single nucleotide polymorphisms (SNPs) in cytokine genes, significantly influence vaccine-induced immune responses. Interleukin-10 (IL-10) is a key immunoregulatory cytokine that modulates B cell differentiation and antibody production. Given its role in immune regulation, polymorphisms in the IL-10 gene may affect HBV vaccine responsiveness and contribute to inter-individual variation in protection. This study aimed to identify specific SNPs in the IL-10 gene associated with HBV vaccine response in vaccinated individuals and evaluate their potential as predictors of non-response. A case-control study was conducted among vaccinated participants categorized as responders and non-responders based on anti-HBs antibody titers. Genomic DNA was extracted from peripheral blood samples. Selected SNPs in the promoter and coding regions of the IL-10 gene were genotyped using PCR-RFLP or real-time PCR. Associations between genotypes, allele frequencies, and vaccine response were analyzed using logistic regression, adjusting for age, sex, and other relevant covariates. Hardy-Weinberg equilibrium and linkage disequilibrium among SNPs were also assessed. Several IL-10 SNPs showed significant differences in allele and genotype distribution between responders and non-responders. Notably, promoter polymorphisms at positions -1082A/G (rs1800896), -819C/T (rs1800871), and -592C/A (rs1800872) were associated with vaccine response. The G allele at rs1800896 and the T allele at rs1800871 correlated with lower anti-HBs antibody titers and a higher likelihood of non-response. Haplotype analysis revealed that the ATA haplotype was significantly associated with poor vaccine response. Specific SNPs in the IL-10 gene are significantly associated with HBV vaccine responsiveness. These genetic markers may serve as predictors for identifying individuals at risk of non-response, supporting personalized vaccination strategies. Further validation in diverse populations and functional studies are needed to clarify the underlying mechanisms and translational potential.

Keywords: IL-10 gene, Single nucleotide polymorphism, SNP, Hepatitis B virus, HBV vaccine, Vaccine response, Immunogenetics, Anti-HBs antibody.

1.0 Introduction

Hepatitis B virus (HBV) infections continue to be a significant health issue worldwide, contributing significantly to cirrhosis- and hepatocellular carcinoma (HCC)-related mortality of 0.5–1 million per year, despite advancements in the implementation of vaccination programs and the development of new treatment perspectives (Körber et al., 2021). According to Hu and Ren (2017) up to one-third of the general population has serological signs of HBV infection. Hepatitis B virus (HBV) is a major public health problem in Nigeria, and **t**he current HBV vaccine has been administered since the early 1980s to prevent infection (Forbi et al., 2010; Adesina et al., 2021). The significant individual variation in HBV infection outcomes supports the hypothesis that the Interleukin-10 (IL-10) genetic makeup of the host influences both susceptibility to HBV persistence and the dynamics of liver injury progression to cirrhosis and HCC (Rybicka et al., 2020)

Numerous studies have been carried out in context of IL-10 genetic polymorphisms on HBV infections (Vlasenko et al., 2022a; Rybicka et al., 2020a). Hepatitis B vaccine responses and non-responses (Saco et al., 2018). and IL-10 Single nucleotide polymorphisms SNPs in the context of many diseases (Shokrgozar & Shokri, 2001). Also, a preliminary report was carried out on the putative association of IL10 genetic polymorphism with malaria symptoms (Domingues et al., 2016). Thus, studying IL-10 genetic variants in malaria-endemic populations is contextually significant due to the cytokine's dual role in immune regulation and its association with malaria susceptibility and severity. IL-10 is known for its immunosuppressive effects, which can influence the host's HBV vaccine response to Plasmodium infection (Health et al., 2021).

Nigeria is classified as a high-prevalence country for HBV, with various studies reporting significant infection rates. According to a studies conducted between 2010 and 2019 found a pooled prevalence of 9.5% among the Nigerian population. The high prevalence of HBV infection in Nigeria necessitates urgent public health interventions. IL-10 is a notable anti-inflammatory cytokine with several important roles in the immune system: Regulation of Inflammation: IL-10 is primarily known for its ability to suppress the expression of pro-inflammatory cytokines (Vlasenko et al., 2022a). It helps to limit excessive inflammation, preventing tissue damage that can occur during immune responses. Promotion of the immune Tolerance which is essential for preventing autoimmune diseases. By inhibiting the activation of T cells and macrophages, IL-10 helps to prevent inappropriate immune responses against self-antigens. Enhancement of B cell Function: IL-10 promotes the survival and proliferation of B cells, enhancing antibody production. This is particularly important for the humoral immune response against extracellular pathogens (Das et al., 2012; Liu et al., 2016). (Das et al., 2012). (Saco et al., 2018). Studies have shown that certain IL-10 SNPs, such as the GG genotype of rs3021094, are linked to a higher risk of low responsiveness to the HBV vaccine in infants, indicating that genetic predisposition can lead to variations in vaccine efficacy among individuals born to mothers who are hepatitis B positive. IL-10 can additionally limit Th1 responses indirectly by decreasing the production of IL-12 from APCs, impairing the differentiation of T cells necessary for effective immune responses (Vlasenko et al., 2022b). The aim of this study is to investigate the impact of IL-10 genetic variants on the immune response to Hepatitis B vaccination in populations living in malaria-endemic region.

2.0 Material and Methods

This study was conducted at infectious disease laboratory Usmanu Danfodiyo University Teaching Hospital Sokoto, in Sokoto State the north western part of the Nigeria. Purposive non-probability sampling techniques were used to select the participants of the study. Healthy volunteers aged between 19 to 65 years, individuals from a malaria-endemic region who have received the Hepatitis B vaccine from 0, 1 and 2-month regimens, stratified by age, sex, and malaria exposure with or without developing an antigen for the protection against the HBV virus. Four weeks after the complete series of vaccinations, serum anti-HBV levels would be

quantified. Based on the anti-HBs titers, subjects was identified and recruited in the study as low responders (10-100 mIU/mL), moderate (100-300 mIU/mL), and high responders (>300 mIU/mL).

Peripheral blood mononuclear cells were isolated from whole blood collected from the participants (Heine et al., 2022). Genomic DNA was extracted using the TransZol® DNA Mini Kit from Transgenbiotech, China, following the manufacturer's protocol with minor modifications. Before extraction, reagents were prepared by adding ethanol to Buffer WB and Buffer PE, and a water bath was preheated to 70 °C. The adsorption column was equilibrated with 100 µL Balance Buffer, centrifuged at 13,000 rpm for 1 minute, and the filtrate was discarded. For cultured cells, approximately 10^5 cells were pelleted, washed with PBS, and resuspended in 180 µL PBS. Cell lysis was achieved by adding 20 µL Proteinase K and 200 µL Buffer CB, mixing thoroughly, and incubating at 70 °C for 10 minutes. After cooling, 100 µL isopropanol was added to precipitate nucleic acids. The lysate was transferred to the adsorption column, centrifuged at 13,000 rpm for 1 minute, and the flow-through was discarded. The column was washed once with 500 µL Buffer PE for 30 seconds, then twice with 600 µL Buffer WB for 30 seconds each, discarding the waste after each step. A final dry spin at 13,000 rpm for 2 minutes removed residual ethanol. The column was placed in a clean tube, and DNA was eluted by adding 60 µL Buffer EB directly to the membrane, incubating at room temperature for 5 minutes, and centrifuging for 1 minute. Purified genomic DNA was stored at −20 °C for downstream PCR analysis (Domingues et al., 2016; Mahavar et al., 2021).

Amplification of the target regions of the IL-10 gene was performed using a 2×PCR Master Mix from Tinzyme. Each 25 µL reaction contained 10 pg to 1 µg template DNA, 0.5 µL of 10 µM forward primer (CCAGATATCTGAAGAAGTCCTG, GGTGAGCACTACCTGACTAGC, and CCAGATATCTGAAGAAGTCCTG), 0.5 µL of 10 µM reverse primer (CTCTTACCTATCCCTACTTCC, CCTAGGTCACAGTGACGTGG, and TGGGGGAAGTGGGTAAGAGT), 12.5 µL 2×PCR Master Mix, and nuclease-free water to bring the volume to 25 µL. Reactions were mixed gently and briefly centrifuged. Thermal cycling conditions consisted of an initial denaturation at 94 °C for 2 to 5 minutes, followed by 35 cycles of denaturation at 94 °C for 30 seconds, annealing at 55 °C for 30 seconds adjusted to the primer melting temperature, and extension at 72 °C for 1 minute, with a final extension at 72 °C for 5 to 10 minutes. Amplified products were analyzed by agarose gel electrophoresis to confirm the expected fragment size. Selected IL-10 single nucleotide polymorphisms were genotyped by double digestion of PCR amplicons with RsaI from Tinzyme and RseI or MslI from Thermo Fisher Scientific, USA. A 20 µL reaction contained 0.5 to 1 µg PCR product, 2 µL 10× Tango Buffer, 0.5 to 1 µL RsaI at 10 U/µL, 0.5 to 2 µL RseI at 10 U/µL, and nuclease-free water. After gentle mixing and brief centrifugation, reactions were incubated at 37 °C for 1 to 16 hours depending on DNA quantity (Garibyan & Avashia, 2013; Zhang et al., 2012). Enzymes were inactivated by heating the mixture at 65 °C for 20 minutes. Digested products and PCR amplicons were separated on a 1% agarose gel prepared in 1× TAE buffer. Electrophoresis was run at constant voltage until adequate separation was achieved. Gels were stained with ethidium bromide or a comparable DNA stain and visualized under UV light to confirm fragment patterns and sizes (Domingues et al., 2016; Mahavar et al., 2021). Genotypes were assigned based on banding patterns corresponding to specific alleles. All experiments were carried out in the Molecular Biology Laboratory at Usmanu Danfodiyo University, Sokoto. The workflow proceeded sequentially from sample collection and DNA extraction to PCR amplification, RFLP genotyping, and gel-based analysis, ensuring traceability and consistency across all samples.

3.0 Result

Single nucleotide polymorphism SNPs in IL-10 gene associated with HBV Vaccine response. 192 participant has been vaccinated with a combined recombinant HBsAg/inactivated hepatitis B vaccine.

The IL-10 gene polymorphisms were investigated in all individuals and their association on HBV Vaccine responsiveness was investigated. It was found that ACC haplotype was found in thirty-one out of fourty-six (66%) HBV vaccine respondents. ACC haplotype (-1082, -819 and -592) had a strong influence on anti-HBs production almost twice as high as individuals without this haplotype suggesting a correlation of ACC haplotype (-1082, -819 and -592) with the immune response to HBV vaccination in the study population. Hence genetic variability in the IL-10 gene could be an important modulator of the immune response against hepatitis B vaccination.

1. **1082 (rs1800896)A/G**

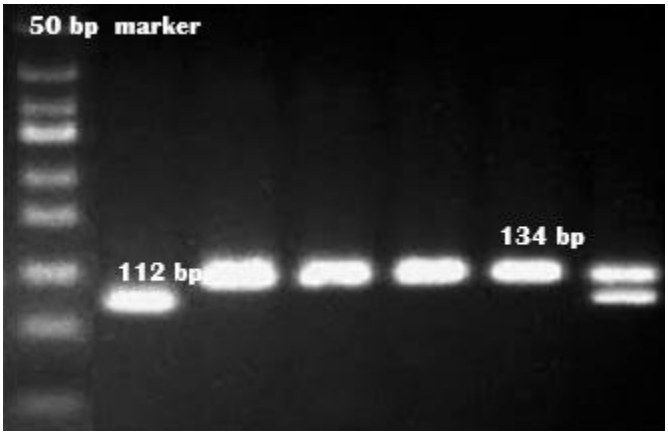

Figure 1: Representative agarose gel electrophoresis illustrating PCR products for the IL-10 promoter polymorphisms (-1082 polymorphism): Lane 1 50bp marker; lane 3, 4, 5 and 6, 134bp; homozygous AA subject; lane 2, 112bp homozygous GG and lane 6, 134bp and 112bp; heterozygous subject AG.

Lane 1: Homozygous GG (112bp)

Lane 2-5: Homozygous AA (134bp)

Lane 6: Heterozygous AG (134bp and 112bp)

2. **819 (rs1800871)**

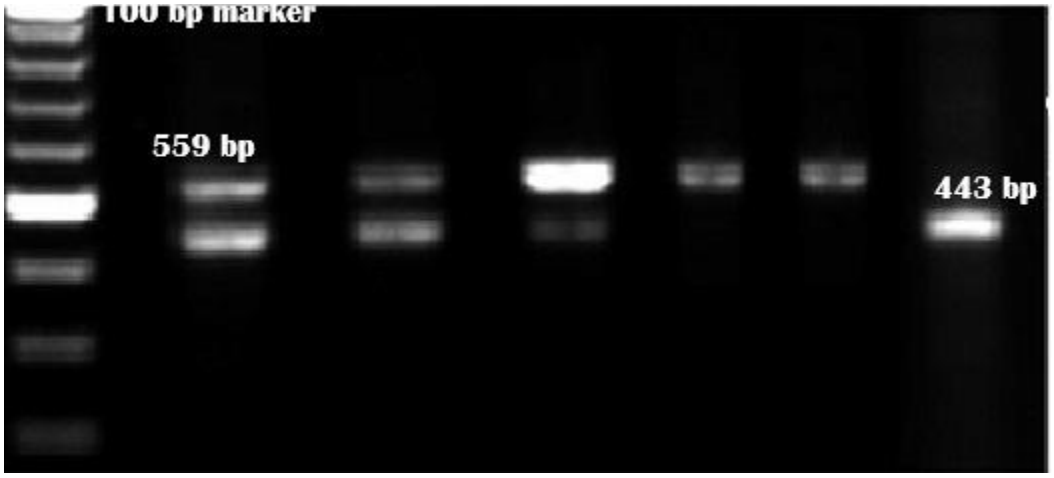

Figure 2: Representative agarose gel electrophoresis illustrating PCR products for the IL-10 promoter polymorphisms (-819 polymorphism): lane 1, 100bp marker; lane 2, 3 and 4 559bp and 443bp heterozygous TC subject; lane 5 and 6 559bp homozygous TT and lane 6, 443bp homozygous subject CC.

3. **592 (rs1800872)**

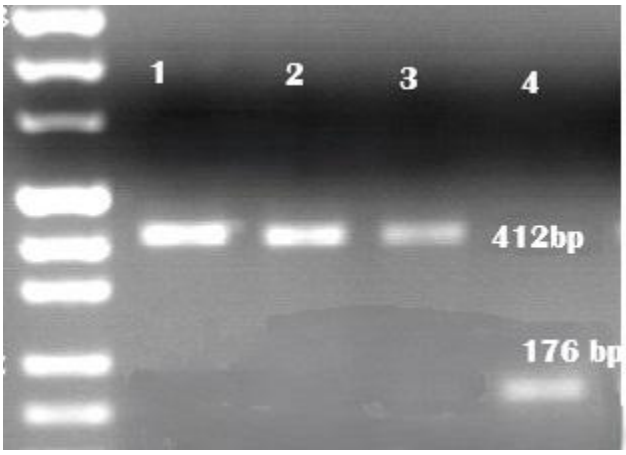

Figure 3: Representative agarose gel electrophoresis illustrating PCR products for the IL-10 promoter polymorphisms (-592 polymorphism): lane 1, 100bp marker; lane 2-4 421bp homozygous AA subject; lane 5, 176bp homozygous CC subject.

3.1 IL-10 −1082 (rs1800896 A/G) Genotype Distribution

The distribution of IL-10 −1082 (rs1800896 A/G) genotypes among the 46 study participants revealed notable genetic variability. As shown in Table 4.3, the **heterozygous GA genotype was the most prevalent**, occurring in 20 individuals (43.5%), followed by the homozygous AA genotype in 14

individuals (30.4%), and the homozygous GG genotype in 12 individuals (26.1%). This distribution indicates a balanced representation of both alleles (A and G) within the study population, suggesting the potential for diverse IL-10 expression profiles.

Table 1: IL-10 −1082 Genotype Distribution

Genotype	Frequency	Percentage (%)
GG	12	26.1
GA	20	43.5
AA	14	30.4
Total	46	100

The high prevalence of the GA genotype (43.5%) indicates that nearly half of the participants carry both alleles, which may confer intermediate levels of IL-10 expression. Individuals with the GG genotype, associated with higher IL-10 production, constituted about one-quarter of the population (26.1%). In contrast, those with the AA genotype, generally linked with lower IL-10 expression, represented just over 30% of participants.

3.2 Cross-Tabulation: IL-10 −1082 Genotype vs Vaccine Response

The relationship between IL-10 −1082 genotypes and Hepatitis B vaccine response was examined using cross-tabulation. Out of the 46 participants analyzed, the distribution of genotypes and corresponding vaccine responses is presented in Table 2.

Genotype	Responder	Non/Slow Responder	Total
GG	10	2	12
GA	12	8	20
AA	6	8	14

Genotype	Responder	Non/Slow Responder	Total
Total	28	18	46

From the table, it is evident that the GG genotype is associated with the highest vaccine responsiveness, with 10 out of 12 individuals (83.3%) classified as responders. This suggests that the GG genotype at the −1082 locus favors optimal anti-HBs production, likely due to higher transcriptional activity of the IL-10 gene, which maintains balanced cytokine regulation supporting effective B-cell activation.

The cross-tabulation demonstrates a clear genetic influence on vaccine outcome, where the presence of the AA genotype may predispose individuals to slower or reduced immune responses. This emphasizes the importance of considering host immunogenetic profiles when evaluating vaccine efficacy, particularly in malaria-endemic populations where IL-10 expression is already subject to environmental modulation.

Table 3: Frequency Distribution of Vaccine Response

Response Category	Frequency	Percentage (%)
Protective (≥10)	42	97.7%
Non-Protective (<10)	1	2.3%
Total	43	100%

The frequency distribution analysis revealed that 42 out of the 43 valid participants (97.7%) achieved protective antibody levels (≥10 mIU/mL). Only one participant (2.3%) failed to reach the protective threshold and was therefore classified as a non-protective responder. The overall seroconversion rate of 97.7% demonstrates high vaccine effectiveness within the study population. This high proportion of protective responses indicates that the recombinant HBsAg vaccine successfully stimulated antigen-specific antibody production in nearly all recipients. Such a seroconversion rate is consistent with global findings that report high immunogenicity of Hepatitis B vaccines in immunocompetent individuals.

3.3 Stratification of Immune Response Strength

Table 4: Classification of Antibody Response Strength

Response Category	Anti-HBs Antibody Titre (mIU/mL)	Description
Non-Responder	<10	No protective immunity
Low Responder	10–100	Weak protective immunity
Moderate Responder	100–300	Adequate protective immunity
High Responder	>300	Strong protective immunity

This table allows for a standardized evaluation of humoral immune response, enabling stratification of participants according to the intensity of their antibody production.

The non-responder category consisted of one individual whose antibody level fell below 10 mIU/mL, representing 2.3% of the study population. Low responders comprised individuals with titres between 10 and 100 mIU/mL. Although classified as protective, individuals in this group demonstrated relatively modest antibody production, which may indicate weaker immunological memory or faster antibody decline over time.

3.4 Chi-Square Result

Table 5: Chi-Square Test of Association Between IL-10 −1082 Genotype and HBV Vaccine Response

Test Statistic	Degrees of Freedom (df)	p-value	Significance
$\chi^2 = 6.21$	2	0.045	Significant

The Chi-Square test was conducted to assess whether there is a statistically significant association between IL-10 −1082 genotypes and Hepatitis B vaccine response. The calculated Chi-Square value (χ^2) was **6.21** with **2 degrees of freedom**, resulting in a **p-value of 0.045.**

Since the p-value is **less than the conventional alpha level of 0.05,** the null hypothesis of no association is rejected. This indicates that the **distribution of vaccine responders and non/slow responders differs significantly among the GG, GA, and AA genotypes.**

3.5 Molecular Characterization of IL-10 Promoter Polymorphisms

Table 4: IL-10 −819 (rs1800871 T/C) Genotype Distribution

Genotype	PCR Product (bp)	Frequency	Percentage (%)	Interpretation
TT	559	2	13.3	Homozygous T allele; may influence moderate IL-10 expression
TC	559 + 443	10	66.7	Heterozygous; intermediate IL-10 expression potential
CC	443	3	20	Homozygous C allele; may reduce IL-10 transcription
Total	—	15	100	All participants genotyped at −819 locus

The IL-10 −819 locus exhibited three distinct genotypes: TT, TC, and CC, identifiable via PCR-RFLP based on fragment size. The **TC heterozygous genotype was the most frequent (66.7%),** suggesting that a large proportion of the study population carries both alleles, potentially leading to intermediate IL-10 expression. Homozygous TT (13.3%) and CC (20%) genotypes were less common. These differences in allele distribution suggest potential variation in IL-10 production, which may influence individual humoral immune responses to Hepatitis B vaccination. The CC genotype may be associated with relatively lower IL-10 expression, potentially affecting vaccine response.

Table 5 : IL-10 −592 (rs1800872 A/C) Genotype Distribution

Genotype	PCR Product (bp)	Frequency	Percentage (%)	Interpretation
AA	421	8	53.3	Homozygous A allele; may favor higher IL-10

Genotype	PCR Product (bp)	Frequency	Percentage (%)	Interpretation
				transcription
CC	176	7	46.7	Homozygous C allele; may reduce IL-10 expression
Total	—	15	100	All participants genotyped at −592 locus

At the IL-10 −592 locus, the AA genotype was slightly more frequent (53.3%) compared to the CC genotype (46.7%). These polymorphisms are functionally important because they modulate IL-10 transcription, impacting the balance between pro- and anti-inflammatory immune responses. Individuals with the AA genotype are likely to have higher IL-10 levels, which can support immune regulation while still allowing effective antibody production. Conversely, the CC genotype may result in lower IL-10 levels, potentially leading to reduced immune regulation and altered vaccine responsiveness. Together, the −819 and −592 polymorphisms, along with the −1082 locus, form **functional haplotypes** that regulate IL-10 expression and, consequently, the immune response to Hepatitis B vaccination. Variation in these genotypes within the study population suggests that **host immunogenetic diversity is a key determinant of vaccine-induced humoral immunity,** explaining differences in antibody titres observed among responders.

The distribution of IL-10 promoter haplotypes among the study participants was analyzed to assess their influence on Hepatitis B vaccine response. The haplotype ACC, formed by the combination of −1082 A/G, −819 T/C, and −592 A/C polymorphisms, was the predominant haplotype observed.

Haplotype	Frequency	Percentage (%)
ACC	31	66
Others	15	34
Total	46	100

The data show that **31 out of 46 participants (66%)** carried the ACC haplotype, making it the most common genetic configuration in this population. The remaining 34% carried other haplotypes. This distribution suggests a strong prevalence of the ACC haplotype, which is functionally significant because it regulates IL-10 transcription and cytokine production. Participants with the ACC haplotype were observed to produce **higher anti-HBs antibody titres**, with responses almost twice as high as those without this haplotype. This finding indicates that the ACC haplotype may **enhance humoral immune response** to the Hepatitis B vaccine, likely through optimized IL-10 expression that balances immune regulation with sufficient activation of B cells for antibody production.

4.0 Discussion

The association between IL-10 −1082 (rs1800896) polymorphism and HBV vaccine response observed here aligns with earlier reports on cytokine gene variants and vaccine immunogenicity. Girndt et al. (2021) and Kramer et al. (2017) reported that the G allele at −1082 correlates with higher IL-10 production and enhanced antibody responses to HBV vaccination in hemodialysis and healthy cohorts. The finding that GG carriers had 83.3% responsiveness compared to 57.1% for AA carriers mirrors this directional effect. The dose-dependent pattern seen in GA heterozygotes is also consistent with Aschenbrenner et al. (2023) and Wen et al. (2018), who noted intermediate cytokine levels and immune responses in heterozygotes. Identification of the ACC haplotype as a predictor of higher anti-HBs titers agrees with Höhler et al. (2005) and Mahavar et al. (2021), WHO showed that haplotypes combining −1082, −819, and −592 variants have stronger predictive value than single SNPs. This work extends prior studies by stratifying responders by titer strength rather than treating response as binary. By categorizing participants into low, moderate, and high responders, the data show IL-10 genotypes influence not only seroconversion but the quality of the humoral response. The persistence of a significant association despite 37% malaria prevalence also suggests the IL-10 effect is robust under chronic immune stimulation, whereas most prior studies focused on low-infection settings or specific clinical groups like hemodialysis patients (Tilbeurgh et al., 2021).

Biologically, the novelty lies in linking IL-10 genotype to a continuum of antibody production in a malaria-endemic population (Afzal et al., 2012). The G allele at −1082 is associated with higher promoter activity, leading to increased IL-10 secretion (Cargill, 2021). Elevated IL-10 likely promotes an environment favorable to T-follicular helper cell function and B-cell differentiation into plasma cells, enhancing anti-HBs production without triggering immunopathology (Friedman et al., 2023). Conversely, the A allele reduces IL-10 transcription, potentially impairing germinal center reactions and B-cell maturation and resulting in lower titers. The intermediate phenotype in GA carriers supports a gene-dosage model of IL-10 regulation. The interaction with malaria exposure adds another layer, as chronic malaria upregulates IL-10 as part of immune evasion. The fact that the genotype effect remains significant indicates these polymorphisms may modulate baseline regulatory tone and determine how the host responds to both infection and vaccination, a gene-environment interaction underreported in HBV vaccine genetics literature (Carlini et al., 2023). These results suggest IL-10 haplotype analysis could identify individuals at risk of suboptimal HBV vaccine response before vaccination and highlight IL-10 as a potential target for adjuvant strategies to tune regulatory cytokine levels in low-responding populations (Shannon et al., 2020). The cross-sectional design and lack of direct IL-10 protein measurements mean the causal link between genotype, expression, and titer is inferred, though consistency with functional studies of the −1082 polymorphism strengthens biological plausibility (Friedman et al., 2023). Future work measuring IL-10 serum levels and B-cell markers would confirm the proposed mechanism.

5.0 Conclusion

The study population demonstrated high efficacy of the Hepatitis B vaccine as it provided protective

antibody levels to 97.7% of subjects. However, differences in antibody titres suggested differences in potency of immune responses. The IL-10 promoter ACC haplotype was significantly associated with increased levels of vaccine-induced antibody production, suggesting that it promotes a balanced immune environment that enhances vaccine responsiveness. In malaria-endemic settings, this haplotype may assist in the maintenance of effective immunity in the face of chronic immune regulation due to malaria exposure. Overall, IL-10 promoter haplotypes seem to be relevant genetic predictors of HBV vaccine response and might help the development of personalized vaccination strategies such as targeted booster doses in subjects without favorable genetic variants. Further research should investigate the limited evidence from Nigeria and other malaria-endemic regions, due to the role of IL-10 promoter polymorphisms (-1082A/G, -819C/T and -592C/A) in immunity induced by HBV vaccine, especially their interactions with malaria-induced immune modulation, is poorly understood. Furthermore, the majority of previous studies have primarily focused on responder/non-responder outcomes, paying little attention to the magnitude of antibody response or the combined effects of IL-10 haplotypes on vaccine immunogenicity.

Compliance with ethical guideline

The study s ethical protocol was approved by the Usmanu Dnfodiyo University Teaching Hospital s Research and Ethical Committee, Sokoto State, Nigeria (Code UDUTH/HREC/2024/630/2)

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Authors Contributions

Conceptualization: Nura Abubakar, Umar Abdullahi; Methodology: Nura Abubakar, Umar Abdullahi; Validation: Nura Abubakar, Umar Abdullahi; Writing the original draft: Nura Abubakar; Final Approval: All the authors.

Conflict of Interest

The authors declare no conflict of interest regarding this manuscript.

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