RESEARCH ARTICLE

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Interleukin-13 (rs20541 A/G) Gene Polymorphism and Chance of Acquiring Hepatitis B in the Egyptian Population

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Abstract

Context and Objective: An important worldwide health concern is infection with the hepatitis B virus (HBV), especially in underdeveloped nations. Gene polymorphisms encoding pro- and anti-inflammatory cytokines can influence how an HBV infection presents clinically. As mediators, cytokines play important functions in the immunological and inflammatory systems. A strong pleiotropic cytokine is interleukin-13 (IL-13). The research attempts to look into the relationship between HBV infection in Egyptians and variations in a single nucleotide in the IL-13 (rs20541 A/G) gene. **Materials and methods:** One hundred and twelve hepatitis B cases and fifty control subjects were involved in the investigation. Utilizing an allelic discrimination test pre-validated TaqMan™ MGB probe (Applied Biosystem). To investigate the relationship between the SNP of (IL-13) (rs 20541 A/G) gene and HBV, we used real-time PCR. **Results:** The IL13 (rs20541 A/G) gene polymorphism study identified more frequent occurrences of the A/G and A/A genotypes among the patients (OR = {62.536, 21.25}, CI = {[19.276-202.889], [3.055-147.8]}, P = {0.0001, 0.002}). In the patient group, the A allele frequency was markedly different from the control group's (CI = 2.614-8.229, OR = 4.638, P < 0.0001). Nevertheless, the current investigation did not find a connection between HBV fibrosis and the gene polymorphism of IL-13(rs 20541 A/G). **Conclusion:** The rs20541 single nucleotide polymorphism (SNP) in IL-13 gene is linked to an increased risk of HBV.

Keywords: HBV- IL-13 (rs20541 A/G)- single nucleotide polymorphism(SNP)

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Introduction

The HBV genome, which is 3.2kb in size and belongs to the Hepadnaviridae family, is relaxed circular in nature. The research indicates that it selectively damages hepatocytes, resulting in acute liver injury. To create a molecular pattern that supports the viral RNA mediator, the viral DNA is then reverse-transcribed back into the genomic DNA after being converted into the stable covalently closed circular DNA (cccDNA).

A low therapy level is maintained due to cccDNA attributes [1]. The largest ORF in the viral polymerase gene generates the protein responsible for reversing transcription. The virus envelope harbors genes for the L, M, and S surface antigens (HBsAg). The viral capsid's capsomers are constructed by the core protein and pre-core genes. One encoded regulatory protein is called HBx. Hepatocellular carcinoma (HCC) [2] is the most common kind of liver cancer and is mostly brought on by the multifunctional control of the HBx protein [3].

Africa, Southern Europe, Asia, the Pacific Islands, and Latin America are endemic for chronic HBV infection. Around 300 million individuals globally are long-term carriers of HBsAg, increasing their risk of hepatic decompensation, HCC, and liver cirrhosis [4, 5]. Approximately one million deaths occur annually due to acute or chronic infection with the Hepatitis B virus [6]. Chronic HBV infection has five distinct phases, each representing a different level of viral replication and inflammation. The five phases, without strict sequentiality, are the basis for making treatment decisions. Antiviral medications enhance patient outcomes by inhibiting

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viral replication and minimizing liver damage due to new insights into HBV biology and cause. A functional cure is successful for only a minority of patients [7, 8].

Every year, one million deaths worldwide result from liver cirrhosis and HCC caused by HBV infection [9]. An HBV infection can occur in older children through contaminated blood from intravenous drug use or sexual interaction. Chronically infected patients with hepatitis B (CHB) had a yearly incidence of 4% HCC and a 50% chance of developing liver cirrhosis. HBV-induced liver damage is primarily due to the host's immune response [10]. Antibodies against hepatitis B development elicited by hepatitis B vaccination or endogenous HBV infection are linked to multiple genotypes, possibly driven by IL13 [11].

The crucial cytokine interleukin-13 (IL-13), secreted by helper T cell type 2 (TH2), controls inflammatory immune responses. Immunoglobulin E (IgE) and IL-13 cause B lymphocytes to release Major Histocompatibility Complex (MHC) class II molecules.

Moreover, TNF-α, IL-1α, IL-4R, and IL-8 production of pro-inflammatory cytokines can be inhibited by it [12]. Chromosome 5q31 contains the human IL-13 gene, which has a length of 2938 base pairs. It is only slightly correlated with single nucleotide polymorphisms (SNPs). Exon 4 at location 130 has one common coding SNP, IL-13 SNP rs20541, which causes a shift in codon use from G to A [13-15]. rs1800925 is another frequent SNP found in the 5' flanking region that frequently results in a substitution from C to T [16]. The binding of STAT transcription factors may also be impacted by individual differences in the rs1800925 IL-13 polymorphism, which might thus have an impact on the amount of IL-13 produced by activated T cells [14, 17].

IL-13 is an important immunoregulatory mediator in a variety of cell types because it minimizes macrophage activity and stops chemokines and pro-inflammatory cytokines from being produced. Genetic differences in IL-13 and its receptor components have been associated with increased illness prevalence rates, and it is activated in response to inflammatory conditions [18].

Receptor complex type 2 recruits IL-4Rα when IL-13 binds to the IL-13Rα1 receptor. In order to suppress IL-13 signal transduction, one can impede binding to either the IL-4Rα or IL-13Rα1 receptor [19]. It is thought that IL-13 serves as the main cause of asthma attacks [20]. Through TH2 helper cells, IL-13 promotes B lymphocyte development, which in turn modulates the humoral immune response at the cellular level [21]. Furthermore, IL-13 suppresses macrophage activation and increases matrix metalloproteinases (MMPs), for instance, in the respiratory tract and gingival fibroblasts [22].

It has been established that the main effector cytokine is IL-13 in hepatic fibrogenesis resulting from a variety of reasons [23, 24]. Patients with non-alcoholic steatohepatitis (NASH) have considerably higher blood IL-13 levels. The function of IL-13 in the liver's reaction to metabolic stress is complex. Hepatic stellate cells (HSCs) that have been activated overexpress IL-13, which exacerbates NASH fibrosis [25, 26]. Thus, the purpose of this investigation was to examine any possible connections between Egyptian patients' HBV and the IL13 rs20541A/G gene polymorphism.

Materials and Methods

Subjects

The study sample included 50 healthy control subjects (34% male and 66% female; mean age 46.08 ± 11.47 years) who had no history of infectious, autoimmune, malignant, or liver/kidney issues, and 112 people from the National Liver Institute at Kafer El-Sheikh University in Egypt who had a clinical diagnosis of chronic HBV infection (mean age 46.42 ± 8.93 years; 73.2% male and 27.8% female) (Table 1).

Patients' ethics declaration

The National Research Center's Medical Research Ethics Committee (MREC) authorised the study (44512012023), and each participant completed an informed consent form.

Blood samples

A 3-millilitre blood sample was drawn from each participant under very rigorous sterile conditions for common routine laboratory tests, complete blood picture, and DNA extraction.

ALT, AST, AFP, Hgb, albumin, total bilirubin, inorganic phosphorus, white blood cells, red blood cells, and platelets are some common biochemical and hematological markers that were measured at admission for each patient using standard techniques in a typical clinical laboratory.

DNA extraction from peripheral whole blood

Whole blood samples should be treated (for both patients and controls) while EDTA was present as an anticoagulant, according to the manufacturer's instructions. Thermo Scientific™, (cat. Number: K0781), the Gene JET whole blood genomic DNA purification micro kit, was utilized to extract all of the genomic DNA from the sample. DNA purity and concentration were assessed using a NanoDrop™ 2000 spectrophotometer (Thermo Scientific™). All extracted DNA samples were stored at -80°C until used for genotyping [27].

Genotyping of IL-13 (interleukin-13) (rs20541 A/G) polymorphism

Utilizing a revalidated TaqMan™ MGB probe for allelic discrimination assay from Applied Biosystems, real-time PCR was applied to identify SNP on IL-13 gene rs20541 A/G. 1.25 µL of a 40X combined primer and probe mix (cat. Number: 4351379) (ABI/Life Technologies, USA) was added to 12.5 µL of 2X TaqMan Universal PCR master mix (cat. Number: 4371353) (ABI/Life technologies, USA) in a 25 µL final volume of DNAse/RNAse-free water (Invitrogen/Life Technologies,USA) and template. The cycle conditions included ten minutes at 95°C, fifteen seconds at 95°C, and one minute at 60°C make up the cycle. Forty rounds were applied to the last two phases. The PCR run was carried out using Real time-PCR system (Max3005P QPCR system, Stratagene,

Table 1. Baseline and Demographic Data of Patients

	Patients No=112(%)	Control No=50 (%)	P
Gender			
Male	82 (73.2%)	17 (34%)	0.001*
Female	30 (26.8%)	33 (66%)	
Age/year	46.42 ± 8.93	46.08 ± 11.47	0.853
Clinical Data			
Free	55 (49.1%)	none	
Fatty liver	25 (22.3%)		
Cirrhotic liver	22 (19.6%)		
HCC	10 (8.9%)		
HBV markers			
HBV Ag	3 (2.7%)	none	
HBV Ab	1 (0.9%)		
HBs Ag	112 (100%)		
HIV Ab	0	0	
Medical history (HCC)	1 (0.9%)	0	
Family history (Colonindistentes)	1 (0.9)	0	
ALT (IU/L)	32.61±11.82	30.02±1.97	0.492
AST (IU/L)	35.89 ± 17.34	23.96 ± 3.02	<0.001*
Total bilirubin (mg/dL)			
Median	0.8	0.8	0.018
Min. – Max.	0.60 – 5.40	0.70 – 1.0	
Direct Bilirubin (mg/dL)			
Median	0.2	0.6	<0.001*
Min. – Max.	0.10 – 0.80	0.50 – 0.70	
Albumin (g/dL)	4.39 ± 0.51	3.99 ± 0.27	<0.001*
HB (%)	13.90 ± 1.62	12.49 ± 0.98	<0.001*
WBC (x $10^3/mm^3$)	6.60 ± 1.83	7.19 ± 1.35	0.024*
Platelets (x$10^3/mm^3$)	210.73±59.17	215.60±44.81	0.234
INR	1.13±0.1	0.98±0.06	<0.001*
AFP (IU/L)			
Median (IQR)	4.70 (2.55 – 6.0)	3.0 (2.0 – 5.0)	<0.001*

Median (IQR), Inter quartile range; HCC, Hepatocellular carcinoma; AFP, Alpha-Fetoprotein; p, p value for comparison between the studied two groups; *, Statistically significant at $p \leq 0.05$

Agilent biotechnology, USA).

Statistical analysis

Version 20.0 of IBM SPSS was the program we used to analyze the data. Numbers and percentages were used to quantify the data. A normal distribution was shown via the Kolmogorov-Smirnov test. We used measures such as range, mean, standard deviation, median, and interquartile range to characterize the data. At a confidence level of five percent, the results were considered statistically significant. Both quantitative measurements and categorical data were compared using independent student t-tests. In categorical data analysis, the chi-square test was employed to evaluate group differences. The data was analyzed using logistic regression analysis, which produced 95% confidence intervals for the odds ratios of HBV association with each genotype. Statistical significance was indicated by a p-value of less than 0.05.

Results

Participant demographics

Table (1) presents the baseline and demographic data of patients with HBV infection and the control group.

Those with HBV had both HBV-DNA and HBsAg but were negative for HCV antibodies. HBV-DNA, HCV antibodies, and HsAg, on the other hand, were all negative in all controls. Male patients with the condition were more likely to have it; of the patients, 49.1% had no fibrosis, 22.3% had fatty liver, 19.6% had cirrhosis, and 8.9% had HCC. AST, total bilirubin, albumin, AFP, INR, and HB were all statistically significantly different between the patient group and the control group ($P < 0.05$). White blood cell and direct bilirubin levels in HBV patients are significantly lower in the patient group than in the control group ($P < 0.05$). Age, ALT, and platelet levels did not vary meaningfully.

Table 2. Distribution of Genotypes and Alleles Frequencies of IL-13 (rs 20541 A/G) Gene polymorphism in HBV and Healthy Control Subjects

IL-13 (rs 20541) gene polymorphism	Patients No=112(%)	Control No=50 (%)	OR	0.95% CI	P-value
Genotypes					
AA	5 (4.5%)	2 (4%)	21.25	3.055-147.8	0.002*
AG	103 (92%)	14 (28%)	62.536	19.276-202.880	0.0001*
GG	4 (3.6%)	34 (68%)	1		
HWE	0.716	0.001			
Alleles					
A	113 (50.4%)	18 (18.0%)	4.638	2.614-8.229	0.0001*
G	111 (49.6%)	82 (82.0%)			
Model of inheritance					
Dominant	GG vs AA+AG		0.017	0.005-0.056	0.0001*
Co-dominant	AG vs AA+GG		29.429	11.735-73.798	0.0001*
Recessive	AA vs AG+GG		1.121	0.210-5.986	1

IL-13, Interleukin-13; CI, confidence interval; OR, odds ratio; P, p value for comparing between the different studied groups. *, Statistically significant at $p \leq 0.05$.

Table 3. Distribution of IL-13 (rs20541A/G) Genotypes According to Fibrosis Stages in HBV Patients

		IL-13 (rs20541 A/G) genotypes			P-value
		AA	AG	GG	
		N (%)	N (%)	N (%)	
Fibroscan	F0-F1	2 (40.0%)	49 (47.6%)	4 (100.0%)	0.339
	F1-F2	2 (40.0%)	23 (22.3%)	0 (0.0%)	
	F2-F3	0 (0.0%)	22 (21.4%)	0 (0.0%)	
	HCC	1 (20.0%)	9 (8.7%)	0 (0.0%)	

IL-13, Interleukin-13; F0-F1, Normal; F1-F2, Moderate scarring; F2-F3, Severe scarring; HCC, Hepatocellular carcinoma; P, p value for comparing between the different studied groups

The IL13 gene rs20541 analysis's genotype and allele distribution were shown in (Table 2). Greater frequencies of the A/G (CI = 19.276–202.889, OR = 62.536, P = 0.0001) and A/A (CI = 3.055–147.8, OR = 21.25, P = 0.002) genotypes were seen in the patients. The frequency of the A allele differed significantly between the patients and control groups (CI = 2.614-8.229, OR = 4.638, P < 0.0001). Nonetheless, the current investigation demonstrated a relationship between HBV and the IL-13 (rs20541 A/G) gene polymorphism.

The examination of the IL-13 (rs20541 A/G) genotypes distribution in relation to fibrosis stages is shown in Table 3.

In HBV patients, the distribution of IL-13 (rs20541 A/G) genotypes did not significantly differ between fibrosis stages (P=0.339). In F0-1 individuals, the occurrence of the AG genotype was highest (47.6%), while among HCC patients, it was the lowest (8.7%). 100% of F0-F1 patients had the maximum GG frequency.

There was no significant link between the AA genotype and the development of F1-2, F2-3, and HCC in comparison to F0-1, with adjusted OR's of 0.815 (95% CI: 0.058-3.272), 1.415 (95% CI: 1.223-1.673), and 0.340 (95% CI: 0.028-4.147) and p-values of 0.242, 0.428, and P=ns, respectively. In contrast to F0-1, the GG+AG genotypes' frequency did not show a significant correlation with the fibrosis development in F1-2, F2-3, and HCC (0.815, 95% CI: 0.058-3.272; 1.415, 95% CI: 1.223-1.673; P = 0.242 and 0.340, 95% CI: 0.028-4.147; P = 0.428, respectively) (Table 4).

Table 4. In HBV Patients, the Distribution of IL-13 (rs20541 A/G) Genotypes is Related to Fibrosis Stages.

IL-13 gene polymorphism	AA	(GG+AG)	OR	95% CI	P
IL-13 (rs20541 A/G)					
F0-1	2 (3.6%)	53(96.4%)	----	----	----
F1-2	2 (8%)	23(92%)	0.434	0.058-3.272	0.37
F2-3	0 (0%)	22 (100%)	1.415	1.223-1.673	0.242
HCC	1 (10%)	9 (90%)	0.34	0.028-4.147	0.428

IL-13, Interleukin-13; F0-F1, Normal; F1-F2, Moderate scarring; F2-F3, Severe scarring; HCC, Hepatocellular carcinoma; CI, confidence interval; OR, odds ratio; P, p value for comparing between the different studied groups

Discussion

A major global health risk is infection with the hepatitis B virus, particularly in developing countries [28]. Approximately one million people die and 300 million are chronically infected each year due to the hepatitis B virus (HBV) [29]. The world ranks Egypt among the top countries with high HCV prevalence rates [30].The hepatitis B virus was successfully prevented in 1992; however, the prevalence of HBsAg in Egypt remained between 2 and 7% [30]. Despite this, it is still unclear with precision how common HBV is across Egypt as a whole. In 2015, the WHO reported that hepatitis B would be eradicated by 2030. Liver transplantation may eventually be necessary for end-stage HBV- related liver illness, and graft failure in recipients of immunocompromised liver transplants can be exacerbated by HBV recurrence [31]. For HCC brought on by HBV, the male-to-female ratio is around 5-7 times higher in men than in women [32]. More cases and deaths from HBV-related liver illnesses occurred in males compared to females [33, 34]. The current study included more men (73.2%) than women (26.8%) in the HBV group.

Numerous pieces of evidence clearly indicate that host genetic variables may be important in the development of HBV, and as such, they are being extensively researched for the different consequences of HBV infection [35-37]. The frequency of hepatitis B surface antigen positive in matching twins is higher than in twins who are fraternal, suggesting that host-related genetic variables influence the HBV infection cycle. Gene polymorphisms can change the biological function, protein structure, and amino acid sequence [38, 39].These hereditary gene polymorphisms have the potential to increase an individual's susceptibility or resistance to a particular disease [37].

The hepatic microenvironment's condition throughout the inflammatory process may be evaluated thanks to cytokines, which are important players and strong immuno-modulatory agents [40]. Immunological differences within the host may be the cause of the various clinical manifestations of HBV infection. The severity of infections is influenced by gene polymorphisms that impact the production of pro- and anti-inflammatory cytokines [38]. The genetic information about cytokines and other mediators can be important in identifying high-risk individuals for developing chronic hepatitis and in planning preventive measures and therapy for these individuals [37, 41]. Modern research primarily focuses on the impact of cytokine gene polymorphisms on infectious disease outcomes, vaccine responses, and therapeutic courses. Individual disparities in clinical outcomes may primarily stem from polymorphisms in cytokine-producing genes; hence, these polymorphisms can be utilized to identify individuals with chronic hepatitis who face an elevated risk of contracting hepatocellular carcinoma [42]. Prior research has demonstrated that genetic variables may be crucial in influencing how an HBV intrauterine infection turns out.

Numerous epidemiological investigations have been conducted to determine whether IL-13 polymorphisms affect a person's propensity to develop cancer. The IL-13 rs1800925, IL-13 rs20541, and IL-13 rs1295685 polymorphisms have been linked to asthma and serum IgE, respectively, in accordance with haplotype findings [43, 44]. IL-13 rs1800925 was strongly connected with rhinitis [45, 18].

Previous studies had reported that there may be a higher risk of HBV due to the IL-13 rs20541 polymorphism. According to current research, 50.4% of HBV patients carried the A allele, while only 18% of healthy controls did. Our findings initially reported, a 2019 study [46] revealed that Iranian HBV patients had a larger distribution of the A/A genotype and A allele at IL-13/+110 (36.7% and 8.6%, respectively) compared to controls (9.3% and 6.4%, respectively).Patients with HCC associated with HBV and IL-13 genetic variations might have an increased risk linked to the functional IL-13 rs20541 polymorphism [44].

In conclusion, current research suggests that the rs20541 SNP polymorphism in IL-13 gene may increase the risk of HBV. Future research would offer a more thorough explanation of how IL-13 gene polymorphisms contribute to the progression of HBV illness.

Author Contribution Statement

NEI played a major role in formulating the hypothesis, performing molecular techniques, biochemical analyses, manuscript writing, and final review. AEGSO, FGY, AAE conducted biochemical analyses, statistical work. MMSF, AAEBM managed patient care and clinical examinations and contributed to manuscript review. MS contributed to biochemical analysis, data interpretation, and manuscript revisions. All authors reviewed and approved the final manuscript..

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Data availability (if pertinent to your study)

The information created or analysed during this inquiry is contained in this published paper (and its additional information files).

Data Availability Statement

The author has chosen not to share the data.

Approval

Ethical approval was granted by the Medical Ethical Committee of the National Research Centre, Dokki, Giza [No. 05430123].

Conflict of Interest

The authors declare no conflicts of interest related to

this work.

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