BIOLOGICA NYSSANA
16 (1) June 2025: 287-296
DOI: 10.46793/BiolNyss.16.1.15A

Role of 11β-hydroxysteroid dehydrogenase gene polymorphisms rs846910 and rs12086634 in the etiology of hepatocellular carcinoma

Original Article

Ahmed Mudher Al-Khaykanee
General Directorate of Education of Babylon Governorate, Iraq
ahmedmudher14@gmail.com (corresponding author)

Soura Alaa Hussein
Department of Technical Nursing, Technical Institute-Baghdad, Middle Technical University, 10074, Iraq

Z Muhsen M Ali
Department of Technical anesthesia Technical Institute-Baghdad, Middle Technical University, 10074, Iraq

Received: December 06, 2024
Revised: February 17, 2025
Accepted: March 17, 2025

Abstract:

In Asia, the most frequent cause of hepatocellular carcinoma (HCC) is chronic hepatitis B. The hepatitis B virus's (HBV) genomic integration is probably a precursor to carcinogenesis. The integrated HBV genome may directly activate nearby cellular genes to give the liver cells a selective growth advantage. Our study's goal was to determine if genetic variants in 11β-HSD1, rs846910 and rs12086634 could be linked to chronic hepatitis B virus (HBV) infection and hepatocellular carcinoma (HCC). 150 samples were collected from people suffering from hepatitis B with HCC, HCC, and healthy people. The samples were genotyped for 11β HSD1 (rs846910 and rs12086634) using allele-specific real-time PCR. After performing genotyping of the 11β-HSD1 gene using real-time PCR, both alleles G and A of rs846910 were found to be more prevalent in the two groups of hepatocellular carcinoma and hepatitis B. This gives a clear indication about the possibility of contracting hepatocellular carcinoma and hepatitis B. A different result was found than previously, as the TT genotype of rs12086634 showed a protective effect against hepatocellular carcinoma and hepatitis B virus infection, while the AG genotype of rs846910 increased the risk of hepatocellular carcinoma. These genetic variations are clearly significant biomarkers for hepatocellular carcinoma.

Key words:
single nucleotide polymorphism, 11β HSD1, Hepatocellular carcinoma (HCC)

Apstrakt:

Uloga polimorfizama gena 11β-hidroksisteroid dehidrogenaze rs846910 i rs12086634 u etiologiji hepatocelularnog carcinoma

U Aziji, najčešći uzročnik hepatocelularnog karcinoma (HCC) je hronični hepatitis B. Genomska integracija hepatitis B virusa (HBV) je verovatno prekursor karcinogeneze. Integrisani HBV genom može direktno aktivirati obližnje ćelijske gene, omogućavajući ćelijama jetre selektivnu prednost u rastu. Cilj naše studije bio je da ispita da li genetske varijante u 11β-HSD1, rs846910 i rs12086634 mogu biti povezane sa hroničnom infekcijom hepatitis B virusa (HBV) i hepatocelularnim karcinomom (HCC). Ispitano je 150 uzoraka sakupljenih od osoba sa hepatitisom B i HCC, osoba sa HCC, kao i zdravih ispitanika. Genotipizacija uzoraka na 11β-HSD1 (rs846910 i rs12086634) izvršena je uz pomoć alel-specifične real-time PCR metode. Nakon genotipizacije 11β-HSD1 gena uz pomoć real-time PCR metode, utvrđeno je da su oba alela, G i A, polimorfizma rs846910 zastupljenija u grupama pacijenata sa hepatocelularnim karcinomom i hepatitisom B, što ukazuje na povećan rizik od obolevanja od ovih bolesti. Nasuprot ranijim rezultatima, genotip TT polimorfizma rs12086634 pokazao je zaštitni efekat protiv hepatocelularnog karcinoma i infekcija izazvanih hepatitis B virusom, dok je AG genotip rs846910 bio povezan sa povećanim rizikom od hepatocelularnog karcinoma. Ove genetske varijacije predstavljaju značajne biomarkere za hepatocelularni karcinom.

Ključne reči:
jednonukleotidni polimorfizam (SNP), 11β HSD1, hepatocelularni karcinom (HCC)

Introduction

Liver cancer ranks sixth in terms of prevalence and number of cases in the world, and fourth in terms of the number of deaths resulting from it. It is a global health problem and one of its causes is non-alcoholic fatty liver disease, a risk factor for this type of cancer (Brown et al., 2023). Hepatocellular carcinoma is currently the most common in North Africa, Southeast Asia, and East Asia (Rumgay et al., 2022).

The risk of developing hepatocellular carcinoma increases when there is cirrhosis of the liver, and it rarely occurs in a healthy liver. One of the main causes of infection is the hepatitis B virus, which is responsible for about 50% of cases of this type of cancer (Akinyemiju et al., 2017). The 5-year survival rate for hepatocellular carcinoma is approximately 18.4% (Leowattana et al., 2023).

Hepatitis B virus (HBV) is a member of the Hepadnaviridae family and consists of only 3,200 nucleotides and is the smallest virus that infects humans. The absence of a proofreading mechanism in HBV reverse transcriptase facilitates the emergence of a varied range of genomic variants throughout different stages of infection. Analysis of HBV genomic sequence divergence has identified several sub genotypes and ten HBV genotypes (Trépo et al., 2014; Razavi-Shearer et al., 2018). The lack of a proofreading mechanism in HBV reverse transcriptase facilitates a diverse array of genomic variations for selective proliferation throughout various stages of infection. Analysis of HBV genomic sequence divergence has identified multiple sub genotypes and eleven HBV genotypes (Assefa et al., 2024). Hepatitis B virus (HBV) belongs to the Hepadnaviridae family. It is an epidemic liver disease. People who carry this virus are more susceptible to liver cancer. It has the ability to multiply within liver cells and interacts with many proteins. It also leads to gradual liver fibrosis and is considered a risk factor for HCC or hepatocellular carcinoma, adversely affecting the survival of people with hepatitis B virus, while concomitant hepatitis D virus infection exacerbates the condition. Evidence indicates that HBV infection correlates with the likelihood of developing HCC, irrespective of the presence of underlying liver cirrhosis, through multiple direct and indirect pathways that facilitate hepatocarcinogenesis (Rizzo et al., 2022).

The human chromosome 1 has the HSD11B1 gene. In humans, the gene located on chromosome 16 encodes 11-HSD2. The two types of 11-Hydroxysteroid dehydrogenases are microsomal enzymes associated with the cellular membrane of the endoplasmic reticulum. 11-HSD1 is expressed in the brain, hepatic adipose tissue, and arteries. Its function is to promote the enactment of the glucocorticoid receptor by facilitating the centralization of the dynamic type of glucocorticoids in the tissue. As a result, 11-HSD2 is present in tissues connected to mineralocorticoid activity, the kidney, the placenta, and the salivary organs (Studzińska et al., 2018; de Kloet et al., 2019). Increased cortisol levels are observed during the bipolar episode, suggesting activation of the HPA (Watson et al., 2012).

Various analyses have suggested that 11β-HSD1 plays a major and helpful role in the metabolic cycles that underlie various diseases. In animals lacking 11β-HSD1, the lack of glucocorticoid recovery in the liver and adipose tissue provided a protective effect against insulin resistance and hyperglycemia (Kotelevtsev et al., 1997; Morgan & Tomlinson, 2010). One Single Nucleotide Polymorphism (SNP) of the HSD11β1 quality that has been studied is rs846910, which is located in the 5' promoter region of the HSD11β1 gene revealed a conflicting association between metabolic disorders and type 2 diabetes in different populations (Nair et al., 2004).

We speculate that 11β-HSD1 gene polymorphisms, particularly rs846910 and rs12086634, may be linked to the onset of HCC based on the findings of this investigation.

Materials and Methods

This study included 150 samples divided into three groups. The first group included 50 samples from individuals with hepatocellular carcinoma and hepatitis B virus carriers. The second group included 50 samples from individuals carrying only hepatitis B virus. The third group included 50 samples from healthy individuals. Samples were collected from Marjan Teaching Hospital in the Babylon Governorate, Department of Oncology and Gastroenterology, between 2022 and 2024. Ethical approval was obtained from the relevant committees in compliance with the Helsinki principles. All participants provided informed consent. The control group comprised 50 healthy adults devoid of any history of liver disease, hypertension, renal illness, diabetes, or other chronic conditions. They were also free of hepatitis B or C virus infections, or HIV. There were 25 males and 25 females among the control group.

Sample collection

Blood samples of 8 mL were collected from each participant and processed as follows: 2 mL were placed in EDTA tubes for DNA extraction, 2 mL were used for a complete blood count (CBC) analysis, and the remaining 4 mL were placed in plain

tubes, allowed to clot for 15 minutes, centrifuged at 3000 rpm for 10 minutes, and then divided into aliquots for liver function testing. Hepatitis markers and alpha-fetoprotein (AFP) were analyzed using an electrochemiluminescence assay (ECLA), and HBV-RNA quantification was performed using the COBAS TaqMan HBV Quantitative Assay, version 2.0. HBV genotypes were determined using the linear probe assay with the INNO-LiPA HBV 2 kit from Innogenetics (UK).

SNP assay of 11β HSD1 rs846910 and rs12086634 and DNA extraction

Genomic DNA was extracted using PureLink Genomic DNA Extraction Kits (USA) according to the manufacturer's instructions (Qiagen). Single nucleotide polymorphism (SNP) assays for 11β-HSD1 rs846910 and rs12086634 were conducted using TaqMan genotyping test kits with the Applied Biosystems 7500 Real-Time PCR instrument (Foster City, CA, USA).

The primer and probe sequences for 11β-HSD1 rs846910 were as follows: forward primer 5′-CTCT-GTTGCTTGCTTGCTTGATTC-3′, reverse primer 5′-AGAGCAGGCTTTCAGCAGA-TA-3′, and probe 5′-CTGGTGGGAAT[VIC]/[FAM]TCAAATCAGAGAGA-3′(GenBank NC_000001.11:209701908:A:G).

For 11β-HSD1 rs12086634, the forward primer was 5′-GGAGGAGAATGGGAAAGGTAT-CAAC-3′, the reverse primer was 5′-TCCTCCT-GCAAGAGATGGCTATATT-3′, and the probe was 5′-CCCAGAGGATTTCT[VIC]/[FAM]CAGATGATTTCT-3′(GenBank NC_000001.11:209706913:T:G).

The PCR reaction (25 µL) mixture contained 12.5 µL of TaqMan Master Mix, 1.25 µL of the SNP Assay, 6.25 µL of nuclease-free water, and 5 µL (10 ng/µL) of genomic DNA template. Negative controls included 5 µL of DNase-free water. The mixture was thoroughly mixed, centrifuged briefly, and loaded onto the PCR cycler (Applied Bio Systems ® 7500 Real-Time PCR). Genotypes were determined using the TaqMan Allelic Discrimination test, and unidentified samples were categorized as homozygous or heterozygous based on allelic differentiation analysis.

Laboratory analyses

Liver function tests included the measurement of alkaline phosphatase (ALP), albumin, total protein, aspartate aminotransferase (AST), and alanine aminotransferase (ALT) using the Monarch-240 Clinical Chemistry Analyzer. Hepatitis B surface antigen (HBsAg) was assessed using a chemiluminescence assay kit from Siemens Healthcare Diagnostics. CBC was performed with the SYSMEX XP-300 Fully Automated 3-Part Cell Counter (Japan). Routine assessments for hepatic and renal functions, hepatitis markers, AFP measurement, and HBV-RNA detection were conducted for all groups.

Statical analysis

Data were analyzed using SPSS version 20. Numerical variables were expressed as mean ± standard deviation (SD), while categorical variables were presented as frequencies and percentages. The Mann-Whitney U test was employed to compare nonparametric variables between two groups, and the Chi-square test was used to compare categorical variables. Correlations between numerical variables were analyzed using Spearman's correlation coefficient (rs). Ors were calculated using logistic regression with CI 95%. A p-value≤0.05 was considered statistically significant, with p<0.01 indicating a highly significant result.

Results and discussion

This study included 150 samples, consisting of 50 patients with hepatocellular carcinoma (HCC) and hepatitis B virus (HBV), 50 patients with HBV infection, and 50 healthy controls. The demographic and laboratory data for the patient and control groups are summarized in **Tab. 1.**

No statistically significant differences were observed for age and sex between the groups, indicating adequate matching. However, statistically significant differences were detected between the HBV and HCC groups compared to the controls regarding the laboratory tests (**Tab. 1**).

The results revealed significant differences in the distribution of genotypes and alleles for the rs12086634 and rs846910 polymorphisms among the HBV, HCC, and control groups, suggesting a potential association between these polymorphisms and the development of HBV and HCC (**Tab. 2**). In the case of 11β-HSD1 rs12086634, the GG and TG genotypes were more prevalent in the HBV (18% and 72%, respectively) and HCC patients (16% and 80%, respectively), whereas the control group exhibited the highest frequency of the TT genotype (82%, p<0.001). Allelic distribution comparisons revealed that the G allele was significantly more frequent in the HBV (54%) and HCC (56%) groups compared to the control group (13%, p<0.001). This suggests that the G allele may contribute to an increased risk of both diseases. In contrast, the T allele was the most common in the control group (87%) compared to HBV (46%) and HCC (44%). This allele may play a protective role against disease

Table 1. Demographic and laboratory data for the HBV, HCC, and control groups

Variable Mean ± SD.	HBV n=50	HCC n=50	Control n=50	*p*-value
Gender:				
Male n. (%)	22 (46)	18 (42)	25 (64)	0.325
Female n. (%)	28 (54)	32 (58)	25 (36)	0.325
Age (years)	56.55±4.45	60.7±1.3	58.55±6.18	0.121
WBCs (x 10^3/µl)	6.11±2.87[a]	5.12±1.88[a]	7.22±0.11	<0.001*
Hb (gm/dl)	9.45±1.43[a]	8.87±0.11[a]	11.78±1.22	<0.001*
Platelets (x 10^3/µl)	119.6±40.31[a]	98.8±20.37[a]	271.6±20.41	<0.001*
P.C.V (%)	70.80±9.53[a]	69.21±5.55[a]	89.45±5.65	<0.001*
AST (IU/L)	43.86±12.15[a]	103.7±18.31[a]	17.4±4.66	<0.001*
ALT(IU/L)	58.64±12.50[a]	189.6±264.22[a,b]	13.11±6.58	<0.001*
T. bilirubin (mg/dl)	2.88±1.86[a]	0.68±0.05[a]	2.96±0.1	<0.001*
Albumin (gm/dl)	2.96±0.22[a]	2.7±0.65[a,b]	4.56±0.19	<0.001*
T. protein (gm/dl)	7.33±1.02[a]	6.44±0.96[a]	7.88±0.65	<0.001*
Alkaline phosphatase (IU/L)	68.06±44.82[b]	130.5±57.32[a]	67.14±11.40	<0.001*
AFP (ng/ml)	11.24±2.60	28.27±20.64[a]	-	<0.001*
Viral load (IU)	698.96.9±1067.4	7435.21±1153.6[a]	-	<0.001*

* statistically significant at $p \leq 0.05$, a - significantly differs from control group, b - significantly differs from HBV group

Table 2. The distribution of genotypes and alleles for the 11β-HSD1 rs846910 and rs12086634 gene polymorphisms among the HBV, HCC, and control groups

	HBV (n=50)		HCC (n=50)		Control (n=50)		χ^2	*p*
	No.	%	No.	%	No.	%		
rs12086634								
GG	9	18%	8	(16%)	4	(8%)		
TG	36	72%	40	(80%)	5	(10%)	50.47*	<0.001*
TT	5	(10%	2	(4%)	41	(82%)		
Allele								
G	54	(54%)	56	(56%)	13	(13%)	46.83*	<0.001*
T	46	(46%)	44	(44%)	87	(87%)		
rs846910								
AA	24	(48%)	22	(44%)	46	(92%)	71.51*	<0.001*
AG	26	(52%)	28	(56%)	4	(8%)		
Allele								
G	26	(26%)	28	(28%)	96	(96%)	65.264*	<0.001*
A	74	(74%)	72	(72%)	4	(4%)		

* statistically significant at $p \leq 0.05$

progression. The genotype distribution of the 11β-HSD1 rs846910 polymorphism also showed a clear difference between the three studied groups, with the AA genotype being the most common in the control group (92%), HBV (48%), and HCC (44%). The AG genotype was the most common in the HCC group (56%), less common in the HBV (52%), and very rare in the control group (8%). The results indicate that the distribution of the A allele may be associated with the risk of infection with hepatitis B virus and hepatocellular carcinoma, and the exact opposite for the G allele, as it was more widespread and distributed in the control group (96%) compared to its prevalence in the liver cancer group (28%) and in the hepatitis B virus group (26%), so it is considered a protective factor. These distributions of the genetic patterns in both rs12086634r and rs846910 indicate that they may have an important role in the genetic predisposition to infection with the hepatitis B virus and its development into hepatocellular carcinoma. The overrepresentation of specific alleles in the disease groups highlights their potential as genetic markers for susceptibility or protection. The findings provide evidence of significant associations between the rs12086634 and rs846910 polymorphisms and HBV and HCC. The G allele in rs12086634 and the A allele in rs846910 appear to be risk factors, while the T allele in rs12086634 and the G allele in rs846910 might have protective effects.

Additionally, we analyzed the association of 11β-HSD1 rs846910 and rs12086634 polymorphisms across the three groups by comparison of their genotypic frequencies. This provided a valuable insight into the potential influence of these polymorphisms on the risk of HCC and HBV infection. Regarding the rs12086634 polymorphism, the analysis revealed significant differences in the genotypic distributions between the groups. By comparing hepatitis B virus (HBV) with hepatocellular carcinoma (HCC), the TG genotype showed a strong association (OR=25.11, $p<0.001$), indicating an increased risk of HCC in individuals carrying the TG genotype for rs12086634. Additionally, the TT genotype also showed a significant association with both the HCC subset compared to the control group (OR=0.009, $p=0.0133$) and HBV versus the control group (OR=0.024, $p<0.001$). This suggests that the TT genotype is a protective factor against HBV and HCC for rs12086634. Significant results emerged, as the T allele consistently showed a lower odds ratio compared to the G allele in all groups studied. Therefore, the T allele for rs12086634 is considered to reduce the risk of hepatocellular carcinoma and hepatitis B virus infection. The GG genotype of the rs846910 polymorphism showed a significant association with a low odds ratio (OR=0.045, $p<0.001$) when comparing the hepatocellular carcinoma group with the hepatitis B virus group. This indicates that it is a protective factor against hepatocellular carcinoma in individuals carrying this genotype. In contrast, the GA genotype was a risk factor for hepatocellular carcinoma compared to the hepatitis B virus (OR=21.77, $p<0.001$) and control groups (OR=19.11, $p<0.001$), representing a risk factor for hepatocellular carcinoma. In the comparison between HBV and control, the GA genotype was associated with a very high odds ratio (OR=40.77, $p<0.001$), suggesting a strong correlation with HBV infection risk. The A allele was consistently associated with higher odds of both HBV and HCC, with G allele showing a protective role. The *p*-values for the majority of comparisons between the groups were statistically significant, particularly for the TG and GA genotypes, indicating a strong association between these genotypes and the presence of liver disease.

The distribution of observed and expected genotypic frequencies for rs12086634 and rs846910 polymorphisms was also analyzed across the three groups (**Tab. 4**). The chi-square test (χ^2) and *p*-values were used to assess deviations from Hardy-Weinberg equilibrium (HWE) within these groups. In the caase of rs12086634, the observed frequencies of the GG, TG, and TT genotypes in the HCC group showed a significant deviation from the expected frequencies ($\chi^2=0.271$, $p=0.018$), indicating disequilibrium, reinforcing the hypothesis that the rs12086634 polymorphism may play a role in liver cancer susceptibility. Conversely, the HBV and control groups showed no significant deviations ($\chi^2=1.69$, $p=0.184$; $\chi^2=3.87$, $p=0.325$ for the HBV and control groups, respectively), indicating that the distribution of rs12086634 genotypes in both healthy individuals and the HBV group follows the expected patterns (**Tab. 4**).

For rs846910, the HCC group showed a significant deviation from HWE ($\chi^2=0.214$, $p=0.015$), mainly due to an overrepresentation of the GA genotype compared to the expected frequencies (28 vs. 9.4, **Tab. 4**). This suggests a potential association between the GA genotype and increased HCC susceptibility. In contrast, the HBV and control groups did not show a significant deviation ($\chi^2=4.22$, $p=0.251$, $\chi^2=6.32$, $p=0.536$ for the HBV and control groups, respectively), suggesting that rs846910 may not play a major role in HBV susceptibility in the control group.

The significant deviations from HWE observed in the HCC group for both polymorphisms suggest that rs12086634 and rs846910 may influence susceptibility to HCC, potentially through their

Table 3. Genotypic frequencies and associations of 11β-HSD1 rs846910 and rs12086634 in HBV, HCC, and control groups

	p_1	OR_1 (CI. 95%)	p_2	OR_2 (CI. 95%)	p_3	OR_3 (CI. 95%)
rs12086634						
Genotype						
GG	0.42	0.69 (0.26-1.83)	0.036	3.63 (1.082-12.18)	0.14	2.52 (0.722-8.81)
TG	<0.001	25.11 (8.36-71.22)	<0.001*	23.14 (7.61-70.30)	<0.001*	23.14 (7.61-70.30)
TT	<0.001*	0.03 (0.002-0.087)	0.0133*	0.009 (0.002-0.044)	<0.001*	0.024 (0.0076-0.078)
Allele						
G [R]						
T	<0.001*	0.12 (0.08-0.74)	<0.001*	0.01 (0.05-0.20)	<0.001*	0.12 (0.063-0.52)
rs846910						
Genotype						
GG	<0.001*	0.045 (0.016-0.130)	<0.001*	0.53 (0.018-0.03)	<0.001*	0.024 (0.007-0.083)
GA	<0.001*	21.77 (7.68-61.74)	<0.001*	19.11 (0.51-0.64)	<0.001*	40.77 (12.02-138.29)
Allele						
G [R]						
A	<0.001*	0.84 (0.48-1.48)	<0.001*	18.10 (6.17-53.08)	<0.001*	15.86 (5.39-46.66)

p1 - HCC vs HBV, p2 - HCC vs Control, p3 – HBV vs Control, OR1 - HCC vs HBV, OR2 - HCC vs Control, OR3 - HBV vs Control, CI - Confidence interval, * - statistically significant at $p \leq 0.05$

roles in regulating biological processes associated with liver disease progression. The defect in the hepatitis B virus 11β-HSD1 gene rs12086634 demonstrates its importance in the pathogenesis of this virus and highlights the importance of the 11β-HSD1 rs846910 and rs12086634 gene polymorphisms in understanding the genetic basis of hepatocellular carcinoma and hepatitis B virus. Future studies require increasing the sample size and further functional analyses to confirm the results and to elucidate the mechanisms underlying this association.

Hepatocellular carcinoma (HCC) constitutes a significant public health issue, with an expected 905,677 new cases and 830,180 fatalities reported globally in 2020. Consequently, HCC is projected to be the third most fatal cancer form, mostly due to diagnostic delays and insufficiently efficient treatment techniques (Sung et al., 2021). Nearly 90% of all HCC cases are associated with identifiable risk factors, namely chronic viral hepatitis and alcohol misuse. Chronic infection with hepatitis B virus (HBV) is the primary cause of HCC globally, succeeded by chronic infection with hepatitis C virus (HCV) (Galle et al., 2018; Al-Khaykanee et al., 2021). Consequently, the World Health Organization has designated HBV and HCV as oncoviruses (Mesri et al., 2014). Hepatitis B contributes directly or indirectly to liver cancer by destabilizing the cell genome and producing genetic modifications in the host DNA, leading to chromosomal reconfiguration and aberrant

Table 4. Observed vs. expected genotypic frequencies and Hardy-Weinberg Equilibrium analysis for 11β-HSD1 rs846910 and rs12086634 polymorphisms

	Observed	Expected	χ^2	*p*
rs12086634				
HCC (n=50)				
GG	8	12	0.271	0.018*
TG	40	83		
TT	2	5		
HBV (n=50)				
GG	9	10	1.69	0.184
TG	36	34		
TT	5	6		
Control (n=50)				
GG	4	5	3.87	0.325
TG	5	7		
TT	41	38		
rs846910				
HCC (n=50)				
AA	22	21	0.214	0.015
GA	28	29		
HBV (n=50)				
AA	24	23	4.22	0.251
GA	26	27		
Control (n=50)				
AA	46	44	6.32	0.536
GA	4	6		

* statistically significant at $p \leq 0.05$

activation of oncogenes and tumor suppressor genes through integration or mutation of host genes. It may also induce malignant transformation of hepatocytes by activating various cancer-related signaling pathways (Jiang et al., 2021). 11Beta-hydroxysteroid dehydrogenase type 1 (11β-HSD1) catalyzes the conversion of glucocorticoids from the inactive cortisone to the active cortisol, serving a vital role in glycemic regulation. Growing evidence suggests that heightened glycolytic activity is significantly associated with postoperative recurrence and prognosis of hepatocellular carcinoma (HCC) (Liu et al., 2015).

In this study, the polymorphism of the 11β-HSD1 gen G/T was evaluated in the three studied groups (HCC, HBV and control group). Analyses revealed significant measurable variations in genotype and allele frequency of the 11β-HSD1 rs12086634 gene. The increase was with the prevalence of the G/T genotype in HCC patients and its presence was higher than in patients infected with HBV only. The TT genotype was the most common in the control group, as the T allele is associated with resistance to HBV infection and is considered defensive against the development of HCC. In this study, we observed the distribution of the 11β-HSD1 rs846910 genotype among the three studied groups, where the GA genotype was slightly more prevalent in HCC patients than in kidney infection only, while the GA genotype was more normal in the control group. In general, the distribution of the AA genotype was less prevalent. In this study, we investigated 11β-HSD1 gene association with certain diseases, explored the relationship of the polymorphism of these gene with HBV risk and HCC contaminated patients. 11β-HSD1 is present in the liver, adipose tissue, and kidneys, among other organs, and performs multiple physiological functions, including intracellular and oxysterol metabolism; its dysregulated expression is linked to insulin resistance, visceral adiposity and hypotension (Seckl et al., 2004). 11β-HSD1 is a microsomal compound that catalyzes the change of the active steroid cortisol to the inactive metabolite cortisone (Michalaki et al., 2012). The 11β-HSD1 gene is considered as hereditary risk factors for polycystic ovary condition and could potentially be used to evaluate for early detection of PCOS (Soliman et al., 2020). Furthermore, the expression level of 11β-HSD1 in subcutaneous adipose tissue was associated with fasting plasma glucose levels and correlated with lipids. The gene expression of 11β-HSD1 significantly increases the risk of diabetes mellitus and hypertension in obese individuals (Aziz et al., 2023). 11β-HSD1 might be a significant protein in the pathogenesis of fatty liver and obesity (Lutz et al., 2016). A study conducted by Shareef & Al-Attar (2019) confirmed that SNP rs2086634 T/G of the 11β-HSD1 gene is significantly associated with polycystic ovary syndrome. In addition, the G allele of this SNP showed a positive association with obesity (Moon et al., 2013). There is a relationship between elevated liver enzymes ALT, liver cells damage, and HSD11B1 polymorphisms (rs12086634) in patients suffering from NAFLD (Devang et al., 2017). Also, there is an association between the T/G genetic polymorphism

in HSD11B1 rs12086634 and increased visceral obesity as a result of increased HSD11B1 activity (Gambineri et al., 2011). 11β-HSD1, containing the two SNPs rs846910 (A) and rs12086634 (T), results in enhanced 11β-HSD1 expression and activity, which supports the development of metabolic disorders (Gambineri et al., 2011). Studies on the association of SNPs rs846910 and rs12086634 with liver disorders have not yet been conducted, despite the fact that there are several studies and discoveries on these SNPs. To confirm the correlations found in this study and clarify the biological processes behind these genetic predispositions, more research is required.

Conclusion

In conclusion, the study provides clear evidence about the relationship between genetic polymorphisms in rs12086634 and rs846910 within the 11β-HSD1 gene and the possibility of developing hepatocellular carcinoma. In the case of people infected with the hepatitis B virus, as the G allele of rs12086634 was found to be more prevalent in the hepatocellular carcinoma group and the hepatitis B virus group, it is considered a risk factor for cancer, while the T allele was found to be protective. For rs846910, GA was the most common genotype in both the liver cancer group and the hepatitis B virus group. Since the GG genotype was predominantly found in the control group, this confirms that the A allele is associated with the risk of liver cancer in people carrying this allele. These genetic variations are considered indicators of the risk of liver cancer.

References

Akinyemiju, T., Abera, S., Ahmed, M., Alam, N., Alemayohu, M.A., Allen, C., ... & Global Burden of Disease Liver Cancer Collaboration. (2017). The Burden of Primary Liver Cancer and Underlying Etiologies From 1990 to 2015 at the Global, Regional, and National Level: Results From the Global Burden of Disease Study 2015. *JAMA Oncology*, *3*(12), 1683-1691. doi: 10.1001/jamaoncol.2017.3055.

Al-Khaykanee, A.M., Abdel-Rahman, A.A., Essa, A., Gadallah, A.N.A.A., Ali, B.H., Al-Aqar, A.A., ... & Shehab-Eldeen, S. (2021). Genetic polymorphism of fibroblast growth factor receptor 2 and trinucleotide repeat-containing 9 influence the susceptibility to HCV-induced hepatocellular carcinoma. *Clinics and Research in Hepatology and Gastroenterology*, *45*(6), 101636.

Assefa, A., Getie, M., Getie, B., Simeneh, T., & Enkobahry, A. (2024). Molecular epidemiology of hepatitis B virus (HBV) in Ethiopia: A review article. *Infection, Genetics and Evolution*, *122*, 105618. doi: 10.1016/j.meegid.2024.105618.

Aziz, H., Raslan, M., El Dahshan, D., Afify, M., Hamimy, W.I., & Gouda, W. (2023). 11β Hydroxysteroid dehydrogenase type 1 gene expression in obesity and its complications. *Egyptian Journal of Chemistry*, *66*(7), 165-174. doi: 10.21608/EJCHEM.2022.157145.6819.

Brown, Z.J., Tsilimigras, D.I., Ruff, S.M., Mohseni, A., Kamel, I.R., Cloyd, J.M., & Pawlik, T.M. (2023). Management of hepatocellular carcinoma: a review. *JAMA surgery*, *158*(4), 410-420. doi: 10.1001/jamasurg.2022.7989.

de Kloet, E.R., de Kloet, S.F., de Kloet, C.S., & de Kloet, A.D. (2019). Top-down and bottom-up control of stress-coping. *Journal of Neuroendocrinology*, *31*(3), e12675. doi: 10.1111/jne.12675.

Devang, N., Satyamoorthy, K., Rai, P.S., Nandini, M., Rao, S., Phani, N.M., & Adhikari, P. (2017). Association of HSD11B1 gene polymorphisms with type 2 diabetes and metabolic syndrome in South Indian population. *Diabetes Research and Clinical Practice*, *131*, 142-148. doi: 10.1016/j.diabres.2017.07.011.

Galle, P.R., Forner, A., Llovet, J.M., Mazzaferro, V., Piscaglia, F., Raoul, J.L., Schirmacher, P., & Vilgrain, V. (2018). EASL clinical practice guidelines: management of hepatocellular carcinoma. *Journal of Hepatology*, *69*(1), 182-236. doi: 10.1016/j.jhep.2018.03.019.

Gambineri, A., Tomassoni, F., Munarini, A., Stimson, R.H., Mioni, R., Pagotto, U., Chapman, K.E., Andrew, R., Mantovani, V., Pasquali, R., & Walker, B.R. (2011). A combination of polymorphisms in HSD11B1 associates with *in vivo* 11β-HSD1 activity and metabolic syndrome in women with and without polycystic ovary syndrome. *European Journal of Endocrinology*, *165*(2), 283-292. doi: 10.1530/EJE-11-0091.

Jiang, Y., Han, Q., Zhao, H., & Zhang, J. (2021). The mechanisms of HBV-induced hepatocellular carcinoma. *Journal of Hepatocellular Carcinoma*, *8*, 435-450. doi: 10.2147/JHC.S307962.

Kotelevtsev, Y., Holmes, M.C., Burchell, A., Houston, P.M., Schmoll, D., Jamieson, P., Best, R., Brown, R., Edwards, C.R., Seckl, J.R., & Mullins, J.J. (1997). 11β-hydroxysteroid dehydrogenase type 1 knockout mice show attenuated glucocorticoid-inducible responses and resist hyperglycemia on obesity or stress. *Proceedings of the National Academy of Sciences USA*, *94*(26), 14924-14929.

doi: 10.1073/pnas.94.26.14924.

Leowattana, W., Leowattana, T., & Leowattana, P. (2023). Systemic treatment for unresectable hepatocellular carcinoma. *World Journal of Gastroenterology*, *29*(10), 1551-1568. doi: 10.3748/wjg.v29.i10.1551.

Liu, X., Tan, X.L., Xia, M., Wu, C., Song, J., Wu, J.J., Laurence, A., Xie, Q.G., Zhang, M.Z., Liang, H.F., Zhang, B.X., & Chen, X.P. (2015). Loss of 11βHSD1 enhances glycolysis, facilitates intrahepatic metastasis, and indicates poor prognosis in hepatocellular carcinoma. *Oncotarget*, *7*(2), 2038-2053. doi: 10.18632/oncotarget.6661.

Lutz, S.Z., Peter, A., Machicao, F., Lamprinou, A., Machann, J., Schick, F., Königsrainer, I., Königsrainer, A., Fritsche, A., Staiger, H., Häring, H.U., Stefan, N., & Kantartzis, K. (2016). Genetic variation in the 11β-hydroxysteroid-dehydrogenase 1 gene determines NAFLD and visceral obesity. *The Journal of Clinical Endocrinology & Metabolism*, *101*(12), 4743-4751. doi: 10.1210/jc.2016-2498.

Mesri, E.A., Feitelson, M.A., & Munger, K. (2014). Human viral oncogenesis: a cancer hallmarks analysis. *Cell Host & Microbe*, *15*(3), 266-282. doi: 10.1016/j.chom.2014.02.011.

Michalaki, M., Kyriazopoulou, V., Antonacopoulou, A., Koika, V., Nikolaou, M., Tsoukas, A., Kalfarentzos, F., Vagenakis, A.G., Voukelatou, G., & Papavassiliou, A.G. (2012). The expression of omental 11β-HSD1 is not increased in severely obese women with metabolic syndrome. *Obesity Facts*, *5*(1), 104–111. doi: 10.1159/000336755.

Moon, S.S., Lee, Y.S., Kim, J.G., & Lee, I.K. (2013). Association of 11β-hydroxysteroid dehydrogenase type 1 gene polymorphisms with serum alanine aminotransferase activity. *Diabetes Research and Clinical Practice*, *99*(3), 343-350. doi: 10.1016/j.diabres.2012.12.020

Morgan, S.A. & Tomlinson, J.W. (2010). 11β-Hydroxysteroid dehydrogenase type 1 inhibitors for the treatment of type 2 diabetes. *Expert Opinion on Investigational Drugs*, *19*(9), 1067-1076. doi.org /10.1517/13543784.2010.504713.

Nair, S., Lee, Y., Lindsay, R., Walker, B.R., Tataranni, P.A., Bogardus, C., Baier, L.J., & Permana, P.A. (2004). 11β-Hydroxysteroid dehydrogenase Type 1: genetic polymorphisms are associated with Type 2 diabetes in Pima Indians independently of obesity and expression in adipocyte and muscle. *Diabetologia*, *47*(6): 1088- 1095. doi: 10.1007/s00125-004-1407-6.

Razavi-Shearer, D., Gamkrelidze, I., Nguyen, M.H., Chen, D.S., Van Damme, P., Abbas, Z., ... & Roberts, S.K. (2018). Global prevalence, treatment, and prevention of hepatitis B virus infection in 2016: a modelling study. *The Lancet Gastroenterology & Hepatology*, *3*(6), 383-403. doi: 10.1016/S2468-1253(18)30056-6.

Rizzo, G.E.M., Cabibbo, G., & Craxì, A. (2022). Hepatitis B virus-associated hepatocellular carcinoma. *Viruses*, *14*(5), 986. doi: 10.3390/v14050986.

Rumgay, H., Ferlay, J., de Martel, C., Georges, D., Ibrahim, A.S., Zheng, R., Wei, W., Lemmens, V.E.P.P., & Soerjomataram, I. (2022) Global, regional and national burden of primary liver cancer by subtype. *European Journal of Cancer*, *161*, 108-118. doi: 10.1016/j.ejca.2021.11.023.

Seckl, J.R., Morton, N.M., Chapman, K.E., & Walker, B.R. (2004). Glucocorticoids and 11beta-hydroxysteroid dehydrogenase in adipose tissue. *Recent Progress in Hormone Research*, *59*, 359-393. doi: 10.1210/rp.59.1.359

Shareef, A.A. & Al-Attar, M.S. (2019). Association study of HSD11B1 rs12086634 (T>G) gene polymorphism with polycystic ovarian syndrome in Erbil Province. *ZANCO Journal of Pure and Applied Sciences*, *31*(5), 36-43. doi:10.21271/zipas.

Soliman, S.E., Abd El Gayed, E M., & Abd El Gayed, A M. (2020). Association of the HSD11B1rs12086634 (T/G) gene polymorphism and IL6 serum level with the risk of polycystic ovary syndrome. *Meta Gene*, *23*, 100638. doi: 10.1016/j.mgene.2019.100638

Studzińska, R., Kupczyk, D., Płazińska, A., Kołodziejska, R., Kosmalski, T., & Modzelewska-Banachiewicz, B. (2018). Thiazolo [3, 2-a] pyrimidin-5-one derivatives as a novel class of 11β-hydroxysteroid dehydrogenase inhibitors. *Bioorganic Chemistry*, *81*, 21-26. doi: 10.1016/j.bioorg.2018.07.033.

Sung, H., Ferlay, J., Siegel, R.L., Laversanne, M., Soerjomataram, I., Jemal, A., & Bray, F. (2021). Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA: A Cancer Journal for Clinicians*, *71*(3), 209-249. doi: 10.3322/caac.21660.

Trépo, C., Chan, H.L., & Lok, A. (2014). Hepatitis B virus infection. *The Lancet*, *384*(9959), 2053-2063. doi: 10.1016/S0140-6736(14)60220-8.

Watson, S., Gallagher, P., Porter, R.J., Smith, M.S., Herron, L.J., Bulmer, S., ... & North-

East Mood Disorders Clinical Research Group. (2012). A randomized trial to examine the effect of mifepristone on neuropsychological performance and mood in patients with bipolar depression. *Biological psychiatry*, *72*(11), 943-949. doi: 10.1016/j.biopsych.2012.05.029.