RESEARCH ARTICLE

Editorial Process: Submission:07/10/2024 Acceptance:01/24/2025

Interleukin-17A and *Interleukin-17F* Gene Polymorphisms in Egyptian Patients with Chronic Hepatitis C and Hepatocellular Carcinoma

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Abstract

Objective: Interleukin *IL-17A* and *IL-17F* are critical cytokines involved in inflammatory processes. Genetic variations in *IL-17A* and *IL-17F* might be linked to chronic hepatitis C (CHC) and an increased risk of hepatocellular carcinoma (HCC), a cancer associated with long-term inflammation. This study aims to examine the relationship between specific polymorphisms in *IL-17A* (rs2275913) and *IL-17F* (rs763780) and their association with HCV-related HCC in an Egyptian population. **Methods:** Authors conducted a case-control study involving 52 patients with chronic hepatitis C, 49 patients with HCV-related HCC, and 51 healthy controls. The study assessed the connection between the *IL-17A* rs2275913 and *IL-17F* rs763780 polymorphisms and chronic hepatitis C patients. Genotyping was performed using real-time PCR with TaqMan MGB-probe allelic discrimination. **Results:** No significant differences in genotype and allele frequencies for *IL-17A* rs2275913 and *IL-17F* rs763780 were observed between CHC or HCC patients and control subjects. However, significant associations were found indicating an increased risk of HCC linked to CHC: the GG genotype of *IL-17A* rs2275913 in a recessive model (P = 0.0129); and CT and CT + CC genotypes as well as the C allele of *IL-17F* rs763780 (P = 0.0038, P = 0.0055 and P = 0.0277, respectively). **Conclusion:** The study identifies a significant association between *IL-17F* rs763780 polymorphisms and a higher risk of HCC in Egyptian patients with chronic hepatitis C. No significant correlation was found between the *IL-17A* rs2275913 polymorphism and either chronic hepatitis C or HCC.

Keywords: Hepatocellular carcinoma- Haplotype- *Interleukin-17*- Polymorphism

Asian Pac J Cancer Prev, **26 (1)**, 153-159

Introduction

Hepatitis C is a severe disease that mainly targets the liver. The hepatitis C virus (HCV), an RNA virus that can result in both acute and chronic forms of the illness, causes it. This virus represents a major global health concern, affecting around 180 million people [1, 2]. Approximately 150,000 new infections occur annually in Egypt, and it is projected that both morbidity and mortality will increase twofold within the next twenty years [3]. Chronic HCV infection leads to persistent inflammation, liver fibrosis, and possibly cirrhosis [4], with up to 3–5% of cirrhotic patients advance to hepatocellular carcinoma (HCC). Hepatocellular carcinoma (HCC) is classified as one of the top five most prevalent malignancies and the second most fatal cancer [5]. Multiple factors, including both genetic and environmental, exert influence on it. The persistent inflammation caused by HCV infection promotes unregulated cell growth, resulting in the development of cancer [6].

Th17 cells, a subtype of pro-inflammatory CD4+ T-cells, produce *IL-17* when activated, which plays a role in tissue inflammation. Among the *IL-17* family of cytokines, *IL-17A* and *IL-17F* are highly similar, sharing a 50% sequence similarity and binding to the same receptor [7]. These cytokines activate various pro-inflammatory mediators in epithelial and fibroblast cells. Excessive Th17 activity and *IL-17A* expression are associated with the onset, progression, and adverse outcomes of liver cancer [8]. The genes for *IL-17A* and *IL-17F* are located on chromosome 6p12.2. Associations have been found between *IL-17A* polymorphisms and several cancers, including breast [9], lung [10], gastric [11], cervical [12], and colorectal cancers [13], while *IL-17F* rs763780

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has been linked to bladder cancer [14] and autoimmune thyroid disorders [15]. However, there has not been much research done on the connection between *IL-17A* and *IL-17F* polymorphisms and chronic hepatitis C and hepatocellular carcinoma.

Materials and Methods

Study Population

The current study involved 51 control subjects, 52 chronic hepatitis C patients, and 49 HCV-related HCC patients from Suez Canal Authority Hospital, Ismailia, and the National Liver Institute, Shibin Al Kawm, Al Minufiyah. Participants needed a history of HCV infection longer than six months. Exclusions were other hepatitis virus infections, liver diseases of mixed etiologies, autoimmune or inflammatory diseases, a family history of HCC or other cancers, and current antiviral or immunomodulatory treatments. Controls were healthy volunteers confirmed HCV-free and without hepatic disease or tumors. Ethical approval was granted by the National Research Center, and informed consent was obtained from all participants. HCV patients were clinically evaluated, including biochemical and serological tests. HCV-RNA levels were measured using the Artus HCV RT-PCR Quantification Kit. HCC diagnosis relied on imaging, with other cancers excluded. Fibrosis stages were classified using the METAVIR scoring system.

DNA Extraction from Peripheral Blood

Three ml of venous blood withdraw from each participant into sterile anticoagulant Ethylenediaminetetraacetic acid (EDTA) tubes for genomic DNA isolation, processed within six hours. Genomic DNA was extracted using (Gene JET whole blood genomic DNA purification mini kit, Thermo Scientific TM, k0781), the quantity and quality of DNA were checked on a Nano Drop spectrophotometer and the DNA was stored at -80°C until further analysis.

Genotyping of Interleukin 17A rs2275913 A/G and Interleukin 17F rs763780 C/T Polymorphisms

Genotyping for *IL-17A* rs2275913 and *IL-17F* rs763780 was done using a real-time PCR protocol with the TaqMan MGB-probe allelic discrimination assay. PCR conditions included 95°C for a period of 10 minutes followed by 40 cycles at 95°C for a period of 15 seconds and 60°C for a period of 1 minute. Genotypes were determined using fluorescence intensity and analyzed with SPSS.

Statistical Analysis

Data were analyzed using SPSS. Genotype distributions were compared with the Chi-squared test, and odds ratios (OR) were calculated. Genotype, allele, and haplotype distributions were examined using Chi-squared or Fisher's exact tests. Linkage disequilibrium and haplotype analyses were done with SHEsis software [16]. Statistical significance was defined as $P < 0.05$.

Results

General Characteristics of Study Subjects

Baseline and clinical characteristics of HCV-infected patients and controls are summarized in Table 1. Older age correlated with a higher risk of chronic HCV infection. Predictive indicators such as BMI, platelet count, and HCV viral load were evaluated. HCC was linked with decreased platelet count and albumin levels and increased AST, ALT, prothrombin time, and total bilirubin. In chronic hepatitis C, no significant differences in parameters were noted between early and late fibrosis stages (Table 2). For

Table 1. Reference Point and Clinical Traits of Patients with HCV and Individuals in the Healthy Group

Variable (Mean ± SD)	Chronic HCV n = 51	HCC n = 49	Healthy control n = 51	ρa
Age (yrs.)	57.94 ± 10.22	58.14 ± 5.32	46.37 ± 11.55	< 0.0001
Sex				
Female count (%)	80%	79%	78%	0.8
Male count (%)	20%	21%	22%	
BMI	29.5 ± 3.1	28.6 ± 3.8	29.27 ± 1.65	0.307
ALT	31.6 ± 21.7	40.9 ± 17.9	30 ± 2	<0.0001
AST	27.7 ± 17.7	51.3 ± 25.4	24 ± 3	<0.0001
AFP (ng/ml)	4.3 ± 2.5	320 ± 196		
Albumin	3.5 ± 0.35	3.4 ± 0.61	3.9 ± 0.2	<0.0001
Total bilirubin	0.73 ±0.33	0.83 ± 0.07	1.4 ± 0.9	<0.0001
INR	1.02 ± 0.12	1.2 ± 0.2	0.98 ± 0.05	<0.0001
HB	13.5 ± 1.6	12.9 ± 2	12.5 ± 1	0.06
WBCx10^3/mm^3	7.3 ± 2.3	6.4 ± 2.2	7.2 ± 1.3	0.057
Platelet (per 10^9/L)	163 ± 108	104 ± 51	216 ± 44.5	<0.0001
HCV viral Load (log 10)	6.08(5.57-6.45)	5.98(2.79-7.24)		0.55

ρa, nonparametric test and one-way ANOVA for continuous data and Chi square test for categorical data. ALT points to alanine aminotransferase; AST, points to aspartate aminotransferase; SD, standard deviation; INR, points to international normalized ratio of prothrombin time; AFP, points to alpha fetoprotein; n, points to the sample; BMI, body mass index; HB, points to hemoglobin.

Table 2. Baseline and Clinical Characteristics of Chronic Hepatitis C Patients with Early (F0-F2) and Late (F3-F4) Fibrosis Stages

Variable (Mean ±SD)	Early fibrosis (F0-F2)	Late fibrosis (F3-F4)	*P*
ALT	26.23 ± 7.88	48.08 ± 37.7	<0.0001
AST	21.28 ± 4.44	47.12 ± 27.13	<0.0001
AFP (ng/ml)	3.93 ± 1.79	5.4 ± 3.9	0.07
Albumin	3.47 ± 0.36	3.5 ± 0.32	0.85
Total bilirubin	0.662 ± 0.3	0.93 ± 0.33	0.008
INR	1.014 ± 0.13	1.06 ± 0.94	0.37
HB	13.7 ± 1.7	12.9 ± 1.3	0.143
WBCx10^3/mm^3	7.5 ± 1.9	6.73 ± 2.9	0.276
Platelet (per 10^9/L)	238.7 ± 69.9	140 ± 65	<0.0001

ALT, points to alanine aminotransferase; AST, points to aspartate aminotransferase; means± SD, standard deviation; INR, points to international normalized ratio of prothrombin time; AFP, points to alpha-fetoprotein; n points to the sample; HB, points to hemoglobin;WBCs, points to white blood cells; significant p value< 0.05.

Table 3. Baseline and Clinical Characteristics of HCC Patients with Early (F0-F2) and Late (F3-F4) Fibrosis Stages

Variable (Mean ±SD)	Early fibrosis (F0-F2) n = 7	Late fibrosis (F3-F4) n = 42	*P*
ALT	29.7 ± 12.17	42.8 ± 18.18	0.074
AST	33 ± 12.3	54.3 ± 25.8	0.038
AFP (ng/ml)	278 ± 136.9	328 ± 206	0 .59
Albumin	3.614 ± 0.6962	3.34 ± 0.6033	0.299
Total bilirubin	0.81 ± .2	0.87 ± 0.44	0 .15
INR	1.17 ± 0.16	1.19 ± 0.2	0.73
HB	14.1 ± 1.5	12.7 ± 2	0.085
WBCx10^3/mm^3	6.9 ± 2.1	6.3 ± 2.2	0.505
Platelet (per 10^9/L)	211.2 ± 55.7	121 ± 38.9	0.000

ALT, points to alanine aminotransferase; AST, points to aspartate aminotransferase; means± SD, standard deviation; INR, points to international normalized ratio of prothrombin time; AFP, points to alpha-fetoprotein; n, points to samples; HB, points to Hemoglobin; WBCs, points to white blood cells, significant p value< 0.05.

HCC patients, no significant differences were observed between fibrosis stages in most variables (Table 3), except for decreased platelet counts in late fibrosis (P < 0.0001).

Hardy-Weinberg Equilibrium of Polymorphisms

Genotype distributions in Interleukin 17A and Interleukin17F genes were consistent with Hardy-Weinberg equilibrium (P > 0.05), indicating the representativeness of the groups.

IL-17A Genotypes and Allele Distribution with Risk to Chronic Hepatitis C and HCC

Table 4 showed the genotypic distributions of *IL-17A* rs2275913 among the groups. Frequencies of AA, AG, and GG genotypes were 2%, 36.7%, and 61.3% in HCC-related HCV-infected patients, 3.8%, 50%, and 46.2% in chronic hepatitis C without HCC, and 5.9%, 51%, and 43.1% in controls. No significant differences were found between controls and chronic hepatitis patients in AG, GG, AG+GG genotypes, or G allele distribution (P > 0.05). The G allele was higher in HCC patients than in controls but was not statistically significant (OR = 1.78, P = 0.071). No significant associations were found in dominant models, but the GG genotype in the recessive model was significantly associated with HCC risk (P = 0.0129).

IL-17F Genotypes and Allele Distribution with Risk to Chronic Hepatitis C and HCC

Table 5 illustrated the genotypic distributions of *IL-17F* rs763780. Frequencies of TT, CT, and CC genotypes were 65.3%, 32.7%, and 2% in HCC-related HCV-infected patients, 88.5%, 7.7%, and 3.8% in chronic hepatitis C without HCC, and 78.4%, 19.6%, and 2% in controls. No significant differences were found between controls and chronic hepatitis patients in CT, CC, CT+CC genotypes, or C allele distribution (P > 0.05). However, the CT and CT+CC genotypes were significantly associated with HCC risk compared to chronic hepatitis C patients (OR = 5.7, P = 0.0038; OR = 3.24, P = 0.0055). The C allele was also associated with HCC progression (P = 0.0277). The dominant model showed a significant association with HCC (P = 0.0055), while no significant association was found in the recessive model.

Distribution of SNPs Genotypes According to Fibrosis Stages (Early versus Late Fibrosis) of chronic hepatitis without HCC and patients with HCC

The rs2275913 GG genotype may act as a marker for early fibrosis and could also play a role in HCC development. It was observed to be more common in early fibrosis (42.3%) compared to late fibrosis (3.8%) in chronic hepatitis C patients without HCC. Moreover, its

Table 5. Genotypic Distribution and Allele Frequency of *IL-17F* rs763780 Polymorphism between Chronic Hepatitis C, HCC, and Healthy Controls

Alleles /Genotypes	Healthy control	HCC	CHC	Control.VS. HCC			Control vs. CHC			HCC VS. CHC		
Il17A rs763780	(n=51)n%	(n=49)n%	(n=52)n%	P	OR	95% CI Lower -Upper	P	OR	95% CI Lower -Upper	P	OR	95% CI Lower -Upper
TT	40 (78.4%)	32 (65.3%)	46 (88.5%)					1 Ref				
CT	10 (19.6%)	16 (32.7%)	4 (7.7%)	0.14	2	(0.8- 5)	0.09	0.35	(0.1-1.19)	0.004	5.7	(1.75-18.8)
CC	1 (2%)	1 (2%)	2 (3.8%)	0.88	1.25	(0.075- 20.8)	0.65	1.73	(0.15-19.9)	0.8	0.72	(0.06-8.27)
Alleles T	90 (88.2%)	80 (81.6%)	96 (92.3%)	1 Ref								
C	12 (11.8%)	18 (18.4%)	8 (7.7%)	0.19	0.6	(0.27- 1.3)	0.32	1.6	(0.62-4.09)	0.027	0.4	(0.15- 0.89)
Dominant Model CT +CCVS. TT	11 (%)	17 (%)	6 (%)	0.15	0.52	(0.21- 1.26)	0.18	2.1	(0.7-6.2)	0.0055	0.25	(0.09-0.2)
Recessive Model CCVS. CT+TT	1 (%)	1 (%)	2 (%)	0.98	0.96	(0.06- 15.8)	0.58	0.5	(0.04-5.7)	0.6	1.9	(0.04-5.7)
HWE P Value	0.69	0.54	0.0009									

Ref refers to the reference group; CI signifies confidence interval; OR denotes odds ratio; SNP stands for single-nucleotide polymorphism, and n represents the number, HWE Hardy-Weinberg equilibrium, and significant p value < 0.05.

Table 4. Genotypic Distribution and Allele Frequency of *IL-17A* rs2275913 Polymorphism between Chronic Hepatitis C, HCC, and Healthy Controls

Alleles /Genotypes	Healthy control	HCC	CHC	Control. vS. HCC			Control vs. CHC			HCC vs. CHC		
Il17A rs2275913	(n=51) n%	(n=49) n%	(n=52) n%	P	OR	95% CI Lower -Upper	P	OR	95% CI Lower -Upper	P	OR	95% CI Lower -Upper
AA	3 (5.9%)	1(2%)	2 (3.8%)					1 Ref				
AG	26 (51%)	18 (36.7%)	26 (50%)	0.53	2.07	(0.2- 21.6)	0.67	1.5	(0.23-9.7)	0.79	1.4	(0.12-16.5)
GG	22 (43.1%)	30 (61.3%)	24 (46.20%)	0.205	4.09	(0.39- 42)	0.605	1.64	(0.25-10.72)	0.45	2.5	(0.21-29.3)
Alleles A	32 (31.3%)	20 (20.4%)	30 (28.8%)					1 Ref				
G	70 (68.7%)	78 (79.6%)	74 (71.2%)	0.078	1.8	(0.94- 3.4)	0.69	1.1	(0.62-2.04)	0.16	1.6	(0.82-3.02)
Dominant Model AG+GGVSAA	48 (94.1%)	48 (97.9%)	50 (96.1%)	0.35	3	(0.3- 29.8)	0.63	1.6	(0.25-9.76)	0.59	1.9	(0.17-21.9)
Recessive Model GGVS AA+AG	22 (43.1%)	30 (61.2%)	24 (46.2%)	0.072	2.08	(0.94- 4.6)	0.76	1.12	(0.5-2.45)	0.013	0.184	(0.049-0.699)
HWE P Value	0.18901	0.35999	0.115916									

Ref, refers to the reference group; CI, signifies confidence interval; OR, denotes odds ratio; SNP, stands for single-nucleotide polymorphism, and n represents the number, HWE, Hardy-Weinberg equilibrium, and significant p value < 0.05.

Table 6. Analysis of *IL-17* Haplotype Frequencies with the Risk of CHC.

ILF	*ILA*	Control	CHC	OR (CI 95%)	p- Value
T	G	0.6561	0.6199	1	-
T	A	0.2468	0.2625	0.75(0.35-1.59)	0.45
C	A	0.0542	0.0513	0.94(0.29- 3.07)	0.92
C	G	0.0429	0.0664	0.28(0.05-1.58)	0.15

CI, signifies confidence interval; OR, denotes odds ratio; CHC, points to chronic hepatitis c patients; *ILF*, pints to *IL17F* rs763780; *IL17A* rs2275913; significant p value < 0.05.

prevalence significantly increased to 61.2% in patients with HCC. Similarly, the rs763780 TT genotype is prevalent in early fibrosis and may also be involved in HCC progression. It is found in 71.3% of chronic hepatitis C patients without HCC in early fibrosis but drops to 17.3% in late-stage fibrosis. In patients who develop HCC, the frequency of the TT genotype rises again to 65.3%.

Haplotype analysis of Interleukin 17 gene polymorphisms and HCC risk

It is thought that haplotype-based analysis more preferable than SNP genotyping. So, linkage disequilibrium (LD) and haplotype-based analysis is important to find out the haplotype frequencies of polymorphisms set in the same chromosome sections in order to derive haplotypes definitely associated with chronic hepatitis C (CHC). It was found linkage disequilibrium (LD) between the alleles of rs2275913 and rs763780, (P = 0.008) however linkage dis- equilibrium analysis of IL17 SNPs among healthy control and HCC patient wasn't significant (P= 0.43).

The haplotype distributions in the chronic hepatitis C patients and healthy Control population shown in Table 6. Four haplotypes derived from the observed genotypes.

Discussion

This research explored the correlation between *IL-17A* and *IL-17F* polymorphisms and the risk of developing chronic hepatitis C and HCC in Egyptian patients. While prior studies identified genetic polymorphisms contributing to liver diseases, including HCC, *IL-17* cytokines' roles have been limitedly examined. Chronic HCV infection can drive liver inflammation, which may culminate in cirrhosis and HCC. Our findings suggest that specific *IL-17* polymorphisms could influence these processes.

Role of IL-17 Polymorphisms in HCV and HCC

The study demonstrates that Interleukin 17A rs2275913 and Interleukin17F rs763780 polymorphisms are related with increased risk of HCC in CHC patients. *IL-17A* and *IL-17F*, through their roles in inflammation, may contribute to the chronic inflammatory environment that promotes hepatocarcinogenesis. The GG genotype of Interleukin 17A rs2275913 and the CT + CC genotypes of Interleukin 17F rs763780 were found to be significantly linked with HCC risk, suggesting a potential genetic predisposition in this cohort. The exact mechanisms by which *IL-17* polymorphisms influence HCC development remain unclear but may involve the regulation of pro-inflammatory cytokines and interactions with other genetic and environmental factors. *IL-17A* and *IL-17F* may modulate immune responses and inflammatory processes that facilitate the transition from chronic inflammation to cancer. Herein, authors found linkage disequilibrium between two SNPs and CHC is statistically significant however, no association haplotypes with these patients While in HCC related HCV patients, no found linkage disequilibrium (LD).

Comparison with Previous Studies

These findings align with previous research linking *IL-17* polymorphisms to various cancers and chronic inflammatory diseases. Similar associations have been observed in studies on gastric [17, 18], bladder [19], breast [20, 21], cervical [22] and colorectal cancers, where *IL-17* polymorphisms contributed to cancer susceptibility. However, this study is among the primary to specifically address the relationship of *IL-17* polymorphisms with HCV-related HCC in an Egyptian population.

Prior studies show the important role that IL17A gene polymorphism plays in inflammatory autoimmune diseases such as rheumatoid arthritis [23, 24], peptic ulcer [25].

In a study devoted to studying and examining the relationship between IL17A gene polymorphisms and the level of interleukin 17 in serum, hepatitis C, and liver cancer related to the virus C. This study, presented no association in rs2275913 between control subjects and chronic hepatitis C infected patients but chronic hepatitis C infection with HCC have significantly higher GG and combined GG+GA than control subjects and chronic hepatitis C infection without HCC. Therefore, the risk of developing liver cancer and developing hepatitis C may be related to IL17A rs2275913 the polymorphism [26]. A comprehensive meta-analysis indicated a close relationship between the risk of cancer, especially stomach cancer, and the hereditary polymorphism of the 17A rs2275913 and IL17 F rs763780, which was conducted by Niu et al. [27].

In a study in 2014, the first of its kind, li et al. reported a positive association between polymorphisms of *IL-17* rs2275913 and liver cancer risk in a Chinese group [28]. On the other hand, there are no clear relationships between the *IL-17A* rs2275913 polymorphism and gastric cancer risk [29]. Moreover, no significant relationship between the rs763780 polymorphism and the risk of gastric [30, 17], cervical [22] or breast cancer [20] could be detected in other studies.

Another study also shows reported that chronic

hepatitis C infection is linked with elevate serum *IL-17* level; however, there were not significant association between the polymorphisms of interleukin 17 rs8193036, rs2275913 and susceptibility of chronic HCV infection in this study's Chinese patients but They not study this relationship to chronic hepatitis C infection with HCC [31].

Limitations and Future Directions

One of the limitations facing this study is the moderately minor sample size and lack of functional assays to explore the mechanistic pathways linking *IL-17* polymorphisms to HCC risk. Future research should involve larger, multi-center studies and functional analyses to elucidate the role of *IL-17* in HCC pathogenesis.

In summary, this study reveals significant associations between *IL-17F* rs763780 polymorphisms and an elevated risk of HCC in Egyptian patients with chronic hepatitis C. The *IL-17A* rs2275913 polymorphism showed no notable correlation with either chronic hepatitis C or HCC. These insights into *IL-17* polymorphisms contribute to understanding genetic factors influencing HCV-related HCC development. More investigations with larger cohorts and diverse populations are essential to verify the accuracy of these findings and explore therapeutic implications.

Author Contribution Statement

Noha E. Ibrahim: Was involved in developing the hypothesis, performing the molecular techniques and biochemical analysis, writing the manuscript, and making substantial revisions. She also reviewed the paper before its submission. Ehab Mabrouk: Conducted molecular and biochemical analyses, contributed to statistical evaluations, participated in writing the manuscript, and played a role in reviewing and revising drafts as well as the study proposal. Mohamed Mansour: Managed patient follow-ups, conducted the recommended medical tests, and contributed to the manuscript review. Menha Swellam: Engaged in biochemical analysis, data interpretation, and provided critical revisions. All authors have read and approved the final version of the manuscript.

Acknowledgements

General

The devices registered in the present study were purchased through a grant from Science and Technology Development Fund (STDF) through Capacity Building Grant Fund (CBG) [No. 4940].

Data Availability Statement

The author has decided not to share the data.

Ethical Approval

The Medical Research Ethics Committee of National Research Centre, Dokki, Giza, Egypt (Approval No. 05430123) approved the study.

Conflicts of Interest

The authors declare no conflicts of interest.

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