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MOLECULAR CHARACTERIZATION OF INTERLEUKIN IN CHRONIC HCV.

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ABSTRACT

A Single nucleotide polymorphism upstream of the interferon-λ3 gene, strongly linked to unprompted and treatment-induced HCV infection clearance. the present study was to assess the role of interleukin- 28 gene polymorphism (rs12979860 CC and rs8099917 TT) on HCV type 4 Egyptian patients treated with sovaldi. A total of 100 patients with HCV infection was included in this study. the diagnosis was based on elevated alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), plasma albumin level, total bilirubin, direct bilirubin, platelet and HB. Molecular characterization of 2 SNPs (rs 12979860CC and rs 8099917 TT) in heparinase gene: by molecular techniques (ARMs-PCR & RFLP). IL28B rs8099917 TT genotype is predominant among patients as well as the control followed by GT and the least prevalent was the GG genotype. Regarding iL28B rs8099917 Allele, HCV group was higher in G than the control group, while regarding to T, a control group was higher than HCV group. For polymorphism rs8099917, being higher among patients than controls. Regarding iL28B rs12979860, HCV group was higher in CT and TT than the control group, while regarding to CC, control group was higher than the HCV group. Regarding iL28B rs12979860 Allele, the HCV group was higher in T than control group, while regarding to C, a control group was higher than HCV group. patients with IL28B rs8099917 TT genotype are associated with a higher probability of spontaneous and treatment-induced HCV clearance than IL28B rs8099917 GT and GG allele carriers. HCV spontaneous clearance was higher in patients with the IL28B rs12979860 CC genotype compared to those with the CT and TT genotypes.

***Conclusively**, treatment with sovaldi can be suggested in patients with IL28B TT genotype and L28B rs12979860 CC genotype to be more effective.*

Keywords: Interleukin- 28 gene polymorphism, HCV type 4, sovaldi.

INTRODUCTION

Hepatitis C virus (HCV) infects more than 175 million people worldwide (Lauer, *et al.,* 2001) . Egypt has the highest prevalence of HCV worldwide with 9% countrywide and up to 50 % in certain rural areas and the highest prevalence of HCV of genotype 4, which is responsible for almost 90% of infections and is considered a major cause of chronic hepatitis, liver cirrhosis, hepatocellular carcinoma (HCC) and liver transplantation in the country (Abdel-Hamid *et al.,* 2007).

The pathogens is continues uncertain, but not only the virus but also the virus' interaction with the immune system of the host may be important in determining the infection course and treatment reaction [(4)]. Cytokines have recently recognized functional gene polymorphisms such as IFN- λ which shows possible relations among these genotypes and the clinical results of liver disease linked to HCV (Sarrazin *et al.,* 2012).

Cytokines have a role in the mechanisms of host defines against infectious agents. They induce inflammatory responses that can lead to tissue injury and serve as antiviral effectors as well. Cytokine synthesis is regulated by genetic mechanisms resulting in differences between individuals in their ability to produce cytokines. This individual variability may be due to single-nucleotide polymorphisms within the coding regions of cytokine genes. Cytokine genes are polymorphic, and some of these variants modify the production of the specific cytokines thereby affecting the host immune response. In HCV infection, secretion of inappropriate amounts of cytokines may be associated with developments of chronic disease or resistance to interferon (IFN) treatment. (Kotenko, *et al.,* 2003)

Interleukin- 28B (IL- 28B) is a cytokine gene that encodes a protein interferon λ3 (IFNL3)12 and IL- 28B gene recently rebaptized as interferon λ3. Cytokines are antiviral effectors, which induce an inflammatory reaction as a predominant mechanism of host defines against infections (Khan *et al*., 2018).

It is conveyed by mononuclear peripheral blood cells dendritic cells after viral infection. IL-28B exhibits antiviral activity, having an impact on the natural clearance of HCV (Par *et al.,* 2011).

Using IL-28B polymorphisms as a predictive instrument will have a significant effect on chronic HCV infection therapy strategies regarding to

emerging therapies and direct-acting agents. It can assist to identify patients who are likely to have success with treatment(Ge *et al*., 2009). The of the present study aimed to evaluate the role of interleukin- 28 gene polymorphism (rs 12979860CC and rs 8099917 T T) on HCV type 4 Egyptian patients treated with sovaldi.

Subjects And Methods

This case-control study was performed on 100 persons with HCC, All subjects were Egyptians being treated at the National Liver Institute Hospital, Menoufia University, Egypt. The patients and control samples were collected over the period from March 2018 to April 2019. This study was approved by Institutional Ethics Committee and informed consent was obtained from all subjects. The subjects were divided into two groups: *Group (A):*50 patients ranged in age between 30.0 – 65.0 years with a mean age 52.32 ± 6.70 years for the control group. *Group (B):* 50 patients ranged in age between 30.0 – 65.0 years with a mean age of 50.82 ± 7.54 years for the HCV group.

Assessment:

The diagnosis will base on elevated alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), gamma-glutamyltransferase (GGT), plasma albumin level, total bilirubin, direct bilirubin, plt and hb. Serum Alpha-Fetoprotein (AFP): COBAS CORE used to measure serum of AFP.

Molecular characterization of 2 SNPs (rs12979860CC& rs8099917 TT): by molecular techniques (PCR RFLP).

Genotyping: Genotyping for the of theIL-28B (rs12979860CC& rs8099917 TT) polymorphism was performed using PCR-based restriction fragment length polymorphism (RFLP) assay.

***Principal of RFLP-PCR*:**

PCR-RFLP is a PCR-based technique that involves endonuclease digestion of the PCR-amplified DNA. It involves a sole PCR reaction followed by restriction enzymatic reaction which is analysed by 3.5% to 4% agarose gel or polyacrylamide gel electrophoresis if the fragments have a small size. The presence of an SNP always creates new restriction site(s) or abolishes the existing one(s), thus allowing the detection (Figure 1).

Therefore, if the SNP created a restriction site, the amplified product of this segment containing the SNP will be cut by the enzyme while the enzyme will not be able to cut the wild strand due to the absence of the restriction site. On the other hand, SNP may abolish the restriction site of a certain enzyme so

by digestion of amplified product of this site, the enzyme will not able to cut the mutant strand while it can cut the wild strand which has the pre-requisite restriction site. Thus, analysis of restriction products will reveal whether there is polymorphism or not. This method is advantageous over some other methods since it is an inexpensive, simple, and convenient method for SNP genotyping.

SNB **(rs12979860CC)** was genotyped in our case-control populations using a PCR-RFLP assay (**Figure 1).**

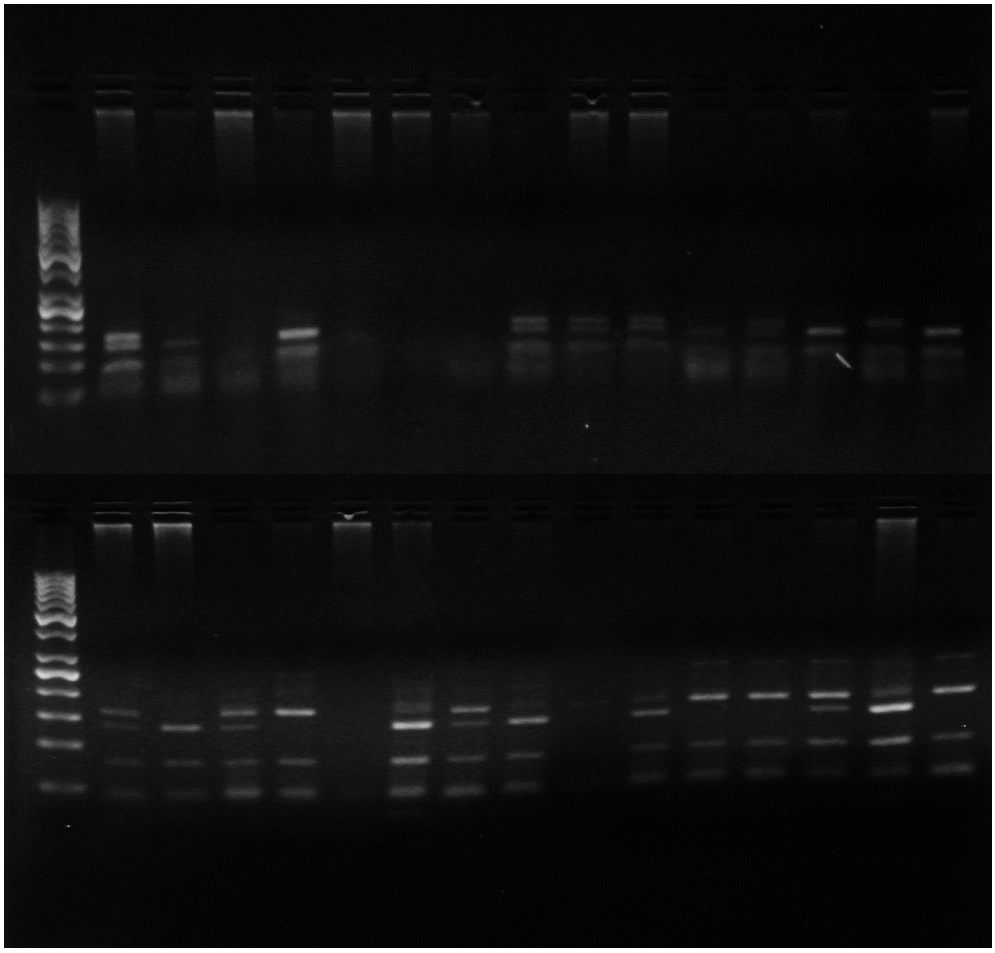

Figure 1. PCR products of SNB **(rs12979860CC)**

SNB**(rs12979860CC**was genotyped in our case-control populations using a PCR-RFLP assay(**Figure 2).**

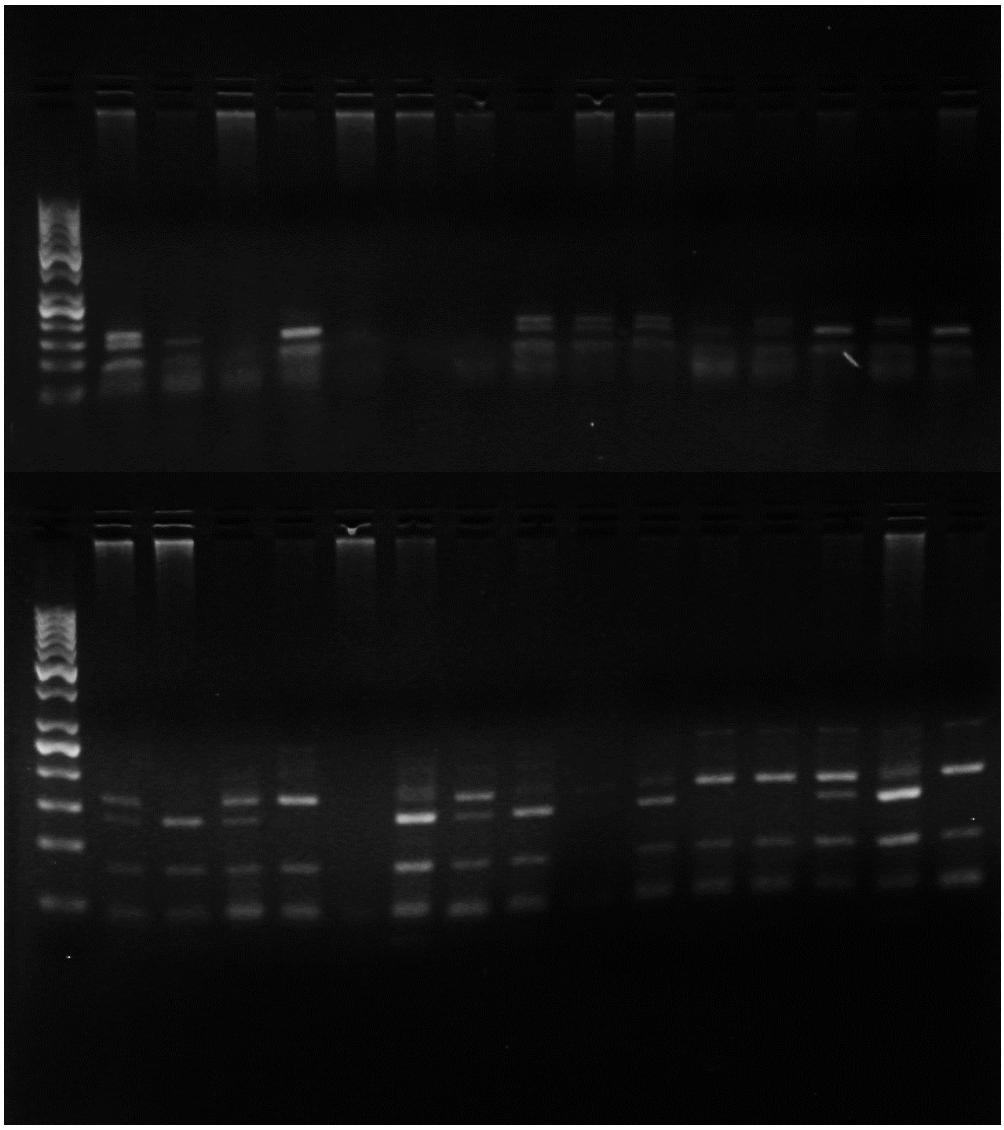

Figure 2. PCR products of SNB **(rs12979860CC)**

Statistical analysis of the data

Data were fed to the computer and analysed using IBM SPSS software package version 20.0. (Armonk, NY: IBM Corp).The Kolmogorov- Smirnov was used to verify the normality of distribution of variables, Comparisons between groups for categorical variables were assessed using the Chi-square test. Student t-test was used to compare two groups for normally distributed

quantitative variables while Mann Whitney test was used to compare between two groups for not normally distributed quantitative variables.

ANOVA was used for comparing the four studied groups. Kruskal Wallis test was used to compare different groups for abnormally distributed quantitative variables. Odds ratio (OR) was used to calculate the ratio of the odds and 95% Confidence Interval of an event occurring in one risk group to the odds of it occurring in the non-risk group. Hardy-Weinberg the population of the studied sample was explored to find its equilibrium with the Hardy-Weinberg equation. The significance of the obtained results was judged at the 5% level.

RESULTS AND DISCUSSION:

Hepatitis C virus genotype 4 (HCV-G4) is the most common type of HCV in the Middle East and Africa, particularly in Egypt, which has the highest prevalence of HCV worldwide (15%), and HCV-G4 represents 90% of all HCV cases[1]. Despite the development of new direct antiviral agents such as protease inhibitors, which have improved response in HCV genotypes (Kamal, 2011& Manns *et al*., 2012), unfortunately G4 has emerged as a resistant genotype to new treatment strategies. Although the mechanisms leading to clearance of acute HCV infection are not completely understood, both innate and adaptive immune responses have been suggested to play crucial roles in viral eradication and response to treatment ([Rehermann, 2009).

Besides immune responses, other host factors have also been associated with treatment induced viral clearance. Higher rates of viral resolution have been reported in women compared with men; however, other factors such as age, race, or route of transmission were not significantly associated with viral resolution (Asselah *et al.*, 2010). Recently, another host factor, a genetic variation in the interleukin-28B (IL28B) gene, was found to predict spontaneous clearance of HCV infection (Thomas *et al.*, 2009).

A single nucleotide polymorphism (SNP) rs12979860 located 3 kb upstream of IL28B, the gene that encodes IFN-λ3, has been strongly associated with the resolution of HCV infection [Ge et al., 2009]. Patients with C/C genotype were more likely to eradicate HCV than those with T/T genotype [Shebl *et al.*, 2011 & Scott *et al*., 2011]. The same SNP has also been associated with treatment-induced viral clearance (Suppiah *et al.*, 2009 & Halfon *et al*., 2011). Patients with the C/C genotype were twice as likely to achieve a sustained viral response (SVR) compared to patients with other IL28B SNP genotypes (Ge *et al.*, 2009).

However, the association between IL28B genotype and response to treatment among individuals infected with HCV-G4 still needs further investigation among the ethnic group living in the Middle East. Therefore, in the present study was to assess the role of interleukin- 28 gene polymorphism (rs12979860 CC and rs8099917 TT) on HCV type 4 Egyptian patients treated with sovaldi.

A total of 100 patients with HCV infection was included in this study, 50 patients ranged in age between 30.0 – 65.0 years with a mean age of 50.82 ± 7.54 years for HCV group and 50 patients ranged in age between 30.0 – 65.0 years with a mean age 52.32 ± 6.70 years for the control group. There was a statistically non-significant difference between the two groups regarding to the mean of age. HCV group had 29 males and 21 females, while the control group had 19 males and 31 females. There was statistically a significant difference between gender distributions in the two groups.

In the present study, the mean Platelet was statistically non-significantly between groups (p=0.092). Regarding Hb: The mean Hb was statistically significant (p=0.020). HCV group showed a higher mean Hb than the Control group. Regarding AFP: The mean AFP was statistically significant (P<0.001). HCV group showed a higher mean AFP than the Control group. the serum AFP level was the most important predictor of HCC for cirrhotic patients. Although the AFP level of almost all patients improves during treatment, the longitudinal AFP level may play a role in early HCC. In previous HCC, cirrhotic patients were significantly more prone to experience HCC recurrence, but the AFP levels at baseline and end of treatment were not significant factors (Ogawa *et al.*, 2018) in contrast, There was no difference between HCV+ patients and controls in terms of mean AFP (Emamaullee *et al.*, 2019). This finding is also in contrast to a previous report by Conti *et al*.,(2016), that reported that liver stiffness by transient elastography was associated with HCC recurrence.15 In fact, among our 21 patients who had HCC recurrence after treatment, (71.4%) had decreased AFP.

Regarding, direct bilirubin: HCV group showed a higher mean Direct bilirubin than Control group. Regarding Total Bilirubin: HCV group showed a higher mean Total Bilirubin than Control group. Regarding ALB: The mean ALB was statistically significant (P<0.001). HCV group showed a lower mean ALB than Control group. Regarding AST: The mean AST was statistically significant (P<0.001*). HCV group showed a higher mean AST than Control group. Regarding, ALT: The mean ALT was statistically significantly (P<0.001*). HCV group showed a higher mean ALT than Control group. ALT and AST elevation is a biochemical surrogate for hepatocytic injury and atypical presentation of CHC. Studies have demonstrated persistent elevation of

ALT and AST is associated with CHC progression and increased risk for cirrhosis, and indication for HCV treatment. For instance, ALT elevation was reported to be present in 75% of patients with CHC (Lynch *et al.,* 2016). In our cohort of patients, baseline serum ALT >48 IU/L and AST >46 IU/L.

The current study showed that, among the 100 Egyptian chronic HCV patients, the IL-28B rs12979860 CC, CT, and TT genotypes were present in 22.0%, 60.0%, and 18.0 % of patients, respectively; thus, the CT genotype was the most common in the studied patients. In accordance, Bakr et al., 2015, showed that, among the 130 Egyptian chronic HCV patients, the IL-28B rs12979860 CC, CT, and TT genotypes were present in 34.6, 42.3, and 23.1% of patients, respectively; thus, the CT genotype was the most common in the studied patients (Table 1).

Nearly similar results were reported in many recent Egyptian studies. For example, Hendy et al. 2011, detected that the incidence of CC, CT, and TT genotypes was 39, 51, and 10, respectively, and Khairy *et al.* (2013) found that the incidence of IL-28 genotypes CC, CT, and TT in Egyptian patients was 25, 56, and 19%, respectively, with the CT genotype being the most common in their study. El-Awady *et al.*(2012) in a study on Egyptian patients, found that the incidence of IL-28B genotypes was 48% CC, 14% TT, and 38% CT in their studied patients and Asselah et al. 2012 found the incidence to be 55% CC, 11% TT, and 34% CT, adding that the CC genotype was the most common in these studies. Similarly, De Nicola *et al.*(2012) found that the incidence of IL-28 genotypes CC, CT, and TT in Italian patients was 23, 63, and 14%, respectively. In the study by Tolmane *et al*.(2012) on the IL-28 gene polymorphism in Latvia, the most common genotype of IL-28B was CT, with an incidence of 53%, followed by the CC genotype (33%) and the TT genotype (14%).

In the present study, the frequency of IL-28B genotypes CC, CT, and TT in healthy controls was 52.0, 40.0, and 8%, respectively. The frequency of the IL-28B C/C genotype was lower in HCV patients than in controls (22.0vs. 52.0%); this difference is not significant. However, there was a significant difference between HCV patients and controls as regards the IL28B alleles, as the frequency of the T allele was lower in HCV patients than in healthy controls (48.0 vs. 28.0%) and the C allele was non-significant. In agreement with our study is the one by Par *et al.* (2011) who reported that the frequency of the IL-28B C/C genotype was lower in HCV patients than in controls; it may be regarded as being protective against chronic HCV infection.

Table (1): Comparison between the two studied groups according to different parameters

Items	HCV (n = 50)	Control (n = 50)	p
Sex			
Male	29 (58.0%)	19 (38.0%)	0.045*
Female	21 (42.0%)	31 (62.0%)	
Age (years)			
Mean ± SD.	50.8 ± 7.5	52.3 ± 6.7	0.296
Median (Min. – Max.)	50(30 – 65)	52(30 – 65)	
Plat			
Mean ± SD.	213.8 ± 53.2	197 ± 50.3	0.092
Median (Min. – Max.)	202(121 – 316)	199(127 – 320)	
Hb			
Mean ± SD.	13.4 ± 1.6	12.7 ± 0.9	0.020*
Median (Min. – Max.)	13.3(10.5 – 16.1)	12.7(12 – 13.5)	
AFP			
Mean ± SD.	246.6 ± 136	1.1 ± 1.5	<0.001*
Median (Min. – Max.)	222(93 – 740)	0(0 – 5)	
Direct bilirubin			
Mean ± SD.	0.5 ± 0.7	0.2 ± 0.03	<0.001*
Median (Min. – Max.)	0.2(0.1 – 3.9)	0.2(0.1 – 0.2)	
Total Bilirubin			
Mean ± SD.	1.4 ± 0.9	0.8 ± 0.2	<0.001*
Median (Min. – Max.)	1.1(0.7 – 5.6)	0.8(0.4 – 1.2)	
ALB			
Mean ± SD.	3.9 ± 0.6	4.6 ± 0.5	<0.001*
Median (Min. – Max.)	4(2.9 – 4.8)	4.6(3.5 – 5.6)	
AST			
Mean ± SD.	46.5 ± 24.9	28.7 ± 5.3	<0.001*
Median (Min. – Max.)	42.5(19 – 134)	28.5(18 – 40)	
ALT			
Mean ± SD.	48.5 ± 30.3	24.2 ± 6.5	<0.001*
Median (Min. – Max.)	44(19 – 205)	23.5(10 – 45)	
rs8099917			
GG	1 (2.0%)	0 (0.0%)	0.006*
GT	19 (38.0%)	7 (14.0%)	
TT	30 (60.0%)	43 (86.0%)	
Allele			
G	21 (21.0%)	7 (7.0%)	0.004*
T	79 (79.0%)	93 (93.0%)	
iL28B rs12979860			
CC	11 (22.0%)	26 (52.0%)	0.007*
CT	30 (60.0%)	20 (40.0%)	
TT	9 (18.0%)	4 (8.0%)	
Allele			
C	52 (52.0%)	72 (72.0%)	0.004*
T	48 (48.0%)	28 (28.0%)	

χ^2: Chi square test, U: Mann Whitney test, t: Student t-test , P: P value for comparing between the studied groups, *: Statistically significant at $P \leq 0.05$.

The frequency of IL-28B genotypes CC, CT, and TT in healthy controls was 52.5, 32.5, and 15%, respectively. The frequency of the IL-28B C/C genotype was lower in HCV patients than in controls (34.6 *vs.* 52.5%); this difference is not significant. However, there was a significant difference between HCV patients and controls as regards the IL28B alleles, as the frequency of the C allele was lower in HCV patients than in healthy controls (55.8 *vs*. 68.8%) and the T allele was higher in HCV patients than in controls (44.2 *vs*. 31.2%) (Bakr *et al*., 2015).

Regarding rs8099917, the difference between HCV group and control group was statistically significant (P=0.006*) The results showed that the IL28B rs8099917 TT genotype is predominant among the studied patients as well as the control followed by GT and the least prevalent was the GG genotype. A similar result was found by Kalantari *et al*.(2019). Patients with the IL28B rs8099917 TT genotype are reported to be associated with a higher probability of spontaneous and treatment-induced HCV clearance than IL28B rs8099917 G allele carriers (Sharafi *et al.*, 2012).

Regarding iL28B rs8099917 Allele, the difference between HCV group and control group was statistically significant (p=0.004*) HCV group was higher in G than control group, while regarding to T, control group was higher than HCV group.

For polymorphism rs8099917, the distribution of allele G exhibited a significant difference between the groups, being higher among the patients than the controls, and the presence of that allele was associated with HCV. The results of this study point to a possible association between the presence of that SNP and greater susceptibility to HCV (da Silva *et al.*, 2014).

Regarding iL28B rs12979860, the difference between HCV group and control group was statistically significant (P=0.005*) HCV group was higher in CT and TT than control group, while regarding CC, control group was higher than HCV group. Regarding iL28B rs12979860 Allele, the difference between HCV group and control group was statistically significant (P=0.017*) HCV group was higher in T than control group, while regarding to C, control group was higher than HCV group (Table 2).

Taheri *et al.*, 2015, evaluated the rate of IL28B genotypes in patients with Chronic Hepatitis-C (CHC) and healthy control subjects and to examine the characteristics of patients in each IL28B subgroup. In the patients with chronic HCV-genotype 1b and 4 infections, the IL28B rs12979860 (C>T) gene polymorphism frequency of the TT genotype and T allele was higher than in healthy control subjects. This result indicates that the TT genotype may be more effective in the progression of HCV infection than other genotypes.

Table (2): Comparison between the two studied groups according to iL28B rs12979860

iL28B rs12979860	**HCV (n = 50)**	**Control (n = 50)**	**p**	**OR**	**95% C.I**
CC	11 (22.0%)	26 (52.0%)		1.000	
CT	30 (60.0%)	20 (40.0%)	0.005*	3.546*	1.436 – 8.755
TT	9 (18.0%)	4 (8.0%)	0.017*	5.318*	1.348 – 20.985
Allele					
C	52 (52.0%)	72 (72.0%)		1.000	
T	48 (48.0%)	28 (28.0%)	0.004*	2.374	1.320 – 4.269

χ^2: **Chi square test** OR: Odds ratio CI: Confidence interval
p: p value for comparing between the studied groups
*: Statistically significant at $P \leq 0.05$.

In a study performed in African or European populations, HCV spontaneous clearance was three-fold higher in patients with the IL28B rs12979860 CC genotype compared to those with the CT and TT genotypes (Thomas *et al.,* 2009). In a study performed in Egypt, the incidence of the CC genotype (48%) was higher than that of the CT (38%) and TT (14%) genotypes in healthy control subjects (El-Awady *et al.,* 2012). Furthermore, in these subjects, the C:T allele ratio was 67:33, indicating that the IL28BCC genotype protects against chronic infection progression by spontaneous clearance during the acute phase (Liao *et al.,* 2011). in another Egyptian study, there was a significant difference in the distribution of the IL28B rs12979860 (C>T) genotypes between 440 HCV genotype-4 infected patients and 220 healthy control people (Pasha *et al.,* 2013).

Conclusively, patients with IL28B rs8099917 TT genotype are associated with a higher probability of spontaneous and treatment-induced HCV clearance than IL28B rs8099917 GT and GG allele carriers. HCV spontaneous clearance was higher in patients with the IL28B rs12979860 CC genotype compared to those with the CT and TT genotypes. Thus, treatment with sovaldi can be suggested in patients with IL28B TT genotype and L28B rs12979860 CC genotype to be more effective.

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التوصيف الجزيئي للإنترلوكين في التهاب الكبد المزمن

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تعدد أشكال النوكليوتيدات المنفردة في منبع الإنترفيرون 3λ- جين، يرتبط بقوة بإزالة عدوى فيروس التهاب الكبد C العفوية والمستحثة بالعلاج. كان الهدف من هذه الدراسة هو تقييم دور الإنترلوكين -28 من أشكال العمل الجيني rs12979860 CC) و rs8099917 TT)على مرضى فيروس التهاب الكبد C من النمط 4 المعالجين بالسوفالدي. تم تضمين ما مجموعه 100 مريض مصابين بعدوى فيروس التهاب الكبد C في هذه الدراسة. تم التشخيص على أساس رفع ناقلات أمين الألانين(ALT) ، ناقلات أمين الأسبرتات(AST) ، الفوسفاتيز القلوي(ALP) ، مستوى ألبومين البلازما، البيليروبين الكلي، البيليروبين المباشر، الصفائح الدموية و .HB التوصيف الجزيئي لـ 2 SNPs (rs 12979860CC and rs 8099917 TT)في جين الهيبارياناز: بواسطة التقنيات الجزيئية .(ARMs-PCR & RFLP) النمط الوراثي IL28B rs8099917 هو السائد بين المرضى، فضلا عن السيطرة تليها GT والأقل انتشارا كان GG النمط الوراثي. فيما يتعلق بـ iL28B rs8099917 أليل، كانت مجموعة HCV أعلى في مجموعة التحكم، بينما فيما يتعلق بـT ، كانت مجموعة التحكم أعلى من مجموعة .HCV لتعدد الأشكال rs8099917 يكون أعلى بين المرضى من الشواهد. فيما يتعلق بـ iL28B rs12979860، كانت مجموعة HCV أعلى في CT و TT من المجموعة الضابطة، بينما فيما يتعلق بCC ، كانت مجموعة الضابطة أعلى من مجموعة .HCV فيما يتعلق بـ iL28B rs12979860 أليل، كانت مجموعة HCV أعلى في T من مجموعة المراقبة، في حين فيما يتعلق بC ، كانت مجموعة المراقبة أعلى من مجموعة .HCV يرتبط المرضى الذين يعانون من النمط الجيني IL28B rs8099917 TT مع احتمال أعلى من التهاب الكبد الفيروسي ج الناجم عن العلاج والعفوية.
التوصية: يمكن اقتراح العلاج باستخدام سوفالدي في المرضى الذين يعانون من النمط الجيني IL28B TT والنمط الجيني L28B rs12979860 CC ليكون أكثر فعالية.