Journal of Communicable Diseases
Volume 56, Issue 2 - 2024, Pg. No. 22-30
Peer Reviewed & Open Access Journal

Research Article

Detect the *IFNL4* Polymorphism (rs12979860) and level of *IFNL4* in serum of Hepatitis C Virus in Iraqi Province

Zahraa Basim Naser[1], Raya Ezat Maroof[2], Khalied Yassen Zakair[3]

[1,2]College of Health and Medical Techniques, Middle Technical University (MTU), Baghdad, Iraq.
[3]Kut Technical Institute, Middle Technical University, Baghdad, Iraq.
DOI: https://doi.org/10.24321/0019.5138.202428

I N F O

Corresponding Author:
Zahraa Basim Naser, College of Health and Medical Techniques, Middle Technical University (MTU), Baghdad, Iraq.
E-mail Id:
zbassim33@gmail.com
Orcid Id:
https://orcid.org/0009-0008-9362-1653
How to cite this article:
Naser Z B, Maroof R E, Zakair K Y. Detect the *IFNL4* Polymorphism (rs12979860) and level of *IFNL4* in serum of Hepatitis C Virus in Iraqi Province.J Commun Dis. 2024;56(2):22-30.

Date of Submission: 2024-03-18
Date of Acceptance: 2024-05-06

A B S T R A C T

Introduction: Hepatitis C virus (HCV) presents a significant and impending threat to the well-being of the global public. In this study, *IFNL4* in the serum of HCV patients and SNPs (rs12979860) was to be evaluated in both the patient and control groups.

Method: Sixty specimens were obtained from patients diagnosed with HCV (divided into infected undetectable viral load and detectable viral load), and thirty samples from individuals deemed to be in fair health (control group) from the Teaching Hospital for Gastroenterology and Hepatology, the National Center for Blood Transfusion, and the Al-Wasiti Teaching Hospital. HCV antibodies were detected in all patient samples, and virus loads were determined. A total of ninety samples were collected from individuals aged 20 to 60 years. The number of viruses was identified by GeneXpert® Systems. ELISA quantified *IFNL4*. The *IFNL4* gene (rs12979860) was determined from blood samples using the polymerase chain reaction and was subsequently transmitted to Macrogen, Korea, for sequencing.

Result: The mean *IFNL4* value was significantly higher in the group with undetectable viral load ($p < 0.0001$). According to the ROC curve study, *IFNL4* has 100% sensitivity and 97.0% specificity in the control and undetectable viral load groups. The assay's specificity is 96.0% for the control group and 97.0% for the detectable viral load group. The primer identifies *IFNL4* gene amplification at the rs12979860 region. Geneious software analysis showed SNP variations: CC to CT (rs12979860), GG to GA (rs1288377676), CC to CG (rs1254026524), GG to GT (rs1414880542), GG to GA (rs574801123), and AA to AG (rs1600456091). *IFNL4* was more prevalent in the undetectable viral load HCV-infected group.

Conclusion: The presence of genetic polymorphisms in the *IFNL4* gene may be of help in planning the treatment course for patients with HCV.

Keywords: HCV, *IFNL4*, Detectable Viral Load, Undetectable Viral Load, SNPs

Introduction

The hepatitis C virus (HCV), which is a serious public health concern, affects around 250 million individuals worldwide. Human liver infection from it can result in acute, temporary, and chronic illnesses.[1,2] In many aspects, the liver is a sign of one's health, hence, it should be given priority in global public health initiatives.[3,4] HCV, an RNA virus classified under the Flaviviridae family, impacts around 3% of the world's populace.[5] Spontaneous clearance occurs in approximately 30% of individuals who have newly contracted HCV (SC). 70%, however, develop chronic hepatitis C. (CHC).[6] Stages of cirrhosis and hepatocellular cancer may develop from CHC. Stages of cirrhosis and hepatocellular cancer may develop from CHC.[7] However, discrepancies in the incidence of SC indicate that host immunological variables and viral genotypes may play a role.[8] Two research groups found the initial three interferon lambda genes under different naming systems.[9,10] This was accomplished by imitating HCV infection and utilising polyinosinic polycytidylic acid to induce the synthesis of interferon lambda genes in human hepatocytes (poly I: C).[11] The discovery of a fourth gene in this region occurred in 2013. According to RNA sequencing, the interferon lambda region now contains *IFNL4*, which was previously unknown. The locus of the interferon lambda genes is 19q13.13 on chromosome 19. *IFNL4* is positioned between IFNL3 and IFNL2. The complete *IFNL4* protein comprises 179 amino acids and five exons that contain the *IFNL4* gene. Researchers have identified the potential of the *IFNL4* protein to activate the Janus kinase (JAK) signal transducer and transcription activator and combat viruses. Further, sustained virological response (SVR) is facilitated by these single nucleotide polymorphisms (SNPs) in HCV-positive patients who are treated with ribavirin (RBV) and pegylated interferon-alpha (peg IFN-α).[12] Serum *IFNL4* concentrations in patients are the secondary aims of this investigation to analyse this genetic variation in the Iraqi populace.

Materials and Methods

This study included 90 blood samples (of people aged 20–60 years) that underwent HCV-AB analysis and viral load measurement of HCV-AB positive samples. They were divided into three groups. The first group comprised 30 HCV-infected patients, while the second group comprised 30 HCV-infected patients with undetectable viral load. The last group consisted of 30 healthy individuals for comparison purposes. A case-control study was conducted at the Teaching Hospital for Gastroenterology and Hepatology, the National Center for Blood Transfusion, and the Al-Wasiti Teaching Hospital from December 2022 to May 2023. The GeneXpert® system determines the viral load tests, and *IFNL4* was detected by ELISA technology. The procedure (USCN/ USA) follows the manufacturer's protocol.

Polymerase Chain Reaction Amplification and DNA Sequencing

The rs12979860 *IFNL4* SNP gene was identified using a standard polymerase chain reaction (PCR). Following primer design, a 617 bp fragment is replicated by the reverse GACGAGAGGGCGTTAGA and forward CACGGTGATCGCAGAAG primers. The PCR was conducted at a final volume of 25 µL, utilising 1 µL of forward and reverse primers, 12.5 µL of Promega green master mix, 7.5 µL of nuclease-free water, and 3µl of genomic DNA per micro-tube PCR. The concentration of the PCR mixture was 1 µL. The optimal outcomes were achieved using a series of 30 cycles consisting of 30 denaturation steps at 94 °C for 5 minutes, followed by 30 cycles of annealing for 30 seconds, denaturation at 94 °C for 30 seconds, extension at 72 °C for 1 minute, and a final extension step at 72 °C for 10 minutes. Agarose gel electrophoresis (1.5% concentration) was utilised to validate the existence of amplification after PCR amplification. Subsequently, the PCR results were subjected to Sanger sequencing using abi3730xl, an automated DNA sequencer manufactured by Microgen Corporation in Korea that relies entirely on the extracted DNA standards. Once the findings were obtained by email, they were examined with the Genius software.

Statistical Analysis

Patients' information was gathered, and statistical analysis was conducted using SPSS version 20. The significance level for the ANOVA test-analysed differences was statistically significant ($p < 0.05$). By constructing an ROC curve and analysing the area under the curve, the optimal cutoff value of *IFNL4* for case detection was determined. P values below 0.05 were deemed to indicate statistical significance, and the frequencies and percentages of the variables representing the distribution of SNPs in the study group were utilised.

Ethical Approval

Before collecting information and blood samples, consent was obtained from all participants after a comprehensive explanation of the study's objectives and methodologies. The study was carried out under the Helsinki Declaration, and the Research Committee of Baghdad Medical City-Training and Human Development Center No. 6627 also approved the study.

Results

There was a statistically significant difference between the mean frequencies of *IFNL4*, as shown in Table 1, with a p value of less than 0.0001. The control group had an undetectable viral load of 3.412 ± 0.8295, an undetected viral load of 5.366 ± 0.8698, and an undetectable viral load of 1.623 ± 0.08468.

ISSN: 0019-5138
DOI: https://doi.org/10.24321/0019.5138.202428

Table 1.Comparison Between the Mean Concentrations of *IFNL4* in HCV Patient Groups With the Control Group

IFNL4	Infected Detectable VL	Infected Undetectable VL	Control	p Value
Mean	3.412	5.366	1.623	< 0.0001**
SD	0.8295	0.8698	0.4638	
SE	0.8295	0.8698	0.08468	
n	30	30	30	

VL: Viral Load, **: Highly significant

According to the data presented in Table 2, the *IFNL4* exhibited an area under the curve (AUC) of 0.9978 (p < 0.0001), a sensitivity of 100.0%, and a specificity of 97.0% when the cut-off value was ≥ 2.693 U/L in patients with undetectable viral load relative to the control groups. Similarly, when the cut-off value was ≥ 2.2 U/L in patients with detectable viral load relative to the control groups, the *IFNL4* demonstrated an AUC of 0.9522 (p < 0.0001), a sensitivity of 96%, and a specificity of 97%.

Table 2.Analysis of the Receiver Operating Characteristic Curve (ROC) for *IFNL4* in the Cohort Under Study

Parameters		Sensitivity (%)	Specificity (%)	Cut-off (U/L)	AUC	p Value
IFNL4	Control and infected undetectable viral load	100.0	97.0	> 2.693	0.9978	< 0.0001
	Control and infected detectable viral load	96.0	97.0	> 2.200	0.9522	< 0.0001

Figure 1 shows the ROC curve in serum *IFNL4* between the control and infected groups. The undetectable viral load is determined by the sensitivity and specificity of *IFNL4* (100%, 97.0%), respectively.

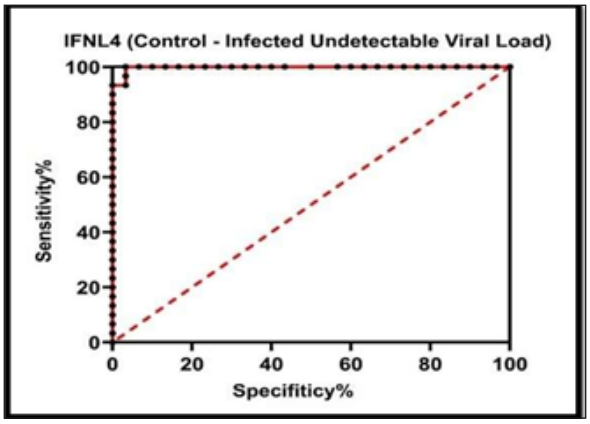

Figure 1.ROC Curves in Serum of Control and Infected Undetectable Viral Load

ISSN: 0019-5138
DOI: https://doi.org/10.24321/0019.5138.202428

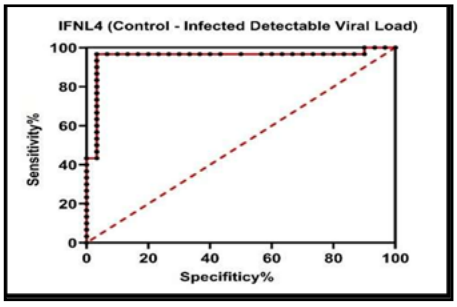

Figure 2.ROC Curves in Serum of Control and Infected Detectable Viral Load

Figure 2 shows the ROC Curve in Serum *IFNL4* Between the Control and Infected Groups. The detectable viral load is found to have a sensitivity of 96.0% and a specificity of 97.0%.

PCR Amplification Result

Fifty-six blood samples were chosen for molecular study. The DNA of these 56 isolates was extracted and amplified for *IFNL4* genes by specific primers. Gel electrophoresis on agarose was compared with DNA ladder marker 100 pb (Promega, USA). The result is shown in Figures 3–6.

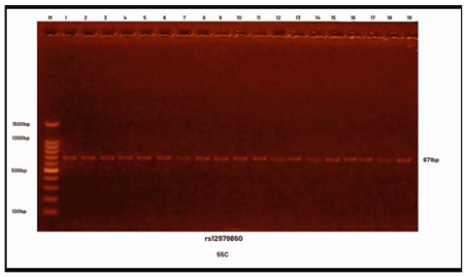

Figure 3.Results of the Amplification of the rs12979860 Specific Gene Region of the Patients and Control Fractionated on 1.5% Agarose Gel Electrophoresis Stained With Eth. Br. at 100 volts/ 50 mAmp for 60 Minutes. M: 100 bp Ladder Marker. Lanes 1-19 Resemble 671 bp PCR Products.

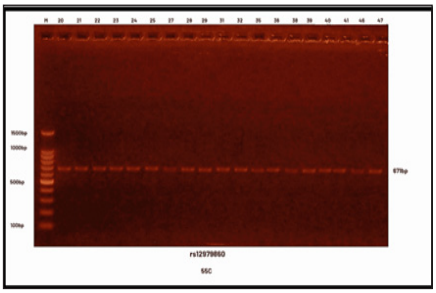

Figure 4.Results of the Amplification of rs12979860 Specific Gene Region of Patients and Control were Fractionated on 1.5% Agarose Gel Electrophoresis Stained With Eth. Br. at 100 volts/ 50 mAmp for 60 minutes. M: 100 bp Ladder Marker. Lanes 20-47 Resemble 671 bp PCR Products.

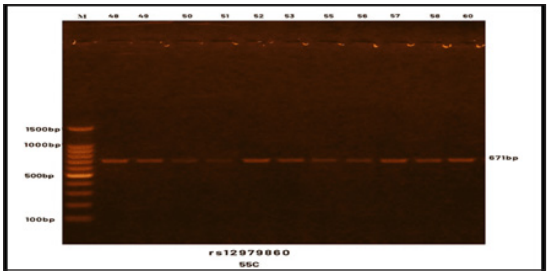

Figure 5.Results of the Amplification of rs12979860 Specific Gene Region of Patients and Control were Fractionated on 1.5% Agarose Gel Electrophoresis Stained With Eth. Br. at 100 volt/ 50 mAmp for 60 minutes M: 100 bp Ladder Marker. Lanes 48-60 Resemble 671 bp PCR Products.

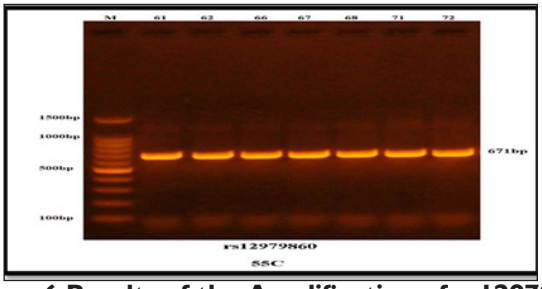

Figure 6.Results of the Amplification of rs12979860 Specific Gene Region of HCV Patients and Control were Fractionated on 1.5% Agarose Gel Electrophoresis Stained With Eth. Br. at 100 volt/ 50 mAmp for 60 Minutes. M: 100 bp Ladder Marker. Lanes 61-72 Resemble 671 bp PCR Products.

Sequencing of Virulence Gene

Sequencing of the *IFNL4* gene (rs12979860) in the 56 DNA samples from blood samples was sent to Macrogen-Korea for Sanger sequencing while studying this gene to detect the SNPs (rs12979860). This study also found another SNP (rs1288377676, rs1254026524, rs1414880542, rs574801123, rs529794067) and (rs1600456091) is near rs12979860. Email delivery of the results was followed by analysis with the Geneious program. Table 3 shows the distribution of SNPs observed in the study samples.

According to SNPs, twelve DNA sequences were recorded in the National Center for Biotechnology Information (NCBI) from a single person in the *IFNL4* regions (partial sequences). Other DNA samples did not show any change in their DNA sequences. The result in Table 4 shows that the percentage point substitution mutations of GA (G>A) was 7 (12.5%) in rs574801123 and 2 (3.5%) in rs1288377676, while the percentage of point substitution mutations C>T was 2 (3.5%) in the rs12979860. The percentage of G>T point substitution mutations found in SNPs rs529794067 and rs1414880542 were 3 (5.3%) and 2 (3.5%), respectively.

ISSN: 0019-5138
DOI: https://doi.org/10.24321/0019.5138.202428

Table 3.Distribution of SNPs in Study Samples Documented in NCBI

SNPs	rs1288377676	rs1254026524	rs1414880542	rs12979860	rs574801123	rs529794067	rs1600456091	Accession No
Wild	GG	CC	GG	CC	GG	GG	AA	-
Variation	G>A	C>G	G>T	C>T	G>A	G>T	A>G	-
1	GG	CC	GG	CC	GG	GG	AA	Zrkiraq1LC780671.1
4	GG	CG	GG	CC	GG	GG	AA	Zrkiraq4 &LC780672.1
7	GG	CG	GT	CC	GG	GG	AG	Zrkiraq7&LC780673.1
10	GG	CG	GG	CC	GA	GG	AA	Zrkiraq10 &LC780988.1
20	GA	CC	GG	CC	GG	GG	AA	Zrkiraq20& LC780989.1
25	GA	CC	GT	CC	GA	GG	AA	Zrkiraq25& LC780990.1
28	GG	CG	GG	CC	GA	GT	AA	Zrkiraq28& LC780991.1
40	GG	CC	GG	CT	GG	GG	AA	Zrkiraq40& LC780992.1
57	GG	CC	GG	CT	GA	GG	AA	Zrkiraq57&LC780993.1
58	GG	CG	GG	CC	GA	GT	AA	Zrkiraq58& LC780994.1
67	GG	CG	GG	CC	GA	GG	AA	Zrkiraq67& LC780995.1
68	GG	CG	GG	CC	GA	GT	AA	Zrkiraq68& LC780996.1

ISSN: 0019-5138
DOI: https://doi.org/10.24321/0019.5138.202428

Table 4.Distribution of the Percentage of SNPs in the Study Group

SNPs	Genotypes	n (%)
rs12979860	CC	54 (96.4)
	CT	2 (3.5)
	TT	0 (0.0)
rs1288377676	GG	54 (96.4)
	GA	2 (3.5)
	AA	0 (0.0)
rs1254026524	CC	48 (85.7)
	CG	8 (14.2)
	GG	0 (0.0)
rs1414880542	GG	54 (96.4)
	GT	2 (3.5)
	TT	0 (0.0)
rs574801123	GG	49 (87.7)
	GA	7 (12.5)
	AA	0 (0.0)
rs529794067	GG	53 (94.6)
	GT	3 (5.3)
	TT	0 (0.0)
rs1600456091	AA	55 (98.0)
	AG	1 (1.7)
	GG	0 (0.0)

Discussion

Additional study is required to establish the precise mechanism by which persistent HCV infection induces liver diseases.[13] The results of our study do not match with those of a study by Farid et al., which found that the mean level of *IFNL4* concentration was 49.85 in the control group.[14] While in patient samples, 39.43. Other studies also indicated that levels of IL-29 (IFN-lambda 1) in the blood were at least two times greater than levels of IL-28 AIL-28 B (IFN-lambda 2/3).[15] Many studies have proven that interferon may prevent the replication of many viruses,[9,10,16] including HCV and HBV[17,18]. This is consistent with our study, where the *IFNL4* level was higher in the group with undetectable viral load compared to the other groups. Furthermore, high *IFNL4* levels made the HCV infection more likely to resolve on its own. As a result, IFN-4 appears to be crucial in managing hepatitis C.

Regarding *IFNL4*, the result did not match with that of El-Khazragy et al.;[19] the area under the curve (AUC) value for serum *IFNL4* was 0.8, with a sensitivity of 85.7% and specificity of 30.2%. Chen et al. found an AUC value of 0.84, a sensitivity of 82.4%, and 90% specificity.[20] The ROC can be used to compare different tests, calculate the appropriate cutoff value, and evaluate the assessed substances' AUC, sensitivity, and specificity. *IFNL4* strong candidates are diagnostic markers for HCV infection because they can effectively differentiate between HCV-infected and HCV-uninfected patients. The discrepancy in disease results reported in multiple studies may be due to differences in differential immune responses or may also be due to differences in the sensitivity of the ELISA kit and small population size.

Conversely, so it stands. The C-to-T transition polymorphism of the rs12979860 intron (*IFNL4*) is linked to both treatment-induced and spontaneous clearance of HCV infection. Hepatocellular carcinoma and other liver illnesses connected with HCV may be impacted by this particular component as well (HCC).[13] Our findings contradicted those of an Iranian study,[21] which found that the frequencies of rs12979860 CC, CT, and TT genotypes in HCV samples were 10 (19.6%), 35 (68.6%), and 6 (11.8%), respectively in addition to another study in Iran conducted by Sharafi et al.[22] Among 104 patients with chronic hepatitis C, the rs12979860 CC, CT, and TT genotypes frequency was 40.4%, 47.1% and 12.5%. Another similar study was conducted in Iran.[23] CT and TT are obvious polymorphisms of rs12979860. The most prevalent genetic variations of the rs12979860 polymorphisms in patients were CC (33.3%), CT (43.3%), and TT (23.3%); in healthy individuals, the equivalent frequencies were CC (50%), CT (32%), and TT (23.3%) (17%). Further inquiry undertaken in the United Kingdom (UK) unveiled that rs12979860 was prevalent (40 instances, or 33%), with CC, CT, and TT comprising 15 cases, 13%, and 65 points, or 54%, respectively. Among individuals, the CT genotype is the most widespread.[24]

Other studies matched our study, including one conducted in Pakistan by Aziz et al.[25] It has been established that patients with homozygous C/C have a greater likelihood of achieving SVR; as a result, the IL28B polymorphism predicts how well HCV-infected patients would respond to PEG-IFN and ribavirin treatment. Another study showed the IL28 gene polymorphisms rs12979860 and rs8099917, found on chromosome 19, are unmistakably linked to viral eradication at 12 weeks of treatment.[26] The rs12979860 genotype might be utilised to predict the efficacy of anti-viral medications in individuals with HCV genotypes 2 and 3. It provided evidence of a comparable outcome. The diminished prevalence of the CC genotype might impact the reduced incidence of SVR among HCV patients receiving PEG-IFN and ribavirin. Another study in Japan found that The CC allele of rs12979860 was correlated with an SVR rate two to three times greater than that of the CT or TT alleles. At two to three times the SVR rate of the CT or TT alleles, the CC allele of rs12979860 exhibited a correlation.[15,27] The study's results indicated that subjects with the rs12979860 CC genotype had significantly greater concentrations of IL28A/B and IL29 in their serum than

ISSN: 0019-5138
DOI: https://doi.org/10.24321/0019.5138.202428

those with the TT genotype.

Based on an Italian study on the impact of immunogenic IL28B polymorphism on chronic hepatitis C, found a lower frequency of the C allele than those whose HCV naturally cleared itself.[28,29] Participants who were under the age of 40, had a baseline viral load of less than 4 x 105 IU/mL, and possessed the responder genotypes of SNPs rs12979860 or rs8099917 were found to be significant independent predictors of rapid viral response to therapy.[30] The genotype CC of the Egyptian cohort is linked to the successful elimination of the virus during the initial infection. The prevalence of the CC genotype was significantly lower in individuals with chronic hepatitis C compared to healthy individuals, and it was virtually absent in individuals with end-stage liver disease (ESLD). This implies that this particular genotype plays a crucial role in halting the advancement of HCV illness. A study conducted on individuals from Africa and Europe revealed that those possessing the IL-28B CC genotype (rs12979860) had a threefold higher likelihood of spontaneous HCV clearance than those with the CT and TT genotypes. This matches our study, where the CT genotype appeared in one patient in the viral load group who had been infected for 20 years and used the treatment for six months when he was infected. Still, the viral load remained at high levels, accompanied by strong symptoms, which means the treatment did not serve its purpose because he carried the CT genotype. The discrepancy in our result may be due to several reasons, such as sample size, age, sex, body mass index, race, patient immune response, viral load, and *IFNL4*, which may be crucial in the anti-viral response against HCV.

Conclusion

The presence of different genetic variations (polymorphisms) in the *IFNL4* gene can assist in determining the course of treatment for patients with HCV. Nevertheless, it is important to undertake a comprehensive and precise assessment to plan and execute more extended research on a greater magnitude in different areas of Iraq.

Acknowledgement

We sincerely thank the management of the Teaching Hospital for Gastroenterology and Hepatology, the National Center for Blood Transfusion, and the Al-Wasiti Teaching Hospital for their support in conducting this study and all willing volunteers who kindly provided blood samples.

Source of Funding: None

Conflict of Interest: None

References

1. Karimkhanilouyi S, Ghorbian S. Nucleic acid vaccines for hepatitis B and C virus. Infect Genet Evol. 2019;75:103968. [PubMed] [Google Scholar]
2. Najlaa Fattah-Allah R, Hind Salman J, Ahmad Saadi H. Assessment of some heavy metals and trace elements in a sample of patients with viral hepatitis in Baghdad. J Techn. 2022;4(3):8-13. [Google Scholar]
3. Al-Azzawi KG, Al-Naqeeb AA, Zeidan MA. Impact of chronic liver diseases on specific health-related quality of life among a sample in Babylon Governorate. J Techn. 2022;4(Special Issue):86-90. [Google Scholar]
4. Marcellin P, Kutala BK. Liver diseases: a major, neglected global public health problem requiring urgent actions and large-scale screening. Liver Int. 2018;38:2-6. [PubMed] [Google Scholar]
5. Chen SL, Morgan TR. The natural history of hepatitis C virus (HCV) infection. Int J Med Sci. 2006;3(2):47-52. [PubMed] [Google Scholar]
6. Hoofnagle JH. Course and outcome of hepatitis C. Hepatology. 2002;36(5 Suppl 1):S21-9. [PubMed] [Google Scholar]
7. Hanafiah KM, Groeger J, Flaxman AD, Wiersma ST. Global epidemiology of hepatitis C virus infection: new estimates of age-specific antibody to HCV seroprevalence. Hepatology. 2013;57(4):1333-42. [PubMed] [Google Scholar]
8. Thomas DL, Thio CL, Martin MP, Qi Y, Ge D, O'Huigin C, Kidd J, Kidd K, Khakoo SI, Alexander G, Goedert JJ, Kirk GD, Donfield SM, Rosen HR, Tobler LH, Busch MP, McHutchison JG, Goldstein DB, Carrington M. Genetic variation in IL28B and spontaneous clearance of hepatitis C virus. Nature. 2009;461(7265):798-801. [PubMed] [Google Scholar]
9. Kotenko SV, Gallagher G, Baurin VV, Lewis-Antes A, Shen M, Shah NK, Langer JA, Sheikh F, Dickensheets H, Donnelly RP. IFN-lambdas mediate antiviral protection through a distinct class II cytokine receptor complex. Nat Immunol. 2003;4(1):69-77. [PubMed] [Google Scholar]
10. Sheppard P, Kindsvogel W, Xu W, Henderson K, Schlutsmeyer S, Whitmore TE, Kuestner R, Garrigues U, Birks C, Roraback J, Ostrander C, Dong D, Shin J, Presnell S, Fox B, Haldeman B, Cooper E, Taft D, Gilbert T, Grant FJ, Tackett M, Krivan W, McKnight G, Clegg C, Foster D, Klucher KM. IL-28, IL-29 and their class II cytokine receptor IL-28R. Nat Immunol. 2003;4(1):63-8. [PubMed] [Google Scholar]
11. Prokunina-Olsson L, Muchmore B, Tang W, Pfeiffer RM, Park H, Dickensheets H, Hergott D, Porter-Gill P, Mumy A, Kohaar I, Chen S, Brand N, Tarway M, Liu L, Sheikh F, Astemborski J, Bonkovsky HL, Edlin BR, Howell CD, Morgan TR, Thomas DL, Rehermann B, Donnelly RP, O'Brien TR. A variant upstream of IFNL3 (IL28B) creating a new interferon gene *IFNL4* is associated with impaired clearance of hepatitis C virus. Nat Genet. 2013;45(2):164-71. [PubMed] [Google Scholar]

12. Suppiah V, Moldovan M, Ahlenstiel G, Berg T, Weltman M, Abate ML, Bassendine M, Spengler U, Dore GJ, Powell E, Riordan S, Sheridan D, Smedile A, Fragomeli V, Müller T, Bahlo M, Stewart GJ, Booth DR, George J. IL28B is associated with response to chronic hepatitis C interferon-alpha and ribavirin therapy. Nat Genet. 2009;41(10):1100-4. [PubMed] [Google Scholar]
13. de Bitencorte JT, Rech TF, Lunge VR, Dos Santos DC, Álvares-da-Silva MR, Simon D. Association of interferon lambda-4 rs12979860 polymorphism with hepatocellular carcinoma in patients with chronic hepatitis C infection. World J Hepatol. 2021;13(1):109. [PubMed] [Google Scholar]
14. Farid S, Rashed L, Sweilam S. Interferon Lambda 4 gene (*IFNL4*) linked to hepatitis C virus clearance, treatment. Egypt J Hosp Med. 2017;67(2):635-44. [Google Scholar]
15. Langhans B, Kupfer B, Braunschweiger I, Arndt S, Schulte W, Nischalke HD, Nattermann J, Oldenburg J, Sauerbruch T, Spengler U. Interferon-lambda serum levels in hepatitis C. J Hepatol. 2011;54(5):859-65. [PubMed] [Google Scholar]
16. Brand S, Beigel F, Olszak T, Zitzmann K, Eichhorst ST, Otte JM, Diebold J, Diepolder H, Adler B, Auernhammer CJ, Göke B, Dambacher J. IL-28A and IL-29 mediate antiproliferative and antiviral signals in intestinal epithelial cells and murine CMV infection increases colonic IL-28A expression. Am J Physiol Gastrointest Liver Physiol. 2005;289(5):G960-8. [PubMed] [Google Scholar]
17. Pagliaccetti NE, Eduardo R, Kleinstein SH, Mu XJ, Bandi P, Robek MD. Interleukin-29 functions cooperatively with interferon to induce antiviral gene expression and inhibit hepatitis C virus replication. J Biol Chem. 2008;283(44):30079-89. [PubMed] [Google Scholar]
18. Zhu H, Butera M, Nelson DR, Liu C. Novel type I interferon IL-28A suppresses hepatitis C viral RNA replication. Virol J. 2005;2:80. [PubMed] [Google Scholar]
19. El-Khazragy N, El Sayed N, Salem AM, Hassan NS, Abdelmoeaz AT, Maher AM, Mansy AE. IL-28β gene polymorphism determines virological response to PEGylated interferon therapy in hepatitis C virus genotype 4 Egyptian patients. J Cell Biochem. 2019;120(5):8154-9. [PubMed] [Google Scholar]
20. Chen Q, Coto-Llerena M, Suslov A, Teixeira RD, Fofana I, Nuciforo S, Hofmann M, Thimme R, Hensel N, Lohmann V, Ng CK, Rosenberger G, Wieland S, Heim MH. Interferon lambda 4 impairs hepatitis C viral antigen presentation and attenuates T cell responses. Nat Commun. 2021;12(1):4882. [PubMed] [Google Scholar]
21. Fateh A, Aghasadeghi M, Siadat SD, Vaziri F, Sadeghi F, Fateh R, Keyvani H, Tasbiti AH, Yari S, Ataei-Pirkooh A, Monavari SH. Comparison of three different methods for detection of IL28 rs12979860 polymorphisms as a predictor of treatment outcome in patients with hepatitis C virus. Osong Public Health Res Perspect. 2016;7(2):83-9. [PubMed] [Google Scholar]
22. Sharafi H, Pouryasin A, Alavian SM, Behnava B, Keshvari M, Mehrnoush L, Salimi S, Kheradvar O. Development and validation of a simple, rapid and inexpensive PCR-RFLP method for genotyping of common IL28B polymorphisms: a useful pharmacogenetic tool for prediction of hepatitis C treatment response. Hepat Mon. 2012;12(3):190-5. [PubMed] [Google Scholar]
23. Koolivand M, Allamehzadeh Z, Ahmadi A, Taheri RA, Hassanpour K, Zeini A, Farnoosh G. The study of IFNL3 gene rs12979860 polymorphism in the hepatitis C virus patients and healthy population in Tehran province, Iran. Jundishapur J Microbiol. 2020;13(5):e95798. [Google Scholar]
24. Sy A, McCabe L, Hudson E, Ansari AM, Pedergnana V, Lin SK, Santana S, Fiorino M, Ala A, Stone B, Smith M, Nelson M, Barclay ST, McPherson S, Ryder SD, Collier J, Barnes E, Walker AS, Pett SL, Cooke G; STOP-HCV-1 Trial Team. Utility of a buccal swab point-of-care test for the *IFNL4* genotype in the era of direct acting antivirals for hepatitis C virus. PLoS One. 2023;18(1):e0280551. [PubMed] [Google Scholar]
25. Aziz H, Raza A, Ali K, Khattak JZ, Irfan J, Gill ML. Polymorphism of the IL28B gene (rs8099917, rs12979860) and virological response of Pakistani hepatitis C virus genotype 3 patients to pegylated interferon therapy. Int J Infect Dis. 2015;30:91-7. [PubMed] [Google Scholar]
26. McCarthy JJ, Li JH, Thompson A, Suchindran S, Lao XQ, Patel K, Tillmann HL, Muir AJ, McHutchison JG. Replicated association between an IL28B gene variant and a sustained response to pegylated interferon and ribavirin. Gastroenterology. 2010;138(7):2307-14. [PubMed] [Google Scholar]
27. Matsuura K, Watanabe T, Tanaka Y. Role of IL28B for chronic hepatitis C treatment toward personalized medicine. J Gastroenterol Hepatol. 2014;29(2):241-9. [PubMed] [Google Scholar]
28. De Re V, Caggiari L, Garziera M, De Zorzi M, Repetto O. Molecular signature in HCV-positive lymphomas. Clin Dev Immunol. 2012;2012:623465. [PubMed] [Google Scholar]
29. Mücke MM, Maasoumy B, Dietz J, Mücke VT, Simon CO, Canchola JA, Cornberg M, Marins EG, Manns MP, Zeuzem S, Wedemeyer H, Sarrazin C, Vermehren J. Utility of the new cobas HCV test for viral load monitoring during direct-acting antiviral therapy. PLoS One. 2019;14(11):e0224751. [PubMed] [Google Scholar]
30. El-Awady MK, Mostafa L, Tabll AA, Abdelhafez TH, Bader El Din NG, Zayed N, El Shenawy R, El Abd Y, Hasan RM,

Zaghlol H, El Khayat H, Aziz AO. Association of IL28B SNP with progression of Egyptian HCV genotype 4 patients to end stage liver disease. Hepat Mon. 2012;12(4):271-7. [PubMed] [Google Scholar]

ISSN: 0019-5138
DOI: https://doi.org/10.24321/0019.5138.202428