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Original article

The Evaluation of Interferon Lambda 4 rs368234815 Polymorphism in Patients with Chronic Hepatitis C

Yasser M. Esmaeil, Samah S. Ahmed, Rana A. khashaba, Seham G. Ameen

Clinical and Chemical Pathology Department, Faculty of Medicine Benha University, Egypt.

Corresponding to:
Dr Samah S. Ahmed..
Clinical and Chemical Pathology Department, Faculty of Medicine Benha University, Egypt.

Email:
samahsabrymohameda@gmail.com

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Abstract:

Background: Interferon lambda 4(FNL -4 rs368234815) predicts the HCV clearance and assess the predictive value of the IFNL4 polymorphism in the treatment of chronic HCV in Egyptian patients and its allele frequency in HCV patients compared with controls .Direct-acting antivirals (DAAs) has seen a significant increase of the patients with hepatitis C virus (HCV) clearing their infection. The INFL -4 rs368234815 was a powerful predictor of sustained virological response (SVR). **Methods:** Evaluation for IFNL4 rs368234815 polymorphism was performed by restriction fragment length polymorphism analysis (PCR- RFLP) in all participants. **Results:** Among 80 chronic HCV patients with IFNL4 rs368234815 Genotypes TT/TT, TT/GG, GG /GG, were present in 33.8%, 46.3%, and 20% of patients respectively, but among 20 persons that apparently healthy persons act as controls, the frequency was 80%, 15 %and 5% for TT/TT, TT/ GG, and GG /GG, respectively. IFNL4 GG genotype is correlated with poorer treatment reaction relative to TT genotype. The probability of spontaneous HCV clearance for IFNL4 rs368234815 TT/TT patients was higher than for the GG carriers. Determining IFNL4 SNPs before initiating treatment will be cost-effective and will reduce adverse effects. The INFL -4 rs368234815 was a powerful predictor of sustained virological response (SVR). **Conclusions:** In Hepatitis C virus patients, identifying the homozygosity in the variant GG of rs368234815 means a more potent prediction of HCV infection in HCV subjects that we observe in the variant homozygosity TT patients. InterferonL4 rs 368234815 polymorphism plays a prominent role in treatment and clearance of hepatitis C virus infection.

Keywords: Chronic hepatitis C virus (HCV); sustained virological response (SVR); Polymerase Chain Reaction (PCR); Interferon lambda 4.

Introduction

HCV has multiple genotypes; Genotype 4a is most common in Egypt and the Middle East [1].

Pegylated interferon (PEG-IFN) and ribavirin (RBV) were used for treatment. Antiviral agents known as direct-acting antivirals (DAAs) have been developed and introduced for treatment of HCV infection Although DAAs are more effective than PEG-IFN/RBV combination therapy, given this new regimen [2].

HCV treatment was tied to combination therapy consisting of PEG-IFN/RBV treatments of HCV are not affordable and available in many countries; PEG-IFN and RBV are colloquially known to remain the alternative HCV treatment [3].

Studies have shown that response to PEG-IFN/RBV combination therapy has been affected by host and virus genetic factors [4].

Among the host genetic factors is, rs368234815 polymorphism within exon-1 of the interferon lambda 4 (IFNL4) gene [5].

The INF lambda 4 gene a 2543 base-pair (bp) length and 5 exons, is located on chromosome 19q13.2. The rs368234815 polymorphism is classified as a deletion/insertion genetic variation (TT/GG). [6]

Single nucleotide polymorphisms (SNPs) located in the interferon-λ genetic region (IFNL) on chromosome 19q13 are associated with antiviral protection In humans, polymorphism. [6]

The interferon-λ4 gene (IFNL4) located on chromosome 19q13.2 upstream of IFNL3 that harbours the dinucleotide frame shift (variant rs368234815 (TT/GG).The polymorphism rs368234815 located within the first IFNL4 exon, is classified as addition/insertion genetic variation (TT/GG).The IFNL rs368234815 polymorphism controls a generation of the functional protein – interferon-λ4 (IFN-λ4) [7].

The ancestral- IFNL4 GG allele creates an open reading frame for IFN-λ4, whereas the alternative IFNL4 TT variant eliminates IFN-λ4 [8].

IFNL4 rs368234815 influences the signaling pathway between interferon-λ3 receptor1 (IFN-λR1) and interferon-stimulated response element (ISRE). Overexpression of IFNL4 suppresses IFN induction-and promoter activation [9].

The favorable outcome of HCV infection correlates with the inability to encode IFN-λ4.An association between IFNL polymorphisms and HCV clearance was studied mainly in HCV Egyptian patients. [10].

IFNL4 rs368234815 currently designated as the most promising predictor of HCV resolution. [11, 12]

Subjects and Methods

Subjects:

The study is a case control study that was approved by the ethical Committee of Faculty of Medicine, Benha University (MS14-11-2019) during the period from June 2019 to Jan 2021 and all patients gave an informed consent. It involved 100 patients from those attending the

of Clinical and Chemical Pathology and the outpatient Clinic of Benha University Hospitals. This study included 100 subjects had been classified into 2 groups:-

- Group (1): included 80 patients with chronic hepatitis C infection
- Group (2): included 20 apparently healthy persons who match the patient group for age and sex.

All patients suffered from compensated liver disease and documented chronic HCV infection by serum hepatitis C antibody testing and positive PCR.

The Inclusion criteria include:

- All patient group show the criteria for HCV infection chronicity which include patients that having positive results for HCV anti bodies and HCV- RNA for period longer than 6 months
- Age group includes young, old age, male and female.

The Exclusion criteria include:

- Any viral infection other than HCV
- Auto immune diseases

Laboratory investigations done were:

A. Complete blood count (CBC) including

- Hb(gm|dl)
- Platelets count(c|mm3)
- WBC(c|mm3)

B. Biochemical Liver Tests-:

- Alanine transaminase (ALT) (U/L)
- Aspartate transaminase (AST) (U/L)
- Bilirubin (direct and indirect) (mg/dL)
- Albumin (g/dL)
- Prothrombin time (PT/INR) (secs)
- AlkalinePhosphatase(ALP) (U/L)
- Alpha Feto Protein (AFP)

C. Viral markers: -

- HCV Ab detection by ELISA
- HCV RNA detection: HCV-RNA levels were determined by real-time-PCR using a commercial kit (Thermo Fisher-USA,Thermocycler peqLab Germany)
- Genomic DNA will extract from whole blood and then will determine genotypes for INFL -4 rs368234815 polymorphism by (PCR-RFLP).

Treatment Regimens

Patients received double and triple combination therapy with 400 mg sof once daily, Peg-INF (180 mcg/0.5 ml; fixed dose/week) plus RBV (1000 mg for ≤75 Kg or 1200 mg for >75 Kg) for 12 weeks

IFNL4 Genotyping via PCR-RFLP

IFNL4 rs368234815 polymorphism (TT/TT, GG/TT,GG/GG) was genotyped by a polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) method.

IFNL4-F primer (5'GACGCAGGACCCCTTGGGACAGGA-3') and IFNL4-R primer (5'-TCTGGGCCGCAGTGGCCGCGAGG-3') used as a Forward and reverse primer pair. The PCR reactions were performed by Thermo scientific Phusion High-Fidelity PCR SuperMix Lot #F-553S).For the RFLP analysis, the PCR product of rs368234815 was digested with 10 units of **BstUI** (New England BioLabs) restriction endonuclease (RE).

Statistical analysis

Data were analysed using SPSS software, version 22.0 (IBM, Armonk, NY, USA). Categorical data were presented as number and percentages, Chi square ($\chi 2$) and Fisher's exact tests were used to analyze them. Odds ratio (OR) and the corresponding 95% confidence intervals (95% CI) were calculated when appropriate. Quantitative data were tested for normality using Shapiro-Wilks test assuming normality at $P>0.05$. Normally distributed variables were expressed as mean ±standard deviation and analyzed by Student "t" test for 2 independent groups, while non-parametric ones were presented as median and inter-quartile range (IQR), and analyzed by Mann Whitney U test. $P \leq 0.05$ was considered significant.

Results

Patients

Patients with a TG genotype had a 7.3-fold and patients with a GG genotype had 9.5-fold Odds of developing Chronic Hepatitis C compared with patients with the TT genotype ($p<0.05$).these characters are shown in table 1and fig 1.The number of copies of G was significantly associated with Patients with Chronic Hepatitis C (P value=0.001 as in Table (1)

Table (1): Comparison between the studied groups as per liver INF L -4 rs368234815 polymorphism

INFL-4 (T>G)	rs368234815	Patients (n=80)		Controls (n=20)		OR (95%CI)	P
		No.	%	No.	%		
Genotypes	**TT**	27	33.8	16	80.0	**Ref**	**----**
	TG	37	46.3	3	15.0	**7.3 (1.9-27.6)**	**0.003 (S)**
	GG	16	20.0	1	5.0	**9.5 (1.1-78.4)**	**0.037 (S)**
Allele	**T**	91	56.9	35	87.5	**5.3**	**=0.001 (HS)**
	G	69	43.1	5	12.5	**(1.98-14.3)**	

Results of genotypes polymorphism before digestion by BSH12361 enzyme

PCR products were found at 227 bp before digestion by RE (BSH12361) as in fig (1).

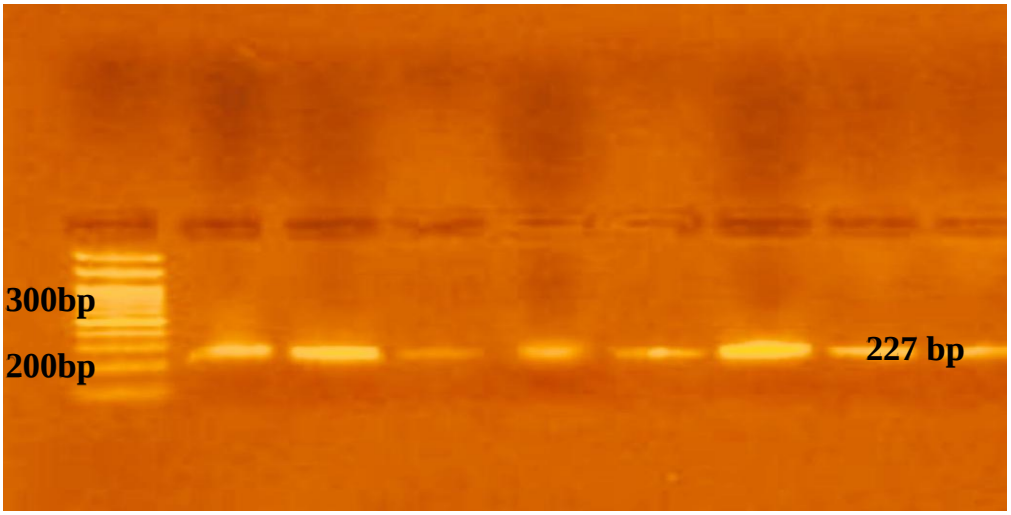

Figure (1) (PCR-RFLP) electrophoresis results of IFNL4 rs368234815 polymorphism before digestion by restriction enzyme.

Results of genotypes polymorphism after digestion by BSH12361 enzyme

Digestion of this product with BSH12361 in individuals with the GG/GG genotype showed 2 fragments of 175 bp and 51 bp , 3 fragments of 227, 175, and 51 bp in the TT/GG genotype and a 227-bp fragment in the TT/TT genotype Fig(2).

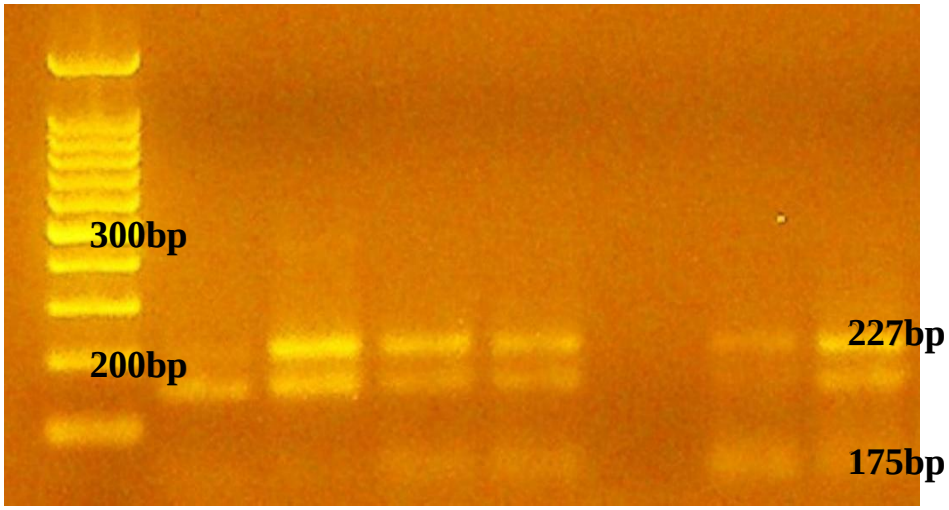

Figure (2) (PCR-RFLP) electrophoresis results of IFNL4 rs368234815 polymorphism after digestion at 227bp,175 bp and 51bp.lane ,1,2,3 was genotyped as GG/GG, TT/TT, TT/GG, respectively

Validation Results

The results of genotyping of the rs368234815 polymorphism by PCR-RFLP were concordant with those of PCR sequencing in all 100 individuals (100%) and showed the 100% analytical sensitivity and specificity of the PCR-RFLP method. In both methods, the frequencies of TT/TT, TT/GG, and GG/GG were 33.8%, 46.3%, and 20%, respectively.

Discussion

The final target of HCV treatment is the eradication of the virus, which also can be determined by sustained virologic response (SVR) or a negative result for HCV RNA 6 months or longer after treatment termination.

Diagnostic instruments, such as genotyping IFNL3 and IFNL4, can predict those most likely to spontaneously clear HCV that could be postponed in therapy. These instruments may also stratify people and prioritize DAAs therapy to those less likely to react to interferon-containing regimens or recognize those likely to react well to shortened therapy [13].

The studies have shown that response to PEGIFN/ RBV combination therapy has been affected by host and virus genetic factors.

Among the host genetic factors, rs 368234815 polymorphism within exon-1 of the interferon lambda 4 (IFNL4) genes were discovered which plays a prominent role in spontaneous and treatment induced clearance of HCV infection and be the strongest host genetic factor for prediction of HCV treatment response [14]. Designing a simple, inexpensive and rapid method for genotyping of the IFNL4 rs368234815 polymorphism might be helpful for predicting response to treatment.

The present work aimed to assess the predictive value of the IFNL4 polymorphism in the treatment of chronic

HCV in Egyptian patients and its allele frequency in HCV patient compared with controls.

This study show that the 80 chronic HCV patients with the rs368234815 Genotypes TT/TT, TT/ GG, GG /GG , were present in 33.8%, 46.3%, and 20% of patients Respectively, but for 20 persons act as controls the frequency was 80%, 15% and 5% for TT/TT, TT/ GG, and GG /GG, respectively.

This shows that presence of TT allele increase possibility of HCV Clearance and increase predictive value for treatment.

Additionally, frequency of IFNL4 genotype Egyptian patients with an TG genotype had a 7.3-fold and patients with a GG genotype had 9.5-fold odds of developing Chronic Hepatitis C compared with patients with the TT genotype ($p<0.05$). The number of copies of GG genotype was significantly associated with Patients with Chronic Hepatitis C

Until now, several studies, have genotyped IFNL4 rs368234815 with probe-based assays, including (the TaqMan and Invader assays), mass spectrometry and the high resolution assay (HRA).

In genotyping of IFNL4 rs368234815 via PCR-RFLP was concordant with PCR sequencing in all individuals. Among these patients with chronic HCV, the frequency of rs368234815 TT/TT, TT/GG, and GG/GG were 44.8%, 37.9%, and 17.3%, respectively [15].

Also, study aimed to investigate the relation between IFNL4 polymorphisms and clearance of HCV genotype 4 for HCV patients. SNP genotyping assay for IFNL4 which formerly known as IL28B (rs368234815) was examined for genomic DNA. The DNA was extracted from whole blood of one hundred patients who documented to have infection with chronic HCV genotype 4 (positive PCR) and treated with SOF and RBV. Patients were diagnosed, previously, as HCV genotype 4 and classified according to drug response into two groups (responders, non-responders). All samples were compared with 50 of non-infected (negative PCR) people (control group). The TT/TT homozygous represents 48% of patients and 66% of non-infected people while the homozygous GG/GG is 21% and 12%, respectively. There is significance to IFNL4 genotypes for the treatment response with the probability value $p < 0.001$. The percentages of the appearance of genotypes TT/TT, TT/GG and GG/GG for responders were 60%, 28% and 12%, respectively [16].

A study used the PCR sequencing method to genotype the IFNL4 rs368234815 polymorphism. It showed that the polymorphism rs368234815 (GG) resulted in a frame shift mutation and therefore produced a new gene designated as interferon-lambda 4 (IFNL4). Homozygous individuals with IFNL4 TT genotype could not create this gene. Researchers have indicated that IFNL4 GG genotype is correlated with poorer treatment reaction relative to TT genotype [17]

Also, study detected IFNL4 rs368234815 genotype using the high-resolution melting (HRM) assay. The genotyping success rate of rs368234815 by HRM assay was 100% and no deviation from Hardy–Weinberg equilibrium ($p >0.05$) was observed. The genotypic frequencies of rs368234815 variant (37% for TT/TT, 49.5% for TT/GG and 13.5% for GG/GG) matched that of rs12979860 polymorphism (37% for GG, 50% for GT and 13% for TT) achieved previously by TaqMan assay, confirming their high linkage disequilibrium . As the

only patient with mismatched genotype was a non-responder to combined treatment, the predictive value of the IFNL4 rs368234815 and rs12979860 variants is not different. [18]

Genotyped rs368234815 using the mass spectrometry method in which SVR was more frequent in TT/TT genotype compared to TT /GG and GG /GG (OR = 4.439, 95% CI: 3.410 - 5.778). Genotype stratification analyses revealed rs368234815 TT/ TT was associated with higher SVR in G1, G2/3 and G4 HCV patients [19].

The role of Interferon-Lambda 4 gene polymorphisms in predicting treatment Response in Egyptian HCV Genotype 4 patients was studied [20]. It was concluded that of the 50 patients, 40 (80%) achieved sustained virological response (SVR). Of the 23 patients with rs368234815 TT/TT genotype, 21 (91.3%) achieved SVR, while in 27 patients with non-TT/TT genotypes, 19 (70.4%) achieved SVR [20].

The PCR RFLP method for detecting IFNL4 rs368234815 genotypes and the associated Sustained Virologic response was used. The genotypes of rs12979860, rs8099917 were identified by polymerase chain reaction (PCR) and restriction fragment length polymorphism while the genotype rs368234815 detected by amplification-refractory mutation system-PCR. The rate of RVR and SVR were 43/71 (60.6%) and 46/71 (64.8%), respectively. Achieving an SVR in patients with rs368234815, TT/TT genotype 20/24 (83.3%) was found to be higher than other SNPs. The correlation coefficient of rs368234815 was strongly associated with rs12979860 ($r = 0.788$, $P < 0.001$) [21].

In, of the 92 patients, 63 (68.5%) achieved sustained virological response (SVR). Of the 43 patients with rs368234815 TT/TT genotype, 36 (83.7%) achieved SVR, while in 49 patients with non-TT/TT genotypes, 27 (55.1%) achieved SVR. Other pretreatment parameters predicted SVR were patients' body mass index, HCV genotype, rs12979860, and rs8099917 SNPs. IFNL4 rs368234815 was a strong predictor of SVR; however, the prediction power of this SNP was the same as that of rs12979860 SNP in the patients of the current study [22].

IFNL4 rs368234815 SNP can be considered for decision-making in the treatment of HCV-infected patients

Although the present PCR-RFLP method is not acceptable as a high-throughput method, it can serve as a high-speed method for genotyping of a small number of specimens. The present method and almost all of the aforementioned methods require a control specimen for assessment of the validity of the testing procedures.

The present study is primer-dependent; synthesis of the primers can be performed even by local providers.

The PCR-RFLP method that we have developed for genotyping of rs368234815 is accurate, inexpensive, rapid, and easy to perform. This method is comparable to the PCR sequencing method, which is the criterion-standard method for detecting genetic markers, and so it can be used for clinical and research work.

The rs368234815 was a powerful predictor of SVR. In Egyptian HCV-positive patients with genotype 4, IFNL4 rs368234815 SNP is an autonomous predictor of SVR to DAAs treatment.

Conclusion

InterferonL4 rs 368234815 polymorphism plays prominent role in treatment and clearance of hepatitis C

virus infection. The INFL -4 rs368234815 was powerful predictor of sustained virological response (SVR). IFNL4 GG genotype is correlated with poorer treatment reaction relative to TT genotype. Determining IFNL4 SNPs before initiating treatment will be cost-effective and will reduce adverse effects. Studies have shown that response to PEG-IFN/RBV combination therapy has been affected by host and virus genetic factors, among the host genetic factors are IFNL4 rs368234815 polymorphism.

Conflict of interest

None of the contributors declared any conflict of interest

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