Relation between HLA-DP/DQ Polymorphisms, Serum IP-10 and Response to Direct Acting Antiviral Therapy among HCV Infected Patients

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HCV infection represents a worldwide health problem with many attempts to control. This study aimed to assess the relation between HLA-DQ-rs3920 SNP, HLA-DP-rs3077 SNP, serum IP-10 levels and response to direct acting antiviral (DAA) drugs among HCV infected Egyptian patients. The study included 100 HCV infected patients (received sofosbuvir, Daclatsvir and Ribavirin) and 50 apparently healthy volunteers as controls. Serological, hematological and viral investigations were done to all participants. Whole DNA was extracted, HLA-DQ-rs3920 SNP and HLA-DP-rs3077 SNP were evaluated using RT-PCR and serum IP-10 levels were determined. Higher frequencies of HLA-DQ rs3920 AG and HLA-DP rs3077 AA variants was observed among HCV infected patients (*P*<0.001* and P=0.029*, respectively). There was a statistically significant association between both genotypes and response to DAA. However, HLA-DQ rs3920 A allele was markedly expressed among non-responders group and could be correlated with resistance to DAA therapy. IP-10 levels were significantly decreased among the non-responder group with 95% sensitivity and 15% specificity. We concluded that HLA-DP-rs3077 and/or HLA-DQ-rs3920 SNP may represent independent predictors for susceptibility to infection and response to direct antiviral drugs among HCV infected Egyptian patients. Serum IP-10 could be a predictive marker for disease progression and response to DAA.

Hepatitis C virus (HCV) infection represents a worldwide health problem with nearly 170-200 million chronically infected patients, in 2018, and most of them deteriorate with time to cirrhosis, hepatocellular carcinoma (HCC) and hepatic failure [1, 2]. Many health programs aimed to complete HCV eradication. New promising direct-acting antiviral drugs (DAAs) have been developed in the past few years with higher effectiveness, safety, and tolerability, than interferon therapy [2].

Genome-wide associated studies (GWASs) have confirmed the role of HLA class II gene, antigen-presentation genes, in viral hepatitis [3, 4] and these host genetic factors could influence HCV responses to antiviral drugs [1, 5]. However, the impact of these genes variants on response to DAAs

has not been fully investigated. Previously we have suggested an association of ingle nucleotide polymorphisms (SNP) of HLA-DPA1 rs3077 and HLA-DQB2 rs7453920 with breast cancer, ovarian cancer patients, and HBV infection among Egyptian Patients [6-8]. However, data for correlations between these two SNPs and HCV is still deficient.

Furthermore, interferon-gamma inducible protein-10 (IP-10) binds to CXCR3 receptors on effector T cells thus it has a role in T-lymphocytes' recruitment [9]. It is secreted by hepatic cells during viral infection leading to activation of cellular immunity and hepatitis. IP-10 level could predict progression or regression of inflammation during antiviral therapy [10].

Therefore, this study aimed to assess the relation between HLA-DQ-rs3920 SNP, HLA-DP-rs3077 SNP, serum IP-10 levels and response to direct acting antiviral gents (sofosbuvir, Daclatsvir and Ribavirin) among HCV infected Egyptian patients.

Subjects and Methods

Subjects and sample collection

This study included 150 participants: 100 HCV infected patients diagnosed and followed up after treatment at Internal Medicine department, Faculty of Medicine, Kafrelskeikh University and 50 apparently healthy volunteers as controls. Participants were divided into 3 groups; group 1 (responders) involved 50 HCV infected patients having sustained viral response (SVR), group 2 (non-responders) included 50 HCV infected patients who did not respond to DAA or had a relapse and group 3 (control group) involved 50 age and sex matched volunteers; seronegative for anti-HCV antibodies. History taking and thorough clinical examination were done for all participants participated in the study. Inclusion criteria of HCV infected patients include ages ranged between 26 and 56 years old, positive for anti-HCV antibodies, and have past or recent HCV-RNA viral loads. Exclusion criteria include ages below 26 or above 56 years, metabolic disorder, alcoholic liver, autoimmune hepatitis and drugs-induced liver injury, previous interferon and/or ribavirin therapy, HCC, co-infected with HBV, and/or schistosomiasis [1].

Direct antiviral drug regimen was daily sofosbuvir (400 mg, 1 tab.), Daclatsvir (60 mg, 2 tab.) and Ribavirin for twelve weeks. All patients were monitored at 16^{th} and 24^{th} weeks by PCR for HCV-RNA; negative serum HCV RNA at 16^{th} week indicates early viral response (EVR) and at 24^{th} week indicates sustained viral response (SVR). Relapse means re-appearance of HCV-RNA during follow-up of participants with previous end of treatment response (ETR).

Ethics approval and patient assent

The study protocol was reviewed and approved by the ethics review committee of Faculty of Medicine, Kafrelskeikh University, Egypt, January 2018. Informed written consents (for participation in the study and sample collection) were collected from all participants under the study.

Samples collection

A total of seven ml venous blood was obtained from each study participant; of these 4 mls were collected in plain tubes (for serum separation to be used for viral investigations) and 3 mls put in tubes with EDTA (for DNA extraction and molecular assays).

Viral load

HCV-RNA extraction was accomplished using QIAamp viral RNA mini kit, Qiagen (Hilden, Germany), according to the manufacturer's instruction, then the extracted RNAs were reverse transcribed and amplified using real time PCR, according to the method described by Rashwan, *et al.*, (2015) [11]. The viral load was expressed in international unit per ml. In each run of PCR, four standards and one blank sample were included. Sample with no C.T was considered negative [11].

Genotyping of HLA-DQ-rs3920 SNP and HLA-DP-rs3077 SNP:

Genomic DNA was extracted from whole blood samples in EDTA tubes using the PureLink® Genomic DNA extraction kit (Invitrogen, Life Technologies, USA) then DNA concentration and purity were assessed using Nano drop spectrophotometer (DE Thermoscientific, USA). The extracted DNA was stored at -80ºC till used.

HLA-DQ-rs3920 SNP and HLA-DP-rs3077 SNP were genotyped using 5' nuclease assay with a

TaqMan MGB probe in an *StepOne*™ Real-Time PCR System (Applied Biosystems, Life Technologies, USA). Data for HLA-DP-rs3077 SNP and HLA-DQ-rs3920 SNP were obtained from NCBI SNP bank (figure 1a, 1b). In PCR tubes, 2 µl genomic DNA, 7 µl DNase-free water, 10 µl TaqMan Universal PCR Master Mix (2X) and 1 µl working stock of SNP genotyping assay (20X) were mixed. The assay contained forward and reverse primers to amplify the required sequence, two TaqMan® MGB probes with NFQ (one VIC®-labeled probe to detect Allele 1 sequence, one FAM™-labelled probe to detect Allele 2 sequence). Sterile water was used as a negative control. Thermal cycling conditions were adjusted to be 10 min. at 95 C followed by 40 PCR cycles each consists of 15 sec at 92 C and 1 min. at 60 C. All steps were conducted blindly without knowing the participants' clinical data. Randomly selected 5 samples were repeated in runs and each SNP yield 100% consistency.

Serum IP-10 Levels

IP-10 levels were determined in all serum samples, using commercial human IP-10 ELISA kit (eBioscience, USA), according to manufacturers' instructions, IP-10 levels are expressed in pg/ml [8].

Statistical Analysis

Data was analyzed using statistical package for social sciences (IBM SPSS Statistics for Windows, Version 23.0, IBM Corp., Armonk, N.Y., USA). Mean and standard deviation were used to describe continuous variables while frequency and percentage were used to describe categorical data. Chi square or Fischer exact test was applied to determine the difference between categorical variables. Levine's test was used to validate equal variance among comparable groups. Independent samples T-test or one-way ANOVA was applied for significant difference in means across two or more categories respectively. Enter method for logistic regression was applied to determine the association between genotype variability and response to antiviral therapy after controlling for age, gender, SGPT and SGOT. Significance was judges at *P* value < 0.05 [14].

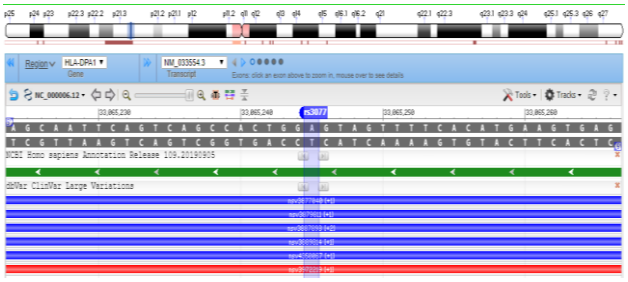

Figure 1a. HLA-DP-rs3077 SNP [12].

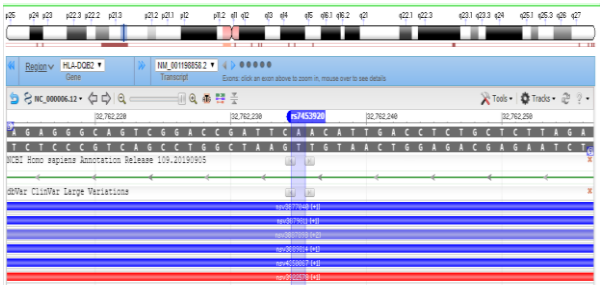

Figure 1b. HLA-DQ-rs3920 SNP [13].

Results

Genotyping of HLA-DQ-rs3920 SNP and HLA-DP-rs3077 SNP

HLA-DQ rs3920 AG and HLA-DP rs3077 AA genotypes were more frequent among HCV infected patients than controls (*P*<0.001* and *P*=0.029*, respectively) (Table 1). Both variants were significantly expressed in both responders and non-responders' groups. Regarding correlations with response to treatment with DAA, there was a significant correlation between each of HLA-DP-rs3077 AA and HLA-DQ rs3920 AG genotypes with response to treatment. However, HLA-DQ rs3920 A allele was markedly expressed among the non-responder group.

Table 1. Comparison of the distribution of HLA-DQ-rs3920 and HLA-DP rs3077 genotypes among studied groups.

Genotype		Group			*P value
		Responders	Non Responders	Control	
		No. (%)	No. (%)	No. (%)	
HLA-DP rs3077	AG	11 (22%)	24 (48%)	34 (68%)	*P*<0.001
	AA	39 (78%)	26 (52%)	16 (32%)	
Total		50 (100%)	50 (100%)	50 (100%)	
HLA-DQ rs3920	GG	13 (26%)	5 (10%)	34 (68%)	*P*=0.029
	AG	33 (66%)	30 (60%)	14 (28%)	
	AA	4 (8%)	15 (30%)	2 (4%)	
Total		50 (100%)	50 (100%)	50 (100%)	

*Pearson Chi-Square, *P*<0.05 is significant

Serum IP-10 levels

The means and medians of IP-10 serum levels were markedly increased among non-responder group in comparison to other groups (*P* = 0.001*) (Table 2, Figure 2a). Roc curve was used to analyze the specificity and sensitivity of IP-10 in predicting response to treatment among HCV infected patients (Figure 2b). IP-10 showed 15% specificity and 95% sensitivity; with area under curve (AUC) of 0.889 (95% Confidence Interval= 0.776-1.001, *P*=.00001*); indicating a good negative test. Correlations between IP-10 level and both of HLA-DQ rs3920 and HLA-DP rs3077 genotypes displayed marked elevation of IP-10 levels among all genotypes of non-responder groups (Table 3 and Figure 3).

Table 2. Comparison of IP-10 serum levels among HCV infected patients and controls

IP-10 (pg/ml)	Group			^{H}P value
	Responder	Non Responder	Control	
Mean ± SD	37.3±32.3	134.2±14.2	50.4±12.9	0.001*
Median	20.1	132.0	53.7	

H: Kruskal-Wallis test, * *P*<0.05 is significant

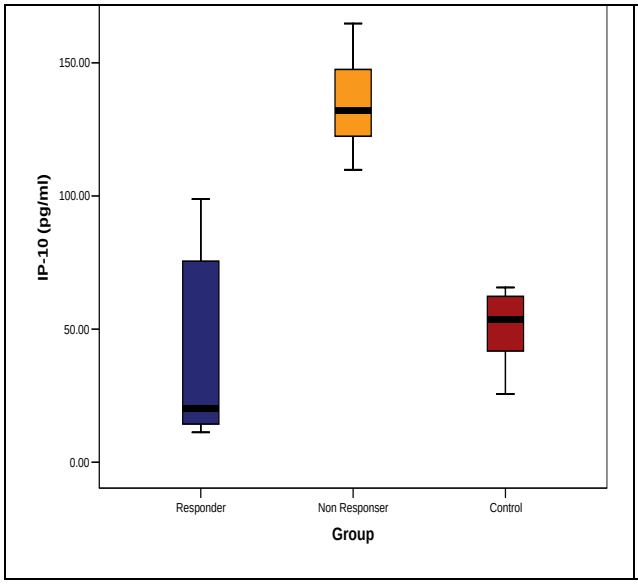

Figure 2a. The means and medians of IP-10 serum levels among HCV infected patients (responder and non-responder) and controls

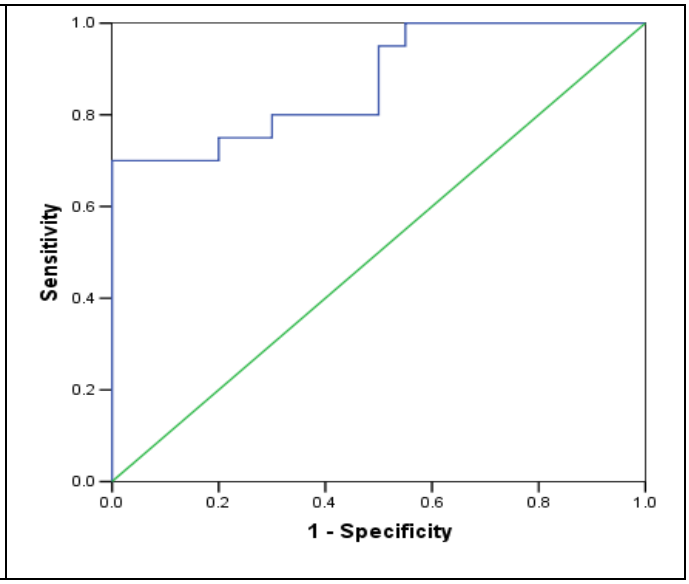

Figure 2b. Roc curve analysis for specificity and sensitivity of IP-10 in predicting response of HCV infected patients to DAA.

Table 3. Correlation between IP-10 level and both of HLA-DQ-rs3920 and HLA-DP rs3077 in HCV infected patients.

Genotypic allele		Median of IP-10 level (pg/ml)			^{H}P value
		Responder	Non Responder	Control	
HLA-DP-rs3077	AG	19.5	135.9	48.7	0.001*
	AA	20.7	130.8	53.9	0.001*
HLA-DQ-rs3920	GG	18.6	134.7	65.5	0.006*
	AG	21.2	130.8	46.8	0.001*
	AA	56.3	135.9	55.6	0.013*

H: Kruskal-Wallis test, * P<0.05 is significant

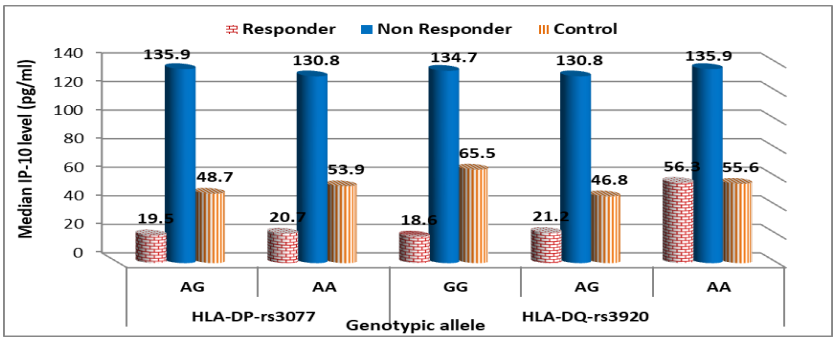

Figure 3. Relation between IP-10 median level and both of HLA-DP-rs3077 and HLA-DQ-rs3920 SNPs among the studied groups.

Discussion

In spite of the significant progress in HCV treatment with direct antiviral drugs (DAAs), HCV infection remains a worldwide health problem [10]. In Egypt, high prevalence of HCV infections resulted in increasing incidence of HCC to become the second cause of cancer mortality among Egyptians [15]. The complex pathogenesis and chronicity of HCV infection is affected by viral genotype, environmental factors, host genetics and host immunity [1]. Human leukocyte antigens (HLA), particularly HLA class II (DP, DR, DQ), play an important role in the specific immunity and immune regulation through the effective viral antigens' presentation to immune cells [16].

Recently researchers have linked variation in HLA-II genes to risk and chronicity of HCV infection [1, 17-19]. A study among Swiss HIV/HCV co-infected individuals has speculated that HLA-A*03 - B*27, DRB1*01:01, and DRB1*04:01 genotypes are linked to viral clearance while DQB1*02:01 is allied with chronicity [17]. GWAS revealed that DQA1* 0201 and DQB1* 0602 alleles were associated with HCV persistence [18]. Hiramatsu and his coinvestigators (2017) [19] have noticed increased HLA-DPB1 gene expression among patients with HCV-related hepatic disease and interrelated with deterioration. In addition, there was a marked difference in the allele frequencies between patients with normal amino-transferases and patients with advanced lever disease.

The current study aimed to assess the relation between HLA-DQ-rs3920 SNP, HLA-DP-rs3077 SNP, serum IP-10 levels and response to direct acting antiviral (DAA) drugs among HCV infected Egyptian patients. Frequencies of HLA-DP rs3077 AA and HLA-DQ rs3920 AG variants were higher among HCV infected patients (P<0.001* and P=0.029*, respectively). Both variants could be considered as genetic risk factor of HCV infection. Regarding response to treatment with DAA, fortunately, there was a statistical significant correlation between each of HLA-DP-rs3077 AA and HLA-DQ rs3920 AG genotypes with response to treatment. However, HLA-DQ rs3920 A allele was markedly expressed among non-responders group and could be considered a marker for failure of treatment with DAA.

It has been shown that HLA-DQ molecules, induced by expression of HLA-DQ genes, regulate antigens presentation to CD4+ T lymphocytes [20, 21]. It is possible that HLA-DQ rs7453920 variation resulted in altered expression of HLA-DQ gene with alternation of non-coding RNA sequences which in turns affects recognition and presentation of viral antigenic peptide, alters the differentiation of T-cells and cytokines' secretion [1]. A previous study detected genetic variants in intron region of HLA-DQ genes also strongly associated with the susceptibility of HCV infection in Chinese population [22].

Our findings are in partial or complete accordance with results of other studies [1, 23-25]; El-Bendary, *et al.*, (2016) [24] have performed a multicenter family-based study and found associations between HLA-DQB1 alleles and HCV infection among Egyptians. Huang and his colleagues (2017) [1] have explored the relationship of HLA-DQ/DP SNP with the consequences of HCV infection and concluded that HLA-DQ rs3920 A allele represents a genetic risk factor of HCV infection among Chinese patients. Sakhaee, *et al.*, (2017) [25] have studied the impact of IL28B, IFNL4

and HLA SNPs on treatment outcomes among chronic hepatitis C (CHC) Iranian patients and indicated that HLA SNP was a good predictor for RVR, EVR and SVR. They suggested that genotyping these SNPs could be helpful prior to treatment of HCV infected patients, especially in countries with limited access to triple or double therapy with viral protease inhibitors.

, many researches [24, 26, 27] have explained persistence of infectious agents by incompetent T-cell response through many mechanisms as epitopes of T-helper cell are highly unrestrained and can be restricted by different HLA class II molecules [26]. Also, genetic association studies have clarified that some HLA class II-restricted epitopes can go unrecognized by T-cells and this may be an evading mechanism of HCV to avoid immune clearance [27].

On the other hand, Xu T., *et al.,* (2017) [28] have reported HLA-DQ rs3920A allele as a protective factor among CHC patients, while HLA-DQ rs3920G allele as a risk factor for HBV infection. Li Y., *et al.* (2017) [29] have investigated the relation between HLA-DP/DQ polymorphisms and post-transplant prognosis among Chinese transplant recipients. They found that HLA-DQ rs3920 was significantly linked to HBV susceptibility, while HLA-DPrs3077 was not risk factor for HBV infection. A retrospective analysis, to investigate the impact of HLA-DP gene polymorphisms on the outcome of HBV infections among Caucasian population, have clarified that HLA-DPA rs3077-T allele is allied with spontaneous clearance in Caucasian population [30]. This could be explained by many factors; first the remarkable difference between HCV and HBV in their molecular virology and specific immune responses, second the genetic and environmental differences between the studied populations. Therefore, further fine mapping studies are recommended.

IP-10 serum levels were remarkably high among the non-responder group when compared with other groups. Roc curve analysis revealed 95% sensitivity and 15% specificity of IP-10 in predicting response to DAA with area under curve (AUC) of 0.889 (95% Confidence Interval=0.776-1.001, *P*=0.00001*); indicating a good negative test. Correlations between IP-10 level and both of HLA-DQ-rs3920 and HLA-DP rs3077 variants showed marked elevation of IP-10 levels among all genotypes of non-responder groups; indicating that they are independent markers.

Such findings are in agreement with a multicenter study on Japanese patients infected with HCV1 and treated with either Telaprevir (TVR) based triple therapy for <8 weeks or Peg-interferon and ribavirin for <24 weeks [10]. The Japanese study found that the median IP-10 pretreatment levels were markedly lower in patients who achieved rapid viral response on TVR-based triple therapy. Patients received peg-IFN/RBV showed both early reduction of HCV and lower serum IP-10 levels. They reported that measuring serum IP-10 levels before treatment could be useful for predicting positive viral response to TVR-based therapy [10].

Finally, this study provides an evidence of association between HLA DP/DQ gene polymorphisms, and the outcome of HCV infection, and response to DAA therapy. Also, IP-10 serum levels could be possible predictor of HCV response to DAA. This may help clinicians and scientists to identify targets for therapy and follow adapted strategy for each patient along with his SNP information. However the main limitation in this study is the relatively small sample size that may not represent all HCV infected

patients. Therefore further research on a large scale is necessary.

Acknowledgment

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