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Genetic Variants in ITPA and TNFSF10A Are Associated with the Risk of HCV Infection Among Egyptian Populations

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Abstract

The liver is a unique organ in the human body. Many vital functions are attributed to it. Hepatitis C is one of the most diseases which intimidate liver integrity. ITPA is a human Inosine Triphosphate Pyrophosphatase (ITPase), which cleaves inosine triphosphate (ITP) and xanthine triphosphate (XTP) as well as their deoxyribose forms into monophosphates. Tumor necrosis factor receptor superfamily member 10A, is a cell surface receptor that bind to tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) and mediate the extrinsic pathway of apoptosis. We aimed to clarify the association between the single nucleotide polymorphism of ITPA and TNFSF10A with the outcome of HCV infection. A total of 264 subjects were recruited and classified into three main groups categorized as (I) spontaneous viral clearance (SVC) (N=55), (II)chronic HCV patients (CHCV) (N=106), and (III) control negative (N=103) where they were genotyped for SNP ITPA and TNFSF10A using allelic discrimination real-time PCR. The carriage of the C allele of ITPA rs7270101 was significantly higher in HCV group compared to that of SVC (odds ratio [OR] 1.6176) and to that of controls (1.8447) (both $P < 0.01$) and carriage of C allele of TNFRSF10A (rs20575) was significantly higher in HCV group compared to that of SVC (odds ratio [OR] 2.1691 and to that of controls (2.1953). Persistence of HCV infection is associated with C alleles of ITPA (rs7270101) and TNFRSF10A (rs20575) in Egyptian populations.

Keywords: Liver, Hepatitis C, DNA, Single nucleotide polymorphism, Real-time PCR

1. Introduction

Hepatitis C virus infection is one of the most chronic health problems globally, affecting more than 170 million people worldwide [1]. Much evidence showed that chronic liver disease, cirrhosis, and hepatocellular carcinoma (HCC) are produced from persistent infection of hepatitis C [2,3]. According to World Health Organization (WHO), Egypt is one of the highest prevalence rate countries in the world with hepatitis C viral infection [4,5]. The detection of hepatitis C antibodies among Egyptians between the ages of 15 and 56 years by the Egypt Demographic and Health Surveys (EDHS) showed that the percentage of hepatitis C virus in 2009 was 14.7%, while in 2015, it was 10.0%, which is the highest percentage worldwide [6]. This high prevalence of HCV infection proved that the immune system is unsuccessful at eliminating the virus for most patients [7,8].

Transmission of HCV can be summarized as the following: Blood transfusion, which is the primary means of HCV infection and represents a 7-10% risk of HCV [6]. Sexual transmission is transmitted by sexual intercourse with an infected partner by mucosal exposure to infectious blood or serum-derived fluids [9]. Intravenous infusion injections, interfamilial transmission [10], parenteral transmission [11], invasive medical procedures [12] and needle sticks [13]. Many previous studies proved that genetic factors are a major determinant of the host response to HCV infection [14].

Inosine triphosphate pyrophosphohydrolase (ITPA) is a house-cleaning enzyme that catalyzes inosine triphosphate (ITP) to inosine monophosphate (IMP) and degrading the other 'rogue' purine nucleotides in cells in addition to exogenous nucleotides derived from purine drugs [15]. ITPA

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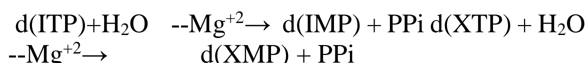
catalyzes the following reaction:



d(ITP)+H_2O --Mg^{+2}→ d(IMP) + PPi d(XTP) + H_2O --Mg^{+2}→ d(XMP) + PPi

The deficiency of ITPA helps predict anemia, anemia management, and response in chronic hepatitis C therapy and its impact on outcomes is a major clinical challenge in the treatment of chronic hepatitis C virus (HCV) infection [16].

Tumor necrosis factor (TNF) is considered as a key regulatory component of the immune system that play important role in regulation of innate and adaptive immunity in addition to initiation and maintenance of inflammation. Macrophages and immune cells are the major source of TNF, that are activated due to infections or tissue damage. Regulation of TNF expression is essential for tissue homeostasis and fight infections. On the other hand, deregulated TNF expression may result in chronic inflammation and tissue damage, in addition to increased levels of TNF were found in patients with autoimmune and degenerative diseases [17]. TNF-α is involved in the apoptotic signaling pathway of hepatocytes infected by HCV [18].

TNF-α inhibitors increase the reactivation of concurrent chronic hepatitis B, but their effect on the hepatitis C virus (HCV) is controversial. Liver transplantation that is considered as one of immunosuppression conditions, may cause an increase in the rate of HCV evolution. Inhibition of TNF-α could result in increased viral replication. Tumor necrosis factor receptor superfamily (TNFRSF) proteins are frequently activated or dysregulated in inflammatory diseases such as rheumatoid arthritis, Crohn's disease and hepatitis Furthermore, genetic variants of TNFRSF10A, TNFRSF5, TNFSF6 and TNFRSF11B influence the immune response to HCV infection [19].

Death receptor 4, that is known as TRAIL receptor 1 or tumor necrosis factor receptor superfamily member 10A. It is a cell surface receptor that bind to tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) and mediate the extrinsic pathway of apoptosis. TNFRSF10A mediates TRAIL-induced apoptosis and contribute to enhancement of apoptosis induced by anticancer drugs [20].

The aim of this work was to study gene polymorphisms of TNFRSF10A and ITPA as the impact of multiple complications of Hepatitis C virus (HCV) in Egyptian patients.

2. Material and Methods:

2.1. Subjects

The study included a total of 264 individuals from the Molecular Genetic Unit in Endemic Hepatogastroenterology and Infectious Diseases (MGUHID), Faculty of Medicine, Mansoura University, between 2017 and 2018. (106 infected participants with chronic hepatitis C (CHC), 103 controls (a household contact negative to HCV), and 55 participants who spontaneously cleared the virus (SVC). The criteria of individuals used in the study according to positive HCV index, positive for HCV markers and, family member negative for HCV infection or liver complications and disorders.

This study was approved by Ethical Board of the Mansoura University. Informed written consent was obtained from all participants, (patients and control subjects), in this study.

2.2. Methods

2.2.1. *Biochemical analysis:*

A blood samples, (5 ml), werecollected and centrifuged to obtain serum for detection of lipid profile, liver enzymes and biochemical parameters levels in HCV patients and control subjects. Liver function tests, kidney function tests, alpha-fetoprotein (AFP) and anti-nuclear antibody (ANA) were tested.

2.2.2. Detection of HCV by Real-time PCR:

Extracting viral RNA from the serum of patients according to the Qiagen RNA extraction kit instructions (QIAGEN GmbH; Hilden's, Germany). Real-time PCR determined the quantitative viral load of the extracted RNA of the samples (Applied Biosystem, Foster City, CA, USA, 7,500 real-time PCR system). DNA extraction, according to manufacturer instructions, genomic DNA was extracted from peripheral blood cells using a DNA extraction kit (QIAmp DNA Mini kit; Qiagen, Hilden's, Germany). All individuals were genotyped for ITPA SNP and TNFRSF10A; by allelic discrimination performed by real-time PCR (PCR Model 7500; Applied Biosystems, Foster City, CA, USA). Real-time allelic discrimination PCR was done using the following validated probes (Invitrogen™ Inc, UK): FAM and VIC for genotyping alleles G allele and C allele, respectively. Plotting is generally done by allele 1 (VIC® dye) on the X-axis and allele 2 (FAM™ dye) on the Y-axis. We purchased TaqMan® Universal Master Mix II (2x) (Applied Biosystems), DNA template, RNase-free water, and

optical plate (MicroAmp® Optical 96-Well Reaction Plate, Applied Biosystems).

3. Statistical analysis

The statistical analysis of data was performed by using SPSS software program version 16. Chi-square and Fisher's exact test were used to compare qualitative variables. $\chi 2$ tests was used for each group separately to assess the Hardy–Weinberg equilibrium (HWE). The number of individuals that carries at least one copy of a specific allele is defined as the allele carriage. The number of the tested allele divided by the total number of alleles in the group was defined as Allelic frequencies. MedCalc software was used to calculate odds ratio at 95% confidence interval (CI) of a specific allele carriage compared to the non-carriage of target allele. The difference was considered significant if P≤.05. The Bonferroni-corrected P-value (Pc) is a correction method of P-values when several dependent or independent statistical tests are performed simultaneously on a single data set.

4. Results

Table 1 showed the clinical and laboratory characteristics (age, sex) of different studied groups. All samples were successfully genotyped for rs7270101. Table 4 shows the distribution of allele carriage and allele frequency, homozygosity, and heterozygosity of SNP among the groups of study.

Table (1) Demographic data of different studied groups:

Groups (n=264)	Sex		Age by years Mean (±SD)
	Male (n)	Female (n)	
Healthy control (n=103)	55	58	38 (10.2)
Chronic HCV (n= 106)	71	35	42.8 (11.9)
Spontaneous clearance (n= 55)	27	18	43.5 (11.2)

Table (2) Liver function tests, creatinine, alpha- (AFP) and anti-nuclear antibody (ANA) in healthy control group and chronic HCV group:

	Healthy control (n=103)	Chronic HCV (n= 106)	
	Mean (±SD)	Mean (±SD)	P value
S. Bilirubin (mg/dl)	0.82 (0.22)	2.3 (0.87)	0.00001*
S. Albumin (gm/dl)	5.1 (0.6)	3.9 (0.7)	0.0001*
AST (IU/L)	25 (11)	41.0 (14.0)	0.00001*
ALT(IU/L)	22 (11)	45.0(15.0)	<0.00001*
ALP (U/L)	37.8 (15.9)	72 (22.0)	<0.00001*
AFP ng/mL	1.8 (4.8)	10.5 (10.7)	<0.00001*
ANA (U)	0.45 (0.13)	0.43 (0.1)	0.0741 NS
S. Creatinine(mg/dl)	0.85 (0.15)	0.8 (0.1)	0.0687 NS

data in each column were represented as; SD: Standard deviation. NS, non-significant and * extremely significant.

S. bilirubin (N: < 40 IU/L); SGPT, alanine aminotransferase (N: < 45 IU/L); ALP, alkaline phosphatase (N: 37–116 U/L); AFP, alpha fetoprotein (N: < 10 ng/mL); ANA, antinuclear antibodies (N: < 1.1 U); S. creatinine (N: < 1.4 mg/dL)

Table (3) Liver function tests, creatinine, alpha-fetoprotein (AFP) and anti-nuclear antibody (ANA) in chronic HCV group and spontaneous clearance group:

	Chronic HCV (n= 106)	**Spontaneous clearance (n= 55)**	
	Mean (±SD)	**Mean (±SD)**	**P value**
S. Bilirubin (mg/dl)	**2.3 (0.87)**	**0.81 (0.12)**	**<0.0001****
S. Albumin (gm/dl)	**3.9 (0.7)**	**4.3 (0.4)**	**0.226** NS
AST (IU/L)	**41.0 (14.0)**	**22 (7.0)**	**<0.0001****
ALT(IU/L)	**45.0(15.0)**	**20 (3.0)**	**<0.0001****
ALP (U/L)	**72 (22.0)**	**457 (12.2)**	**<0.0001****
AFP (ng/ml)	**10.5 (10.7)**	**3.8 (4.5)**	**<0.0001****
ANA (U)	**0.43 (0.1)**	**0.44 (0.1)**	**0.1402** NS
S. Creatinine(mg/dl)	**0.8 (0.1)**	**0.9 (0.1)**	**0.0758** NS

Table (4) Allele carriage of ITPA rs7270101 (A/C) among different groups

	HCV negative group (n=103)	HCV positive group (n=106)	Spontaneous clearance group (n=55)
AA	65	51	33
AC	35	48	19
CC	3	7	3
Hardy-Weinberg X2 P	0.44567846 0.504394		
Allele Frequency A C	0.80 0.20	0.71 0.29	0.78 0.22
Homozygozity	0.661	0.447	0.655
Hetrozygosity	0.339	0.453	0.345
PIC	0.31	0.41	0.31

Table 4 demonstrated the distribution of the ITPA rs7270101 polymorphism amongst the different groups of the study. The table showed that the allele carriage in the HCV negative group was 65(63.1%), 35(33.98%) and 3(2.91%) for AA, AC and CC respectively. While for HCV positive group was 51(48.1%),48(45.28%) and 7(6.6%) for AA, AC and CC respectively. As for the HCV Spontaneous clearance group the carriage was 33(60%), 19(34.54%) and 3(5.45%) for the AA, AC and CC alleles respectively. This results show that A allele is the major allele while C allele is the minor one.

The allele frequency of A allele was 0.80 ,0.71 and 0.78 for the negative, positive and spontaneous clearance groups respectively.

While the allele frequency of the C allele was 0.20, 0.29 and 0.22 for the negative, positive and spontaneous clearance groups respectively.

The heterozygosity of this SNP was estimated to be 0.339, 0.453 and 0.345 for the negative, positive and spontaneous clearance groups respectively.

Also, the polymorphic information content was estimated to be 0.31, 0.41 and 0.31for the negative, positive and spontaneous clearance groups respectively, indicating that the SNP was polymorphic enough for genetic analysis in the study. These results show that C allele is a risk allele.

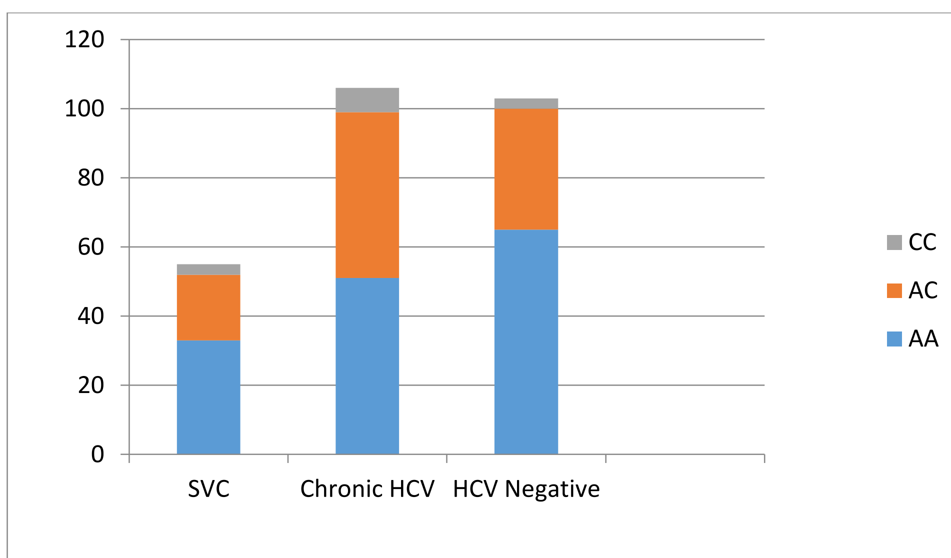


Figure 1: showed genotypes distribution of ITPA rs7270101 SNP in the studied groups

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Table (5) Odds ratio for (ITPA rs7270101) C allele SNP among different studied groups

	HCV vs healthy	HCV vs SC	SC vs Healthy
Odds ratio	1.8447	1.6176	0.8769
95% CI	1.0615 to 3.2056	0.8357 to 3.1312	0.4480 to 1.7167
P	0.0299	0.1535	0.7016

The allele carriage of C allele is significant in positive group compared to spontaneous clearance group with odds ratio 1.6176 , 95% Cl 0.8357 to 3.1312 , P value 0.1535.

Table (6) Allele carriage of TNFRSF10A rs20575 C/G among different groups

	HCV negative group (n=103)	Chronic HCV group (n=106)	SVC group (n= 55)
CC	49	31	26
CG	38	54	21
GG	16	21	8
Hardy-Weinberg X2 P	3.253599146 0.071267		
Allele Frequency C G	0.66 0.34	0.55 0.45	0.66 0.34
Homozygozity	0.631	0.491	0.618
Hetrozygosity	0.369	0.509	0.382
PIC	0.32	0.41	0.34

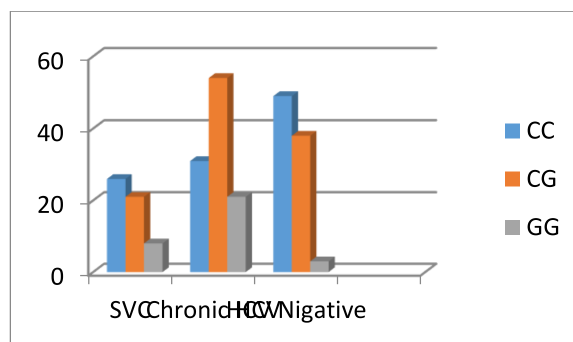

Figure 2: show the genotypes distribution of TNFRSF10A rs20757 SNP in the studied groups.

Table (7) Odds ratio for (TNFRSF10A rs20575 C/G) among different studied groups:

	HCV vs healthy	HCV vs SC	SC vs Healthy
OR	2.1953	2.1691	0.9880
95 % CI	1.2418 to 3.8812	1.1046 to 4.2593	0.5129 to 1.9032
P	0.0068	0.0245	0.9713

Table 6 demonstrated the distribution of the TNFRSF10A rs20575 polymorphism amongst the different groups of the study. It shows the allele carriage in the HCV negative group was 49(47.6%), 38(36.89%) and 16(15.51%) for CC, CG and GG respectively. While for HCV positive group was 31(29.2%),54(50.94%) and 21(19.8%) for CC, CG and GG respectively. As for the HCV Spontaneous clearance group the carriage was 26(47.27%), 21(38.1%) and 8(14.54%) for the CC, CG and GG alleles respectively. This results show that C allele is the major allele while G allele is the minor one.

The allele frequency of C allele was 0.66 ,0.55 and 0.66 for the negative , positive and spontaneous clearance groups respectively. While the allele frequency of the G allele was 0.34 , 0.45 and 0.34 for the negative , positive and spontaneous clearance groups respectively. The heterozygosity of this SNP was estimated to be 0.369 , 0.509 and 0.382 for the negative , positive and spontaneous clearance groups respectively.

Also, the polymorphic information content (PIC) was estimated to be 0.32 , 0.41 and 0.31 for the negative , positive and spontaneous clearance groups respectively , indicating that the SNP was polymorphic enough for genetic analysis in the study. These results show that G allele is a risk allele.

The allele carriage of C allele is significant in positive group compared to spontaneous clearance group with odds ratio 2.1691, 95% Cl 1.1046 to 4.2593, P value 0.0245.

5. Discussion

In the present study, our results showed that ITPA and TNFSF10A are associated with an increased risk of HCV infection in the Egyptian population.

Hepatitis C virus is one of the most infectious diseases, affecting approximately 170 million people worldwide [21]. The danger of the C virus is that it can cause persistent infection in the liver [22]. The leading cause of severe progressive liver disease such as hepatocellular carcinoma is the remaining infection of virus C in the liver that persists for life [23]. A representative sample for HCV antibody was recently tested off the entire country through the Egyptian Demographic Health Survey and showed about 14.7% of people positive for antibody to HCV, which is one of the highest HCV prevalence in the world [24]. Several genetic polymorphism studies showed that SNPs in several genes could be associated with HCV infection susceptibility, either resolution of treatment of HCV infection or development of persistent liver disease such as hepatocellular carcinoma [23].

In this study, we concerned Egyptian C virus patients and their families. Family with at least one positive HCV index, at least one positive HCV member and at least one negative member with exposure to HCV for more 15 years. The inosine triphosphatase (ITPA) gene Polymorphisms is associated with anemia induced by peginterferon (PEG-IFN) plus ribavirin (RBV) treatment for patients with chronic hepatitis C virus (HCV) infection [25].

Ochi, et al. identified a variant located upstream of the ITPA gene on chromosome 20p13, is significantly associated with treatment-induced anemia (combined $P = 6.0 \times 10^{-14}$). Resequencing and fine-mapping revealed SNPs strongly associated with Hb decline, including the nonsynonymous SNP rs1127354 ($P = 3.5 \times 10^{-44}$), which was recently reported for other ethnic groups. Another reported SNP, the splicing variant-related SNP rs7270101, was not polymorphic in the Japanese population. Stratified analysis based on rs1127354 genotype revealed that inosine triphosphate pyrophosphatase expression is not correlated with Hb decline, suggesting that rs1127354 is a direct causal variant in the Japanese population. Multivariate analysis demonstrated that age, baseline Hb, baseline platelet count, and rs1127354 were independently associated with severe anemia (Hb <10 g/dL) [26].

Other study performed on European-Americans suggested the possibility that these two knowns functional ITPA variants are responsible for part or all of the observed association and confer protection against anemia. To test this possibility, they first sequenced the entire coding region of the gene in a subset of 168 samples and found no other obvious reduced function mutations. They then genotyped the known functional SNPs rs1127354 and rs7270101 in our entire cohort [27].

The genetic variation of ITPA reduces the amount and or altered function of ITPA. Homozygosity for minor alleles causes ITPA deficiency and results in strong accumulation of ITP within erythrocytes, which replaces GTP to restore ATP production and protect from RBV-induced hemolysis [28] .

In a study conducted on 997 Chinese showed that a significant association of ITPA rs1127354 CC genotype with a higher risk of hemolysis induced by ribavirin treatment. Also, showed that patients infected with HCV-6 showed prevalence of the ITPA rs1127354 CC genotype 66.7 similar to patients infected with HCV-1 (65.1%; $P > 0.05$). Thus, the possible risk of this adverse event of ribavirin is relatively high in this population [29].

It was reported that patients with ITPA CC genotype showed significant decrease in Hb and were more vulnerable to anemia than patients with ITPA CA/AA genotype during sofosbuvir and ribavirin combination treatment for chronic hepatitis C. There is no significant effect of ITPA CC genotype was observed during treatment with RBV [25].

TRAIL is a death receptor ligand belonging to the tumor necrosis receptor (TNF) super family. It has been detected as a tumor selective molecule that transmits death signal via ligation to its receptors (TRAIL-R1 andTRAIL-R2 or death receptors 4 and 5; DR4 and DR5). TRAIL-induced apoptosis through extrinsic, is subjected to regulation both at the cell surface receptor level as well as downstream at the post mitochondrial level [30]. Several previous studies were carried out on DR4 polymorphisms and cancer risk, these results proved that DR4 polymorphisms are associated with the risk of developing cancers including HCC in HCV patients, and Chronic lymphocytic leukemia [31].

Another study was performed on HIV/HCV-coinfected patients, the results demonstrated that the polymorphism rs4242392 in the TNFSF10A gene is associated with nonresponse to interferon-based therapy in our cohort of HIV/HCV-coinfected patients. This gene encodes the TRAIL R1 [32].

TRAIL receptor expression is associated with the immunopathogenesis of viral infections, including influenza, HIV, and HCV. For example, TRAIL has been argued to contribute to the CD4+ T-cell depletion during progressive HIV disease, has been suggested as a novel therapy to eradicate HIV-infected cells , and polymorphisms in TRAIL have been associated with reduced CD4+ T-cell gains following antiretroviral therapy . In the case of HCV, TRAIL expression on hepatocytes was increased in HCV infected patients. HCV should be cured when TRAIL receptor function is preserved [33].

6. Conclusion

Genetic analysis of subjects taking part in the current study demonstrates the association of ITPA and TNFRSF10A with the fate of HCV infection. The allele frequency of the current study indicates that C alleles of ITPA (rs7270101), and G alleles of TNFRSF10A rs20575 can be considered risk alleles for HCV in Egyptian patients.

7. Conflicts of interest

"There are no conflicts to declare".

8. Formatting of funding sources

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

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