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The X-Ray Repair Cross Complementing 1(XRCC1) Rs25487 Variation and Susceptibility to Cirrhosis in Patients with Chronic Hepatitis C Virus

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ABSTRACT

Background: Around 130–170 million individuals are thought to be affected with the hepatitis C virus (HCV), which is a viral pandemic and the leading cause of persistent liver illness. The frequency of HCV infections is greatest in Egypt, where more than 10% of the general population is affected. **Objective:** The purpose of the current study was to confirm any potential associations between cirrhosis and the XRCC1 rs25487 variant in chronic HCV patients.

Patients and methods: A fibroscan was conducted on 80 HCV +ve patients and 40 control participants for a total of 120 people to determine the extent of hepatic fibrosis. Real-time PCR was used to examine the SNP genotyping in the XRCC1 gene (rs25487). **Results:** There were no substantial variation in the prevalence of different genotypes in XRCC1 A > G (GG and AG) between non cirrhotic and cirrhotic in chronic HCV Egyptian patients. **Conclusion:** By comparing the incidence of the various genotypes (AA, AG, and GG) in the analyzed groups, no clear pattern of relationship could be seen (p=0.225). (P = 0.410) There was no distinguishable pattern of connection between the AA genotype and the other genotypes (GG and AG). Comparing the frequencies of the two alleles (A and G alleles) in the three groups under study revealed no evidence of a connection**.**

Keywords: X-ray repair, rs25487 Variation, cirrhosis, chronic hepatitis C virus, case control study, Cairo University.

INTRODUCTION

The hepatitis C virus is acknowledged as posing a serious risk to public health worldwide. As per to the most current estimates of disease burden, seropositivity has climbed to 2.8% during the last 15 years, translating to more over 185 million infections globally [(1)].

In 2008, Egypt had the largest proportion of HCV infections in the world, with 10% of the population having a chronic infection and 90% of patients having genotype 4 infections [(2)]. With an overall projected 30% fall in HCV occurrence in Egypt between 2008 and 2015, the seropositivity of HCV infection in that country has reduced to 6.3% among the population under study in 2015 [(3)].

Hepatocellular carcinoma (HCC) and cirrhosis are two conditions that are mostly brought on by HCV infection. HCC is more likely to occur in people with liver cirrhosis than in those with less severe fibrosis [(4)].

A multi-protein complex called XRRC1, one of the most important molecules in base excision restoration, joins DNA ligase III, DNA polymeraseβ and poly (ADP-ribose) polymerase to fix the single strand break brought on by the cleaving of the DNA backbone at a basic site, which occurred in an initial phase of the DNA restoration technique [(5)].

An A to G transition at codon 399 (exon 10) of the XRCC1 gene causes a shift from the amino acid arginine (Arg) to the amino acid glycine (Gln) in the XRCC1 protein (XRCC1 rs25487). The addition of Gln may change the protein's function, making DNA repair less successful [(6)].

The study's objective was to determine if there was any connection between the dispersion of the XRCC1 rs25487 A > G variant in chronic HCV patients from Egypt and hepatic cirrhosis.

PATIENTS AND METHODS

Between August 2016 and November 2016, a case control study including HCV patients at the Cairo University Center for Hepatic Fibrosis, Endemic Medicine Department, Kasr Al-Ainy Hospital, and age- and sex-matched healthy participants was conducted.

A total 120 participants were recruited in the present research, who were split into two groups; *Group I* (Control Group) had 40

healthy, age and sex matched controls with normal liver biochemical profile, HCV Ab -ve and HBs Ag -ve. *Group II* (Patient Group) had 80 HCV patients.

Patient Group was split into groups depending on the degree of hepatic fibrosis found by fibroscan; Group IIa included 40 chronic HCV non cirrhotic patients (f0-f2), and Group IIb included 40 chronic HCV cirrhotic patients (f3-f4).

Patient's Inclusion criteria: : Patients diagnosed with chronic HCV (HCV Ab +ve > 6 months, male or female, and subsequently validated by PCR testing for the existence of HCV RNA in blood) must be between the ages of 18 and 65.

Patient's exclusion criteria: Combined HCV and HBV (HBs Ag positive) and other causes of liver cirrhosis.

Patients underwent the following:

- **History taking** including, medical history and possible routes of acquiring HCV infection, as blood transfusion, surgeries, dental care, needle pricks and tattoos.
- **Clinical assessment** including general examinations especially jaundice, lower limb edema, and local

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abdominal examination, especially, hepatomegaly, shrunken liver and ascites.

- Radiological investigation: fibroscan.
- Laboratory investigations for the patients and control: Prothrombin concentration, Serum creatinine and urea. Liver Function tests included determination of Aspartate aminotransferas (AST), Alanine aminotransferase (ALT). Indicators of hepatitis viruses: HBsAg and anti-HCV antibodies were assessed by routine methods using enzyme linked immunosorbant assay (ELISA). Genotyping of XRCC1 gene polymorphism (rs25487) by Real Time PCR.

METHODS

Sample collection: Three divisions of seven milliliters of venous blood were made: Three milliliters into a plain sterile tube for performing routine tests. Two milliliters into a sterile sodium citrate tube for performing prothrombine time. Two milliliters into a sterile ethylene diaminetetra-acetic acid (EDTA) tube and utilized for the genotyping process and kept at -20ºC. Routine chemistry investigation was analyzed on Bechman Synchron CX9 Pro blood chemistry auto analyzer using kits supplied by beckman.

Aspartate Aminotranferase (AST): The International Federation of Clinical Chemistry (IFCC) refers to this enzyme by its other name, serum GOT (glutamic oxalacetic transaminase), which is aspartate aminotransferase (AST) worldwide.

Alanine Aminotransferase (ALT):

This ALT technique uses a modified version of the IFCC-recommended approach and is based on the concepts mentioned. To create pyruvate and glutamate, ALT moves the amino group from alanine to -oxoglutarate [(7)].

Urea: Urease breaks down urea enzymatically to produce carbon dioxide and ammonia. Ammonia and -oxoglutarate are converted to glutamate by L-glutamate dehydrogenase (GLDH) [(8)].

Creatinine: The Jaffe process has been kinetically modified by the creatinine procedure**.** Taq Man® probes and primers were used in Real-Time PCR to identify the genetic polymorphisms of XRCC1 (rs25487) on the applicable biosystem step one Real-Time PCR system.

The test was done in 2 main steps: Genomic DNA was isolated from EDTA-anticoagulated blood's peripheral blood leucocytes, amplified, and then subjected to genotypic analysis using Real-Time PCR.
Genomic DNA Extraction from EDTA Anticoagulant Blood Peripheral Blood Leucocytes: This was done utilizing G-spin™ Total DNA Extraction Kit (Cat. no. 17045).

Assays for Real-time PCR and amplification: The XRCC1gene SNP was identified using real-time PCR and primers specific to certain sequences (rs25487). Taq-Man SNP Genotyping Assays (*Applied Bio Systems, MA, USA) were used to build a real-time PCR allelic discrimination test.

PCR Amplification: Applied Biosystem step one Real-Time PCR System was utilized as the real-time PCR system in this work. This device enabled Real-Time PCR analysis.
Heterozygous Allele 1 A/Allele 2 G, Homozygous Allele 1 A/Allele 1 A, and Homozygous Allele 2 G/Allele 2 G

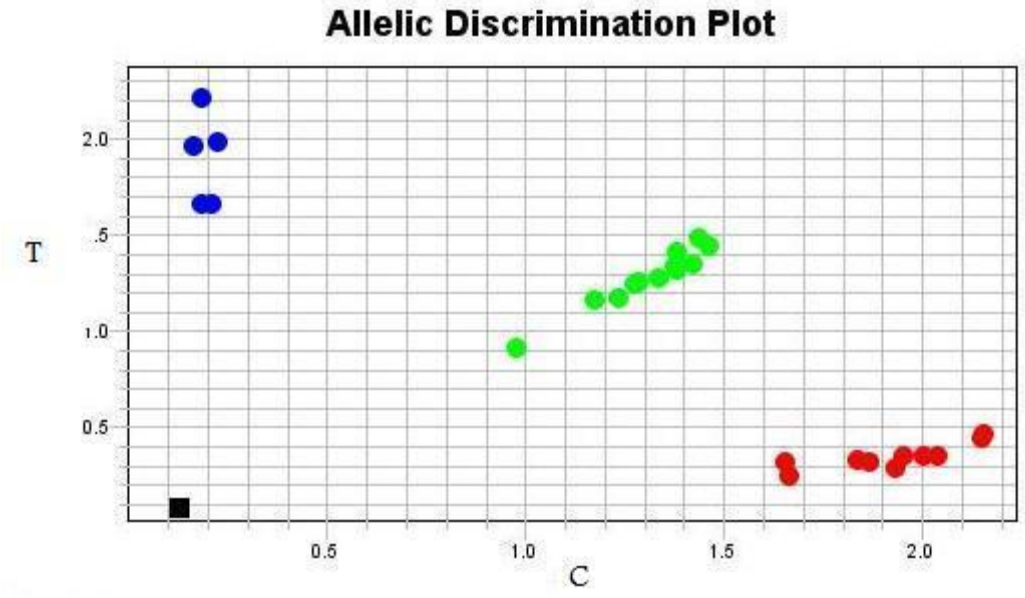

Figure (1): **plate and well layout of the experiment done by Taqman SNP Genotyping Assay on the Applied Biosystem Step one Real time PCR System**

Ethical Approval:

An approval of the study was obtained from Cairo University Academic and Ethical Committee. Every patient signed an informed written consent for acceptance of participation in the study. This work has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for studies involving humans.

Statistical Analysis

The collected data were coded, processed and analyzed using the SPSS (Statistical Package for Social Sciences) version 22 for Windows® (IBM SPSS Inc, Chicago, IL, USA). Qualitative data were described using number and percent. Quantitative data were described using median (minimum and maximum) and inter quartile range for non-parametric data, and mean and standard deviation (SD) for parametric data after testing normality using Kolmogrov-Smirnov test. Chi-Square test was used for comparison of 2 or more groups. Fisher's exact test was used as correction for Chi-Square test when more than 25% of cells have count less than 5.

Student's t-test was used to compare 2 independent groups. One Way ANOVA test was used to compare more than 2 independent groups with Post Hoc Tukey test to detect pair-wise comparison. Mann-Whitney U test was used to compare 2 independent groups. Kruskal Wallis test was used to compare more than 2 independent groups with Mann Whitney U test to detect pair-wise comparison. Utilizing logistic regression, the genotype and allele frequencies of the illness and control groups were compared. The odds ratio (OR) was estimated with 95% confidence intervals. P value $\leq$0.05 was considered significant.

RESULTS

Table 1 summarizes the demographic data of the participants. There is no statistically substantial variation in the group under study's age distribution (P value= 0.073).

Table (1): Distribution of the investigated groups' ages and sexes:

Variable		Control group (n=40)	HCV +ve non cirrhotic gp (n=40)	HCV +ve cirrhotic gp (n=40)
Age (years)		47.32 (SD 5.69)	48.42 (SD 10.2)	51.12 (SD 8.3)
Sex	**Male**	26 (65%)	22 (55%)	22 (55%)
	Female	14 (35%)	18 (45%)	18 (45%)

*Age is shown as mean (SD). *Sex is shown as number and percent (%).

On comparing the control group with HCV +ve group it was found that serum AST and ALT were statistically substantially greater in HCV +ve group (P<0.001), while prothrombin concentration was substantially lower in HCV +ve group (P= 0.001). As regards serum urea and creatinine there were no statistically substantial variations between both groups (P values 0.780 and 0.193, respectively) (**Table 2**).

Table (2): Laboratory data among different studied group.

Parameters	Control group (n=40)	HCV +ve non cirrhotic gp (n=40)	HCV +ve cirrhotic gp (n=40)	P value
ALT (U/l)	26 (13-44)	33.5 (6-220)	38 (13-80)	**<0.001**
AST (U/l)	26 (16-42)	32 (9-128)	40 (3-94)	**<0.001**
Urea (mg/dl)	29.5 (17-91)	28 (16-58)	28 (12-50)	0.780
Creatinine mg/dl)	0.8 (0.5-1.3)	0.9 (0.5-1.4)	0.9 (0.5-1.4)	0.193
PC (%)	86 (75-100)	91 (64-100)	85 (41-100)	**0.001**

*Laboratory data presented as median and range. *P value is substantial P $\leq$0.05.

There was substantial variation could be detected on comparing Jaundice and LL edema with substantially higher in cirrhotic patients with (P values 0.084 and <0.001, respectively) as in **Table 3**.

Table (3): Clinical data among HCV patients.

Variable		HCV +ve non cirrhotic gp (n=40)	HCV +ve cirrhotic gp (n=40)	P value
Jaundice	**Mild**	8 (20%)	15 (37.5%)	
	None	32 (80%)	25 (62.5%)	**0.084**
Lower limb edema	**Ll edema**	0 (0%)	11 (27.5%)	
	None	40 (100%)	29 (72.5%)	**<0.001**

The examined group's genotyping prevalence lacked statistical significance (Table 4).

Table (4): Genetic characterization of the study groups

Genotype	Control gp (n=40)	HCV +ve non cirrhotic gp (n=40)	HCV +ve cirrhotic gp (n=40)	P value
A-A	4 (10%)	10 (25%)	4 (10%)	0.225
A-G	23 (57.5%)	17 (42.5%)	20 (50%)	
G-G	13 (32.5%)	13 (32.5%)	16 (40%)	

The genotype frequency of XRCC1 gene shows no statistically substantial variation between HCV +ve and control groups (P value= 0.410) (**Table 5**).

Table (5): The genotype frequency of the XRCC1 gene among the HCV +ve and control groups

Genotypes		Control group (n=40)	HCV +ve group (n=80)	P value
XRCC1	**AA (wild)**	4 (10%)	14 (17.5%)	0.410
	AG+GG (mutant)	36 (90%)	66 (82.5%)	

The allelic frequency of XRCC1 was no statistically substantial variation among the studied groups (P value= 0.410) (**Table 6**).

Table (6): Allelic frequency of XRCC1 gene across the study groups

Variable	Control group	HCV +ve non cirrhotic group	HCV +ve cirrhotic group	P value
Allele A	31 (38.8%)	37 (46.2%)	28 (35%)	0.410
Allele G	49 (61.2%)	43 (53.8%)	52 (65%)	

There was no statistically substantial variation on comparing genotype frequency of XRCC1 and degree of fibrosis among the HCV +ve cirrhotic patients (**Table 7**).

Table (7): Association of degree of fibrosis among HCV +ve cirrhotic patient and genotype frequency

Variable		XRCC1		P Value
		A-A	**A-G / G-G**	
Fibroscan	**F3**	**0 (0%)**	**1 (2.5%)**	**1**
	F4	**4 (5%)**	**35 (87.5%)**	

DISCUSSION

Hepatitis C virus (HCV) infection is a significant public health concern in Egypt. With 15% of the population seropositive, 10% persistently diseased, and 90% of patients with genotype 4 infection, Egypt had the highest global presence of HCV infection in 2008. [(2)]. With an overall estimated 30% fall in HCV frequency in Egypt between 2008 and 2015, the seropositivity of HCV infections in that country has reduced to 6.3% among the population under study in 2015 [(3)].

Recently, animals with age-related liver malfunction and a buildup of DNA damage showed the importance of DNA repairing affects homeostasis and liver function [(9)].

The study's objective was to determine if there was any connection between the distribution of the XRCC1 rs25487 A > G variant in chronic HCV patients from Egypt and hepatic cirrhosis.

A total of 120 participants were used in this research, who were split into two groups as follows: Group I had 40 healthy, age and sex matched controls with normal liver biochemical profile, HCV Ab -ve and HBs Ag –ve and Group II included 80 patients diagnosed with HCV and categorized by the level of liver fibrosis discovered by fibroscan.

Blood samples were taken from each patient included in this study, for analyzing serum ALT, AST, Urea, Creatinine, HCV PCR, prothrombin concentration (PC) and SNP in XRCC1 gene (rs25487) by Real Time PCR.

In the present study, Between the three investigated groups, it was shown that there was no statistically substantial variation (control, HCV +ve non cirrhotic and HCV +ve cirrhotic group) in Age (P= 0.073), gender (P= 0.062), Urea (P= 0.780) and Creatinine (P= 0.193) and there was highly statistical substantial variation between the control group and HCV +ve group in ALT and AST (P <0.001), While PC was substantially reduced in HCV +ve group (P= 0.001). There was substantial variation on comparing Jaundice and LL edema with significantly higher in cirrhotic patients with (P values 0.084 and <0.001, respectively). Also in the current study, it was found that AA genotype were 4/40 (10%), 10/40 (25%) and 4/40 (10%) in the control, HCV +ve non cirrhotic and HCV +ve cirrhotic groups, respectively, While the frequencies of AG genotypes were 23/40 (57.5%),

17/40 (42.5%) and 20/40 (50%) in the control, HCV +ve non-cirrhotic and HCV +ve cirrhotic groups respectively and the frequencies of GG genotype were 13/40 (32.5%), 13/40 (32.5%) and 16/40 (40%) in the control, HCV +ve non cirrhotic and HCV +ve cirrhotic groups respectively. There was no statistical significance between control group, cirrhotic and non-cirrhotic chronic HCV patients in the distribution of different genotypes in XRCC1 A > G (P= 0.225). Regarding the AA genotype in comparison to the other genotypes (GG and AG), no unique pattern of correlation could be found (P= 0.410). Comparing the frequencies of the two alleles (A and G alleles) in the three groups under study revealed no evidence of a connection. The distinction between the G allele in the control group (61.2%), HCV cirrhotic patient 65%, and HCV non-cirrhotic patient 53.8% was not statistically substantial (P= 0.410).

Similarly, **Leite *et al.*** [10] XRCC1 A>G was investigated in 227 Brazilian patients, 108 of whom had HCV and 119 of whom had HBV (174 non-cirrhotic and 53 cirrhotic). They discovered that there was no distinction between patients with viral hepatitis (either collectively or in each HBV and HCV carrier separately) and the control group in terms of genotypic ratios (Gln/Gln, Gln /Arg, or Arg/Arg), or allelic frequencies (Arg and Gln). Additionally, they discovered that the frequency of the Arg/Gln genotype was substantially greater in cirrhotic patients (56.6%) compared to non-cirrhotic patients (25.8%) (P <0.0001). Independent of sex, age, alcohol use, and tobacco use, the link between this genotype and the occurrence of cirrhosis in patients remained statistically substantial (adjusted OR 3.5; 95% CI 1.7-7.4, P= 0.001). In the cirrhotic group (69.8%), there were substantially more people with at least one Gln allele (Gln/Gln + Arg/Gln) than in the non-cirrhotic group (37.9%) (OR 3.8; 95% CI 1.9-7.3, P <0.0001). This connection, too, was unrelated to the other covariates that were examined (adjusted OR 3.1; 95% CI 1.5-6.3, P= 0.002). Patients with cirrhosis had a frequency of the Gln allele that was substantially greater (0.4) than that of patients without cirrhosis (0.25) (OR 2.1; 95% CI 1.3-3.4, P= 0.001). These findings are highly intriguing and point to a potential involvement for the XRCC1 rs25487 polymorphism in the emergence of more severe illnesses in these individuals.

Another study was done by **Rossit *et al.*** [11] XRCC1 polymorphism among Southeastern Brazilians may be correlated with an increased risk of liver cirrhosis, according to research. The goal of the research was to determine Utilizing 97 liver cirrhosis patients and 96 controls that were matched for age, sex, and ethnicity, we examined the importance of two allelic variants encoding for amino acid alterations in the XRCC1 gene (the polymorphisms Arg194Trp and Arg399Gln). They observed that the genotypes Arg/Gln or Gln/Gln, which are both carriers of the 399Gln allele, increased the relative chance of liver cirrhosis by 1.8 times. The odds ratio (OR) was corrected and was 1.82 (95% CI 1.10-3.30). The Mestiso ethnic group seems to be at the greatest relative risk (OR 2.60; 95% CI 0.92-7.34). In older people over the age of 45, there was a substantial correlation between the 399Gln polymorphism and the risk of liver cirrhosis with an OR of 1.24 (95% CI 0.55-2.78), and OR was 2.70 (95% CI 1.14-6.48) in younger people. The 194Trp polymorphism in XRCC1 was not associated with an increased incidence of liver cirrhosis. According to these early outcomes, the XRCC1 399Gln mutation may significantly affect the chance of developing alcoholic liver cirrhosis.

In our research, cirrhotic patients made up 40% of the population, whereas 32.5% of non-cirrhotic patients had the GG genotype, which contrasts with what was discovered by **Rossit *et al.*** [11]**, Leite *et al.*** [10] Given that HCV genotype 4 infections account for over 90% of reported infections, this may be explained by differences in HCV genotype. **Ruane *et al.*** [12] while genotypes 1, 2, and 3 were used in the other experiments. Ethnic differences might provide as another justification for the variations in outcomes across the research **Sterling *et al.*** [13] and also the limited number of the studied group.

Another study in India by **Bose *et al.*** [14] research on HBV patients looked on the genetic dangers for developing liver disorders linked to the HBV. It was shown that the combining of the Cyp2E1 variation and the XRCC1 variant raised the likelihood of HCC, cirrhosis, and CHBV in a total of 424 patients, including 210 controls, 50 acute HBV (AVH), 84 chronic HBV (CHBV), 25 HBV-related cirrhosis, and 55 HBV-related HCC (p b 0.001).

As severe liver fibrosis or cirrhosis coexists with the majority (70–90%) of HCC patients [15], there have been several investigations looking at the connection across the XRCC1 rs25487 polymorphism and vulnerability to HCC caused by viral hepatitis.

In the meta-analysis of **Liu *et al.*** [16] 2208 HCC patients and 3265 controls were included in 11 case-control investigations. The connection between genetic variants and HCC risk was examined in nine studies including Asian patients, one research involving African patients, and one study involving Caucasian patients. In comparison to the wild-type Arg/Arg homozygote, the different genotypes of Arg399Gln (Arg/Gln and Gln/Gln) were not linked with an increased risk of developing HCC (OR 1.01, 95% CI 0.79-1.28; OR 1.09, 95% CI 0.81-1.45). The findings showed there was no connection at XRCC1 Arg399Gln variant and HCC risk in various ethnic groups. The lack of studies—only two from non-Asians (one Caucasian and one African) were included in this meta-analysis—could be the explanation of the null outcome.

The meta-analysis done by **Qi *et al.*** [17] 15 case-control investigations were conducted to investigate the

relationship between the XRCC1 Arg399Gln polymorphism and the risk of HCC. These studies included 2,554 cases and 3,320 controls. Overall, the variations genotypes of the XRCC1 Arg399Gln gene were linked to a substantially higher risk of HCC in co-dominant models and dominant models. The XRCC1 Arg399Gln variant was shown to be linked with a higher incidence of HCC in Asian populations when the co-dominant model was used. A greater risk of HCC may be linked to the XRCC1 Arg399Gln mutation, particularly in the Asian population.

In summary, Genetic variables have a complicated role in the development of hepatic fibrosis in chronic HCV patients, and their impact is expected to be very variable. An association (whether negative or positive) between XRCC1 gene polymorphism and fibrosis progression, though not proven in this study, requires further confirmation by larger scale or prospective longitudinal.

CONCLUSION

By comparing the prevalence of the various genotypes (AA, AG, and GG) in the analyzed groups, no clear pattern of relationship could be seen (P= 0.225). Regarding the AA genotype in comparison to the other genotypes (GG and AG), no unique pattern of correlation could be found (P= 0.410). Comparing the frequencies of the two alleles (A and G alleles) in the three groups under study revealed no evidence of a connection.

DECLARATIONS

- **Consent for publication:** I attest that all authors have agreed to submit the work.
- **Availability of data and material:** Available
- **Competing interests:** None
- **Funding:** No fund
- **Conflicts of interest:** no conflicts of interest.

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