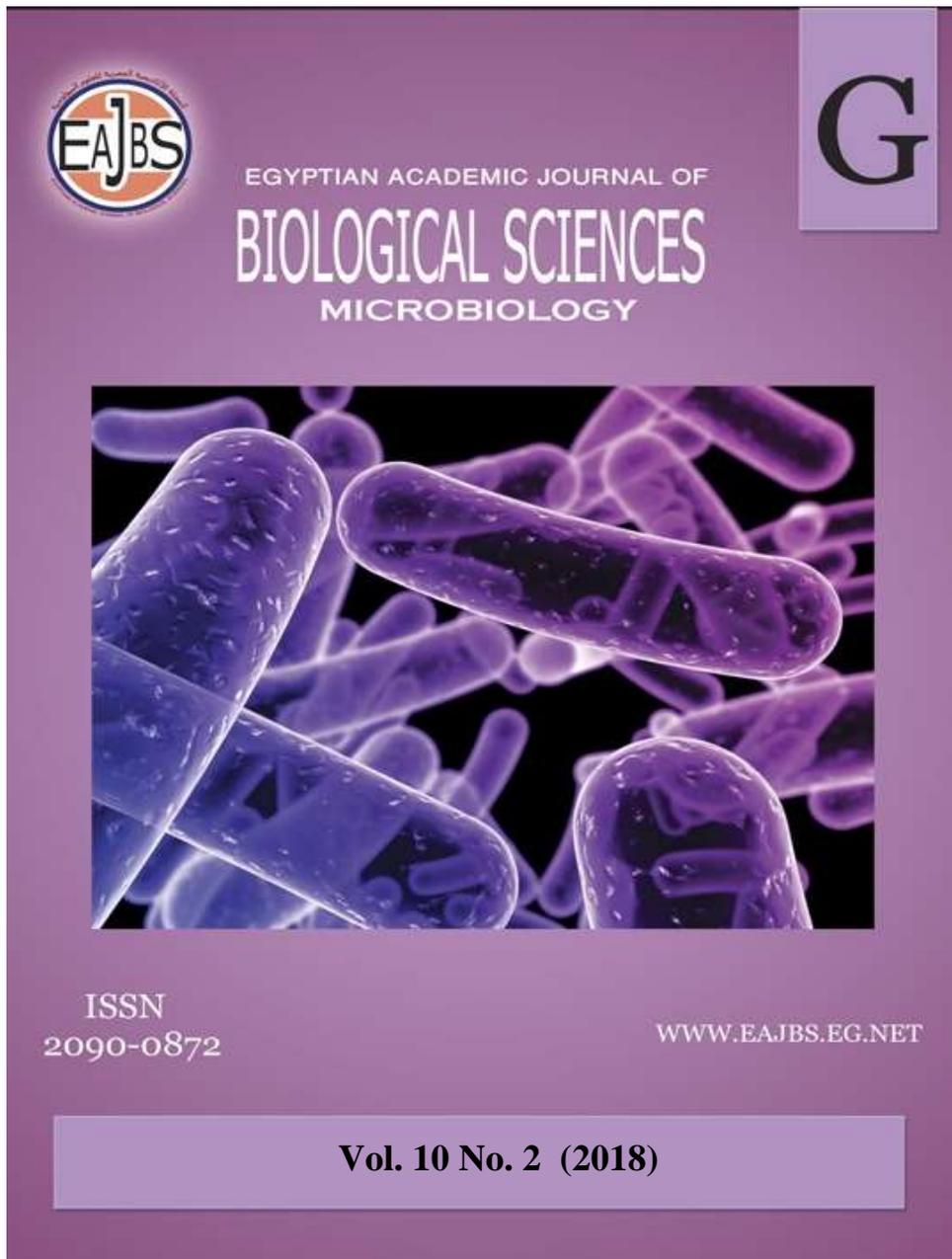


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Citation: *Egypt. Acad. J. Biolog. Sci. (G. Microbiolog) Vol.10 (2)pp. 15- 23 (2018)*



Polymorphisms of COMT Val158Met and the Risk of Hepatocellular Carcinoma Development among Egyptian HCV Infected Patients

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ARTICLE INFO

Article History

Received: 15/8/2018

Accepted: 20/9/2018

Keywords:

Hepatocellular Carcinoma;
Hepatitis C Virus; COMT;
Egypt

ABSTRACT

Chronic viral hepatitis is the most important risk factor for progression to hepatocellular carcinoma (HCC) in Egypt. Catechol-*O*-methyltransferase (COMT) plays a central role in DNA repair and estrogen-induced carcinogenesis. Many recent epidemiologic studies have investigated the association between the COMT Val158Met polymorphism and cancer risk.

In the current study, we investigated the association between COMT Val158Met A/G variations and the risk of HCC development among Egyptian HCV infected patients. This study was conducted on two groups; HCC patients group and healthy control group each included 100 subjects. Single nucleotide polymorphisms (SNPs) have been studied for COMT using real-time PCR.

Our results suggest that COMT is not associated with HCC risk among HCV infected patients. A significant increase was detected regarding the different COMT SNPs in the aged category more than 50 years compared to younger patients. No significant difference was detected on the level of gender, liver cirrhosis, biochemical and hematological parameters.

In conclusion, COMT Val158Met polymorphism could not be considered as a risk factor for HCC risk among hepatitis C virus patients in Egypt.

INTRODUCTION

Hepatocellular carcinoma (HCC) is the most widely recognized primary liver tumor (Balogh et al., 2016; Abdel-Hamid et al., 2018). Incidence varies widely between geographical areas, probably because of variations in the exposure to hepatitis virus and other environmental pathogens (El-Serag, 2001). The clinical risk factors include cirrhosis, chronic

hepatitis C virus (HCV) infection, chronic hepatitis B virus (HBV) infection, co-infection of HBV and HCV viruses, schistosomiasis, aflatoxin B1 (AFB1), and alcoholism. The environmental risk factors include pesticides and cigarette smoking (Anwar *et al.*, 2008). HCV infection causes liver inflammation and a variable grade of damage to the organ that over decades can lead to cirrhosis (Ikeda *et al.*, 1993; Tsukuma *et al.*, 1993; Lauer and Walker, 2001). Egypt has one of the highest prevalence rates of HCV infection. Disease progression is influenced by additional factors such as duration of infection, age at infection, gender, co-infection with HBV, and the level of HCV viremia and its genotype (Anwar *et al.*, 2008).

As with many cancers, variants of genes involved in multistage carcinogenesis may determine an individual's susceptibility to developing HCC. Single nucleotide polymorphisms (SNPs) are the most common type of genomic sequence variation and are thought to be associated with population diversity, susceptibility to disease, and individual response to drug treatment (Shastry, 2002).

Epidemiological and endocrinological studies indicate that sex hormones control normal growth and development of target organs, but can also influence susceptibility to disease and to neoplastic transformation. Researchers implicate sex hormones in the pathogenesis of several cancer types, such as ovary, prostate and breast (Henderson and Feigelson, 2000).

Catechol-O-methyltransferase (COMT) is the main enzyme sequentially participating in the pathways of estrogen and androgen biosynthesis and inactivation. COMT is expressed at high levels in liver, kidney, endometrium and breast (Guldberg and Marsden, 1975). A G-to-A transition at codon 158 leads to substitution of valine to methionine causes a 3–4-fold reduction of enzyme activity (Lachman *et al.*, 1996).

COMT gene is localized on chromosome 22q11.2 and contains six exons

(Grossman *et al.*, 1992). It is a vital enzyme participates in the inactivation of endogenous catecholamine and catechol estrogens which have the capability to destroy DNA and carcinogenic agents (Cavalieri *et al.*, 1997). So, the damage, the loss of or changes in COMT is hypothetically contributed to genomic instability and tumor formation.

Several evidence studies indicate that COMT polymorphisms can affect individual susceptibility to developing cancers (Garner *et al.*, 2002; Sasak *et al.*, 2003; Shen *et al.*, 2006; Tanaka *et al.*, 2006; Zhang *et al.*, 2008). Functional polymorphisms of these genes have been studied in association with hormone-induced cancers (Reichardt *et al.*, 1995; Febbo *et al.*, 1999; Lunn *et al.*, 1999; Makridakis *et al.*, 1999; Jaffe *et al.*, 2000; Haiman *et al.*, 2001; Yamada *et al.*, 2001), but they have been poorly investigated in the setting of chronic liver disease (Yu *et al.*, 2001). The aim of the current study was to investigate the association between COMT Val158Met (rs4680) and the HCC risk among HCV patients in Egypt.

MATERIALS & METHODS

This study was a case-control study. It was conducted on a total number of 200 individuals divided into two groups, group I included 100 HCC cases that were recruited from National Cancer Institute, Cairo University and group II included 100 healthy subjects negative for anti-HCV and HBsAg were recruited from National Liver Institute, Menoufia University (age and gender were considered). Any healthy subject has a history of tumor, liver disease, renal disease, coronary artery disease or other metabolic disorders was excluded (Hao *et al.*, 2014). A written agreement was gained from all contributors and the institutional ethical committee permitted the study.

Ten ml of blood was withdrawn from all patients and healthy controls under a complete aseptic condition in vacutainer tubes containing EDTA. All samples were centrifuged at 2000 rpm for 10 min, plasma and buffy coat were separated, aliquoted and stored at -80°C . Plasma samples were used

for the determination of HCV Ab, HBsAg, and AFP using ADVIA Centaur CP (Switzerland) according to the manufacturer instructions. Assessment of aspartate aminotransferase (AST), alanine aminotransferase (ALT), total bilirubin (TBIL), and Albumin (ALB) was measured using Beckman CX4 chemistry analyzer (USA). Hemoglobin (HB) and platelets were measured using Sysmex XT-1800i (Japan). Also, plasma was used to perform in-house RT HCV PCR for the detection of HCV (Abdel-Hamid et al., 1997). In patients, compensated cirrhosis was determined by Fibro-scan™ > 12.5 kPa (Ibrahim et al., 2018).

Genomic DNA was isolated from the buffy coat of cases and healthy control samples using a DNA isolation kit (QiAamp DNA mini kit, Qiagen, Hilden, Germany). Amplification of genomic DNA samples was used to detect the genetic polymorphisms COMT Val158Met (rs4680) (González-Castro et al., 2013). One of the allelic probes of the gene was labeled with FAM dye and the other with the fluorescent VIC dye using real-time PCR System (Applied Biosystems: Foster City, CA, USA). The PCR reaction was carried out using a TaqMan universal master mix (Applied Biosystems: Foster City, CA, USA) at a probe concentration of 20X. The reaction was performed in a 96-well format in a total reaction volume of 25 µl using 20 ng of genomic DNA. The reaction was heated for 2 min at 50°C, then 10 min at 95°C, followed by 40 cycles of 95°C for 15 sec and 60°C for 1.5 min. Then the fluorescence intensity of each well in the TaqMan assay plate was read.

Data were collected and entered to the computer using SPSS 20 (Chicago, Inc, Illinose). Quantitative data were shown as mean and standard deviation (SD) or expressed as frequency and percent. Chi-

square test and Fisher exact test were used to measure the association between qualitative variables as appropriate. Mann Whitney and independent sample t-tests were done to measure the association between two quantitative variables as appropriate. The Kruskal-Wallis and ANOVA tests were done to measure the association between more than two quantitative variables as appropriate.

RESULTS

Table 1 showed that there is no significant ($P = 0.607$) difference was detected on the level of COMT polymorphisms where (AA as wild genotype), (AG as heterozygous genotype) and (GG as mutant genotype) were detected in HCC group as 45(45.0%), 27(27.0%) and 28(28.0%), respectively, while the indicated genotypes were found in healthy control as 48(48.0%), 21(21.0%) and 31(31.0%), respectively.

Based on gender, no significant percentage ($P = 0.463$) was demonstrated on the levels of AA, AG, and GG polymorphisms in male patients 34(75.6%), 21(77.8%) and 18(64.3%), and in female patients 11(24.4%), 6(22.2%) and 10(35.7%), respectively. Interestingly, the higher percentage was detected with male patients than female (Table 2). On the level of age, a significant increase ($P = 0.018$) was detected regarding the different COMT SNPs in the aged category more than 50 years compared to younger patients. Moreover, No significant difference ($P = 0.138$) was detected in the percentage of liver cirrhosis among the different COMT genetic variants (Table 2).

Studying COMT SNP variants with laboratory findings among patients group showed no significant association between the COMT genotypes and biochemical and hematological studied parameters (Table 3).

Table (1): Comparison of genotype and allele distributions of COMT between the studied groups.

			HCC N = 100	Control N = 100	P-value
COMT	Genotypes	AA	45 (45.0%)	48 (48.0%)	0.607
		AG	27 (27.0%)	21 (21.0%)	
		GG	28 (28.0%)	31 (31.0%)	

Data are presented in terms of numbers of patients (%).

Table (2): The gender, age and liver cirrhosis comparison among the COMT genotypes in the HCC group.

		COMT			P-value
		AA N = 45	AG N = 27	GG N = 28	
Gender	Male	34 (75.6%)	21 (77.8%)	18 (64.3%)	0.463
	Female	11 (24.4%)	6 (22.2%)	10 (35.7%)	
Age	≤50 years	4 (8.9%)	7 (25.9%)	10 (35.7%)	0.018*
	>50 years	41 (91.1%)	20 (74.1%)	18 (64.3%)	
Liver cirrhosis	36/100	14 (31.1%)	13 (48.1%)	9 (32.1%)	0.138

Data are presented in terms of numbers of patients (%).

*P-value < 0.05 was considered significant.

Table (3): The laboratory parameters among the COMT genotypes in HCC group.

	COMT			P-value
	AA N = 45	AG N = 27	GG N = 28	
AFP (ng/ml)	461.3 ± 495.4	599.8 ± 492.6	467.3 ± 467.8	0.400
ALT (IU/L)	52.5 ± 26.70	60.0 ± 38.4	40.6 ± 34.3	0.160
AST (IU/L)	46.5 ± 18.8	70.8 ± 58.8	53.3 ± 36.5	0.234
TBIL (mg/dL)	2.4 ± 1.7	2.6 ± 2.7	2.4 ± 2.2	0.921
ALB (g/dL)	2.9 ± 0.2	3.0 ± 0.4	3.1 ± 0.5	0.376
HB (g/dL)	11.3 ± 1.2	10.6 ± 1.1	11.0 ± 1.3	0.164
Platelets (10 ³ /μL)	117.1 ± 30.6	114.4 ± 35.2	121.9 ± 50.4	0.783

Data are presented in terms of Mean ± SD.

DISCUSSION

COMT is an enzyme belongs to estrogen metabolism enzymes that are the main enzymes involved in disrupting catechol estrogens, which are the most metabolites of estrogens and can cause oxidative DNA damage. It has been shown that Val158Met at codon 158 in exon 4 makes a severe decrease in the enzyme activity (Lachman et al., 1996; Lee et al., 2005).

Some studies have established that estrogen metabolites can bind to DNA and initiate damage, predicting that the estrogens might be endogenous genotoxic agents that can cause genetic alteration and begin tumor development (Cavaliere et al., 2000; Newbold et al., 2000). This concept is supported by the result that women with fewer quantities of the enzymes responsible for removing reactive estrogen metabolites have a higher risk of breast cancer development (Lavigne et al., 1997). Based on the obvious relevance of estrogens in human hepatocarcinogenesis (Neuberger et al., 1986), it is sensible to guess that the same mechanism may occur in HCC.

In our study, there is no association between COMT gene polymorphisms and HCC in Egyptian patients infected with HCV. Consequently, these results are indicating that COMT polymorphism is not associated with HCC risk related to HCV infection. In agreement with our findings, the previous report recorded that COMT Val158Met is not related to the risk of HCV-induced HCC (Rossi et al., 2003). Furthermore, another study found no association between the functional polymorphism of COMT and the risk of HCC caused by HBV infection (Yuan et al., 2008). Other records found to support the theory that estrogen levels are not involved in the modulation of liver disease outcome, which comes from observation that no effect was demonstrated with COMT polymorphism in the studies of other diseases, such as breast and ovarian cancer, where estrogen plays an essential role

(Lavigne et al., 1997; Thompson et al., 1998).

In disagreement with our findings, Yin et al. (2004) had reported that women who have low COMT Val158Met allele activity are strongly associated with the risk of developing HCC in Taiwanese females. The conflicting results could be attributable to differences in demography, ethnicity, lifestyles, type of viral infections, and clinical settings. In addition, other methodological factors in studies, such as small sample size, inadequate adjustment for confounding factors, or failure to correct multiple tests, may lead to inconsistent results.

In the current study, a higher percentage of COMT SNP variants were detected in aged patients than younger ones. Several studies found an obvious association between age and HCC or HCV infection (Abdel-Wahab et al., 2007; Do Carmo et al., 2012; Abdel-Hamid et al., 2018). The intimate relation between HCC, HCV and age might be reflected on COMT SNP studied in this current report.

Lastly, cancer is an illness as a result of a multifactor reaction between different genetic and environmental risk factors. So, the gene only or an environmental factor only is not enough to explain the risk to cancer. In conclusion, our findings do not support associations between the polymorphisms of COMT Val158Met gene and the risk for hepatocellular carcinoma among HCV infected patients in Egypt.

Conflict of Interest:

The author declares no conflict of interest.

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ARABIC SUMMERY

العلاقة بين تعدد الأشكال الجينية ل COMT Val158Met وخطر تطور سرطان الخلايا الكبدية في المرضى المصريين المصابين بفيروس التهاب الكبد الوبائي (سى)

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بعد التهاب الكبد الفيروسي المزمن من أهم عوامل الخطر التي تؤدي الى حدوث سرطان الخلايا الكبدية في مصر. يلعب جين ال COMT دوراً أساسياً في إصلاح الحمض النووي والتسرطن الناتج عن الاستروجين. وقد حققت العديد من الدراسات الوبائية الحديثة العلاقة بين تعدد الأشكال لجين COMT Val158Met وخطر السرطان.

في هذه الدراسة ، قمنا بالتحري عن الارتباط بين تعدد الأشكال لجين COMT Val158Met A/G وخطر تطور سرطان الخلايا الكبدية بين المرضى المصريين المصابين بفيروس التهاب الكبد الوبائي (سى). أجريت هذه الدراسة على مجموعتين. وشملت مجموعة المرضى المصابين بسرطان الخلايا الكبدية ومجموعة الأصحاء كل مجموعة تشمل ١٠٠ فرد. وقد تمت دراسة تعدد الأشكال الفردية (SNPs) لجين COMT باستخدام تفاعل البلمرة التسلسلى Real-time PCR.

نتائجنا تشير إلى أن جين ال COMT لا يرتبط مع خطر الإصابة بسرطان الخلايا الكبدية بين المرضى المصابين بفيروس التهاب الكبد الوبائي (سى). تم الكشف عن وجود علاقة بين جين ال COMT في الفئة العمرية أكثر من ٥٠ سنة مقارنة مع المرضى الأصغر سناً. تم الكشف عن عدم وجود علاقة بين جين ال COMT على مستوى الجنس، حالة الكبد (تليف الكبد) ، و تحاليل البيوكيميائية و الدموية المختلفة محل الدراسة.

في الختام لا يوجد علاقة بين تعدد الأشكال الجينية ل COMT Val158Met وخطر تطور سرطان الخلايا الكبدية في المرضى المصريين المصابين بفيروس التهاب الكبد الوبائي (سى).