BRITISH JOURNAL OF BIOMEDICAL SCIENCE
2019, VOL. 76, NO. 2, 64–69
https://doi.org/10.1080/09674845.2019.1594487

Genetic variants of *XRCC1* and risk of hepatocellular carcinoma in chronic hepatitis C patients

M Arafa[a], T Besheer[a], AM El-Eraky[a], SM Abo El-khair[b] and AZ Elsamanoudy[b,c]

[a]Departments of Tropical Medicine, Faculty of Medicine, Mansoura University, Mansoura, Egypt; [b]Medical Biochemistry and Molecular Biology, Faculty of Medicine, Mansoura University, Mansoura, Egypt; [c]The Department of Clinical Biochemistry, Faculty of Medicine, King Abdulaziz University, Jeddah, Saudi Arabia

ABSTRACT

Background: Hepatitis C virus (HCV) related liver cirrhosis occurs in about 20% of chronically infected patients over a duration of 10–20 years, and within 5 years approximately 10–20% of these cirrhotic patients will develop hepatocellular carcinoma (HCC). Previous studies report that the X-ray repair cross-complementing group1 gene (*XRCC1*) is important in the risk of HCC development; however, results obtained from these studies are conflicting rather than conclusive. We hypothesised an association between single nucleotide polymorphisms (SNPs) in *XRCC1* with the HCC risk on a background of chronic hepatitis C.

Materials and methods: We recruited 210 subjects, 70 with HCC, 70 with cirrhosis and 70 healthy controls. Two SNPs [c.1254C>T(rs2293035) and c.1517G>C(rs139599857)] in *XRCC1* were genotyped using created restriction site-polymerase chain reaction (CRS-PCR) and PCR-restriction fragment length polymorphism (PCR-RFLP) methods.

Results: The TT genotype, CT genotype and T-allele in c.1254C>T (rs2293035) were linked to risk of HCC compared to the CC genotype: OR 3.58 [confidence interval (CI) 95%: 1.19–10.7] p = 0.019; OR 2.16 (CI 95%: 1.04–4.47) p = 0.037 and OR 2.10 (CI 95%: 1.2–3.3) p = 0.006, respectively. Regarding c.1517G>C (rs139599857), the CC genotype, GC genotype and C-allele were linked with higher risk of developing HCC compared to GG genotype: OR 4.77 (CI 95%: 1.3–16.9), p = 0.016; OR 3.02 (CI 95%: 1.46–6.2), p = 0.002 and OR 2.4 (CI 95%: 1.4–4.0), p = 0.001, respectively.

Conclusion: We conclude that the T-allele of c.1254C>T (rs2293035) and the C allele of c.1517G>C (rs139599857) genetic variants may be associated with increased HCC risk among chronic hepatitis C patients.

ARTICLE HISTORY
Received 24 January 2019
Accepted 8 March 2019

KEYWORDS
XRCC1 gene; polymorphisms; HCC; HCV

Introduction

Primary liver cancer is the fifth most common cancer worldwide and the second leading cause of cancer-related mortality [1]. Many environmental factors, such as hepatitis C (HCV) or hepatitis B (HBV) viral infections, alcohol consumption, smoking, and diabetes mellitus, increase risk for developing hepatocellular carcinoma (HCC) [2]. The observation that not all chronically infected subjects progress to HCC demonstrates that genetic variables may play key roles in the pathogenesis of HCC [3]. An increase in reactive oxygen species and DNA damage detected before development of HCC in mice with active chronic hepatitis suggests that both ROS and DNA damage have a role in pathogenesis [4]. Hence, the repair of damaged DNA is vital for cells to prevent incidence of cancer [5].

There are four major DNA repair pathways including nucleotide excision repair (NER), base excision repair, double strand break repair, and mismatch repair [6,7]. Base excision repair is the fundamental repair pathway that protects cells from oxidative DNA injury. The X-ray repair cross-complementing protein 1 (XRCC1) is one of the most essential molecules in base excision repair [8,9]. Additionally, genetic polymorphisms in genes encoding proteins included in DNA repair may affect susceptibility to cancer [10,11]. It has been reported that *XRCC1* is essential in affecting HCC susceptibility [11]. Several previous studies have described possible association between the single nucleotide polymorphisms (SNPs) in *XRCC1* [as arginine (Arg) 194tryptophan (Trp), Arg280histidine (His) and Arg399glutamine (Gln)] and the risk of HCC [12].

We hypothesised an association between two non-synonymous SNPs [c.1254C>T (rs2293035) and 1517G>C (rs139599857)] in *XRCC1* and the presence of HCC in patients with a chronic HCV infection.

Materials and methods

We recruited 140 patients (98 males and 42 females) with chronic HCV infection with positive viremia with or without HCC, recruited from Tropical Medicine Department, Mansoura university hospital. Seventy

CONTACT T Besheer Tarekbesheer@yahoo.com Tropical Medicine Department, Faculty of Medicine, Mansoura University, 35516 Mansoura, Egypt.

age and sex matched healthy subjects were included. All subjects gave written informed consent before enrollment. Approval was provided from the Institutional Review Board (IRB) of faculty of medicine at Mansoura University (MS/611). All subjects had undergone detailed history taking, and clinical assessment. Exclusion criteria were non-HCV-related hepatocellular carcinoma and non-HCV-related liver cirrhosis. Liver function tests (ALT, AST, albumin, bilirubin), prothrombin time, creatinine, complete blood count, virology (HBS Ag, HCV *Ab*), PCR for hepatitis C RNA for HCV *Ab* positive cases, AFP, were evaluated. The HCC diagnosis was done according to EASL-EORTC clinical practise guidelines (2012) for management of hepatocellular carcinoma [13]. Cirrhosis was diagnosed by laboratory tests, endoscopic evidence, sonography finding and tri-phasic multi-slices computed tomography (CT) of the abdomen. Five ml blood was collected by venipuncture and divided in two tubes: 2 ml into EDTA for DNA extraction, and 3 ml into silica/gel separator for routine laboratory tests.

For genotyping of the *XRCC1* polymorphisms, DNA isolation was done using spin column DNA extraction kits [Gene-JET Whole Blood Genomic DNA Purification Mini Kit] according to manufacturer instructions (Thermo-Scientific, USA, Cat. no #K0781). DNA quantification and purity were evaluated using Nanodrop (Thermo scientific NanoDrop 2000 spectrophotometer, USA). DNA concentrations of samples were between 10 and 45 ng/µl. A260/A280 ratio represents the purity of the extracted DNA (~1.8 is generally accepted). The quality of DNA purified was assessed by separation on 1% agarose gel electrophoresis.

Genotyping of *XRCC1* SNPs [c.1254C>T (rs2293035) and 1517G>C(rs139599857)] was analysed by PCR-RFLP. The genotyping of c.1254C>T SNP was performed by creation restriction site-PCR (CRS-PCR) method in which one primer contained a nucleotide mismatch, that make restriction enzyme use for discrimination of sequence variations [14]. The genotyping for c.1517G>C SNP was investigated by PCR-restriction fragment length polymorphism (PCR-RFLP) technique according to [15,16]. PCR amplification was done using the following PCR reaction (25 µl): PCR master mix (12.5 µl), forward primer (2 µl of 10 pmol/µl), reverse primer (2 µl of 10 pmol/µl), 5 µl extracted DNA template (10 ng/µl) and 3.5 µl double distiled water. Primer sequences were: for c.1254C>T SNP; forward primer: 5′-GAGGAGGATGAGGCCTCTCACAC-3′ and reverse primer: 5′-TAAGGAGGGAGAGTGGGTGGGT-3′ while for c.1517G>C SNP; forward primer: 5′-CAAGTCCCAGCTGAGAACTGAG-3′ and reverse primer: 5′-GCTGCTCTGCATGCTCACTC-3′. The PCR amplification condition was initial denaturation (one cycle) at 95°C (5 min), 35 cycles: denaturation at 95°C (30 s), annealing at 59 °C (30 s), and extension at 72 °C (30 s), then final extension (one cycle) at 72 °C (5 min). A 2% agarose gel was used for separation of the DNA-PCR products, then the gel visualised by UV trans-illuminator. PCR product includes two variants [c.1254C>T (218bp) and (c.1517G>C (247bp)]. PCR product cleavage by Hpa II restriction enzyme for c.1254C>T SNP and by Hae III restriction enzyme for c.1517G>C SNP were then performed.

Restriction enzyme digestion reaction contained these constituents in this sequence and volumes: 16 µl double distiled water, 3 µl 10 X Fast-Digest green buffers, 10 µl PCR products, and 1 µl of restriction enzyme to get a net total amount 30 µl. Then, digestion mix was incubated at 37 C in a heat block for 15 min. Finally, the restriction enzyme inactivation was done by heating at 65°C for 5 min. The amplified PCR products and products after restriction enzyme digestion were analysed by 3% agarose gel electrophoresis. The PCR amplified products of c.1254C>T, after digestion with restriction enzyme (*Hpa*II), give three genotypes: CC (195 and 23 bp), CT (218, 195 and 23 bp) and TT (218bp). The PCR amplified products of c.1517G>C, after digestion with restriction enzyme (*Hae*III), give three genotypes: GG (247 bp), GA (247, 168 and 79 bp) and AA (168 and 79 bp).

Analysis of data was done by the SPSS version 17.0. Analysed data were presented as mean ± standard deviation (SD) and frequency (number-percent). The significance of difference was analysed by: analysis of variance (ANOVA) followed by post hoc Tukey, and Mann-Whitney U test, or by Kruskal Wallis test and then Mann-Whitney test for multiple comparisons. The SNPs were tested for Hardy-Weinberg equilibrium and the genotypic and allelic disease association analysis was analysed by DeFinetti programme. Frequencies of polymorphisms and genotype evaluated by the gene counts. X^2 tests were done to calculate significance for different genotype distributions, and odd's ratio (OR) and 95% confidence interval were calculated to detect risk ratio. In all analyses, p values < 0.05 were considered statistically significant.

Results

The general criteria and biochemical parameters are shown in Table 1. The three groups were age (p = 0.07) and sex (p = 0.5) matched, but all laboratory indices were different across the groups (all $p < 0.001$) except albumin, ALT, AST, creatinine and platelets, which were all not different ($p > 0.05$) between cirrhosis and HCC.

Genotyping of *XRCC1* SNPs: The genotype frequencies of both c.1254C>T and c.1517G>C genetic polymorphisms were in Hardy-Weinberg equilibrium. Tables 2 and 3 show the allelic and genotypic frequencies of the two genetic variants. C-allele

Table 1. Demographic and biochemical parameters.

		Controls	Cirrhosis	HCC
Age (years)		56.9 [7.2]	56.4 [5.8]	58.8 [6.1]
Sex	Female/Male	22/48	18/52	24/46
ALT (U/L)		21 (11–34)	38 (20–134)	50 (21–380)
AST (U/L)		24 (12–34)	66 (20–182)	86 (28–256)
AFP (µg/L)		6.2 (2.6–11.6)	13.0 (2.7–116)	75.3 (6.3–5000)
Albumin (g/L)		43 [4.5]	25 [5]	29.5 [6]
Bilirubin (µmol/L)		10 (45–19)	44 (14–391)	27 (12–433)
INR		1.0 [0.1]	1.6 [0.3]	1.4 [0.3]
Creatinine (µmol/L)		71 [18]	88 [27]	88 [18]
WBC ($\times 10^9$/L)		8.1 [0.8]	2.9 [1.0]	4.5 [2.7]
Haemoglobin (g/L)		141 [9]	91 [12.3]	106 [20]
Platelets ($\times 10^9$/L)		189 (155–260)	64 (29–106)	70 (21–334)

Data mean [SD] or median (IQR). HCC: hepatocellular carcinoma; ALT: alanine transaminase; AST: aspartate transaminase; AFP: alpha-fetoprotein; WBC: white blood cell; INR: International Normalised Ratio.

of c.1254C>T (rs2293035) and G-allele of c.1517G>C (rs139599857) genetic variants are the predominant alleles in all studied groups. Table 2 shows that the occurrence of TT genotype and CT genotype was significantly higher in HCC group than in control group [p = 0.019, p = 0.037, respectively]. As regards the allelic analysis, the percentage of individuals having the T allele was 43% of HCC group and 27% of healthy controls. Hence T allele frequency was significantly higher in patients than controls (p = 0.006). Table 3 shows that the occurrence of CC genotype and GC genotype was significantly higher in HCC group than in control group [p = 0.016, p = 0.002, respectively]. As regards the allelic analysis, the percentage of individuals having the C allele was 41% of HCC group and 23% of healthy controls, hence C allele frequency was significantly higher in HCC patients than controls (p = 0.001). Table 4 shows that the occurrence of the haplotypes (CTGC), (TTGC) were significantly higher in HCC group than in control group (both p = 0.001).

Discussion

Hepatitis C virus (HCV) infection is a major cause of chronic hepatitis [17]. Chronic inflammation generates reactive oxygen species that can damage DNA, which triggers short term responses, such as activation of DNA repair, cell cycle checkpoints and when the level of DNA damage exceeds the repair capacity, apoptosis occurs. In the long-term, non-repaired DNA damage may result in mutations and genomic instability which contributes to the development of chronic diseases and carcinogenesis [18]. The XRCC1 protein is an essential molecule in the multi-step base excision repair system [19]. Mutations of *XRCC1* might increase cancer risk through impairment of XRCC1 interaction with further enzymatic proteins and so, induce alterations in DNA repair activity [20,21] and this subsequently may induce carcinogenesis, including tumours of head and neck, lung, breast, oesophagus and multiple other tumours [22,23].

Table 2. Genotype and allele analysis of c.1254 C>T SNPs *XRCC1* gene.

	Controls	Cirrhosis	HCC	OR (CI 95%) Cirrhosis vs control	OR (CI 95%) HCC vs control	OR3 (CI 95%) HCC vs cirrhosis
CC	38 (54.3%)	32 (48.6%)	23 (32.9%)	1(Ref)	1(Ref)	1(Ref)
CT	26 (37.1%)	30 (42.9%)	34 (48.6%)	1.37 (0.67–2.77)	2.16[a] (1.04–4.47)	1.57 (0.76–3.26)
TT	6 (8.6%)	8 (8.6%)	13 (18.6%)	1.58 (0.49–5.04)	3.58[b] (1.19–10.7)	2.26 (0.8–6.3)
C	102 (73%)	94 (67%)	80 (57%)	1(Ref)	1(Ref)	1(Ref)
T	38 (27%)	46 (33%)	60 (43%)	1.3 (0.78–2.19)	2.01[c] (1.2–3.3)	1.5 (0.9–2.5)

HCC = hepatocellular carcinoma, OR = odds ratio, CI = confidence interval. [a]p = 0.037, [b]p = 0.019, [c]p = 0.006.

Table 3. Genotype and allele analysis of c.1517G>C SNPs in *XRCC1*.

	Controls	Cirrhosis	HCC	OR (CI 95%) Cirrhosis vs control	OR (CI 95%) HCC vs control	OR (CI 95%) HCC vs cirrhosis
GG	42 (60.0%)	30 (42.9%)	22 (31.4%)	1(Ref)	1(Ref)	1(Ref)
GC	24 (34.3%)	34 (48.6%)	38 (54.3%)	1.98 (0.98–4.001)	3.02[a] (1.46–6.2)	1.5 (0.7–3.1)
CC	4 (5.7%)	6 (8.6%)	10 (14.3%)	2.1 (0.54–8.09)	4.77[b] (1.3–16.9)	2.27 (0.7–7.2)
G	108 (77.0%)	94 (67.0%)	82 (59.0%)	1(Ref)	1(Ref)	1(Ref)
C	32 (23.0%)	46 (33.0%)	58 (41.0%)	1.56 (0.97–2.8)	2.4[c] (1.4–4.0)	1.4 (0.88–2.35)

HCC = hepatocellular carcinoma, OR = odds ratio, CI = confidence interval. [a]p = 0.002, [b]p = 0.016, [c]p = 0.001.

Table 4. Haplotyping analysis of c.1254C>T and c.1517G>C SNPs of *XRCC1*.

	Controls	Cirrhosis	HCC	OR (CI 95%) Cirrhosis vs control	OR (CI 95%) HCC vs control	OR (CI 95%) HCC vs cirrhosis
CCGG	20 (28.6%)	14 (20.0%)	6 (8.6%)	1(Ref)	1(Ref)	1(Ref)
CCGC	14 (20.0%)	12 (17.1%)	12 (17.1%)	1.2 (0.4–3.4)	2.8 (0.86–9.4)	2.3 (0.67–8.1)
CCCC	4 (5.7%)	6 (8.6%)	5 (7.1%)	2.14 (0.5–9.02)	4.16 (0.84–20.6)	1.9 (0.4–8.9)
CTGG	18 (25.7%)	14 (20.0%)	13 (18.6%)	1.1 (0.4–2.95)	2.4 (0.75–7.66)	2.16 (064–7.3)
CTGC	8 (11.4%)	16 (22.9%)	17 (24.3%)	2.85 (0.96–8.5)	7.08* (2.05–24.5)	2.47 (0.76–8.03)
CTCC	0 (0%)	0 (0%)	4 (5.7%)	**	**	**
TTGG	4 (5.7%)	2 (2.9%)	3 (4.3%)	0.7 (0.11–4.45)	2.5 (0.4–14.4)	3.5 (0.46–26.6)
TTGC	2 (2.9%)	6 (8.6%)	9 (12.9%)	4.28 (0.75–24.4)	15.00* (2.5–89.2)	3.5 (0.85–14.3)
TTCC	0 (0%)	0 (0%)	1 (1.4%)	**	**	**

HCC = hepatocellular carcinoma, OR = odds ratio, CI = confidence interval. *p = 0.001. **Underpowered for analysis.

The association between several SNPs in *XRCC1* (Arg194Trp, Arg280His and Arg399Gln) with the risk of HCC have been assessed in recent years [11,12,23–27]. However, the results are conflicting due to the diversity in cancer types, the source of cases, ethnicities and sample size. Kiran et al. (2009) demonstrated that Arg194Trp, Arg280His and Arg399Gln SNPs were associated with a higher risk for developing HCC on top of HCV infection in Indian patients. They found that Arg/Gln and Gln/Gln genotypes may increase the susceptibility for HCC among patients aged more than 50 years old [11]. However, it is contrary to the protective effect of Gln/Gln genotype reported by previous studies [25]. Pan et al. (2011) reported that the Arg399Gln Arg/Gln is associated with a higher risk for HCC, especially in those exceeding 50 years old or drinking alcohol in the Chinese population [12]. However, Liu et al. (2011) indicated that the Arg399Gln is not associated with increased risk of HCC [28].

The present study revealed that c.1254C>T *XRCC1* SNP showed a significantly higher frequency of CT, TT genotypes and T allele in HCC group more than control. Additionally, c.1517G>C showed a significantly higher frequency of GC and CC genotypes and C allele in HCC group more than control. These results agree with Bi et al. who reported that HCC risk increases significantly with T allele and TT genotype of the c.1254C>T variant; and C allele and CC genotype of the c.1517G>C variant of *XRCC1* [15]. Additionally, several studies report an association between *XRCC1* polymorphisms and a wide variety of cancers. Nissar et al. (2014) conclude that *XRCC1* polymorphic status has a role in the development of colorectal cancer [29]. Yu et al. [20] reported that *XRCC1* 399 Gln/Gln genotype may increase susceptibility to oesophageal squamous cell carcinoma especially in smokers [22]. The meta-analysis of Zhang et al. [30] on 53 individual studies on *XRCC1* Arg280His identified that increased cancer risk (including HCC) was statistically associated with the minor variant His allele and Arg-His/His-His genotypes both in the overall population and in both Caucasians and non-Caucasians. However, no significant difference between cancer types was detected [30].

There are some limitations to this study. The sample size was small, and further investigations and studies on greater population samples are necessary to confirm or refute our results. Prospective studies would be required to demonstrate this risk-based conclusion, e.g. looking at 5- or 10-year progression to HCC in Hep C-infected patients with different genotypes. Moreover, further studies are needed to investigate possible association of XRCC1 and HCV replication and to clarify the impact of genetic variations on HCV treatment and relapse. In recent years, several studies have been performed on genetic factors affecting the course of HCV infection and progression to HCC, such as Toll-like receptors [31,32], IL-28B [33], chemokines (CCL2 and CCL5 [34]) polymorphisms, nuclear phosphoprotein c-Myc and cellular phosphoprotein p53 [35]. Our data on *XRCC1* polymorphisms add to this body of work, and it may be that a combination of these SNPs provide a better perspective for the aetiology of these diseases.

Our data represent an advance in biomedical science in that it indicates that the T-allele of c.1254C>T (rs2293035) and the C allele of c.1517G>C (rs139599857) SNPs may be associated with increased HCC risk among chronic hepatitis C patients.

Summary table

What is known about this subject:
- The fact that not all HCV patients progress to HCC suggest that genetic variables may play key roles in the pathogenesis of HCC.
- Several studies have described possible links between SNPs in *XRCC1* and the risk of HCC.
- c.1254C>T and c.1517G>C genetic variants only reported to affect risk of HCC in Chinese patients.

What this paper adds:
- T-allele of c.1254C>T (rs2293035) and the C allele of c.1517G>C (rs139599857) genetic variants may be associated with increased HCC risk among chronic hepatitis C patients.

Informed consent

Written informed consent was obtained from patients who participated in this study.

Ethics committee approval

Ethics committee approval was received for this study from the Institutional Review Board of Mansoura Faculty of Medicine (Code number: MS/611; Decision Date: 17.06.2014).

Disclosure statement

No potential conflict of interest was reported by the authors.

ORCID

T Besheer http://orcid.org/0000-0002-0583-8860

References

[1] Lafaro KJ, Demirjian AN, Pawlik TM. Epidemiology of hepatocellular carcinoma. Surg Oncol Clin N Am. 2015;24:1–17.
[2] Gomaa AI, Khan SA, Toledano MB, et al. Hepatocellular carcinoma: epidemiology, risk factors and pathogenesis. World J Gastroenterol. 2008;14:4300.
[3] Thorgeirsson SS, Grisham JW. Molecular pathogenesis of human hepatocellular carcinoma. Nat Genet. 2002;31:339–346.
[4] Hagen TM, Huang S, Curnutte J, et al. Extensive oxidative DNA damage in hepatocytes of transgenic mice with chronic active hepatitis destined to develop hepatocellular carcinoma. Proc Natl Acad Sci U S A. 1994;91:12808–12812.
[5] Friedberg EC. DNA damage and repair. Nature. 2003;421:436–440.
[6] Friedberg EC. How nucleotide excision repair protects against cancer. Nat Rev Cancer. 2001;1:22–33.
[7] Wood RD, Mitchell M, Sgouros J, et al. Human DNA repair genes. Science. 2001;291:1284–1289.
[8] Masson M, Niedergang C, Schreiber V, et al. XRCC1 is specifically associated with poly (ADP-ribose) polymerase and negatively regulates its activity following DNA damage. Mol Cell Biol. 1998;18:3563–3571.
[9] Caldecott KW. XRCC1 and DNA strand break repair. DNA Repair. 2003;2:955–969.
[10] Kirk GD, Turner PC, Gong Y, et al. Hepatocellular carcinoma and polymorphisms in carcinogen-metabolizing and DNA repair enzymes in a population with aflatoxin exposure and hepatitis B virus endemicity. Cancer Epidemiol Biomarkers Prev. 2005;14:373–379.
[11] Kiran M, Saxena R, Chawla YK, et al. Polymorphism of DNA repair gene XRCC1 and hepatitis-related hepatocellular carcinoma risk in Indian population. Mol Cell Biochem. 2009;327:7–13.
[12] Pan H-Z, Liang J, Yu Z, et al. Polymorphism of DNA repair gene XRCC1 and hepatocellular carcinoma risk in Chinese population. Asian Pac J Cancer Prev. 2011;12:2947–2950.
[13] European Association for the Study of the Liver. EASL–EORTC clinical practice guidelines: management of hepatocellular carcinoma. J Hepatol. 2012;56:908–943.
[14] Yuan Z, Li J, Li J, et al. SNPs identification and its correlation analysis with milk somatic cell score in bovine MBL1 gene. Mol Biol Rep. 2013;40:7–12.
[15] Bi J, Zhong C, Li K, et al. Association study of single nucleotide polymorphisms in XRCC1 gene with risk of hepatocellular carcinoma in Chinese Han population. Biomed Res Int. 2013;2013:1–6.
[16] Abo El-khair S, Arafa M, Besheer T, et al. The association of XRCC1 gene polymorphisms and chronic hepatitis C induced insulin resistancein Egyptian Patients. Cells. 2018;7:185.
[17] Craxi A, Wedemeyer H, Bjoro K, et al.; European Association for the Study of the Liver. EASL clinical practice guidelines: management of hepatitis C virus infection. J Hepatol. 2011;55:245–264.
[18] Ferguson LR. Chronic inflammation and mutagenesis. Mutat Res. 2010;690:3–11.
[19] Thompson LH, Brookman KW, Jones NJ, et al. Molecular cloning of the human XRCC1 gene, which corrects defective DNA strand break repair and sister chromatid exchange. Mol Cell Biol. 1990;10:6160–6171.
[20] Basso D, Navaglia F, Fogar P, et al. DNA repair pathways and mitochondrial DNA mutations in gastrointestinal carcinogenesis. Clin Chim Acta. 2007;381:50–55.
[21] Tudek B. Base excision repair modulation as a risk factor for human cancers. Mol Aspects Med. 2007;28:258–275.
[22] Yu H-P, Zhang X-Y, Wang X-L, et al. DNA repair gene XRCC1 polymorphisms, smoking, and esophageal cancer risk. Cancer Detect Prev. 2004;28:194–199.
[23] Han X, Xing Q, Li Y, et al. Study on the DNA repair gene XRCC1 and XRCC3 polymorphism in prediction and prognosis of hepatocellular carcinoma risk. Hepato-gastroenterology. 2012;59:2285–2289.
[24] Rossit ARB, Cabral IR, Hackel C, et al. Polymorphisms in the DNA repair gene XRCC1 and susceptibility to alcoholic liver cirrhosis in older Southeastern Brazilians. Cancer Lett. 2002;180:173–182.
[25] Yu M-W, Yang S-Y, Pan I-J, et al. Polymorphisms in XRCC1 and glutathione S-transferase genes and hepatitis B–related hepatocellular carcinoma. J Natl Cancer Inst. 2003;95:1485–1488.
[26] Long XD, Ma Y, Huang HD, et al. Polymorphism of XRCC1 and the frequency of mutation in codon 249 of the p53 gene in hepatocellular carcinoma among Guangxi population, China. Mol Carcinog. 2008;47:295–300.
[27] Li Q-W, Lu C-R, Ye M, et al. Evaluation of DNA repair gene XRCC1 polymorphism in prediction and prognosis of hepatocellular carcinoma risk. Asian Pac J Cancer Prev. 2012;13:191–194.

[28] Liu F, Li B, Wei Y, et al. XRCC1 genetic polymorphism Arg399Gln and hepatocellular carcinoma risk: a meta-analysis. Liver Int. 2011;31:802–809.
[29] Nissar S, Sameer AS, Rasool R, et al. DNA repair gene-XRCC1 in relation to genome instability and role in colorectal carcinogenesis. Oncol Res Treat. 2014;37:418–422.
[30] Zhang K, Zhou B, Wang Y, et al. The XRCC1 Arg280His polymorphism contributes to cancer susceptibility: an update by meta-analysis of 53 individual studies. Gene. 2012;510:93–101.
[31] Sghaier I, Zidi S, Mouelhi L, et al. TLR3 and TLR4 SNP variants in the liver disease resulting from hepatitis B virus and hepatitis C virus infection. Br J Biomed Sci. 2019;76:35–41.
[32] El-Bendary M, Neamatallah M, Elalfy H, et al. The association of single nucleotide polymorphisms of Toll-like receptor 3, Toll-like receptor 7 and Toll-like receptor 8 genes with the susceptibility to HCV infection. Br J Biomed Sci. 2018;75:175–181.
[33] Attallah A, Omran D, Marie M, et al. IL-28B rs12979860 polymorphism affect the course of chronic hepatitis and the development of HCC in Egyptian patients with hepatitis C type 4. Br J Biomed Sci. 2018;75:157–162.
[34] El-Bendary M, Neamatallah M, Elalfy H, et al. Association of genetic polymorphisms of chemokines and their receptors with clearance or persistence of hepatitis C virus infection. Br J Biomed Sci. 2019;76:11–16.
[35] Attallah A, El-Far M, Abdelrazek M, et al. Combined use of nuclear phosphoprotein c-Myc and cellular phosphoprotein p53 for hepatocellular carcinoma detection in high-risk chronic hepatitis C patients. Br J Biomed Sci. 2017;74:170–175.