Int J Clin Exp Pathol 2015;8(10):12949-12954
www.ijcep.com /ISSN:1936-2625/IJCEP0014059

Original Article

A meta-analysis of xeroderma pigmentosum gene D Ls751Gln polymorphism and susceptibility to hepatocellular carcinoma

Yu Wang[1], Yingren Zhao[2], Aiyun Zhang[3], Juan Ma[3], Zhenzhen Wang[3], Xu Zhang[3]

[1]Department of Infectious Diseases, Xi'an Jiaotong University School of Medicine, General Hospital of Ningxia Medical University, Yinchuan 750004, Ningxia, China; [2]Department of Infectious Diseases, First Affiliated Hospital of Xi'an Jiaotong University School of Medicine, Xi'an 710061, Shanxi, China; [3]Department of Infectious Diseases, Infectious Disease Department of General Hospital of Ningxia Medical University, Yinchuan 750004, Ningxia, China

Received August 6, 2015; Accepted September 25, 2015; Epub October 1, 2015; Published October 15, 2015

Abstract: Hepatocellular carcinoma (HCC) is one of most common malignant tumors worldwide, but with unclear mechanisms. Xeroderma pigmentosum gene D (XPD) is one important DNA damage repair gene and can be involved in protein mutation. Currently little has been known about XPD polymorphism and HCC susceptibility in Chinese people. This study used a meta-analysis approach to comprehensively investigate the correlation between XPD polymorphism and HCC susceptibility in Chinese population, based on previously published literatures. A computer retrieval system was used to collect all case-control studies about XPD Lys751Gln polymorphism and HCC susceptibility. Data in literatures were extracted for meta-analysis. After the primary screening, four independent studies, which were published in 3 English articles and one Chinese article, were recruited in this study. There were 1,717 samples included in all studies. Using Gln/Gln + Lys/Gln, Lys/Lys + Lys/Gln and Lys allels as the reference, HCC disease alleles including Lys/Lys, Gln/Gln and Gln had OR values (95% CI, I^2) of 1.007 (0.657~4.672, 91%), 3.516 (0.220~20.661, 48%) and 3.225 (0.278~12.326, 84%), respectively. The polymorphism of XPD751 loci is closely correlated with primary HCC. Lys751Gln polymorphism of XPD gene can be used as one susceptibility factor for HCC.

Keywords: Xeroderma pigmentosum gene D, Lys715Gln, gene polymorphism, hepatocellular carcinoma, meta-analysis

Introduction

Hepatocellular carcinoma (HCC) is one common malignant tumor, especially in China, where about 42.5% of all liver cancer cases worldwide occurs in each year [1, 2]. The pathogenesis of HCC is a complicated process involving multiple genetic and environmental factors that have not been fully illustrated yet. As one important body defense mechanism, DNA repair may contribute to the susceptibility of HCC via mediating DNA repair and damage of liver cells. Xeroderma pigmentosum gene D (XPD) is one of DNA repair genes for the formation of DNA repair signaling pathway. The mutation of XPD may alter the ability of DNA repair, leading to HCC occurrence [3]. Currently there have been reports regarding the polymorphism of XPD Lys751Gln and tumor susceptibility [4, 5]. These studies, however, mainly focused one pulmonary or head/neck tumors. The correlation between XPD Lys751Gln gene polymorphism and HCC susceptibility has been reported but with relatively smaller size and poor consistency, in addition to the insufficient focus on Chinese population. This study thus performed a meta-analysis on those literatures fitting inclusive criteria, and investigated the correlation between XPD Lys751Gln gene polymorphism and HCC incidence of Chinese people via a case-control study approach.

Materials and methods

Literature sources

Inclusive criteria: (1) With complete clinical data, including distribution of genotype frequencies along with related statistical data. (2) All were performed in a case-control manner with consistent baseline and were thus compa-

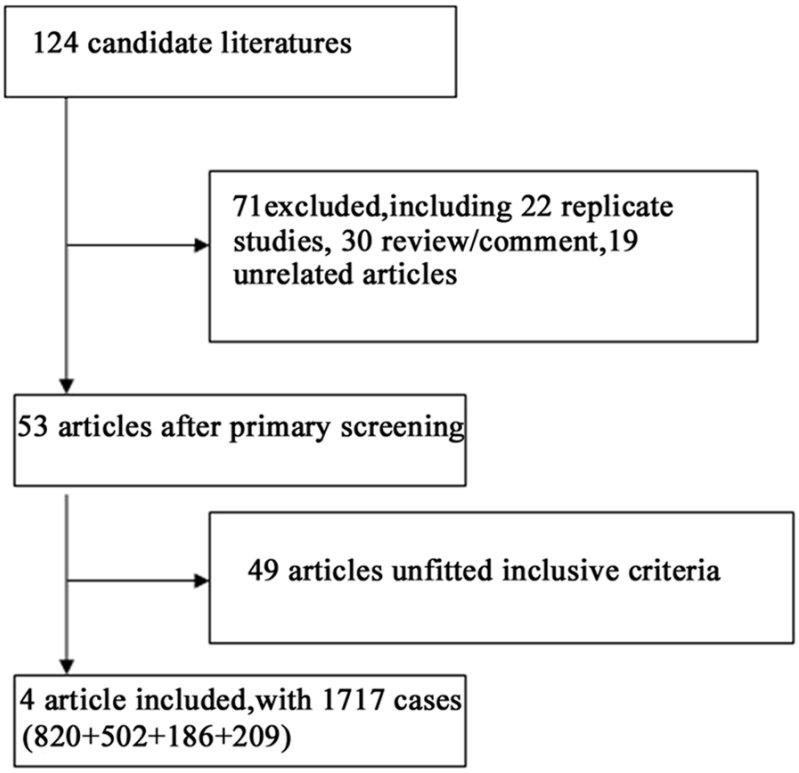

Figure 1. Flow chart of literature screening.

rable. (3) Published research articles between January 2004 and December 2014. (4) The most updated report was selected for replicated studies.

Exclusive criteria: (1) Incomplete data, incomprehensive research contents or objects, or replicated studies. (2) Small-scale study based on single family or local areas; (3) Review article or articles with only abstract accessible.

Literature retrieval

We used computer software to search both Chinese and English medical databases including PubMed, Medline, EmBase, Cochrane, CMBdisc, CNKI, Wanfang and Weipu database between January 2004 and December 2014. Literature retrieval was assisted by manual search. Keywords used in searches included: *Xeroderma pigmentosum group D gene (XPD), genotype, Lys751Gln, polymorphism, hepatocellular carcinoma (HCC)* and *Chinese*.

Data extraction

Two independent researches were responsible for literature selection. Primary screening was performed according to the inclusive/exclusive criteria after reading the abstract and main text of all articles. Inconsistency opinion or uncertainly can be resolved by a third party. Critical points for data extraction included: study background; general information of research objects; comparability of baseline levels and completeness of test parameters.

Statistical analysis

RevMan 5.0 software was used to process all collected data. Heterogeneity test was firstly performed on all included data. Enumeration data were analyzed by OR and 95% CI. A statistical significance was defined when $P<0.05$. The heterogeneity was firstly determined by I^2 value and chi-square test with a significant level $\alpha=0.1$. The rejection of statistical heterogeneity was defined when $P>0.1$ and $I^2<0.5$. Under such circumstances a meta-analysis with fixed effect model was adopted. Those data with statistical heterogeneity were further analyzed for the sources of heterogeneity: those from clinical uncertainly of heterogeneity can be analyzed by random effect model. Otherwise, only descriptive studies were performed.

Results

Inclusive criteria

On-line search of databases obtained 124 related articles. After primary screening by abstract reading, 71 articles with review-nature or unrelated research objects were firstly screened out. The remaining 53 clinical studies were further examined according to the exclusive/inclusive criteria, and leaving only 4 studies, including 3 English articles and 1 Chinese articles. The flow chart of literature inclusion was shown in **Figure 1**, with a list of included literatures in **Table 1**.

Table 1. List of included articles

Author	Approach	Control	P_{HWE}	Disease group (N)			Control group (N)		
				Lys/Lys	Lys/Gln	Gln/Gln	Lys/Lys	Lys/Gln	Gln/Gln
Guo LY et al [6]	PCR-CTPP	HB	0.124	352	30	28	361	37	12
Yuan T et al [7]	PCR-CTPP	HB	0.344	186	29	37	174	65	11
Zhang JJ et al [8]	PCR-CTPP	HB	1.250	58	17	18	64	20	9
Xu L et al [9]	PCR-CTPP	HB	0.135	57	15	0	125	10	2

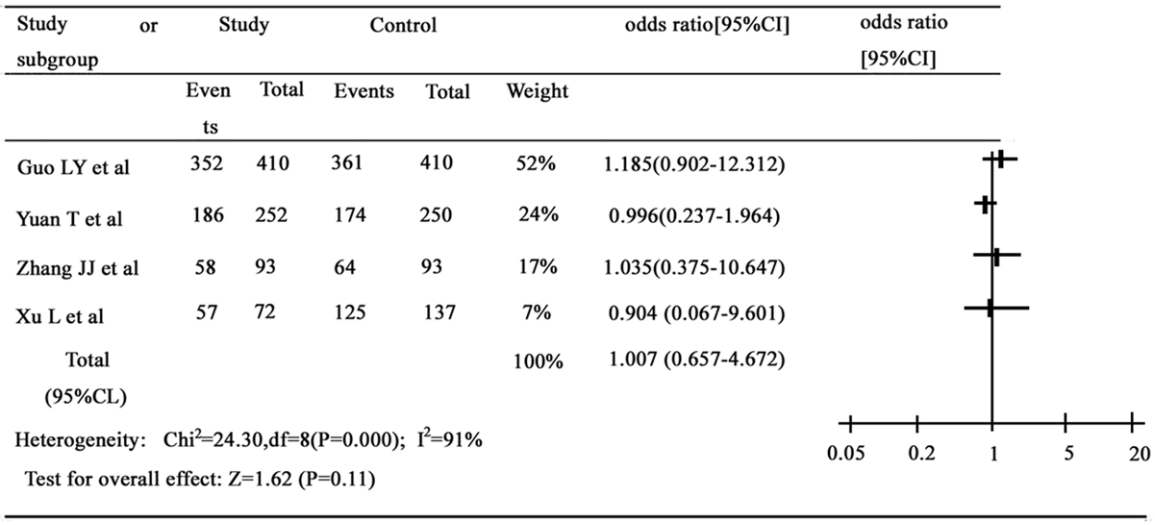

Figure 2. A forest plot between XPD751 polymorphism and HCC susceptibility (Lys/Lys against Gln/Gln + Lys/Gln).

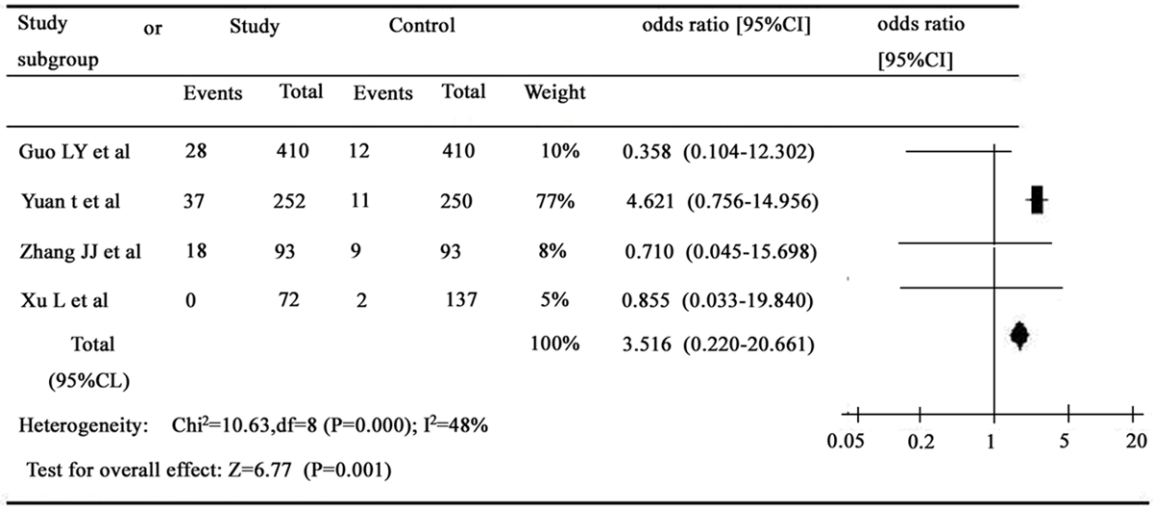

Figure 3. A forest plot between XPD751 polymorphism and HCC susceptibility (Gln/Gln against Lys/Lys + Lys/Gln).

Meta-analysis between XPD751 gene polymorphism and HCC susceptibility

Model analysis data suggested the OR values and 95% CI of Lys/Lys carriers using Gln/Gln + Lys/Gln as the control group, were 1.007 and 0.657~4.672, respectively (**Figure 2**), Using Lys/Lys + Lys/Gln genotype as the baseline, Gln/Gln carriers had OR value and 95% CI at 3.516 and 0.220~20.661, respectively (**Figure**

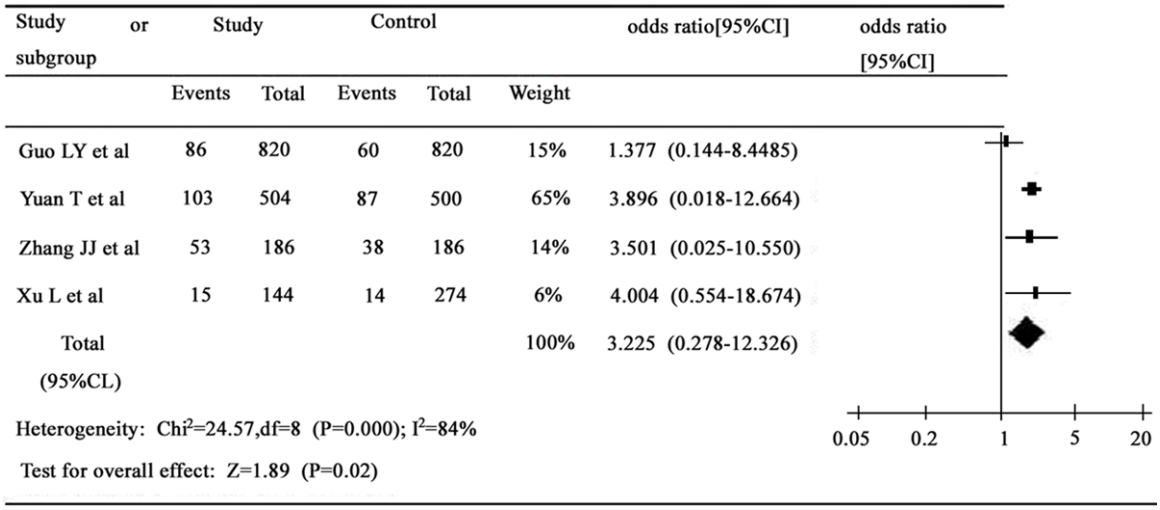

Figure 4. A forest plot between XPD751 polymorphism and HCC susceptibility (Gln allele against Lys allele).

3). Using Lys allele as the reference, we found OR vaues and 95% CI of Gln allele carriers suffering by HCC at 3.225 and 0.278~12.326, respectively (**Figure 4**).

Discussion

As one common and severe malignant tumor, HCC has a relatively higher incidence and mortality rate in China. It has been estimated that more than 120 thousands people in China died from HCC, occupying about 45.4% of total mortality by HCC worldwide [10, 11]. There were seven xeroderma pigmentosum related complementation gene families (XPA~XPG), plus one mutant form related with DNA mismatching repair. All complementation genes were DNA-repair related genes and are involved in the process of nucleotide excision repair (NER). The correlation between XPD gene polymorphism and tumor pathogenesis is one research hotspot in recent years. As on important DNA damage repair gene, XPD encodes for proteins via participating DNA repair pathway and mutation. Most of DNA damage repair genes have single nucleotide polymorphism (SNP), which endows differential abilities for repairing DNA damages, leading to chromosome instability and tumor transformation of normal cells. XPD codes for one ATP-dependent DNA helicase with pluripotent DNA repair functions. This gene is localized in 19q13.2-19q13.3 region of human chromosome and includes 23 exons and introns with highly-conserved AG/GT sequence at the binding sites [12-14]. XPD has known to be involved in p53-induced cell apoptosis, in addition to NER. Currently, there have been lots of studies reporting the XPD gene polymorphism and tumor susceptibility. Six out of twenty-three exons of XPD gene have SNP at loci 199, 201, 312 and 751, leading to abnormal protein translation with the occurrence rate as high as 45% (for loci 312 and 751) [15-17]. Therefore, current studies about XPD gene polymorphism mainly focus on loci 312 and 751. Some reports have suggested the impaired NER abilities with mutant homogenous or heterogeneous (Gln/Gln and Lys/Gln genotype) in XPD-751 carriers [18, 19].

There have been increasing studies about XPD-751 Lys/Gln polymorphism and tumor susceptibility. Due to potential interference from regional, ethical and sample size differences, we performed a meta-analysis to investigate the correlation. A total of 1,717 Chinese objects were included in this study. After meta-analysis, we found that the OR and 95% CI of suffering from HCC in Lys/Lys genotype carriers, with reference to Gln/Gln + Lys/Gln genotypes, were 1.007 and 0.657~4.672, respectively, suggesting that Lys/Lys carriers had 1.007 fold of HCC susceptibility compared to Gln/Gln + Lys/Gln carriers (I^2=91%). Using Lys/Lys + Lys/Gln genotype as the baseline, OR and 95% CI values of Gln/Gln individuals were 3.516 and 0.220~20.661, respectively. This result indicated a 3.516-fold risk of HCC in Gln/Gln individuals against Lys/Lys + Lys/Gln carriers (I^2=48%). Furthermore, meta-analysis revealed OR and

95% CI values of HCC in Gln allele individuals against Lys allele carriers were 3.225 and 0.278~12.326, respectively. Therefore the risk of HCC in Gln allele carriers was 3.225 fold of that in Lys allele carriers (I^2=84%). These results collectively suggest the potential role of XPD-751 Lys/Lys as the protective genotype against HCC in Chinese population, while XPD-751 Gln/Gln might be one HCC-susceptible genotype. Therefore, a close relationship exists between XPD-751 SNP and primary HCC, as XPD Lys751Gln is potentially one inherent susceptibility factor for primary HCC. The major determination factor of inherent susceptibility is genetic variability [20-22], which is mainly manifested with SNP leading to differential biological activities of protein products [23]. These diversity leads to variable susceptibility of the body to the same carcinogen. In summary, this study demonstrated the close relationship between XPD751 gene polymorphism and primary liver cancer, and the potency of XPD Lys751Gln polymorphism as one factor governing inherent HCC susceptibility.

Certain limitations, however, existed in the current study as: (1) Only Chinese and English literature database were included, thus artificially narrowing the study scale; (2) Different TNM stages and backgrounds of HCC patients were included in this study, compromising the reliability; (3) The lack of gene-environment and gene-to-gene interaction analysis due to insufficient original data. As a future perspective, more comprehensive studies about XPD751 gene polymorphism and HCC require larger sample size and optimized design. These studies may provide novel and effective strategies for HCC prevention and treatment in future.

Acknowledgements

Study on relationship between rate of telbivudine on chronic hepatitis B andhumoral immunity in patients with diabetes mellitus and creatinine clearance (Ningxia Natural Science Foundation, NZ14154); Study on the effect of telbivudine on cellular immune function in patients withHBeAg positive chronic hepatitis B response (Natural Science Foundation of Ningxia NZ10118).

Disclosure of conflict of interest

None.

Address correspondence to: Yingren Zhao, Department of Infectious Diseases, First Affiliated Hospital of Xi'an Jiaotong University School of Medicine, Infectious Diseases Division, No. 227, Yanta Road, Shanxi 710061, Xi'an, China. Tel: +86-029-85323112; Fax: +86-029-85323112; E-mail: zhyingren@126.com

References

[1] Yue AM, Xie ZB, Guo SP, Wei QD, Yang XW. Implication of polymorphisms in DNA repair genes in prognosis of hepatocellular carcinoma. Asian Pac J Cancer Prev 2013; 14: 355-8.

[2] Capone F, Guerriero E, Colonna G, Maio P, Mangia A, Marfella R, Paolisso G, Izzo F, Potenza N, Tomeo L, Castello G, Costantini S. The Cytokinome Profile in Patients with Hepatocellular Carcinoma and Type 2 Diabetes. PLoS One 2015; 10: e0134594.

[3] Zeng XY, Qiu XQ, Ji L, Yu HP. [Study on the relationship between hepatocellular carcinoma and the interaction between polymorphisms in DNA repair gene XPD and environmental factors]. Zhonghua Liu Xing Bing Xue Za Zhi 2009; 30: 702-5.

[4] Gong WF. XPD 751 common digestive system tumor susceptibility gene polymorphism and Meta analysis. Nanning: guangxi medical university; 2013. pp. 40-43.

[5] Radwan WM, Elbarbary HS and Alsheikh NM. DNA repair genes XPD and XRCC1 polymorphisms and risk of end-stage renal disease in Egyptian population. Ren Fail 2015; 37: 122-8.

[6] Guo LY, Jin XP, Niu W, Li XF, Liu BH, Wang YL. Association of XPD and XRCC1 genetic polymorphisms with hepatocellular carcinoma risk. Asian Pac J Cancer Prev 2012; 13: 4423-6.

[7] Yuan T, Deng S, Liu H, Liu M, Chen P. Relationship between XRCC1 and XPD polymorphisms and the risk of the development of hepatocellular carcinoma: A case-control study. Exp Ther Med 2012; 4: 285-290.

[8] Zhang JJ and Ma JZ. [Association of the xeroderma pigmentosum group D DNA repair gene with hepatocellular carcinoma]. Zhonghua Gan Zang Bing Za Zhi 2012; 20: 683-7.

[9] Xu L, Wu Y and Jin Y. DNA repair gene XPD polymorphism and HCC risk of cases in a controlled study. Cancer 2004; 24: 526-529.

[10] Peng Q, Li S, Lao X, Chen Z, Li R, Qin X. Association between XPD Lys751Gln and Asp312-Asn polymorphisms and hepatocellular carcinoma risk: a systematic review and meta-analysis. Medicine (Baltimore) 2014; 93: e330.

[11] Schlachterman A, Craft WW Jr, Hilgenfeldt E, Mitra A, Cabrera R. Current and future treatments for hepatocellular carcinoma. World J Gastroenterol 2015; 21: 8478-91.

[12] Liu CY, Yang JS, Huang SM, Chiang JH, Chen MH, Huang LJ, Ha HY, Fushiya S, Kuo SC. Smh-3 induces G(2)/M arrest and apoptosis through calciummediated endoplasmic reticulum stress and mitochondrial signaling in human hepatocellular carcinoma Hep3B cells. Oncol Rep 2013; 29: 751-62.
[13] Sinn DH, Choi MS, Gwak GY, Paik YH, Lee JH, Koh KC, Paik SW, Yoo BC. Pre-s mutation is a significant risk factor for hepatocellular carcinoma development: a long-term retrospective cohort study. Dig Dis Sci 2013; 58: 751-8.
[14] Yeh ML, Huang CI, Huang CF, Hsieh MY, Huang JF, Dai CY, Lin ZY, Chen SC, Yu ML, Chuang WL. Neoadjuvant transcatheter arterial chemoembolization does not provide survival benefit compared to curative therapy alone in single hepatocellular carcinoma. Kaohsiung J Med Sci 2015; 31: 77-82.
[15] Li L, Khan MN, Li Q, Chen X, Wei J, Wang B, Cheng JW, Gordon JR. Li F G31P, CXCR1/2 inhibitor, with cisplatin inhibits the growth of mice hepatocellular carcinoma and mitigates highdose cisplatin-induced nephrotoxicity. Oncol Rep 2015; 33: 751-7.
[16] Bruix J and Colombo M. Hepatocellular carcinoma: current state of the art in diagnosis and treatment. Best Pract Res Clin Gastroenterol 2014; 28: 751.
[17] Dubbelboer IR, Lilienberg E, Ahnfelt E, Sjögren E, Axén N, Lennernäs H. Treatment of intermediate stage hepatocellular carcinoma: a review of intrahepatic doxorubicin drug-delivery systems. Ther Deliv 2014; 5: 447-66.
[18] Wu J, Xu X and Liu X. Xeroderma base skin pigmentation D polymorphism and dimethyl formamide relationship susceptibility to liver function injury. China Industrial Medical Journal 2013; 26: 436-438.
[19] Cui X and Su G. XPD gene polymorphism and the risk of primary liver cancer case-control study. Journal of the National Medicine 2010; 22: 912-915.
[20] Jaitovich-Groisman I, Benlimame N, Slagle BL, Perez MH, Alpert L, Song DJ, Fotouhi-Ardakani N, Galipeau J, Alaoui-Jamali MA. Transcriptional regulation of the TFIIH transcription repair components XPB and XPD by the hepatitis B virus x protein in liver cells and transgenic liver tissue. J Biol Chem 2001; 276: 14124-32.
[21] Vashisht AA, Yu CC, Sharma T, Ro K, Wohlschlegel JA. The Association of the Xeroderma Pigmentosum Group D DNA Helicase (XPD) with Transcription Factor IIH Is Regulated by the Cytosolic Iron-Sulfur Cluster Assembly Pathway. J Biol Chem 2015; 290: 14218-25.
[22] Zhao JH, Li H and Di J. [Relation of polymorphisms of the XPD and GSTM1 genes with susceptibility to hepatocellular carcinoma in Qinghai Tibetans]. Zhonghua Gan Zang Bing Za Zhi 2014; 22: 831-6.
[23] Yang R, Zhang C, Malik A, Shen ZD, Hu J, Wu YH. Xeroderma pigmentosum group D polymorphisms and esophageal cancer susceptibility: a meta-analysis based on case-control studies. World J Gastroenterol 2014; 20: 16765-73.