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RESEARCH ARTICLE

The relationship between five non-synonymous polymorphisms within three *XRCC* genes and gastric cancer risk in a Han Chinese population

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Abstract We aimed to assess the association of five non-synonymous polymorphisms within three X-ray repair cross-complementing group (*XRCC*) genes with gastric cancer risk in Han Chinese. Genotyping was determined in 693 gastric cancer patients and 681 healthy controls. Statistical analyses were completed with SPSS (version 20.0) and Haplo.stats (version 1.6.11). The genotypes of *XRCC1* gene rs25487 polymorphism (P=0.003) differed significantly between patients and controls, even after the Bonferroni correction (P<0.05/5), and this polymorphism was significantly associated with gastric cancer after adjusting for age, sex, body mass index, smoking, drinking, especially under a dominant model (odds ratio or OR; 95 % confidence interval or CI; P 1.59; 1.20–2.00; 0.001). In multiple-marker analysis, the most common allele combination was C-G-G-G-C (alleles in order of rs1799782, rs25489, rs25487, rs3218536, rs861539), which was overrepresented in controls relative to patients (adjusted simulated P=0.0001). Contrastingly, the frequency of allele combination C-G-A-G-C was significantly higher in patients than in controls (adjusted simulated P=0.0009), and this combination was associated with a strikingly increased risk of gastric cancer (OR; 95 % CI; P 2.39; 1.32–4.31; 0.0040) after the Bonferroni correction (P<0.05/11) and adjusting for confounders. Our findings demonstrated that *XRCC1* gene rs25487 polymorphism might play a leading role in pronounced susceptibility to gastric cancer in Han Chinese.

Keywords Gastric cancer · DNA repair system · X-ray repair cross-complementing group · Polymorphism · Case-control association study

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Introduction

Deoxyribonucleic acid (DNA) of a normal cell is vulnerable to internal and external damage, leaving the cell the choice of repairing the damage or dying [1, 2]. DNA repair is essential to restore lost information, maintain genetic integrity, and guard against the entry of normal cells into carcinogenesis. There is a wide recognition that defects in DNA repair system can underlie cancer. Indeed, as human genomes are sequenced and refined, multiple DNA mutations implying abnormal DNA repair are continuing to surface [3, 4]. Therefore, understanding the genetic underpinnings of DNA repair system might open a new window to unravel the pathogenesis of cancer.

X-ray repair cross-complementing group (XRCC) is the family of DNA repair genes that are responsible for the repair of DNA base damage and single-strand breaks [5]. The genes coding XRCC family members are polymorphic and several non-synonymous polymorphisms, such as Arg194Trp,

Arg280His, Arg399Gln in the *XRCC1* gene, Arg188His in the *XRCC2* gene, and Thr241Met in the *XRCC3* gene, have been well-characterized as promising genetic biomarkers for carcinogenesis [6–10]. In view of obvious tumor heterogeneity, we in this study sought to assess the association of the above five non-synonymous polymorphisms with the risk of having gastric cancer in a Han Chinese population. Gastric cancer is established as a polygenic disease and it seems unlikely that individual polymorphisms will make a major contribution to risk prediction [11]. To yield more information, we therefore conducted additional combined genetic analyses for these five polymorphisms to enhance their predictive capability for gastric cancer.

Materials and methods

Study population

In this study, all subjects were recruited from the Gastric and Intestine Department, Yantai Affiliated Hospital of Binzhou Medical University between February 2013 and September 2014. They were reported to be unrelated Han Chinese. This study was approved by the ethics committee of Binzhou Medical University with the protocols consistent with the Declaration of Helsinki Principles. All study subjects completed written informed consent prior to enrollment. In total, 1374 subjects were genotyped in this study, and 693 of them were diagnosed as sporadic gastric cancer patients according to medical history, gastroscopic examination, or computed tomography scanning by experienced surgeons. Patients were excluded if they had gastric cancer of unknown primary source, and if they had a family history of gastric cancer in first-degree relatives. The remaining 681 subjects, who had no clinical evidence of gastric cancer and had no family history of all cancer sites except skin within three generations, formed the control group. The controls were frequency matched with the patients on age and sex.

Baseline characteristics

A bespoke questionnaire was used to collect baseline information of study subjects at the time of enrollment, including age (onset age for patients with gastric cancer and age at enrollment for healthy controls), gender, body weight and height, smoking and drinking habits, and a family history of all cancer sites. Body mass index (BMI) was expressed as body weight in kilograms divided by body height in meters squared. Smoking status was categorized into never smokers and ever smokers (including current and former smokers). Similarly, drinking status was categorized into never drinkers and ever drinkers (including current and former drinkers). After enrollment, 3–5 ml venous blood was extracted from each subject for genomic DNA extraction and mass genotyping.

Genotype determination

Genomic DNA preparations were carried out from 1 ml venous blood with TIANamp Blood DNA Kit (Tiangen Biotect Beijing Co., Beijing, China) according to the manufacturer's instructions. Genotypes of five examined polymorphisms in *XRCC* genes were determined by ligase detection reaction (LDR) method [12]. All study samples have been successfully genotyped for five examined polymorphisms in this study. In detail, two specific probes were designed and synthesized to make a distinction between wild and mutant bases. Firstly, multiplex ligation reaction was performed in a 10-ml reaction volume, including 2 μl of polymerase chain reaction product, 1 μl 10×Taq DNA ligase buffer, 1 μM of each discriminating probe, and 5 U Taq DNA ligase. Secondly, 1 μl multiplex ligation reaction product was mixed with 1 μl ROX passive reference and 1 μl loading buffer (with marker), and then denatured at 95 °C for 3 min and chilled rapidly in ice. Thirdly, the fluorescent LDR products were discriminated with ABI 3730XL sequencer (Applied Biosystems, USA).

Statistical analysis

Comparisons of baseline characteristics and genetic distributions between gastric cancer patients and controls were conducted by unpaired *t* test and Pearson χ^2 test where appropriate. Hardy-Weinberg equilibrium was tested in the control group by Pearson χ^2 test. Each polymorphism was assessed under assumption of additive, dominant, and recessive models for risk prediction of gastric cancer, and effect estimates were expressed as odds ratio (OR) and its 95 % confidence interval (CI) after adjusting for age, sex, BMI, smoking, and drinking in logistic regression analysis. The above statistical analyses were conducted by IBM SPSS Statistics version 20.0. Allele combination frequencies of five examined polymorphisms were estimated by Haploview version 4.2 [13], and their risk prediction for gastric cancer was computed by Haplo.stats version 1.6.11. Unless otherwise indicated, the significance level was set at 5 %. Multiple comparisons were controlled by the Bonferroni method. Statistical power was estimated using the Power and Sample Size Calculations (PS) software version 3.0.

eQTL analysis

The potential functional impact of significant polymorphism on the expression of its coding gene was explored by expression quantitative trait loci (eQTL) method with the Genevar (HapMap3) database available at the website "http://www.sanger.ac.uk/resources/software/genevar/" [14].

Results

Baseline characteristics

Table 1 compares baseline characteristics between gastric cancer patients and controls. The mean levels of age (P=0.135) and male gender (P=0.547) were comparable between the two groups. BMI was slightly higher in patients than in controls (P=0.013). The percentage of ever smokers was significantly higher in patients than in controls, while that of ever drinkers was lower (both P<0.0001).

Single-marker association analysis

At a 5 % test criterion, none of the genotypes of the five examined polymorphisms deviated from the Hardy-Weinberg expectations in the controls. Table 2 provides the genotype and allele distributions of all polymorphisms between gastric cancer patients and controls. The genotypes of the *XRCC1* gene rs25489 (P=0.032) and rs25487 (P=0.003) polymorphisms differed significantly between the two groups, whereas only rs25487 survived the Bonferroni correction (P<0.05/5, here 5 denotes the total number of all examined polymorphisms). As for allele distributions, only rs25487 exhibited statistical significance, but remained nonsignificant after the Bonferroni correction. The statistical power to detect significant allele difference of rs24587 polymorphism between patients and controls was estimated to be 93.5 % at an alpha of 0.05. None of the other genotype and allele comparisons were significant at a level of 5 % for the other polymorphisms (all P>0.05).

The risk prediction of five examined polymorphisms within three *XRCC* genes is summarized in Table 3 before and after adjusting for confounding factors. After the Bonferroni correction (P<0.05/15, here 15 is the product of total number of examined polymorphisms and total number of genetic models), only rs25487 was significantly associated with the risk of having gastric cancer under both additive and dominant models, even after adjusting for age, sex, BMI, smoking, and drinking. For instance, carriers of the mutant allele of rs25487 were 1.59 times more likely to have gastric cancer than the wild homozygotes (95 % CI 1.20–2.00; P=0.001) after adjusting for the abovementioned confounders. No significance was observed for the other polymorphisms.

Table 1 Baseline characteristics of study population

Characteristics	Patients (n=693)	Controls (n=681)	P
Age (years)	59.11±9.99	59.89±9.27	0.135
Gender			
Female	403 (59.18 %)	278 (40.82 %)	0.547
Male	399 (57.58 %)	1174 (77.44 %)	
BMI (kg/m^2)	26.40±6.64	25.40±5.22	0.013
Smoking			
Ever smokers	224 (32.32 %)	149 (21.88 %)	<0.0001
Never smokers	469 (67.68 %)	532 (78.12 %)	
Drinking			
Ever drinkers	147 (21.21 %)	209 (30.74 %)	<0.0001
Never drinkers	546 (78.79 %)	471 (69.26 %)	

BMI body mass index

Multiple-marker association analysis

To test whether all examined polymorphisms act in a dose-dependent manner, a panel of allele combinations were constructed and compared between gastric cancer patients and controls (Table 4). To derive a reliable estimate, analysis was only restricted to the allele combination with an estimated frequency of at least 1 % among all subjects. The most common allele combination was C-G-G-G-C (alleles in order of rs1799782, rs25489, rs25487, rs3218536, and rs861539), which was overrepresented in controls (50.14 %) relative to patients (42.68 %, adjusted simulated P=0.0001), and the statistical power to detect this difference was 97.5 %. By contrast, the frequency of allele combination C-G-A-G-C was significantly higher in patients than in controls (5.07 versus 2.40 %, adjusted simulated P=0.0009) with statistical power of 95.9 %. There was no significance for the rest of the nine derived allele combinations. Moreover, selecting the most common allele combination as a reference group, only allele combination C-G-A-G-C showed significant association with gastric cancer before (OR=2.54; 95 % CI 1.53–4.21; P=0.0003) and after (OR=2.39; 95 % CI 1.32–4.31; P=0.0040) adjusting for confounding factors, even after the Bonferroni correction (P<0.05/11, here 11 is the total number of qualified allele combinations) (Table 4).

Polymorphism-gene expression analysis

The potential functional impact of polymorphism rs25487 on the *XRCC1* gene expression is presented in Fig. 1. This polymorphism was observed to be marginally associated with different expression profiles of the *XRCC1* gene in lymphoblastoid cell lines (permutated P=0.0713).

Discussion

In this candidate gene association study, we examined the contribution of five non-synonymous polymorphisms within three *XRCC* genes, both individually and in combination, to the risk of having gastric cancer in a Han Chinese population. The key finding of the present study was the leading role conferred by *XRCC1* gene rs25487 polymorphism in pronounced susceptibility to gastric cancer. To the authors'

Table 2 Genotype and allele distributions of five examined polymorphisms between gastric cancer patients and controls

Polymorphisms	Groups	Genotypes				Alleles	
XRCC1: rs1799782		CC	CT	TT	P	T	P
Arg194Trp (C>T)	Patients	210 (30.30 %)	362 (52.24 %)	121 (17.46 %)	0.337	43.58 %	0.155
	Controls	227 (33.33 %)	351 (51.54 %)	103 (15.12 %)		40.90 %	
XRCC1: rs25489		GG	GA	AA	P	A	P
Arg280His (G>A)	Patients	468 (67.53 %)	203 (29.29 %)	22 (3.17 %)	0.032	17.82 %	0.072
	Controls	481 (70.63 %)	191 (28.19 %)	8 (1.17 %)		15.22 %	
XRCC1: rs25487		GG	GA	AA	P	A	P
Arg399Gln (G>A)	Patients	337 (48.63 %)	287 (41.41 %)	69 (9.96 %)	0.003	30.66 %	0.021
	Controls	389 (57.12 %)	247 (36.27 %)	45 (6.61 %)		24.74 %	
XRCC2: rs3218536		GG	GA	AA	P	A	P
Arg188His (G>A)	Patients	590 (85.14 %)	98 (14.14 %)	5 (0.72 %)	0.436	7.79 %	0.301
	Controls	564 (82.82 %)	113 (16.59 %)	4 (0.59 %)		8.88 %	
XRCC3: rs861539		CC	CT	TT	P	T	P
Thr241Met (C>T)	Patients	605 (87.30 %)	85 (12.27 %)	3 (0.43 %)	0.750	6.57 %	0.903
	Controls	595 (87.37 %)	81 (11.89 %)	5 (0.73 %)		6.68 %	

knowledge, this is the first report to explore the association of multiple *XRCC* genes and polymorphisms with gastric cancer risk in the literature.

The majority of previous studies focused on only one gene within the XRCC family, while disregarding other genes and overlooking potential joint impact of multiple genes on gastric cancer [15–17]. As the development of gastric cancer is a complex biological process involving multiple physiological pathways and multiple gene products [18, 19], it is reasonably expected that multiple genetic polymorphisms render individuals susceptible or resistant to gastric cancer. To fill this knowledge gap, we in the present study aimed to test whether five non-synonymous polymorphisms within three *XRCC* genes act individually or together in the pathogenesis of gastric cancer.

Our single-marker analysis revealed that only one polymorphism, rs25487 (Arg399Gln), in the *XRCC1* gene was significantly associated with the risk for gastric cancer, even after the Bonferroni correction and adjusting for confounding factors, arguing against the results of several previous meta-analyses that failed to detect any relationship between rs25487 polymorphism and gastric cancer, as well as its cardia type [5, 20, 21]. By contrast, two recent large-scale meta-analyses suggested that this polymorphism might be a prognostic biomarker for gastric cancer patients treated with platinum and oxaliplatin-based chemotherapy [22, 23]. The above observations prompted us to speculate that the *XRCC1* gene rs25487 polymorphism might be associated with the progression and severity of gastric cancer. In addition, we employed the Genevar (HapMap3) database to assess the potential

Table 3 Risk prediction of the five examined polymorphisms for gastric cancer

Polymorphisms	Additive model	Dominant model	Recessive model
Before adjustment			
rs1799782	1.12; 0.96–1.32; 0.142	1.15; 0.92–1.44; 0.228	1.19; 0.89–1.58; 0.242
rs25489	1.21; 0.99–1.49; 0.067	1.16; 0.92–1.45; 0.214	2.76; 1.22–6.24; 0.015
rs25487	1.34; 1.13–1.58; 0.001	1.41; 1.14–1.74; 0.002	1.56; 1.06–2.31; 0.025
rs3218536	0.87; 0.66–1.14; 0.300	0.84; 0.63–1.12; 0.242	1.23; 0.33–4.60; 0.758
rs861539	0.98; 0.73–1.32; 0.904	1.01; 0.73–1.38; 0.969	0.59; 0.14–2.47; 0.468
After adjustment[a]			
rs1799782	1.21; 0.98–1.49; 0.076	1.26; 0.93–1.72; 0.136	1.30; 0.89–1.88; 0.173
rs25489	1.15; 0.87–1.52; 0.343	1.09; 0.80–1.48; 0.581	2.56; 0.86–7.60; 0.090
rs25487	1.44; 1.16–1.80; 0.001	1.59; 1.20–2.11; 0.001	1.59; 0.95–2.66; 0.076
rs3218536	0.83; 0.58–1.20; 0.329	0.79; 0.53–1.16; 0.221	1.99; 0.39–10.05; 0.404
rs861539	0.99; 0.66–1.49; 0.960	1.03; 0.67–1.58; 0.884	0.57; 0.14–2.40; 0.443

Data are expressed as odds ratio, 95 % confidence interval, and *P* value

[a] Adjusting for age, sex, BMI, smoking, and drinking

Table 4 Allele combination distributions and risk prediction for gastric cancer

Allele combinations[a]	All subjects	Patients	Controls	Sim *P*	Adj. Sim *P*	OR; 95 % CI; *P*	Adjusted OR; 95 % CI; *P*
C-G-G-G-C	0.4622	0.4268	0.5014	0.0010	0.0001	Reference	Reference
T-G-G-G-C	0.1043	0.1070	0.0999	0.7894	0.9011	1.28; 0.97–1.7; 0.0865	1.40; 0.96–2.03; 0.0797
T-G-A-G-C	0.0986	0.1059	0.0920	0.1053	0.1032	1.39; 1.04–1.86; 0.0265	1.46; 0.99–2.17; 0.0581
T-A-A-G-C	0.0896	0.0973	0.0824	0.1496	0.1522	1.42; 1.06–1.9; 0.0205	1.44; 0.98–2.13; 0.0665
T-G-G-A-C	0.0732	0.0717	0.0729	0.4320	0.5164	1.18; 0.85–1.63; 0.3272	1.18; 0.77–1.81; 0.4402
C-G-A-G-C	0.0376	0.0507	0.0240	0.0034	0.0009	2.54; 1.53–4.21; 0.0003	2.39; 1.32–4.31; 0.0040
C-A-G-G-C	0.0299	0.0360	0.0252	0.3905	0.3969	1.68; 0.92–3.09; 0.0929	1.47; 0.61–3.54; 0.3933
C-G-G-G-T	0.0264	0.0288	0.0209	0.6947	0.6497	1.86; 1.02–3.41; 0.0436	1.34; 0.53–3.37; 0.5365
T-G-A-G-T	0.0215	0.0235	0.0197	0.8426	0.8974	1.33; 0.71–2.48; 0.3695	1.79; 0.8–4.02; 0.1591
C-A-A-G-C	0.0167	0.0184	0.0138	0.1768	0.2132	1.61; 0.77–3.34; 0.2019	1.69; 0.58–4.89; 0.3345
T-A-G-G-C	0.0144	0.0144	0.0139	0.5901	0.5143	1.43; 0.66–3.13; 0.3643	1.23; 0.38–3.96; 0.7287

Sim P simulated *P* value, *Adj. Sim P* adjusted simulated *P* value, *OR* odds ratio, *95 % CI* 95 % confidence interval

[a] Alleles in order of rs1799782, rs25489, rs25487, rs3218536, and rs861539

functional impact of the rs25487 polymorphism on the *XRCC1* gene expression, and found that this polymorphism might be in cis eQTL with the *XRCC1* gene expression. However, the exact mechanisms underlying the association of the *XRCC1* gene rs25487 polymorphism and gastric cancer remain unclear thus far, and if hypothetically involved, the mutation of this polymorphism (399Arg→399Gln) might reduce the DNA repair capability of XRCC1 through lowering its gene expression, accelerating the transition of normal cells into carcinogenesis.

To see whether there was a joint genetic interaction on gastric cancer susceptibility, we introduced the concept of "allele combination," in parallel to "haplotype," which is composed of different alleles from different genes in the same or different chromosomes [24, 25]. This method could provide more information than analysis with a single polymorphic marker [26]. We therefore utilized this method to construct all possible allele combinations on the basis of five examined polymorphisms within three *XRCC* genes, and interestingly found that when compared with the most common allele combination C-G-G-G-C, allele combination C-G-A-G-C was significantly associated with an increased risk of gastric cancer. The only difference between the significant allele combination and the reference combination was in the third place, the two alleles of the *XRCC1* gene rs25487 polymorphism. The reason for such association may be that the rs25487 polymorphism played a leading role in the development of gastric cancer. Otherwise, antagonistic action might exist or some allele might take a dominant place. Given the complexity of the mechanisms through which genes affect the occurrence of gastric cancer, further validation of our findings is necessary in different ethnic or racial groups.

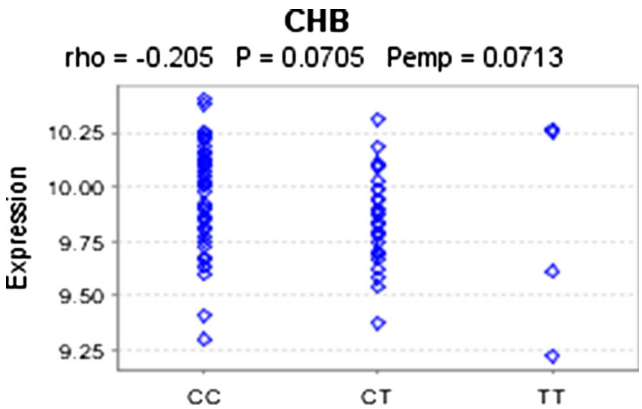

Fig. 1 The eQTL analysis of polymorphism rs25487 with *XRCC1* gene expression

Several drawbacks for this study should be emphasized. Firstly, the sample size of this study might not be large enough to obtain a reliable effect estimate, especially for low-penetrance genes or loci. Secondly, the retrospective case-control study design prevented cause-effect inference. Thirdly, only three genes from the XRCC family were selected and only seven non-synonymous polymorphisms were analyzed. Fourthly, data on the clinical subtypes, progression, and overall survival of gastric cancer were not available for us, limiting further stratified and predictive analyses. Fifthly, the generalizability of our findings to other ethnic groups was limited due to the fact that only Han Chinese subjects were enrolled in this study. Nevertheless, our findings highlight that the *XRCC1* gene rs25487 polymorphism might be a useful genetic marker, which can help identify individuals at high risk for gastric cancer in clinical screening and facilitate the development of preventive strategies.

Taken together, our findings demonstrated that *XRCC1* gene rs25487 polymorphism might play a leading role in pronounced susceptibility to gastric cancer in Han Chinese. Our findings may help direct further efforts to identify the *XRCC1* gene as a biomarker and potential therapeutic target for gastric carcinogenesis in future investigations.

Conflicts of interest None

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References

1. Alli E, Sharma VB, Sunderesakumar P, Ford JM. Defective repair of oxidative dna damage in triple-negative breast cancer confers sensitivity to inhibition of poly(adp-ribose) polymerase. Cancer Res. 2009;69:3589–96.
2. Orlow I, Park BJ, Mujumdar U, Patel H, Siu-Lau P, Clas BA, et al. DNA damage and repair capacity in patients with lung cancer: prediction of multiple primary tumors. J Clin Oncol. 2008;26:3560–6.
3. Aggarwal M, Brosh Jr RM. Functional analyses of human DNA repair proteins important for aging and genomic stability using yeast genetics. DNA Repair (Amst). 2012;11:335–48.
4. Babron MC, Kazma R, Gaborieau V, McKay J, Brennan P, Sarasin A, et al. Genetic variants in DNA repair pathways and risk of upper aerodigestive tract cancers: combined analysis of data from two genome-wide association studies in European populations. Carcinogenesis. 2014;35:1523–7.
5. Dizdaroglu M. Oxidatively induced DNA damage and its repair in cancer. Mutat Res Rev Mutat Res. 2015;763:212–45.
6. Qiao W, Wang T, Zhang L, Tang Q, Wang D, Sun H. Association study of single nucleotide polymorphisms in xrcc1 gene with the risk of gastric cancer in Chinese population. Int J Biol Sci. 2013;9:753–8.
7. Zhao DY, Cheng L, Yu J, Shen H. Xrcc1 genetic polymorphism arg339gln, arg194trp, arg280his and gastric cancer risk: an evidence based decision. Cancer Biomark. 2014;14:449–56.
8. Perez LO, Crivaro A, Barbisan G, Poleri L, Golijow CD. Xrcc2 r188h (rs3218536), xrcc3 t241m (rs861539) and r243h (rs77381814) single nucleotide polymorphisms in cervical cancer risk. Pathol Oncol Res. 2013;19:553–8.
9. Curtin K, Lin WY, George R, Katory M, Shorto J, Cannon-Albright LA, et al. Genetic variants in xrcc2: new insights into colorectal cancer tumorigenesis. Cancer Epidemiol Biomarkers Prev. 2009;18:2476–84.
10. Qin XP, Zhou Y, Chen Y, Li NN, Wu XT. Xrcc3 thr241met polymorphism and gastric cancer susceptibility: a meta-analysis. Clin Res Hepatol Gastroenterol. 2014;38:226–34.
11. McLean MH, El-Omar EM. Genetics of gastric cancer. Nat Rev Gastroenterol Hepatol. 2014;11:664–74.
12. Martinet W, Knaapen MW, De Meyer GR, Herman AG, Kockx MM. Oxidative DNA damage and repair in experimental atherosclerosis are reversed by dietary lipid lowering. Circ Res. 2001;88:733–9.
13. Barrett JC, Fry B, Maller J, Daly MJ. Haploview: analysis and visualization of ld and haplotype maps. Bioinformatics. 2005;21:263–5.
14. Yang TP, Beazley C, Montgomery SB, Dimas AS, Gutierrez-Arcelus M, Stranger BE, et al. Genevar: a database and java application for the analysis and visualization of snp-gene associations in eqtl studies. Bioinformatics. 2010;26:2474–6.
15. Gok I, Baday M, Cetinkunar S, Kilic K, Bilgin BC. Polymorphisms in DNA repair genes xrcc2 and xrcc3 risk of gastric cancer in Turkey. Bosn J Basic Med Sci. 2014;14:214–8.
16. Wang Z, Chen X, Liu B, Li S, Liu M, Xue H. Quantitative assessment of the associations between DNA repair gene xrcc3 thr241met polymorphism and gastric cancer. Tumour Biol. 2014;35:1589–98.
17. Lee SG, Kim B, Choi J, Kim C, Lee I, Song K. Genetic polymorphisms of xrcc1 and risk of gastric cancer. Cancer Lett. 2002;187:53–60.
18. Abdel-Rahman O. Hedgehog pathway aberrations and gastric cancer; evaluation of prognostic impact and exploration of therapeutic potentials. Tumour Biol. 2015;36:1367–74.
19. Zhou J, Liu ZY, Li CB, Gao S, Ding LH, Wu XL, et al. Genetic polymorphisms of DNA repair pathways influence the response to chemotherapy and overall survival of gastric cancer. Tumour Biol. 2015;36:3017–23.
20. Boerner JL, Nechiporchik N, Mueller KL, Polin L, Heilbrun L, Boerner SA, et al. Protein expression of DNA damage repair proteins dictates response to topoisomerase and PARP inhibitors in triple-negative breast cancer. PLoS ONE. 2015;10:e0119614.
21. Sarangi P, Zhao X. Sumo-mediated regulation of DNA damage repair and responses. Trends Biochem Sci. 2015;40:233–42.
22. Kim HM, Colaiacovo MP. New insights into the post-translational regulation of DNA damage response and double-strand break repair in caenorhabditis elegans. Genetics. 2015.
23. Dong H, Shi Q, Song X, Fu J, Hu L, Xu D, Su C, Xia X, Song E, Song Y. Polychlorinated biphenyl quinone induces oxidative DNA damage and repair responses: the activations of nhej, ber and ner via atm-p53 signaling axis. Toxicol Appl Pharmacol. 2015.
24. Niu W, Qi Y, Hou S, Zhai X, Zhou W, Qiu C. Haplotype-based association of the renin-angiotensin-aldosterone system genes polymorphisms with essential hypertension among Han Chinese: The Fangshan Study. J Hypertens. 2009;27:1384–91.
25. Bugawan TL, Angelini G, Larrick J, Auricchio S, Ferrara GB, Erlich HA. A combination of a particular hla-dp beta allele and an hla-dq heterodimer confers susceptibility to coeliac disease. Nature. 1989;339:470–3.
26. Gai LP, Liu H, Cui JH, Ji N, Ding XD, Sun C, et al. Distributions of allele combination in single and cross loci among patients with several kinds of chronic diseases and the normal population. Genomics. 2015;105:168–74.