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The Contribution of Excision Repair Cross-complementing Group 1 Genotypes to Colorectal Cancer Susceptibility in Taiwan

TE-CHENG YUEH[1,2,3*], AN-KUO CHOU[4*], CHI-LI GONG[5*], CHUN-KAI FU[1,2], JEN-SHENG PEI[6], MING-HSIEN WU[2], CHIA-WEN TSAI[3], WEN-SHIN CHANG[3], CHIEH-LUN HSIAO[3], SHIOU-TING YEN[3], HSIN-TING LI[3] and DA-TIAN BAU[1,3,7]

[1]*Graduate Institute of Biomedical Sciences, China Medical University, Taichung, Taiwan, R.O.C.;*
[2]*Taichung Armed Forces General Hospital, Taichung, Taiwan, R.O.C.;*
[3]*Terry Fox Cancer Research Laboratory, Department of Medical Research, China Medical University Hospital, Taichung, Taiwan, R.O.C.;*
[4]*Department of Anesthesiology, China Medical University Hospital, Taichung, Taiwan, R.O.C.;*
[5]*Department of Physiology, China Medical University, Taichung, Taiwan, R.O.C.;*
[6]*Department of Pediatrics, Taoyuan General Hospital, Ministry of Health and Welfare, Taoyuan, Taiwan, R.O.C.;*
[7]*Department of Bioinformatics and Medical Engineering, Asia University, Taichung, Taiwan, R.O.C.*

Abstract. *Aim: To evaluate the contribution of ERCC1 rs11615 and rs3212986 genotypes regarding the risk of colorectal cancer (CRC) in Taiwan. Materials and Methods: In this case–control study, ERCC1 rs11615 and rs3212986 genotypes and their interaction with consumption of cigarettes and alcohol in determining CRC risk were investigated among 362 CRC patients and 362 age- and gender-matched healthy controls. Results: The percentages of CC, CT and TT for ERCC1 rs11615 genotype were 44.2%, 36.2% and 19.6% in the CRC group and 49.7%, 38.4% and 11.9% in the control group, respectively (p for trend=0.0158). The allelic frequency distribution analysis showed that the variant T allele of ERCC1 rs11615 conferred increased CRC susceptibility to the wild-type C allele (odds ratio (OR)=1.34, 95% confidence interval (CI)=1.08-1.67, p=0.0079). As for the gene-lifestyle interaction, there were obvious joint effects of ERCC1 rs11615 genotype on the risk of CRC among ever smokers and alcohol drinkers, but not non-smokers or non-drinkers. There is a positive correlation of ERCC1 rs11615 genotype with lymph node metastasis, but not other CRC prognosis, including tumor size and location. Conclusion: ERCC1 rs11615 T allele serves as a predictive marker for CRC risk and future studies with larger samples and functional evaluation are warranted to validate these findings.*

*These Authors contributed equally to this study.

Correspondence to: Da-Tian Bau, Terry Fox Cancer Research Laboratory, China Medical University Hospital, 2 Yuh-Der Road, Taichung, 404 Taiwan, R.O.C. Tel: +886 422052121 (Ext. 7534), e-mail: datian@mail.cmuh.org.tw; artbau2@gmail.com

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Statistically, nearly one million cases of colorectal cancer (CRC) diagnoses worldwide each year and the incidence, as well as age-adjusted mortality of CRC, keep on increasing in recent years (1). In Taiwan, the incidence and mortality of CRC has occupied the first and third places among the common types of cancer for many years and the high incidence has been proposed to be closely associated with dietary changes to Western food style and a decreased consumption of dietary fiber or grain-made foods. Etiological studies have attributed more than 85% of CRC to risk environmental factors (1-3), particularly meat consumption, cigarette smoking, exposure to carcinogenic aromatic amines, such as arylamines and heterocyclic amines (4, 5). About 15-20% of CRC cases are with strong familial history of cancer that have interested the epidemiologists to figure out additional inherited susceptibility factors (6-8). In Taiwan, although specific biomarkers for CRC prediction and detection have keeping on being reported in recent years (9-16), the genomic susceptibility of CRC and the interactions among the genomic and environmental risk factors are mostly unknown.

Our genome is regularly and frequently damaged by various kinds of endogenous and exogenous mutagens and the DNA repair systems play a vital role in protecting our genome from

irreversible mutations leading to carcinogenesis, among which the nucleotide excision repair (NER) pathway is one of the nuclear DNA repair systems used in correcting subtle DNA lesions and bulky DNA damage (17, 18). Among the DNA repair proteins involved in NER, excision repair cross-complementing group 1 (*ERCC1*) is located on chromosome 19q13.3 and participates as the central rate-limiting enzyme in the multistep NER process. For instance, Shirota and his colleagues have suggested that down-regulation of *ERCC1* expression is associated with increased chemotherapeutic sensitivity and, thus, considered a predictive marker for CRC patients receiving combination of oxaliplatin and fluorouracil chemotherapy (19). In addition, Huang and his colleagues reported that A2251C variants of *ERCC2* were associated with increased risk of early relapse in CRC (20). In the literature, several single-nucleotide polymorphisms (SNPs) of *ERCC1* have been well identified, of which *ERCC1* rs11615 and rs3212986 SNPs (Asn118Asn and C8092A) both have transcriptional moderating effects on their mRNA expression (21). Given the role of *ERCC1* in genomic stability maintenance and carcinogenesis progression, we hypothesized that genomic variations in the *ERCC1* gene may determine the individual susceptibility of Taiwanese to CRC. Therefore, we conducted a hospital-based case-control study to investigate the genotypes of *ERCC1* firstly among Taiwanese and examine the association of *ERCC1* genotypes with the risk of CRC in a Taiwanese population.

Materials and Methods

Investigated population. The investigated population included 724 subjects (362 CRC patients and 362 healthy controls). Patients diagnosed with CRC were recruited at the outpatient clinics of general surgery between 2002 and 2008 at the China Medical University Hospital, Taichung, Taiwan, Republic of China, by the team of Drs. Jeng LB and Yang MD. The clinical characteristics of patients, including histological details, were all graded and defined by expert surgeons (9, 10, 13, 16). All participants have completed a self-administered questionnaire and provided a 5-ml sample of peripheral blood for genotyping work. An equal number of non-cancer healthy volunteers (n=362) were selected as controls by matching for age, gender and some indulgences after initial random sampling from the Health Examination Cohort of the Hospital with the help of colleagues in the Department of Family Medicine. The exclusion criteria of the control group included previous malignancy, metastasized cancer from other or unknown origin and any familial or genetic diseases. This study was approved by the Institutional Review Board of the China Medical University Hospital (IRB project identification coding number: DMR99-IRB-108) and written informed consent was obtained from all participants with the help of Tissue Bank of China Medical University Hospital. The selected patients' characteristics, extracted from personal questionnaires, are summarized in Table I.

Table I. *Summary of selected data of the 362 patients with colorectal cancer and 362 matched non-cancer healthy controls.*

Characteristic	Controls (n=362)		Cases (n=362)		*p*-Value[a]
	n	%	n	%	
Age (years)					
≤60	93	25.7%	95	26.2%	0.8654
>60	269	74.3%	267	73.8%	
Gender					
Male	209	57.7%	203	56.1%	0.6525
Female	153	42.3%	159	43.9%	
Tumor size (cm)					
<5			195	53.9%	
≥5			167	46.1%	
Location					
Colon			257	71.0%	
Rectum			105	29.0%	
Lymph node metastasis					
Negative			210	58.0%	
Positive			152	42.0%	

SD, Standard deviation; [a]based on Chi-square test without Yates' correction.

Genotyping conditions. Genomic DNA from peripheral blood leucocytes of each investigated subject was prepared applying the QIAamp Blood Mini Kit (Blossom, Taipei, Taiwan) and stored at –80˚C until processed as per our recent publications (9, 22, 23). The methodology for *ERCC1* rs11615 and rs3212986 genotyping, including the designing of the specific primers and the selection of restriction enzymes, were firstly designed in our lab. Briefly, the sequences for forward and reverse primer pairs for *ERCC1* rs11615 were 5'-TTAGGAGGAGAGAGAAGCTG-3' and 5'-GGCTTCTC ATAGAACAGTCC-3', respectively. The sequences for forward and reverse primer pairs for *ERCC1* rs3212986 were 5'-AGGC TGTTTGATGTCCTGCA-3' and 5'-AGAGGAAGAAGCAGAGT CAG-3', respectively. The polymerase chain reaction (PCR) cycling conditions were set as one cycle at 94˚C for 5 min; 35 cycles of 94˚C for 30 s, 58˚C for 30 s and 72˚C for 30 s; and a final extension step at 72˚C for 10 min. After PCR amplification, the PCR products were subject to the digestion by *BsrD* I and *MboI* I restriction endonucleases, respectively, for 2 h at 37˚C and separation via 3% agarose gel electrophoresis for 25 min. The ERCC1 rs11615 genotypes were identified as homozygous C/C with 393-bp product, heterozygous C/T with 393-, 228- and 165-bp products, as well as homozygous T/T with 228- and 165-bp products, respectively. The *ERCC1* rs3212986 genotypes were identified as homozygous G/G with 367-bp product, heterozygous G/T with 367-, 233- and 134-bp products, as well as homozygous T/T with 233- and 134-bp products, respectively. All the genotypic processing was repeated by two researchers independently and blindly; all the genotyping results were 100% concordant.

Statistical analyses. The Student's *t*-test was applied for the comparison of ages between the CRC cases and the control groups. Pearson's Chi-square test was applied to compare the distribution of the *ERCC1* genotypes among the subgroups. The associations between *ERCC1* genotypes and CRC risk were estimated by computing odds ratios (ORs) and their 95% confidence intervals (CIs)

Table II. *Excision repair cross-complementing group 1 (ERCC1) genotypes among the 362 patients with colorectal cancer and 362 matched healthy controls*.

Genotype	Controls		Patients		OR (95% CI)	*p*-Value[a]
	n	%	n	%		
rs11615						
CC	180	49.7%	160	44.2%	1.00 (Reference)	
CT	139	38.4%	131	36.2%	1.06 (0.77-1.46)	0.7200
TT	43	11.9%	71	19.6%	1.86 (1.20-2.87)	0.0049*
ptrend						0.0158*
Carrier comparison						
CC +CT	319	88.1%	291	80.4%	1.00 (Reference)	
TT	43	11.9%	71	19.6%	1.81 (1.20-2.73)	0.0043*
CC	180	49.7%	160	44.2%	1.00 (Reference)	
CT+TT	182	50.3%	202	55.8%	1.25 (0.93-1.67)	0.1364
rs3212986						
TT	177	48.9%	181	50.0%	1.00 (Reference)	
GT	139	38.4%	133	36.7%	0.94 (0.68-1.28)	0.6795
GG	46	12.7%	48	13.3%	1.02 (0.65-1.61)	0.9305
ptrend						0.8960
Carrier comparison						
TT+GT	316	87.3%	314	86.7%	1.00 (Reference)	
GG	46	12.7%	48	13.3%	1.05 (0.68-1.62)	0.8250
TT	177	48.9%	181	50.0%	1.00 (Reference)	
GT+GG	185	51.1%	181	50.0%	0.96 (0.71-1.28)	0.7662

[a]Based on chi-square test without Yates's correction; *statistically significant; OR, odds ratio; CI, confidence interval.

from logistic regression analysis. Statistically, any difference at $p<0.05$ was taken as significant between the two groups compared.

Results

The frequency distributions of selected characters, including age and gender for the 362 CRC patients in the case group and 362 non-cancer healthy subjects in the control group, are summarized and compared in Table I. In addition, tumor size, location,and lymph node metastasis status are also summarized in Table I. Since we applied frequency matching to recruit non-cancer healthy subjects as controls, there was no difference in the distributions of age and gender between the control and case groups (p=0.8654 and 0.6525, respectively) (Table I). The patients with tumor size <5 cm and ≥5 cm were 195 and 167, respectively. The patients with tumor location at colon and rectum were 257 and 105, respectively. The patients with and without lymph node metastasis were 152 and 210, respectively (Table I).

The distributions of the *ERCC1* rs11615 and rs3212986 genotypes among the 326 non-cancer controls and the 326 CRC patients are presented and statistically analyzed in Table II. The results showed that the genotypes of *ERCC1* rs11615 were differently distributed between case and control groups (p for trend=0.0158) (Table II). In detail, the *ERCC1* rs11615 homozygous TT, but not the heterozygous CT, was associated with CRC risk, compared with wild-type CC genotype (OR=1.86 and 1.06, 95%CI=1.20-2.87 and 0.77-1.46, p=0.0049 and 0.7200, respectively; Table II). In the recessive model, there was a positive association between the TT genotype of *ERCC1* rs11615 and CRC risk, compared with CC+CT genotypes (OR=1.81, 95%CI=1.20-2.73, p=0.0043, Table II). The genotypes of *ERCC1* rs3212986 were not differently distributed between case and control groups in all models (Table II).

To confirm the results in Table II, analysis of allelic frequency distribution for the *ERCC1* rs11615 and rs3212986 was further conducted and the results are presented in Table III. Supporting the findings that genotype of *ERCC1* rs11615 was associated with CRC risk, the variant allele T was found at 37.7% in the case group, significantly higher than that of 31.1% in the control group (OR=1.34, 95% CI=1.08-1.67, p=0.0079). At the same time, there was no significant difference in the allelic frequencies of *ERCC1* rs3212986 between the case and control groups (Table III).

Since smoking and alcohol drinking habits are well-known risk factors for CRC in Taiwan, we were interested in investigating the interactions between the genotype of *ERCC1*

Table III. *Distribution of allelic frequencies for excision repair cross-complementing group 1 (ERCC1) among the 362 patients with colorectal cancer and 362 matched healthy controls.*

Allele	Controls, n	%	Patients, n	%	OR (95% CI)	*p*-Value[a]
rs11615						
C	499	68.9%	451	62.3%	1.00 (Reference)	
T	225	31.1%	273	37.7%	1.34 (1.08-1.67)	0.0079*
rs3212986						
G	493	68.1%	495	68.4%	1.00 (Reference)	
T	231	31.9%	229	31.6%	0.99 (0.79-1.23)	0.9101

[a]Based on chi-square test without Yates's correction; *statistically significant.

Table IV. *Odds ratios for excision repair cross-complementing group 1 (ERCC1) rs11615 genotype and colorectal cancer after stratification by smoking status.*

Genotype	Non-smokers, n		OR (95% CI)[a]	aOR (95% CI)[b]	*p*-Value	Smokers, n		OR (95% CI)[a]	aOR (95% CI)[b]	*p*-Value
	Controls	Cases				Controls	Cases			
CC	137	126	1.00 (ref)	1.00 (ref)		43	34	1.00 (ref)	1.00 (ref)	
CT	105	101	1.05 (0.73-1.51)	1.07 (0.75-1.55)	0.8096	34	30	1.12 (0.57-2.17)	1.27 (0.61-2.31)	0.7468
TT	36	44	1.33 (0.80-2.20)	1.34 (0.85-2.05)	0.2666	7	27	4.88 (1.90-12.55)	4.41 (1.94-11.53)	0.0006*
Total	278	271				84	91			

[a]By multivariate logistic regression analysis; [b]by multivariate logistic regression analysis after adjusted of age, gender and alcohol drinking status; *statistically significant; CI, confidence interval; aOR, adjusted odds ratio.

Table V. *Odds ratios for excision repair cross-complementing group 1 (ERCC1) rs11615 genotype and colorectal cancer after stratification by alcohol drinking status.*

Genotype	Non-drinker, n		OR (95% CI)[a]	aOR (95% CI)[b]	*p*-Value	Drinkers, n		OR (95% CI)[a]	aOR (95% CI)[b]	*p*-Value
	Controls	Cases				Controls	Cases			
CC	155	146	1.00 (ref)	1.00 (ref)		25	14	1.00 (ref)	1.00 (ref)	
CT	118	117	1.05 (0.75-1.48)	1.11 (0.79-1.49)	0.7683	21	14	1.19 (0.46-3.05)	1.24 (0.47-3.21)	0.7164
TT	38	55	1.54 (0.96-2.46)	1.48 (0.94-2.54)	0.0729	5	16	5.71 (1.72-18.94)	5.46 (1.68-17.87)	0.0029*
Total	311	318				51	44			

[a]By multivariate logistic regression analysis; [b]by multivariate logistic regression analysis after adjusted of age, gender and smoking status; *statistically significant; CI, confidence interval; aOR, adjusted odds ratio.

rs11615 and personal cigarette smoking and alcohol drinking habits. Among smokers, those with TT genotype at *ERCC1* rs11615 were at 4.88-fold odds of having CRC (95% CI=1.90-12.55, *p*=0.0006) conferring a risky effect, while this was not the case for non-smokers (Table IV). After adjusting for age, gender and alcohol drinking status, statistical significance still existed at a similar level (OR=4.41, 95%CI=1.94-11.53, Table IV). On the other hand, among alcohol drinkers, those with TT genotype at *ERCC1* rs11615 were at 5.71-fold odds of having CRC (95% CI=1.72-18.94, *p*=0.0029) conferring a risky effect, while this was not the case for non-drinkers (Table V). After adjusting for age, gender and smoking status, results were equally significant (OR=5.46, 95%CI=1.68-17.87, Table V).

The correlations between genotypes of *ERCC1* rs11615 and clinicopathological features of 362 CRC patients were analyzed and summarized in Table VI. No statistically

Table VI. *Correlation between excision repair cross-complementing group 1 rs11615 genotypes and clinicopathological properties of 362 colorectal cancer patients.*

Characteristics	Case number	Genotypes			*p*-Value[a]
		CC (%)	CT (%)	TT (%)	
Age (years)					
≤60	95	44 (46.3)	35 (36.8)	16 (16.9)	
>60	267	116 (43.4)	96 (36.0)	55 (20.6)	0.7225
Gender					
Male	203	89 (43.8)	70 (34.5)	44 (21.7)	
Female	159	71 (44.6)	61 (38.4)	27 (17.0)	0.5000
Tumor size					
<5 cm	195	85 (43.6)	71 (36.4)	39 (20.0)	
≥5 cm	167	75 (44.9)	60 (35.9)	32 (19.2)	0.9639
Location					
Colon	257	115 (44.7)	92 (35.8)	50 (19.5)	
Rectum	105	45 (42.9)	39 (37.1)	21 (20.0)	0.9471
Lymph node metastasis					
Negative	210	106 (50.5)	73 (34.8)	31 (14.7)	
Positive	152	54 (35.5)	58 (38.2)	40 (26.3)	0.0047*

[a]Based on chi-square test without Yates's correction; *statistically significant.

significant correlation was observed between *ERCC1* rs11615 genotypic distributions and age, gender, tumor size or location (all $p>0.05$). The most important finding was that the *ERCC1* rs11615 genotype was associated with lymph node metastasis ($p=0.0047$) (Table VI).

Discussion

In the literature, genotypes of DNA repair genes may be associated with prognosis of chemotherapy in cancer patients. The DNA repair system plays an important role in maintaining the integrity of human genome that controls the homeostasis of cellular functions via the reversal of all types of DNA damage due to variety of factors, including cancer therapeutic agents. Therefore, overall DNA repair capacity may greatly contribute not only to cancer susceptibility but, also, prognosis (24). *ERCC1* plays a central role in NER pathway and is responsible for a major part of routine DNA damage (25). The *ERCC1* genotypes of rs11615 and rs3212986 may provide predictive information of platinum-based chemotherapy of advanced gastric cancer (26), advanced non-small cell lung cancer (27), testicular germ cell tumors (28), advanced epithelial ovarian cancer (29) and esophageal cancer (30). Molecular studies showed that *ERCC1* rs11615 T allele is associated with diminished mRNA and protein expression levels but represents, however, a controversial predictive marker for cancer therapy (31-35). In the initial steps of carcinogenesis, the defects in DNA repair capacity of cells determined by variant *ERCC1* genotypes may also contribute to increased cancer susceptibility. In the current work, we found that *ERCC1* rs11615 TT genotype is associated with 1.86-fold enhanced CRC risk (Table II), which is further elevated to 4.88-fold odds of having CRC among smokers and 5.71-fold odds among alcohol drinkers (Tables IV and V). This is the first study to reveal joint effects between *ERCC1* rs11615 genotypes with cigarette smoking and alcohol drinking habits on the susceptibility to CRC.

Despite our efforts to conduct an accurate and comprehensive genotyping work and related analysis, there are some limitations that should be noted. Firstly, the lack of recorded follow-ups limited the analysis of the correlation of prognosis indexes, such as survival rates. Table VI only provides evidence for the *ERCC1* rs11615 genotype that did not contribute to the prediction of tumor size, location and metastasis. Secondly, lack of tumor and non-tumor samples limited the study of differential expression of *ERCC1* mRNA and protein levels among the subjects, in addition to the inter-individual difference of the CRC patients. Further molecular investigations of the genotype-phenotype correlation may help in understanding the contribution of *ERCC1* genotypes to not only overall DNA repair capacity but, also, personal susceptibility to CRC and/or other types of cancer. Thirdly, the relatively small sample size, especially in subgroup analysis, such as those in Tables IV and V, may have caused some bias and reduced the statistic power of our estimates.

In conclusion, this study provides evidence that the T allele at *ERCC1* rs11615 may interact with smoking and alcohol drinking status to determine personal susceptibility to CRC;

however, more research should be conducted to reveal the detailed alteration of DNA repair capacity in relation to CRC susceptibility and prognosis of chemotherapy.

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References

1 Torre LA, Bray F, Siegel RL, Ferlay J, Lortet-Tieulent J and Jemal A: Global cancer statistics, 2012. CA Cancer J Clin *65*: 87-108, 2015.
2 Jemal A, Siegel R, Xu J and Ward E: Cancer statistics, 2010. CA Cancer J Clin *60*: 277-300, 2010.
3 Jemal A, Bray F, Center MM, Ferlay J, Ward E and Forman D: Global cancer statistics. CA Cancer J Clin *61*: 69-90, 2011.
4 Nagini S: Carcinoma of the stomach: A review of epidemiology, pathogenesis, molecular genetics and chemoprevention. World J Gastrointest Oncol *4*: 156-169, 2012.
5 Jayasurya R, Sathyan KM, Lakshminarayanan K, Abraham T, Nalinakumari KR, Abraham EK, Nair MK and Kannan S: Phenotypic alterations in Rb pathway have more prognostic influence than p53 pathway proteins in oral carcinoma. Mod Pathol *18*: 1056-1066, 2005.
6 Butterworth AS, Higgins JP and Pharoah P: Relative and absolute risk of colorectal cancer for individuals with a family history: A meta-analysis. Eur J Cancer *42*: 216-227, 2006.
7 Houlston RS and Tomlinson IP: Polymorphisms and colorectal tumor risk. Gastroenterology *121*: 282-301, 2001.
8 Rasool S, Rasool V, Naqvi T, Ganai BA and Shah BA: Genetic unraveling of colorectal cancer. Tumour Biol *35*: 5067-5082, 2014.
9 Chang WS, Yueh TC, Tsai CW, Ji HX, Wu CN, Wang SC, Lai YL, Hsu SW, Hsieh MH, Hsiao CL, Hung YW, Shih TC and Bau DT: Contribution of DNA repair Xeroderma Pigmentosum Group D genotypes to colorectal cancer risk in Taiwan. Anticancer Res *36*: 1657-1663, 2016.
10 Huang CY, Tsai CW, Hsu CM, Chang WS, Shui HA and Bau DT: The significant association of CCND1 genotypes with colorectal cancer in Taiwan. Tumour Biol *36*: 6533-6540, 2015.
11 Yang MD, Tsai CW, Chang WS, Tsou YA, Wu CN and Bau DT: Predictive role of XRCC5/XRCC6 genotypes in digestive system cancers. World J Gastrointest Oncol *3*: 175-181, 2011.
12 Yang MD, Tsai RY, Liu CS, Chang CH, Wang HC, Tsou YA, Wang CH, Lin CC, Shyue SK and Bau DT: Association of Caveolin-1 polymorphisms with colorectal cancer susceptibility in Taiwan. World J Gastrointest Oncol *2*: 326-331, 2010.
13 Bau DT, Yang MD, Tsou YA, Lin SS, Wu CN, Hsieh HH, Wang RF, Tsai CW, Chang WS, Hsieh HM, Sun SS and Tsai RY: Colorectal cancer and genetic polymorphism of DNA double-strand break repair gene XRCC4 in Taiwan. Anticancer Res *30*: 2727-2730, 2010.
14 Yeh YS, Tsai HL, Huang CW, Wang JH, Lin YW, Tang HC, Sung YC, Wu CC, Lu CY and Wang JY: Prospective analysis of UGT1A1 promoter polymorphism for irinotecan dose escalation in metastatic colorectal cancer patients treated with bevacizumab plus FOLFIRI as the first-line setting: study protocol for a randomized controlled trial. Trials *17*: 46, 2016.
15 Shi MD, Chen JH, Sung HT, Lee JS, Tsai LY and Lin HH: CXCL12-G801A polymorphism modulates risk of colorectal cancer in Taiwan. Arch Med Sci *9*: 999-1005, 2013.
16 Yang MD, Hsu YM, Kuo YS, Chen HS, Chang CL, Wu CN, Chang CH, Liao YM, Wang HC, Wang MF and Bau DT: Significant association of Ku80 single nucleotide polymorphisms with colorectal cancer susceptibility in Central Taiwan. Anticancer Res *29*: 2239-2242, 2009.
17 De Silva IU, McHugh PJ, Clingen PH and Hartley JA: Defining the roles of nucleotide excision repair and recombination in the repair of DNA interstrand cross-links in mammalian cells. Mol Cell Biol *20*: 7980-7990, 2000.
18 Braithwaite E, Wu X and Wang Z: Repair of DNA lesions: mechanisms and relative repair efficiencies. Mutat Res *424*: 207-219, 1999.
19 Shirota Y, Stoehlmacher J, Brabender J, Xiong YP, Uetake H, Danenberg KD, Groshen S, Tsao-Wei DD, Danenberg PV and Lenz HJ: ERCC1 and thymidylate synthase mRNA levels predict survival for colorectal cancer patients receiving combination oxaliplatin and fluorouracil chemotherapy. J Clin Oncol *19*: 4298-4304, 2001.
20 Huang MY, Fang WY, Lee SC, Cheng TL, Wang JY and Lin SR: ERCC2 2251A>C genetic polymorphism was highly correlated with early relapse in high-risk stage II and stage III colorectal cancer patients: A preliminary study. BMC Cancer *8*: 50, 2008.
21 Yu JJ, Lee KB, Mu C, Li Q, Abernathy TV, Bostick-Bruton F and Reed E: Comparison of two human ovarian carcinoma cell lines (A2780/CP70 and MCAS) that are equally resistant to platinum, but differ at codon 118 of the ERCC1 gene. Int J Oncol *16*: 555-560, 2000.
22 Chang WS, Liao CH, Tsai CW, Hu PS, Wu HC, Hsu SW, Hsiao CL, Hsu CH, Hung YW and Bau DT: Association of enhancer of Zeste 2 (EZH2) genotypes with bladder cancer risk in Taiwan. Anticancer Res *36*: 4509-4514, 2016.
23 Chang WS, Liao CH, Tsai CW, Hu PS, Wu HC, Hsu SW, Ji HX, Hsiao CL and Bau DT: The role of IL-10 promoter polymorphisms in renal cell carcinoma. Anticancer Res *36*: 2205-2209, 2016.
24 Li Y, Liu Z, Liu H, Wang LE, Tan D, Ajani JA and Wei QY: ERCC1 and ERCC2 variants predict survival in gastric cancer patients. PLoS One *8*: e71994, 2013.
25 Wang Z, Chen JQ, Liu JL, Qin XG and Huang Y: Polymorphisms in ERCC1, GSTs, TS and MTHFR predict clinical outcomes of gastric cancer patients treated with platinum/5-Fu-based chemotherapy: A systematic review. BMC Gastroenterol *12*: 137, 2012.
26 Mokmeli S, Tehrani GA, Zamiri RE and Bahrami T: Investigating the frequency of the ERCC1 gene C8092A polymorphism in Iranian patients with advanced gastric cancer receiving platinum-based chemotherapy. Asian Pac J Cancer Prev *17*: 1369-1372, 2016.
27 Zhou C, Ren S, Zhou S, Zhang L, Su C, Zhang Z, Deng Q and Zhang J: Predictive effects of ERCC1 and XRCC3 SNP on efficacy of platinum-based chemotherapy in advanced NSCLC patients. Jpn J Clin Oncol *40*: 954-960, 2010.

28 Mendoza J, Martinez J, Hernandez C, Perez-Montiel D, Castro C, Fabian-Morales E, Santibanez M, Gonzalez-Barrios R, Diaz-Chavez J, Andonegui MA, Reynoso N, Onate LF, Jimenez MA, Nunez M, Dyer R and Herrera LA: Association between ERCC1 and XPA expression and polymorphisms and the response to cisplatin in testicular germ cell tumours. Br J Cancer *109*: 68-75, 2013.
29 Moxley KM, Benbrook DM, Queimado L, Zuna RE, Thompson D, McCumber M, Premkumar P, Thavathiru E, Hines L and Moore KN: The role of single nucleotide polymorphisms of the ERCC1 and MMS19 genes in predicting platinum-sensitivity, progression-free and overall survival in advanced epithelial ovarian cancer. Gynecol Oncol *130*: 377-382, 2013.
30 Rumiato E, Cavallin F, Boldrin E, Cagol M, Alfieri R, Basso D, Castoro C, Ancona E, Amadori A, Ruol A and Saggioro D: ERCC1 C8092A (rs3212986) polymorphism as a predictive marker in esophageal cancer patients treated with cisplatin/5-FU-based neoadjuvant therapy. Pharmacogenet Genomics *23*: 597-604, 2013.
31 van Huis-Tanja LH, Kweekel DM, Lu X, Franken K, Koopman M, Gelderblom H, Antonini NF, Punt CJ, Guchelaar HJ and van der Straaten T: Excision repair cross-complementation group 1 (ERCC1) C118T SNP does not affect cellular response to oxaliplatin. Mutat Res *759*: 37-44, 2014.
32 Zaanan A, Dalban C, Emile JF, Blons H, Flejou JF, Goumard C, Istanbullu M, Calmel C, Alhazmi K, Validire P, Louvet C, de Gramont A, Laurent-Puig P, Taieb J and Praz F: ERCC1, XRCC1 and GSTP1 single nucleotide polymorphisms and survival of patients with colon cancer receiving oxaliplatin-based adjuvant chemotherapy. J Cancer *5*: 425-432, 2014.
33 Pare L, Marcuello E, Altes A, del Rio E, Sedano L, Salazar J, Cortes A, Barnadas A and Baiget M: Pharmacogenetic prediction of clinical outcome in advanced colorectal cancer patients receiving oxaliplatin/5-fluorouracil as first-line chemotherapy. Br J Cancer *99*: 1050-1055, 2008.
34 Spindler KL, Andersen RF, Jensen LH, Ploen J and Jakobsen A: EGF61A>G polymorphism as predictive marker of clinical outcome to first-line capecitabine and oxaliplatin in metastatic colorectal cancer. Ann Oncol *21*: 535-539, 2010.
35 Viguier J, Boige V, Miquel C, Pocard M, Giraudeau B, Sabourin JC, Ducreux M, Sarasin A and Praz F: ERCC1 codon 118 polymorphism is a predictive factor for the tumor response to oxaliplatin/5-fluorouracil combination chemotherapy in patients with advanced colorectal cancer. Clin Cancer Res *11*: 6212-6217, 2005.

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