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The Significant Interaction of Excision Repair Cross-complementing Group 1 Genotypes and Smoking to Lung Cancer Risk

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Abstract. *Background: The study aims to evaluate the contribution of excision repair cross-complementing group 1 (ERCC1), which plays an important role in genome integrity maintenance, to lung cancer risk. Materials and Methods: ERCC1 rs11615 and rs3212986 genotypes were identified by polymerase chain reaction-restriction fragment length polymorphism analysis and their association with lung cancer risk was examined among 358 lung cancer patients and 716 controls. Results: The proportions of CC, CT and TT for the rs11615 genotype were 43.6%, 41.6% and 14.8% in the case group and 50.0%, 41.1% and 8.9% in the control group, respectively (p for trend=0.0082). Allelic analysis showed that ERCC1 rs11615 T-allele carriers have a 1.32-fold higher risk of lung cancer than wild-type C-allele carriers [95%confidence interval (CI)=1.09-1.60, p=0.0039]. In addition, a significant interaction between the rs11615 genotype and smoking status was observed. Conclusion: The T allele of ERCC1 rs11615 jointly with smoking habits may contribute to a higher lung cancer risk in Taiwan.*

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According to the most recent report on cancer incidence and mortality by the International Agency for Research on Cancer, lung cancer has remained as the leading cause of cancer deaths all over the world (1). An estimated 2.1 million new lung cancer cases and 1.8 million cancer-related deaths occurred worldwide in 2018 (1). The rapidly increasing cases and the high death rate have urged us to look for effective marker(s) for the prediction of the risk of lung cancer, the outcome of the prognosis and the responsiveness of patient drug treatment. The initiation and development of lung cancer is related to multiple exogenous and endogenous factors including behavioral, environmental and genetic discrepancies, among which the consumption of cigarettes is the most significant factor to be associated with lung cancer risk (2). On the other hand, the fact that about 10% to 25% of lung cancer patients are non-smokers worldwide indicates that the individual genomic influences also play a critical part for personal lung cancer etiology (3). In Taiwan, the incidence and mortality of lung cancer has been ranked on the third and first place, respectively, among different types of cancer, for several years (4). Although several biomarkers for the early detection of lung cancer are being examined during recent years (5-11), the continuous search for effective clinically practical markers and the undermining mechanisms is still largely ongoing.

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 it from irreversible mutations that can lead to carcinogenesis (12, 13). Concerning non-small cell lung cancer, genomic instability was

significantly higher in patients older than 50 and those with adenocarcinoma compared to squamous-cell carcinoma. In addition,genomic instability was negatively correlated with tumor grade (12). In 2018, a study reported that mice lacking geminin, a DNA replication inhibitor in charge of ensuring faithful DNA replication, develop a higher number of lung tumors,have a larger tumor burden and reduced survival compared tosham-treated controls, in a urethane-induced lung carcinogenesis model (13). Most importantly, the DNA repair systems are the gatekeepers for genomic stability maintenance and initiation of carcinogenesis, while the nucleotide excision repair (NER) pathway is one of the DNA repair machineries involved in removing subtle DNA mutations and bulky DNA adducts (14, 15). Among the DNA repair proteins involved in NER, excision repair cross-complementing group 1 (*ERCC1*) teams up together with *ERCC4* (XPF), participating as the central rate-limiting endonucleases in the multistep NER process. From late 1990s, evidence have been accumulating showing that in cancers, such as ovarian and gastric cancer, the expression level of ERCC1 may be a useful marker for clinical drug resistance for those patients with platinum-based chemo-treatments (16). In addition, it has also been suggested that ERCC1 downregulation is associated with increased chemotherapeutic sensitivity and, thus, considered as a predictive marker for lung patients receiving platinum-based chemotherapy (17-20). However, *ERCC1* genotype is seldom evaluated as a predictor for lung cancer risk. In the literature, several single-nucleotide polymorphisms (SNPs) of *ERCC1* have been well identified, of which *ERCC1* rs11615 (Asn118Asn) and rs3212986 (C8092A) both have transcriptional regulatory effects on their mRNA and subsequent protein expression levels (21). Knowing the role of *ERCC1* in the maintenance of genomic stability and cancer drug responsiveness and resistance, we hypothesized that genomic variations in the *ERCC1* gene may determine the individual susceptibility of Taiwanese to lung cancer at the early cancer initiation step. 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 lung cancer in a Taiwanese population. The interaction of *ERCC1* genotypes and smoking status on lung cancer risk was also examined.

Materials and Methods

Collection of lung cancer patients and age- and gender-matched controls. In total, three hundred and fifty-eight patients with lung cancer were histologically confirmed and recruited at China Medical University Hospital, as previously described (6, 7, 11). In brief, the exclusion criteria were as follows: a) the cases should be free of any history of malignancy or cancer; b) the cases should also be free of any other pulmonary diseases, such as chronic obstructive pulmonary disease (COPD), pneumothorax, and asthma. After carefully checking that each case has complete records and has donated blood, two healthy volunteers were selected for each lung cancer patient. Patients were selected from the databank of Health Examination Cohort of China Medical University Hospital with more than 15,000 individuals as controls, matched for the indexes of age (differences less than 5), gender and smoking behavior (we aimed to remove the influence of smoking as much as possible). The exclusion criteria for the recruited controls were as follows: a) they should be free of any history of malignancy or cancer; b) they should also be free of any metastasized cancer from other known or unknown origin; c) they should be free of any genetic or familial diseases. The controls and cases are all Taiwanese and several indexes of the population are summarized in Table I.

Genotyping conditions for ERCC1 rs11615 and rs3212986. The extraction of genomic DNA from the peripheral blood leukocytes of each participant was conducted within 24 h after blood collection with a QIAamp Blood Mini Kit (Blossom, Taipei, Taiwan) as described previously (22, 23). The DNA was then quantified, stored long-term at –80˚C, diluted and aliquoted for genotyping as a working stock at –20˚C (24-26). 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'-GGCTTCTCATAGAACAGTCC-3', respectively. The sequences for forward and reverse primer pairs for *ERCC1* rs3212986 were 5'-AGGCTGTTTGATGTCCTGCA-3' and 5'-AGAGGAAGAAGCAG AGTCAG-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 were separated via 3% agarose gel electrophoresis for 25 min. The *ERCC1* rs11615 genotypes were identified as homozygous C/C with a 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 a 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. Genotyping was repeated by two researchers independently and blindly; all the genotyping results were 100% concordant.

Statistical analysis. The Student's *t*-test was adopted in comparisons of the distributions of ages between the case and control groups. The Pearson's Chi-square methodology was adopted in comparisons of the distributions of *ERCC1* rs11615 and/or rs3212986 genotypes among the subgroups in addition to stratification analysis for the interaction between *ERCC1* genotypes and smoking status. The associations between *ERCC1* genotypes and lung cancer risk are also estimated by calculating the odds ratios (ORs) and their corresponding 95% confidence intervals (CIs) within logistic regression analysis. Statistically, in any comparison with *p*-value less than 0.05 the comparison is identified as significant.

Results

The frequency distributions of the indexes of age, gender and smoking status for the investigated 358 lung cancer

Table I. *Summary of selected demographics of the 358 patients with lung cancer and the 716 matched controls.*

Characteristics	Controls (n=716)			Patients (n=358)			*p*-Value[a]
	N	%	Mean (SD)	n	%	Mean (SD)	
Age (years)			64.8 (6.8)			64.0 (6.9)	0.5871
Gender							
Male	488	68.1%		254	70.9%		
Female	228	31.9%		104	29.1%		0.3642
Smoking status							
Ever smokers	563	78.6%		293	81.8%		
Non-smokers	153	21.4%		65	18.2%		0.2282
Histology							
Adenocarcinoma				218	60.9%		
SCC				106	29.6%		
Other				34	9.5%		

[a]Based on Chi-square test without Yates' correction; SCC, squamous cell carcinoma; SD, standard deviation.

patients and their matched 716 (double in size) non-cancer healthy controls, are shown in Table I. In addition, the histology of the lung cancer patients is also shown at the bottom of Table I. Since we have applied frequency matching strategies focusing on age, gender and smoking status to recruit those 716 non-cancer healthy subjects as controls, the data showed that there was no difference in respect to the distributions of age, gender and smoking behavior between the two groups (all *p*-values >0.05) (Table I). Please note that since we matched the frequency of lung cancer smoking when choosing controls, the percentage of smokers in the control group is rather high (78.6%) and it does not represent the whole Taiwanese population. Among the lung cancer patients, 60.9% (218 out of 358) had adenocarcinoma, 29.6% (106 out of 358) had squamous cell carcinoma type and 9.5% (34 out of 358) had other types.

The genotypic distributions of *ERCC1* rs11615 and rs3212986 among the 716 non-cancer controls and the 358 lung cancer patients are presented and analyzed in Tables II and III, respectively. Firstly, the results showed that the genotypes of *ERCC1* rs11615 were differently distributed between the lung cancer and healthy control groups (*p* for trend=0.0082) (Table II). More specifically, the *ERCC1* rs11615 homozygous variant TT genotype, but not the heterozygous CT variant genotype, was associated with an elevated lung cancer risk, compared to the wild-type homozygous CC genotype (OR=1.90 and 1.16, 95%CI=1.26-2.86 and 0.89-1.53, *p*=0.0019 and 0.2770, respectively; Table II). In the recessive model, there was a 1.77-fold elevated lung cancer risk for those TT genotype carriers with *ERCC1* rs11615, compared to those carrying CC+CT genotypes (OR=1.77, 95%CI=1.20-2.61, *p*=0.0036, Table II). In the dominant model, there was a significant 1.29-fold elevated lung cancer risk for those CT+TT genotype carriers of *ERCC1* rs11615, compared to those carrying CC genotypes (OR=1.29, 95%CI=1.00-1.67, *p*=0.0469, Table II). Second, the results showed that the genotypes of *ERCC1* rs3212986 were non-differently distributed between the lung cancer and healthy control groups (*p* for trend=0.7013 (Table III). The genotypes of *ERCC1* rs3212986 were not differently distributed between the case and control groups in recessive and dominant models (Table III).

To confirm the results in Tables II and III, allelic frequency distribution analysis for the *ERCC1* rs11615 and rs3212986 was conducted and the results are shown in Table IV. Supporting the findings that genotype of *ERCC1* rs11615 was associated with lung cancer risk, the variant allele T was found at 35.6% in the lung cancer group, significantly higher than that of 29.5% in the control group (OR=1.32, 95%CI=1.09-1.60, *p*=0.0039). In addition, there was no significant difference in the allelic frequencies of *ERCC1* rs3212986 between the lung cancer and control groups (Table IV).

Since personal smoking habit is a famous risk contributor to lung cancer both in Taiwan and all over the world, we were interested in examining the interactions between the genotype of *ERCC1* rs11615 and personal cigarette smoking habits via stratification analysis. The results showed that among smokers, those with *ERCC1* rs11615 TT genotype were at 1.85-fold odds of having lung cancer (95%CI=1.17-2.92, *p*=0.0077), while this was not the case for non-smokers (Table V). After adjusting for age, gender and alcohol drinking status, the statistical significance still existed at a similar level (OR=1.98, 95%CI=1.24-3.37, Table V). There is no such differential interaction present for the *ERCC1* rs11615 TT genotype and personal alcohol drinking habits (data not shown).

Table II. *Excision repair cross-complementing group 1 (ERCC1) rs11615 genotypes among the 358 patients with lung cancer and 716 healthy controls.*

Genotype	Controls		Patients		OR (95% CI)	*p*-Value[a]
	N	%	n	%		
rs11615						
CC	358	50.0%	156	43.6%	1.00 (Reference)	
CT	294	41.1%	149	41.6%	1.16 (0.89-1.53)	0.2770
TT	64	8.9%	53	14.8%	1.90 (1.26-2.86)	0.0019*
ptrend						0.0082*
Carrier comparison						
CC +CT	652	91.1%	305	85.2%	1.00 (Reference)	
TT	64	8.9%	53	14.8%	1.77 (1.20-2.61)	0.0036*
CC	358	50.0%	156	43.6%	1.00 (Reference)	
CT+TT	358	50.0%	202	56.4%	1.29 (1.00-1.67)	0.0469*

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

Table III. *Excision repair cross-complementing group 1 (ERCC1) rs3212986 genotypes among the 358 patients with lung cancer and 716 healthy controls.*

Genotype	Controls		Patients		OR (95% CI)	*p*-Value[a]
	n	%	n	%		
rs3212986						
GG	329	45.9%	167	46.6%	1.00 (Reference)	
GT	315	44.0%	150	41.9%	0.94 (0.72-1.23)	0.6419
TT	72	10.1%	41	11.5%	1.12 (0.73-1.72)	0.5970
p_{trend}						0.7013
Carrier comparison						
GG+GT	644	89.9%	317	88.5%	1.00 (Reference)	
TT	72	10.1%	41	11.5%	1.16 (0.77-1.74)	0.4819
GG	329	45.9%	167	46.6%	1.00 (Reference)	
GT+TT	387	54.1%	191	53.4%	0.97 (0.75-1.25)	0.8287

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

Discussion

DNA repair is a house-keeping system of defenses evolved to protect genomic integrity and prevent carcinogenesis. The main pathways of the DNA repair system are the base excision repair (BER), nucleotide excision repair (NER), mismatch repair (MMR) and double-strand break repair (DSBR), while inter-individual differences in subtle DNA repair capacities may contribute to differential susceptibility to all cancer types (27). *ERCC1*, encoded from its 14-exon gene located at 19q13.32, plays a central role in NER pathway assembling with *ERCC4* (XPF) to form a heterodimer, which is responsible for 5' incision of DNA lesions (28). In the literature, there have been several *ERCC1* SNPs examined for their cancer risk and s11615 and rs3212986 have been the most frequently studied. For example, identifying the *ERCC1* rs11615 genotype may help in predicting a positive or poor outcome of platinum-based chemotherapy for patients with colorectal (29), advanced gastric (30-32) and breast cancer (33) as well as testicular germ cell tumors (34), ovarian (35, 36), esophageal (37), and most importantly, non-small cell lung cancer (17-20). Molecular studies consistently provided evidence showing that *ERCC1* rs11615 T allele is associated with relatively lower expression of ERCC1 at both the mRNA and protein levels; however, its role as a predictive marker for cancer therapy is controversial (38-42). It is likely that in the initial step of carcinogenesis, the subtle defects in DNA repair capacity of lung cells may contribute to the increased cancer susceptibility of those carrying this *ERCC1* T allele. In the current work, we found that the *ERCC1* rs11615 TT genotype is associated with 1.90-fold enhanced CRC risk (Table II), which is further elevated to 1.98-fold odds of having lung

Table IV. *Distribution of allelic frequencies for excision repair cross-complementing group 1 (ERCC1) among the 358 patients with lung cancer and 716 healthy controls.*

Allele	Controls, n	%	Patients, n	%	OR (95% CI)	*p*-Value[a]
rs11615						
C	1010	70.5%	461	64.4%	1.00 (Reference)	
T	422	29.5%	255	35.6%	1.32 (1.09-1.60)	0.0039*
rs3212986						
G	973	67.9%	484	67.6%	1.00 (Reference)	
T	459	32.1%	232	32.4%	1.02 (0.84-1.23)	0.8703

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

Table V. *Odds ratios for excision repair cross-complementing group 1 (ERCC1) rs11615 genotype in lung cancer risk 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	77	28	1.00 (ref)	1.00 (ref)		281	128	1.00 (ref)	1.00 (ref)	
CT	63	27	1.18 (0.63-2.20)	1.09 (0.75-1.55)	0.6061	231	122	1.16 (0.86-1.57)	1.23 (0.69-1.78)	0.3385
TT	13	10	2.12 (0.83-5.37)	1.93 (0.86-1.95)	0.1100	51	43	1.85 (1.17-2.92)	1.98 (1.24-3.37)	0.0077*
Total	153	65				563	293			

[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.

cancer among smokers after adjusting for confounding factors (Table V). Cigarette smoking is the major environmental contributor for lung cancer risk, and lots of compounds in cigarettes are reported to induce DNA damage, initiating and promoting lung carcinogenesis (43). This current study is the first one to reveal joint effects between *ERCC1* rs11615 genotypes with cigarette smoking habits on the susceptibility to lung cancer.

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-up limited the analysis of the correlation of prognosis indexes, such as survival rates. We also analyzed the potential for *ERCC1* rs11615 and rs3212986 genotypes to the prediction of tumor size, stage and metastasis, but no significant association was found (data not shown). Secondly, insufficient tumor and non-tumor samples limited the current study of differential expression of *ERCC1* mRNA and protein levels among subjects, in addition to the inter-individual differences of the lung cancer patients. Further molecular investigations of the genotype-phenotype correlation may help in understanding the contribution of *ERCC1* genotypes not only to overall DNA repair capacity but personal susceptibility to lung cancer. Thirdly, the relatively small sample size, especially for the subgroup analysis, such as those in Table V, may have caused some bias and reduced the statistical power for further evaluations.

In conclusion, this study provides evidence that the T allele at *ERCC1* rs11615 may interact with the smoking status to determine personal susceptibility to lung cancer. Further investigations should be conducted to reveal the detailed alteration of DNA repair capacity in relation to lung cancer susceptibility and prognosis.

Conflicts of Interest

The Authors declare no conflicts of interest regarding this study.

Authors' Contributions

Research Design: Chen LH, Shen TC and Chiu KL; Patient and Questionnaire Summary: Shen TC, Li CH and Hsia TC; Experiment Data Clearing and Checking: Hsiau YC, Wang YC and Chang WS; Statistical Analysis: Chen LH, Wang ZH and Gong CL; Manuscript Writing: Tsai CW and Bau DT; Reviewing and Revising: Bau DT, Chang WS and Tsai CW.

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