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Polymorphisms in ERCC1 and ERCC2/XPD Genes and Carcinogen DNA Adducts in Human Lung

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Abstract

Objectives—In this exploratory study, we aimed to investigate whether polymorphisms in excision repair cross-complementing group 1 (ERCC1) and excision repair cross-complementing group 2/xeroderma pigmentosum group D (ERCC2/XPD) in the nucleotide excision repair (NER) pathways associated with DNA adducts in human lung tissue. We also analyzed the association stratified by the major histologic subtypes of non-small cell lung cancer (NSCLC): adenocarcinoma (ADC) and squamous cell carcinoma (SQCC).

Methods—The study population consisted of 107 early stage NSCLC patients from the Massachusetts General Hospital (MGH) in Boston who underwent curative surgical resection. Genotyping was completed for SNPs in ERCC1 [C8092A (rs3212986) and C118T (rs11615)] and ERCC2/XPD [Asp312Asn (rs1799793) and Lys751Gln (rs1052559)] using a PCR-RFLP method and the PCR with fluorescent allele-specific oligonucleotide probes (Taqman). DNA adduct levels were measured as relative adduct levels per 10¹⁰ nucleotides by ³²P-postlabeling in non-tumor lung tissue.

Results—After adjusting for potential confounders, lung DNA adduct levels increased by 103.2% [95% confidence interval (CI), –11.5 to 366.6] for ERCC2/XPD rs1799793AA genotype compared with their corresponding wild type homozygous genotypes in overall NSCLC, but the difference did not reach statistical significance. When we stratified by the subtypes of NSCLC, we found that DNA adducts levels in lung increased by 204.9% (95% CI, 0.8 to 822.2, P = 0.059) for ERCC2/XPD rs1799793AA genotype in subjects with SQCC and the trend was statistically significant (P for trend = 0.0489).

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Conclusions—Polymorphisms in ERCC2/XPD Asp312Asn may be associated with increased DNA adduct levels in the lung, especially among subjects with SQCC. Further large scale studies are needed to confirm our findings.

Keywords

ERCC1; ERCC2/XPD; DNA repair; DNA adduct; non-small cell lung cancer

1. Introduction

DNA adducts serve as a marker of exposure to tobacco-associated carcinogen such as polycyclic aromatic hydrocarbons (PAHs), listed as Group 1 (carcinogenic to humans) by IARC, and also as one of the early hallmarks of cancer [1]. If damaged DNA is not repaired, DNA adducts may cause permanent mutations and thereby lead to development of lung cancer, by far the leading cause of cancer deaths in men and women in the United States, 2014 [2].

The nucleotide excision repair (NER) pathway, a major and well-developed cellular repair mechanism, is responsible for the repair of DNA damage including PAH-DNA adducts [3]. The two genes, excision repair cross-complementing group 1 (ERCC1) and excision repair cross-complementing group 2/xeroderma pigmentosum group D (ERCC2/XPD), are the major components of NER pathway. The ERCC1 protein, interacting with XPA/XPF and other NER proteins, is responsible for recognition of DNA damage and incision of the damaged strand during NER. The ERCC2/XPD gene is a core component of transcription factor IIH (TFIIH), which involved in gene transcription and NER by unwinding DNA around the lesion [4]. Both ERCC1 and ERCC2/XPD contain polymorphisms that may modulate repair capacity and thus influence susceptibility of lung cancer [5-9]. A few in-vitro studies have reported their effects on DNA adduct levels in peripheral blood lymphocytes, a surrogate for target lung tissue [10, 11]. However, no studies have examined their role in DNA adducts in target human lung tissue.

Therefore, we aimed to assess whether polymorphisms in ERCC1 and in ERCC2/XPD in the NER pathways influence DNA adduct levels in target human lung tissue in non-small cell lung cancer (NSCLC), a major form of lung cancer, accounting for about 85% of all lung cancer [12]. We further analyzed the association stratified by two major histologic subtypes of NSCLC: adenocarcinoma (ADC) and squamous cell carcinoma (SQCC). In the present study, we included a more comprehensive list of four NER SNPs: ERCC1 C8092A and ERCC1 C118T (rs3212986 and rs11615) and ERCC2/XPD Lys751Gln and ERCC2/XPD Asp312Asn (rs1052559 and rs1799793) which have been implicated in the risk of lung and other types of cancer development by our prior studies as well as others [5-9, 13-15].

2. Materials and methods

2.1 Study Population

The Committees on the Use of human Subjects in Research at the Massachusetts General Hospital (MGH) and the Harvard School of Public Health approved our study. The study population consisted of 135 consecutively enrolled lung cancer patients at MGH (Boston, MA), as we described previously [16-18]. Of the 135 patients, genotyping and complete clinical data was available on 107 Caucasian patients. Information on demographic and detailed smoking history was obtained using a modified American Thoracic Society (ATS) questionnaire [19] by trained personnel.

2.2. DNA Adducts

We used previously reported data on DNA adducts in human lung samples determined by the ³²P-postlabeling assay [20, 21]. These adducts are considered primarily to represent tobacco-derived aromatic hydrophobic adducts, mainly PAH-DNA adducts [20, 21]. The half-life of DNA adduct in the lung tissue of lung cancer patients has been reported to be approximately 1.7 years, indicating that DNA adduct persist longer in lung tissues than other tissues [22]. Surgically resected non-involved lung tissue was sampled from the same lobe, distal to tumor in patients at the time of diagnosis for lung cancer. The collected specimens were frozen immediately on dry ice and stored deep-frozen at -80 until DNA adduct analysis. Total relative DNA adducts were measured in the diagonal reactive zone plus discrete adducts as in prior studies [21]. Each sample was repeated at least twice as a validation analysis and average adducts levels were obtained from the combination of all experiments of the relative adduct levels. The coefficient of variation for the repeated measurements was 14% for the positive control sample of DNA containing benzo[a]pyrene diol epoxide (BPDE) labeled deoxyguanosine [21].

2.3. Genotyping

DNA was extracted from peripheral blood samples using the Puregene DNA Isolation Kit (Gentra Systems, Minneapolis, MN). Four NER SNPs: ERCC1 C8092A and C118T (rs3212986 and rs11615) and ERCC2/XPD Lys751Gln and Asp312Asn (rs1052559 and rs1799793) were genotyped using the Taqman[®] assays with an ABI 7900HT sequence detection system (Applied Biosystems, Foster City, CA). For quality control, a random 5% of the samples were repeated. All genotyping results were blindly and independently verified by two researchers (LS and a research technologist).

2.4. Statistical analysis

The dependent variable, DNA lung adduct per 10¹⁰ nucleotides, was transformed using natural logarithm to improve normality and to stabilize the variance. Genotypes were coded as wild type (major-allele homozygote), minor-allele homozygote and minor-allele heterozygote. Potential confounders including age at diagnosis (tertile), gender (male and female), smoking status (ex-smoker and current smoker), pack-years of smoking (continuous), and histology (ADC, SQCC, and others) were adjusted in the multiple linear regression analysis. We estimated the percent change in DNA lung adduct levels for the risk

genotype compared with the common allele as $[e^{\beta} - 1] \times 100\%$, with 95% CI $[e^{(\beta \pm 1.96 \times SE)} - 1] \times 100\%$, where β and SE are the estimated regression coefficient and its standard error from multiple regression analysis. To assess the linear trend in associations, trend tests were conducted by treating each category as a continuous variable in regression models. In addition, we performed stratified analysis by histologic subtypes, ADC and SQCC. We also conducted post hoc power analyses, based on the number of individuals in our population. All statistical analyses were performed using SAS version 9.4 (SAS Institute Inc., Carry, NC, USA).

3. Results

3.1. Lung DNA adduct levels by general characteristics

DNA adduct levels in lung by demographic and clinical variables of the study population are presented in Table 1. The study population is all Caucasian, consisting of 59 (55%) men and 48 (45%) women, with a mean age of 66 years. The geometric mean (GM) of DNA adduct levels was 89.4 adducts per 10^{10} nucleotides in lung tissue (mean, 172 adducts per 10^{10} nucleotides). To check for possible selection bias due to lack of genotyping data (21% of the population), we tested whether differences exist between the two groups, cases with ERCC1 or ERCC2/XPD genotypes ($n=107$) and cases without ERCC1 or ERCC2/XPD genotypes ($n=28$). There were no statistical significant differences in age, gender, smoking status, histology, pack-years, and DNA adduct levels in the lung.

3.2. Lung DNA adduct levels by ERCC1 and ERCC2/XPD genotypes

Genotype frequencies and lung adduct levels by each genotype are given in Table 2. For ERCC1 rs3212986, the frequency of C-allele was 0.77 and A-allele was 0.22, for ERCC1 rs11615 the frequency of T-allele was 0.58 and C-allele was 0.42. Similarly, for ERCC2/XPD rs1799793, the frequency of G-allele was 0.71 and A-allele was 0.29; and for ERCC2/XPD rs1052559 the frequency of T-allele was 0.58 and G-allele was 0.42. The geometric mean (GM) of DNA adduct levels in lung were high in individuals with variant minor-allele homozygote genotype of each SNP.

3.3. Associations between ERCC1 and ERCC2/XPD genotypes and DNA adduct in lung

Table 3 shows the associations between ERCC1 and ERCC2/XPD genotypes and DNA adduct levels in lung. After adjusting for potential confounders, DNA adduct levels in lung increased by 91.4% [95% confidence interval (CI), -32.5 to 442.5] for ERCC1 rs3212986 AA genotype and by 52.3% (95% CI, -23.1 to 201.5) for ERCC1 rs11617 CC genotype. Similarly, DNA adduct levels in lung increased by 103.2% (95% CI, -11.5 to 366.6) for ERCC2/XPD rs1799793AA genotype and by 42.0% (95% CI, -31.0 to 192.2) for ERCC2/XPD rs1052559GG genotype compared with their corresponding wild type homozygous genotypes, though the difference did not reach statistical significance. When stratifying major histologic subtype, SQCC and ADC, elevated DNA adducts levels in the lung were higher - 204.9% (95% CI, 0.8 to 822.2, $P = 0.059$) for ERCC2/XPD rs1799793AA genotype in SQCC than those in ADC and the trend was significant (P for trend = 0.0489). Post-hoc power analyses indicated that the power to detect a similar effect

as observed in ERCC/XPD rs1799793AA genotype was 51% among the patients with SQCC.

When we also stratified by smoking status, greater increase in DNA adduct levels of 1,425.2% (95% CI, 222.4 to 7,114.5, $P = 0.005$) for ERCC2/XPD rs1799793AA genotype was found in former smokers than those in current smokers of 38.9% (95% CI, -78.2 to 786.4) among lung SQCC and the trend was significant (P for trend = 0.034).

4. Discussion

To our knowledge, this is the first study examining the association between polymorphisms in NER pathway genes and DNA adducts in target human lung tissue. In this study, we found that genetic polymorphisms in ERCC2/XPD Asp312Asn were associated with an increase in DNA lung adducts levels, especially among subjects with SQCC, implying that ERCC2/XPD Asp312Asn may be one of the underlying mechanisms for modulating DNA damage in target lung tissue.

To date, there is no clinical or epidemiological evidence regarding the role of ERCC1 and/or ERCC2/XPD genes on DNA adducts in human lung tissue. A few in vitro studies have reported their influence on DNA adduct levels in peripheral blood lymphocytes (PBLs) [10, 11], used as surrogate tissue in molecular epidemiology studies of lung cancer. In a study of healthy non-Hispanic white, BPDE-induced DNA adduct levels in PBLs larger than median value were associated with the genotypes ERCC1 rs3212986 TT and ERCC2/XPD rs238406 AA compared with their wild-type homozygous genotypes [11]. In the other in vitro study of healthy Han individuals from the northeast of China, ERCC1 rs3212986 A-allele variant was associated with increased in vitro-induced BPDE-DNA adducts in PBLs [10], whereas individuals with ERCC2 rs1799793 AA genotype had lower BPDE-DNA adduct levels than those with the wild-type genotype. However, some limitations in those studies should be noted. The half-life of DNA adduct in PBLs has been reported to be approximately 9 to 13 weeks [23], indicating a relatively short half-life than DNA adduct levels in lung tissues (1.7 years) [22]. In addition, there were large variations in the levels of in vitro-induced DNA adduct in PBLs [11] and in vitro-induced DNA adducts in PBLs were only detected in 34% (282 of 818) of the study participants [10], which may limit generalizability.

A few studies have reported significant associations between ERCC2/XPD Asp312Asn and risk of lung [6, 7, 9] and other types of cancer, including esophageal squamous cell carcinoma [14] and squamous cell carcinoma of the head and neck [15]. In an in vitro study of human lung tissue explants, DNA adduct levels were significantly higher in patients with SQCC than those in patients with ADC [24]. In a case-control study of lung cancer in a Chinese population, subjects with the variant Asp312Asn genotypes had an increased risk of lung cancer (OR: 10.33, 95% CI: 1.29 to 82.50), and the increased association was only evident among lung SQCC, with the ORs being 20.50 (95% CI: 2.25 to 179.05) for the variant Asp312Asn genotype, but not ADC and other subtypes of lung cancer [25]. This finding may be due to cigarette smoking, which causes all types of lung cancer but is linked more strongly with SQCC than with other histologic subtypes of NSCLC [12]. Tobacco carcinogens such as PAHs can bind preferentially at the mutational p53 hot spot to induce

DNA adduct formation that is repaired mainly by the NER pathway [26, 27]. A case-control study reported the interaction between smoking and DNA repair capacity (DRC) in peripheral lymphocytes, especially in the patients with SQCC or other histologic types of NSCLC other than ADC [28]. Thus genetic variants of ERCC2/XPD Asp312Asn, which may have reduced NER capacity [29], may modulate DNA damage and thus influence the susceptibility of smoking-related lung SQCC [25]. We found a strong DNA adduct-ERCC2/XPD Asp312Asn association in former smokers compared with current smokers among lung SQCC that, in current smokers, influence of smoking may mask the effects of genetic polymorphisms in ERCC2/XPD Asp312Asn on DNA adduct levels.

Although the underlying mechanisms have not yet been fully understood, the NER is the major pathway that is responsible for the repair of DNA damage, including DNA adducts induced by tobacco carcinogens such as PAHs [26, 27]. The two genes, ERCC1 and ERCC2/XPD, exert an important role in repairing DNA damage and NER function. The ERCC1 protein is responsible for recognition of DNA damage and removal of the damaged DNA by 5' incision [30]. The ERCC2 codes for an evolutionarily conserved helicase, a subunit of TFIIH complex which is essential for transcription and NER [4]. Genetic polymorphisms in SNPs in ERCC1 and ERCC2/XPD may influence their protein activity, resulting in differences of individual NER and DNA repair capacity (DRC) that may modulate the level of DNA damage and affect susceptibility to lung cancer [10, 31].

The major limitations of our study include the relatively small sample size and the inclusion of Caucasian-only population which limited generalizability across other populations, as have been discussed in our previous reports [16-18]. Further studies with large sample sizes are needed to confirm our findings.

In conclusion, our findings suggest that DNA adduct levels in target lung tissue may influenced by genetic polymorphisms in ERCC2/XPD Asp312Asn, especially among subjects with lung SQCC, implying that ERCC2/XPD Asp312Asn may be one of the underlying mechanisms for modulating DNA damage in target lung tissue in smoking-related lung cancer.

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Abbreviations

ADC	adenocarcinoma
BPDE	benzo[a]pyrene diol epoxide
ERCC1	excision repair cross-complementing group 1
DRC	DNA repair capacity

ERCC2/XPD	excision repair cross-complementing group 2/xeroderma pigmentosum group D
GM	geometric mean
GSD	geometric standard deviation
NER	nucleotide excision repair
NSCLC	non-small cell lung cancer
PAHs	polycyclic aromatic hydrocarbons
SQCC	squamous cell carcinoma
TFIIH	transcription factor IIH

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Highlights

- We assessed whether polymorphisms in NER genes influence DNA lung adducts in NSCLC.
- Increased lung adducts were found for *ERCC2/XPD* rs1799793AA genotype among SQCC.
- Further large scale studies are warranted to confirm our findings.

Table 1

Lung DNA adduct levels (per 10^{10} nucleotides) by general and clinical characteristics of study subjects (N = 107)

	N (%)	GM $\pm$ GSD [†]
Total	107 (100.0)	86.2 $\pm$ 4.7
Age at diagnosis (tertile)		
<62	37 (34.6)	112.2 $\pm$ 4.1
62-71	36 (33.6)	68.7 $\pm$ 6.6
>71	34 (31.8)	92.1 $\pm$ 2.6
Gender		
Male	59 (55.1)	105.8 $\pm$ 2.9
Female	48 (44.9)	72.6 $\pm$ 6.5
Smoking		
Current	47 (43.9)	168.3 $\pm$ 2.8
Former	60 (56.1)	54.4 $\pm$ 5.0
Pack-years (tertile)		
<41	34 (31.8)	49.7 $\pm$ 5.2
41-70	37 (34.6)	88.8 $\pm$ 5.1
>70	36 (33.6)	156.5 $\pm$ 2.3
Histology		
Adenocarcinoma (ADC)	51 (47.7)	73.3 $\pm$ 5.1
Squamous cell carcinoma (SQCC)	36 (33.6)	107.3 $\pm$ 3.1
Others	20 (18.7)	106.6 $\pm$ 5.3

[†] Geometric mean $\pm$ geometric SD

Table 2

Distribution of lung adducts by *ERCC1* and *ERCC2/XPD* genotypes

SNP	Genotype	Allele frequency	Overall			ADC			SQCC		
			N	GM	GSD	N	GM	GSD	N	GM	GSD
<i>ERCC1</i> (C8092A), rs3212986 (n=103)	AA	A 0.23	7	182.1	2.6	4	130.8	2.6	3	282.9	2.4
	CA		34	66.5	5.4	17	69.8	5.2	11	99.2	3.9
	CC	C 0.77	62	96.0	4.2	29	67.5	5.6	20	99.6	2.9
<i>ERCC1</i> (C118T), rs11615 (n=103)	CC	C 0.42	23	108.5	4.9	19	74.7	7.4	7	164.6	3.6
	CT		38	80.4	4.2	20	74.2	4.7	16	96.2	4.1
	TT	T 0.58	42	87.1	4.8	20	68.5	5.0	11	100.9	2.0
<i>ERCC2/XPD</i> (Asp312Asn), rs1799793 (n=95)	AA	A 0.29	12	161.6	3.0	6	152.6	3.8	5	212.5	2.2
	GA		31	82.4	4.0	13	64.4	6.2	12	119.2	2.7
	GG	G 0.71	52	71.8	5.1	26	54.2	5.4	16	64.5	3.1
<i>ERCC2/XPD</i> (Lys751Gln), rs1052559 (n=95)	GG	G 0.42	18	117.0	3.2	10	93.3	3.3	6	150.7	3.0
	TG		37	81.6	4.9	15	78.2	5.2	13	115.1	2.8
	TT	T 0.58	40	72.7	4.9	20	59.7	6.9	14	66.6	3.2

ADC, adenocarcinoma; SQCC, squamous cell carcinoma

Table 3
Adjusted percent changes and 95% CIs in lung adduct levels associated with *ERCC1* and *ERCC2/XPD* genotypes

SNP	Overall				ADC				SQCC			
	% Change [†]	95% CI	Power [§]	% Change [‡]	95% CI	Power [§]	% Change [‡]	95% CI	95% CI	Power [§]	% Change [‡]	95% CI
<i>ERCC1</i> (C8092A)	AA	91.4	-32.5 to 442.5	0.230	48.6	-69.5 to 622.9	0.071	182.9	-36.3 to 1,157.3	0.278	-13.0	-64.8 to 115.3
	CA	-20.1	-54.3 to 39.8	0.003	10.5	-54.1 to 166.0	0.041	Reference	Reference	0.012	Reference	Reference
	CC	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference
<i>P</i> trend	0.7147			0.6354			0.4133					
<i>ERCC1</i> (C118T)	CC	52.3	-23.1 to 201.5	0.227	45.8	-53.4 to 356.2	0.097	47.6	-55.5 to 389.5	0.093	-36.0	-75.0 to 63.6
	CT	8.9	-40.5 to 99.4	0.046	45.4	-42.0 to 264.2	0.123	Reference	Reference	0.002	Reference	Reference
	TT	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference
<i>P</i> trend	0.2405			0.4424			0.6799					
<i>ERCC2/XPD</i> (Asp312Asn)	AA	103.2	-11.5 to 366.6*	0.386	104.0	-49.4 to 721.8	0.169	204.9	0.8 to 822.2*	0.508	62.6	-24.0 to 247.8
	GA	16.3	-33.9 to 104.7	0.076	15.7	-58.4 to 222.0	0.046	Reference	Reference	0.239	Reference	Reference
	GG	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference
<i>P</i> trend	0.1188			0.3478			0.0489					
<i>ERCC2/XPD</i> (Lys75Gln)	GG	42.0	-31.0 to 192.2	0.156	44.0	-55.1 to 361.5	0.089	68.0	-40.8 to 376.1	0.164	12.3	-52.0 to 162.6
	TG	11.3	-37.5 to 98.1	0.056	33.5	-53.9 to 286.7	0.076	Reference	Reference	0.046	Reference	Reference
	TT	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference
<i>P</i> trend	0.3522			0.4984			0.3575					

* p < 0.1.

[†] Adjusted for age, gender, smoking status, pack-years, and histology (SQCC, ADC and others).

[‡] Adjusted for age, gender, smoking status, and pack-years.

[§] Observed Power = $1 - \phi \left(\frac{\beta}{SE} - 1.96 \right)$, where β and SE are the estimated regression coefficient and its standard error from mixed analysis [32].