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Modulation of Nucleotide Excision Repair Capacity by XPD Polymorphisms in Lung Cancer Patients[1]

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Abstract

Sequence variations have been identified in a number of DNA repair genes, including *XPD*, but the effect of these polymorphisms on DNA repair capacity (DRC) is uncertain. We therefore examined *XPD* polymorphisms at *Lys751Gln* and *Asp312Asn* in 341 white lung cancer cases and 360 age-, sex-, ethnicity-, and smoking-matched controls accrued in a hospital-based molecular epidemiological study of susceptibility markers for lung cancer. As previously reported, DRC was statistically significantly lower in the cases than in the controls (7.8% *versus* 9.5%; $P < 0.001$), which represents an average 18% reduction among the cases. The variant *Lys751Gln* and *Asp312Asn* allele frequencies were 0.36 and 0.29, respectively, for the cases and 0.33 and 0.27, respectively, for the controls. For subjects homozygous for the variant genotype at either locus, the adjusted odds ratio [95% confidence interval (CI)] was 1.84 (1.11–3.04; $P = 0.018$, for trend). Both cases and controls with the wild-type genotypes exhibited the most proficient DRC. The risk (95% CI) for suboptimal DRC (defined as less than the median DRC value among the controls) was 1.57 (0.74–3.35) for those with the *Gln/Gln751* genotype. For cases with the *Asn/Asn312* genotype, the risk (95% CI) was 3.50 (1.06–11.59). For cases who were homozygous at either locus, the risk was 2.29 (1.03–5.12; $P = 0.048$, for trend). The pattern was less evident among the controls, although there was a nonsignificant 41% increase in the risk of suboptimal DRC for controls who were homozygous at either locus. These results suggest that the two *XPD* polymorphisms have a modulating effect on DRC, especially in the cases.

Introduction

NER[3] is the repair pathway that eliminates the widest variety of damage to the human genome, including UV-induced photoproducts, bulky monoadducts, cross-links, and oxidative damage (1). There is an expanding body of evidence that suboptimal DRC constitutes a risk factor for cancer (2). At the extreme end of this spectrum are patients with xeroderma pigmentosum, who have a defect in NER, and who exhibit a 1000-fold increase in risk of skin cancer (3). We recently demonstrated that there are interindividual differences in DRC within both cancer patients and healthy subjects, and that the ability to repair BPDE-induced adducts in peripheral lymphocytes is a significant predictor of lung cancer risk (4).

XPD (originally named excision repair cross complementing group 2) is one of the seven genetic complementation groups encoding for proteins involved in the NER pathway. XPD has a dual function: (*a*) in nucleotide excision repair; and (*b*) in basal transcription. It functions as an evolutionary conserved ATP-dependent helicase within the multisuûbunit transcription repair factor complex, TFIIH. Different mutation sites in genes encoding the TFIIH complex lead to differing clinical phenotypes (5). Because TFIIH is required for all transcription by RNA polymerase II, *XPD* is considered an essential gene (5). In fact, inactivation of the gene is embryolethal in mice (6).

Extensive screening of DNA genes for sequence variations is under way in an effort to understand interindividual differences in DRC (7). The overall effect of conservative mutations in *XPD* may be subtle, because they would not alter XPB and XPD helicase activity, and multiple alterations might be needed before any effect was noted (8).

We have DRC data available on a substantial number of lung cancer cases and controls (4). The assay used to assess DRC is the host cell reactivation assay, which measures the expression level of damaged reporter genes. This assay uses undamaged cells, is relatively fast, and is an objective way of measuring intrinsic cellular DRC (9) for removing damage induced by B(*a*)P, a major constituent of tobacco smoke (10). BPDE can irreversibly damage DNA by covalent binding or oxidation (11). Such BPDE-DNA adducts are repaired by the NER pathway that is responsible for the restoration of normal DNA structure (12).

We therefore genotyped our population at *Lys751Gln* (exon 23) and *Asp312Asn* (exon 10) of the *XPD* gene. We hypothesized that these *XPD* mutations could have an effect on host capacity for removing bulky adducts induced by exposure to B(*a*)P. If there were such a functional relevance to the polymorphisms, we might detect differences in DRC in individuals of different *XPD* genotypes. Functional assays that require viable lymphocytes are not currently suitable for large-scale population-based epidemiological studies of cancer susceptibility. Therefore, our objective was to identify genotypes that predict DRC and are amenable to high-throughput analysis.

Materials and Methods

Case and Control Recruitment. The cases and controls were accrued in a molecular epidemiological study of susceptibility markers for lung cancer described previously (13). This study recruited newly diagnosed, untreated lung cancer patients at The University of Texas M. D. Anderson Cancer Center. There were no age, histological, or stage restrictions, but all cases were histologically confirmed. We had also created a pool of control subjects, recruited from the largest multispecialty managed-care organization in the Houston metropolitan area (14). For this analysis, we used 341 case subjects for whom we had complete epidemiological and DRC data. From the total control pool, we selected 360 control subjects frequency-matched to these cases on age, sex, and smoking status (never, former, and current). The exclusion criteria were previous radiotherapy or chemotherapy (for the cases) and previous invasive cancer and any recent blood transfusion (for all subjects). Because of the small numbers of minority subjects recruited, we report here only the data for white participants. Information on the subjects' sociodemographics, smoking history, alcohol consumption, medical history, and

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[3] The abbreviations used are: NER, nucleotide excision repair; DRC, DNA repair capacity; BPDE, benzo(*a*)pyrene diol epoxide; B(*a*)P, benzo(*a*)pyrene; OR, odds ratio; CI, confidence interval; TFIIH, transcription factor IIH; CAT, chloramphenicol acetyltransferase.

family history of cancer was collected, and blood samples were drawn as reported previously (13).

Genotyping Methods. The *XPD* genotypes were determined by PCR-RFLP analysis of DNA samples collected previously (4). The PCR primers for the *Lys751Gln* gene were: forward, 5′-GCCCGCTCTGGATTATACG-3′; and reverse, 5′-CTATCATCTCCTGGCCCCC-3′. PCR was performed in 50-μl containing 2 mM $MgCl_2$, 0.04 mM deoxynucleotide triphosphates, 2.5 units of Taq polymerase, and the manufacturer's buffer [20 mM Tris-HCl (pH 8.4) and 50 mM KCl]. After an initial denaturation at 94°C for 3 min, there were 38 cycles of 45 s at 94°C, 45 s at 60°C, and 60 s at 72°C, and then a final extension step of 7 min at 72°C. After overnight digestion of the PCR product with *Pst*I, 15 μl of the digested products were resolved on a 3% agarose gel (5 V/cm) containing ethidium bromide. The homozygous wild-type allele (*Lys 751*) produced two DNA bands (290 and 146 bp), whereas the mutant allele (*Gln 751*) produced three DNA bands (227, 146, and 63 bp). Heterozygotes displayed all four bands (290, 227, 146, and 63 bp).

For amplification of the exon 10 region of *XPD*, which contains the polymorphic *Sty*I restriction site (15), we used the oligonucleotide primers 5′-CTGTTGGTGGGTGCCCGTATCTGTTGGTCT-3 (bases 22872–22901 of *XPD*) and 5′-TAATATCGGGGCTCACCCTGCAGCACTTCCT (bases 23592–23616 of *XPD*). PCR was performed in 25 μl reaction mixtures containing 1.5 mM $MgCl_2$, 0.2 mM deoxynucleotide triphosphates, 3% DMSO, 0.2 μM primers, 1 μg of template DNA, and 1.5 units of Taq polymerase in PCR buffer [10 mM Tris-HCl (pH 9.0 at 25°C), 50 mM KCl, and 0.1% Triton X-100 (Promega)]. After an initial denaturation at 94°C for 4 min, the DNA was amplified by 30 cycles of 30 s at 94°C, 30 s at 60°C, and 60 s at 72°C, and then by a final extension step of 5 min at 72°C. Fifteen μl of the PCR product was digested with *Sty*I for 8 h at 37°C. The digestion products were then resolved on a 3% agarose gel (5 V/cm) containing ethidium bromide. The homozygous wild-type *(Asp/Asp)* was identified by two DNA bands (507 and 244 bp), the homozygous mutant type *(Asn/Asn)* produced three bands (474, 244, and 33 bp); and heterozygotes *(Asp/Asn)* displayed all four bands (507, 474, 244, and 33 bp). These exon 10 genotype data were available for only 195 cases and 257 controls.

DNA Repair Assay. The host cell reactivation assay measures the activity of the *CAT* gene, a bacterial drug resistance gene, in cells that have been transfected with BPDE-treated plasmids (9, 16). Because a single unrepaired DNA adduct can effectively block CAT transcription (17), any CAT activity will reflect the ability of the transfected cells to remove BPDE-induced adducts from the plasmids. Therefore, this assay provides a quantitative measurement of the DRC of the host cells. CAT activity in transfected cells was measured as described previously (9).

Statistical Methods. Demographic data were merged with laboratory data. An individual who had smoked at least 100 cigarettes in his or her lifetime was defined as an "ever" smoker. Ever smokers included former smokers, current smokers, and recent quitters (those who had quit within the previous year). "Former" smokers were those who had quit smoking at least 1 year before diagnosis (for cases) or 1 year before the interview (for controls). Pearson's χ^2 was used to test the differences in the distributions between cases and controls. Hardy-Weinberg equilibrium was tested by a goodness-of-fit χ^2 test to compare the observed genotype frequencies with the expected genotype frequencies among the cases and controls (18). ORs were calculated as an estimate of the relative risk. Multivariate logistic regression was performed to control for confounding by age, sex, and smoking status where appropriate. Trend tests for the ordered variables (pack-years and age) were performed by assigning the score j to the j^{th} exposure level of the categorical variable. The categorical variable was treated as an interval predictor in the unconditional multivariate logistic models. A P of 0.05 for any test or model was considered to be statistically significant.

Linkage disequilibrium between the two polymorphisms was also evaluated (19). Briefly, we estimated the linkage disequilibrium parameter D as the difference between the estimated proportion of double heterozygotes minus the marginal probabilities of double heterozygotes. The normalized disequilibrium coefficients D′ were also calculated (20).

DRC data from the previous study (4) were analyzed as a continuous variable before and after natural logarithmic transformation. Student's t test was used to compare DRC in cases and controls. We compared DRC for each *XPD* genotype and also dichotomized DRC at the median control value to calculate crude ORs and 95% CIs. Values greater than the median were considered proficient DRC; values below the median were considered suboptimal DRC. Adjusted ORs were calculated by fitting unconditional multivariate logistic regression models with adjustments for age, sex, smoking status, and pack-years smoked. All statistical tests were two-sided and were performed with Statistical Analysis System software (Version 6: SAS Institute Inc., Cary, NC).

Results

There were 341 lung cancer cases and 360 controls in this analysis. Table 1 summarizes selected characteristics of the subjects (about half were male), and the mean ages of the cases and controls were similar (61.9 and 61.4 respectively), suggesting that matching on these two variables was adequate. There was a slightly higher percentage of current smokers (39.9%) among the cases than the controls (36.7%), but this difference was not statistically significant ($P = 0.608$). The cases also reported more cigarette pack-years smoked (51.8) than the controls did (48.6), but this difference, too, was not statistically significant ($P = 0.236$). The cases were more likely than the controls (33.8% *versus* 18.1%; $P < 0.001$) to report a family history of lung cancer in a first-degree relative. Similarly, there was a statistically significantly higher percentage of cases compared with controls (68.7% *versus* 56.9%) reporting any cancer in a first-degree relative.

As we reported previously (4), DRC was statistically significantly lower in the cases than in the controls (7.8% *versus* 9.5%; $P < 0.001$), representing an average 18% reduction in DRC among the cases (Table 1). This difference remained statistically significant after natural log transformation of the data, and so all results presented are for untransformed DRC.

There were no statistically significant differences in the distribution of *Lys751Gln* or *Asp312Asn* genotypes by case-control status (Table 2). The variant allele frequencies at codons 751 and 312 for the cases were 0.36 and 0.29, respectively, compared with 0.33 and 0.27, respectively, for the controls, which is compatible with previous reports (7, 21–23). The allele frequencies for the cases and controls were in Hardy-Weinberg equilibrium by the goodness-of-fit χ^2 statistic. For the *Lys751Gln* locus, the P for the Hardy-Weinberg test for cases and controls combined was 0.803 (0.906 for controls and 0.639 for the cases). The comparable Ps for the *Asp312Asn* locus were 0.485, 0.875, and 0.165 (data not shown). Twenty-five percent of the cases (compared with 17.5% of the controls) had two or more variant alleles (Table 2). When the data were partitioned by family history of any cancer in a first-degree relative, 28.5% of the positive family history cases, compared with 16.4% of the cases without a positive family history, had two or more variant alleles. There was a similar pattern among the controls (19.3% and 15.3%; data not shown).

On logistic regression analysis, the adjusted ORs for the variant

Table 1 *Distribution of select variables by case control status*

Variable	Cases *n* (%)	Controls *n* (%)	P^a
Male	170 (49.9)	198 (55.0)	
Female	171 (50.1)	162 (45.0)	0.173
Total	341 (100)	360 (100)	
Mean age in years (SD)	61.9 (9.4)	61.4 (10.3)	0.485
Smoking status			
Never	34 (10.0)	34 (9.4)	
Former	171 (50.1)	194 (53.9)	
Current	136 (39.9)	132 (36.7)	0.608
Mean number of cigarettes smoked/day (SD)	27.3 (16.0)	27.7 (16.7)	0.760
Mean pack-years smoked (SD)	51.8 (35.6)	48.6 (35.0)	0.236
Family history (% yes)[b]			
Lung cancer	54 (33.8)	34 (18.1)	<0.001
Any cancer	233 (68.7)	203 (56.9)	0.001
Mean DRC (%; SD)	7.8 (2.8)	9.5 (4.5)	<0.001

[a] Two-sided χ^2 test.
[b] Data missing in five subjects.

Table 2 *Distribution of XPD genotypes and DRC by case and control status*

Variable	Cases *n* (%)	Controls *n* (%)	Crude OR (95% CI)	Adjusted OR[a] (95% CI)
Total subjects	341 (100)	360 (100)		
Lys751Gln				
Lys/Lys	141 (41.3)	159 (44.2)	1.00	1.00
Lys/Gln	153 (44.9)	162 (45.0)	1.07 (0.78–1.46)	1.07 (0.78–1.47)
Gln/Gln	47 (13.8)	39 (10.8)	1.36 (0.84–2.20)	1.36 (0.84–2.20)
Trend test[a]			$P = 0.260$	$P = 0.260$
Asp312Asn[b]				
Asp/Asp	102 (52.3)	135 (52.5)	1.00	1.00
Asp/Asn	72 (36.9)	104 (40.5)	0.92 (0.62–1.36)	0.93 (0.63–1.39)
Asn/Asn	21 (10.8)	18 (7.0)	1.54 (0.78–3.05)	1.51 (0.76–3.00)
Trend test[a]			$P = 0.517$	$P = 0.535$
Lys751Gln + Asp312Asn				
Both wild-type	67 (31.5)	105 (39.2)	1.00	1.00
1 variant allele	92 (43.2)	116 (43.3)	1.24 (0.82–1.87)	1.28 (0.85–1.94)
2+ variant alleles	54 (25.3)	47 (17.5)	1.80 (1.10–2.96)	1.84 (1.11–3.04)
Trend test[a]			$P = 0.022$	$P = 0.018$
DRC (%)[a]				
Proficient	117 (65.7)	183 (50.8)	1.00	1.00
Suboptimal	224 (34.3)	177 (49.2)	1.98 (1.46–2.68)	2.00 (1.47–2.72)

[a] Obtained from the logistic regression model with adjustment for age (in yr), sex, and smoking status.
[b] Genotype data available for 195 cases and 257 controls.
[c] As described previously (4).

Lys751Gln or *Asp312Asn* genotypes were 1.36 and 1.51, respectively, although neither estimate was statistically significant. Finally, we evaluated the risk associated with combined genotypes. For individuals homozygous for the variant genotype at either locus, the adjusted risk estimate was 1.84 (1.11–3.04; $P = 0.018$, for trend; Table 2). The calculated linkage disequilibrium parameter D for the combined sample of cases and controls was 0.124974 (data not shown), with a χ^2 test statistic of 193.49. The estimates of δ were 0.124037 for cases and 0.125332 for controls, with χ^2 test statistics of 81.14 and 112.59, respectively. All *P*s with 1 degree of freedom were $<10^{-6}$. Hence, the null hypothesis was rejected, and we concluded that there was strong evidence for linkage disequilibrium. The estimated values of the normalized disequilibrium, D′, were 0.6679 for the combined sample, 0.6662 for controls, and 0.6700 for the cases. Thus we were able to reject the null hypothesis of no association between the two polymorphisms.

Next we determined genotype-phenotype correlations (Table 3). Among the cases, DRC was 8.21% for those with the *Lys/Lys 751* common genotype. This was higher than the DRC of the *Lys/Gln* heterozygotes (7.65%, $P = 0.10$) and significantly higher than the DRC of *Gln/Gln* homozygotes (7.20%; $P = 0.041$). The *P* for the trend was 0.017. A similar trend ($P = 0.008$) was evident for DRC among the cases for the *Asp312Asn* genotypes (8.37%, 7.50%, and 6.84%, for wild-type homozygotes, heterozygotes, and variant homozygotes, respectively). These patterns were less evident among the controls, although wild-type homozygous and heterozygous controls exhibited the most proficient DRC (Table 3). When we combined both genotypes, individuals who were homozygous wild-type at both loci exhibited the best DRC among both cases and controls. Cases and controls who were homozygous for the variant allele at one or both loci exhibited the poorest repair capacity. Again, the trend was only statistically significant among the cases ($P = 0.001$).

The risk (95% CI) for exhibiting suboptimal DRC was 0.85 (0.52–1.39) for individuals with the *715Lys/Gln* genotype and 1.57 (0.74–3.35) for those with the *751Gln/Gln* genotype (Table 4). For cases with the variant *codon 312 Asn/Asn* genotype, the risk for suboptimal DRC was 1.31 (0.68–2.51). For cases with at least one homozygous mutant genotype, the risk was 3.50 (1.06–11.59; Table 4). There was evidence of a gene-dosage effect, with a *P* of 0.046 for the trend. Again, there were no significant patterns among the controls, although there was a nonsignificant 41% increase in the risk of suboptimal DRC for controls who were homozygous at either locus.

We also analyzed the data by "current," "former," and "never"

Table 4 *XPD genotypes and risk for suboptimal DRC*

Genotypes	Cases DRC (Poor/good)[b]	Cases OR[a] (95% CI)	Controls DRC (Poor/good)[b]	Controls OR[a] (95% CI)
Lys751Gln				
Lys/Lys	93/48	1.00	74/85	1.00
Lys/Gln	96/57	0.85 (0.52–1.39)	83/79	1.22 (0.79–1.90)
Gln/Gln	35/12	1.57 (0.74–3.35)	20/19	1.19 (0.59–2.42)
Trend test[c]		$P = 0.499$		$P = 0.428$
Asp312Asn				
Asp/Asp	61/41	1.00	55/80	1.00
Asp/Asn	47/25	1.31 (0.68–2.51)	49/55	1.29 (0.77–2.18)
Asn/Asn	17/4	3.50 (1.06–11.59)	9/9	1.48 (0.55–3.98)
Trend test[c]		$P = 0.046$		$P = 0.269$
Lys751Gln + Asp312Asn				
Both wild-type	39/28	1.00	45/60	1.00
1 variant allele	58/34	1.23 (0.63–2.39)	51/65	1.04 (0.60–1.78)
2+ variant alleles	40/14	2.29 (1.03–5.12)	24/23	1.41 (0.70–2.82)
Trend test[c]		$P = 0.048$		$P = 0.393$

[a] Adjusted for age, sex, and smoking status.
[b] Dichotomized at the median DRC of controls.
[c] Obtained from a logistic regression model adjusting for age, sex, and smoking status.

Table 3 *DRC (%) by XPD genotype*

	Cases *n*	Cases DRC, % (SD)	Cases P^a	Controls *n*	Controls DRC, % (SD)	Controls P^a	P^b
Lys751Gln							
Lys/Lys	141	8.21 (3.09)	Ref.[c]	159	9.70 (4.26)	Ref.[c]	<0.001
Lys/Gln	153	7.65 (2.73)	0.100	162	9.33 (4.58)	0.469	<0.001
Gln/Gln	47	7.20 (2.27)	0.041	39	9.38 (5.25)	0.690	0.012
Trend test[d]		$P = 0.017$			$P = 0.502$		
Asp312Asn[e]							
Asp/Asp	102	8.37 (3.26)	Ref.[c]	135	10.34 (4.97)	Ref.[c]	<0.001
Asp/Asn	72	7.50 (2.53)	0.060	104	9.33 (4.19)	0.097	0.001
Asn/Asn	21	6.84 (2.15)	0.042	18	9.78 (6.46)	0.666	0.058
Trend test[d]		$P = 0.008$			$P = 0.190$		
Lys751Gln + Asp312Asn							
Both wild-type	67	8.80 (3.14)	Ref.[c]	105	10.00 (4.36)	Ref.[c]	0.052
1 variant allele	92	7.65 (2.94)	0.012	116	9.94 (5.05)	0.925	<0.001
2+ variant alleles	54	7.23 (2.19)	0.000	47	9.20 (4.99)	0.319	0.010
Trend test[c]		$P = 0.001$			$P = 0.409$		

[a] Two-sided *t* test for difference between genotypes.
[b] Two-sided *t* test for difference between cases and controls.
[c] Ref., reference value.
[d] From a general linear model.
[e] Genotype data available for 195 cases and 257 controls.

smoking status, and the results were similar (data not shown). There were also no differences in mean age at lung cancer diagnosis or mean pack-years smoked by genotype (data not shown).

Discussion

Proteins involved in DNA repair pathways are often multifunctional, resulting in a variety of phenotypes. This is exemplified by the XPD protein, which has a role in both NER and basal transcription. The *XPD* gene is highly conserved in eukaryotes, with homology to *Rad3* and *Rad15*. The amino acid substitution *Lys751Gln* in exon 23 does not reside in a known helicase/ATPase domain (7), but is at an amino acid residue identical in human, mouse, hamster, and fish XPD, suggesting a functional relevance for such a highly evolutionary conserved sequence.

Recently Lunn *et al.* (15) reported that possessing the *Lys/Lys* 751 common *XPD* genotype is associated with an increased risk of exhibiting suboptimal DRC (as reflected in the number of X-ray-induced lymphocyte chromatid aberrations). They found no effect with the *Asn312* allele. However, their study included only 31 women, some of whom were classified as at high risk for breast cancer. Dybdahl *et al.* (22) also reported that individuals with the wild-type *Lys/Lys751* genotype were at higher risk of basal cell carcinoma and had an earlier age of onset, and that the variant allele might be protective. On the other hand, Sturgis *et al.* (23) reported that the *Gln/Gln751* homozygous genotype is more common in patients with upper aerodigestive tract cancer (16.4%) than in controls (11.5%) and is associated with a borderline increased risk (adjusted OR = 1.55; 95% CI = 0.96–2.52) for these cancers. Moller *et al.* (24) reported no relationship of the *Lys751Gln* polymorphism with DRC (measured by the host cell reactivation assay or the comet assay) in 80 subjects, including 20 healthy subjects. Recently, in another small sample of 76 healthy subjects, no association was noted between sister chromatid exchange frequencies or the presence of polyphenol DNA adducts by the *Lys751Gln* genotype (25).

Our study on DNA repair phenotype and *XPD* genotypes is the largest to date and includes both healthy controls and lung cancer patients. We report that the variant *Gln751Gln* and *Asp312Asn* genotypes were associated with less optimal DRC as assessed by the host cell reactivation assay. Similarly, Hu *et al.* (26) correlated DRC with *XPD* genotypes in a small group of 66 prostate cancer cases and 54 controls. Both cases and controls homozygous for the variant allele had lower DRC (8.7% and 6.4%, respectively) than those with the wild-type genotype (11.1% and 10.9%).

Because many different mutations have been identified in the *XPD* gene, TFIIH transcriptional activity is probably relatively tolerant to amino acid changes in the XPD protein. It is also possible that mutations could destroy or alter repair function without affecting transcriptional activity. As Lunn *et al.* (15) suggested, the *Lys* allele may have different effects in different repair pathways assessed by different repair assays.

In our dataset, these two *XPD* polymorphisms were consistently associated with lower DRC in cases with a statistically significant trend and in controls with a nonstatistically significant trend. In other words, the results suggest that these two *XPD* polymorphisms had a dominant effect on DRC in cases and a smaller effect on DRC in controls. For a complex disease like cancer, multiple genes, each with a small effect, probably act independently, or with other genes, to influence the disease phenotype. The overall difference in DRC between lung cancer patients and controls, which was not explained by these two *XPD* polymorphisms, suggests that genetic alterations of other repair genes involved in NER may also play a role in the etiology of lung cancer. Although our data suggest that the polymorphisms have functional relevance, biochemical and biological characterization of the variants are needed to validate our findings.

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