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Gene-environment and gene-gene interactions between *CHRNA3* rs1051730, *XRCC1* rs25487, and *ERCC1* rs735482 variants highly elevate the risk of lung cancer

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Abstract

Background: Gene-gene and gene-environment interactions play an important role in cancer susceptibility. In this work, we studied the association of *XRCC1* rs25487, *ERCC1* rs735482, and *CHRNA3* rs1051730 variants with lung cancer and assessed the modulatory effect of potential interaction between these variants on disease risk.

Results: In this study, 86 primary lung cancer patients and 64 control subjects were genotyped for *CHRNA3* rs1051730, *XRCC1* rs25487, and *ERCC1* rs735482 by real-time PCR. The frequency of the three studied variants was higher among lung cancer patients than in control subjects, but with no statistical significance. *ERCC1* rs735482 variant was associated with 6.9-fold increased risk to develop lung cancer among smokers ($p = 0.03$). Concomitant presence of *CHRNA3* and *ERCC1* wild alleles was associated with 2.7-fold elevated risk of lung cancer ($p < 0.0001$), while concomitant presence of *CHRNA3* rs1051730 variant allele with *ERCC1* wild allele was associated with 20-fold elevated risk ($p < 0.000$). Concomitant presence of both variants, *ERCC1* rs735482 and *CHRNA3* rs1051730, was associated with 9.9-fold elevated risk ($p < 0.0001$). Meanwhile, the concomitant presence of XRCC1 rs25487 with either *ERCC1* rs735482 or *CHRNA3* rs1051730 or both was not associated with increased risk of the disease.

Conclusion: Our results emphasize the role of gene-gene interaction in the pathogenesis of lung cancer. Large-scale further studies to clarify the underlying mechanisms are needed.

Keywords: Lung cancer, Smoking, *XRCC1*, *ERCC1*, *CHRNA3*, Polymorphism

Background

Lung cancer is a leading cause of death with a poor survival rate worldwide [1]. Although smoking is the main cause of lung cancer, yet it cannot fully elucidate the epidemiologic incidences of disease among nonsmokers [2]. Gene-gene and gene-environment interactions are currently believed to play a major role in individual's susceptibility to lung cancer [3, 4].

Polymorphisms of DNA repair genes have been reported as potential markers for disease susceptibility and prognosis [5]. Subjects with low expression and/or activity of DNA repair enzymes have impaired ability to remove tobacco-induced DNA damage and are more likely to develop lung cancer. Excision repair cross complementing group 1 (ERCC1) and X-ray repair cross-complementing group 1 (XRCC1) enzymes are needed to clear DNA damage and have been highlighted as potential biomarkers of clinical outcome in cancer [6–10].

XRCC1 gene is involved in base excision repair (BER) and single-stranded break repair (SSBR) [11] and helps in removing oxidative DNA damage induced by exposures to ionizing radiation or alkylating agents [12]. *XRCC1* rs25487 variant is a single-nucleotide polymorphism resulting from a nucleotide substitution at

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Table 1 General characteristics of the studied lung cancer patients and control subjects

Variable	Lung cancer (*N* = 86)	Controls (*N* = 64)	*p* value	OR (95% CI)/ *P*
Age (years)				
Mean ± SD (Range)	54.2 ± 10.5 (27–75)	50.2 ± 8.5 (37–70)	0.08[a]	
Age group				
< 45 year *n (%)*	14 (16.3)	18 (28.1)	0.2[b]	2.0 (0.6–6.1)/ 0.2
≥ 45 year *n (%)*	72 (83.7)	46 (71.9)		
Gender				
Male *n* (%)	70 (81.4)	26 (40.6)	0.001*[b]	6.4 (2.2–18.1)/< 0.001*
Female *n* (%)	16 (19.6)	38 (59.4)		
Histological type *n* (%)				
SCLC	12 (14)			
NSCLC	74 (86)			
Adenocarcinoma	52 (70.3)			
Squamous cell carcinoma	6 (8.1)			
Others[d]	16 (21.6)			
Smoking (Yes/No)				
Non-smokers *n* (%)	26(30.3)	50(78.2)	< 0.0001*[b]	8.2(2.8-23.7)/ < 0.0001*
Smoker *n* (%)	60(69.7)	14(21.8)	< 0.0001*[b]	
Pack-year (mean)	44.9	28.7	0.001*[c]	1.0 (0.9-1.1)/ 0.03*

NSCLC non-small cell lung cancer, *SCLC* small cell lung cancer
carcinoma, anaplastic
*Significant *P*
[a]*P* value for independent *t* test
[b]*P* value for χ^2 test
[c]*P* value for Mann–Whitney *U* test
[d]Large cell carcinoma, undifferentiated, spindle, mucinous, Broncho alveolar carcinoma, carcinoid, sarcomatoid

Table 2 Genotypes and alleles frequencies of the studied SNP in lung cancer patients and control subjects

	Lung cancer patients (*n* = 86) *f* %	Controls (*n* = 64) *f* %
rs1051730		
A/A	14 (16.2)	8 (12.5)
A/G	46 (53.5)	34 (53.1)
G/G	26 (30.3)	22 (34.4)
P-value	0.8	
Allele A	74 (42.0)	50 (39.1)
Allele G	98 (58.0)	78 (60.9)
HWE	*p* value = 0.36	*p* value = 0.43
rs25487		
A/A	56 (65.1)	48 (75.0)
A/C	26 (30.2)	16 (25.0)
C/C	4 (4.7)	0
p value	0.3	
Allele A	138 (80.2)	112 (87.5)
Allele C	34 (19.8)	16 (12.5)
HWE	*p* value = 0.09	*p* value = 0.6
rs735482		
A/A	38 (44.2)	38 (59.4)
A/G	40 (46.5)	20 (31.2)
G/G	8 (9.3)	6 (9.4)
p value	0.3	
Allele A	116 (67.4)	96 (75.0)
Allele G	56 (32.6)	32 (25.0)
HWE	*p* value = 0.1	*p* value = 0.8

HWE Hardy–Weinberg equilibrium

codon 399 with an amino acid change from arginine (Arg) to glutamine (Gln) and has been associated with an altered DNA repair activity [13]. Previous studies on *this variant and its role in* susceptibility to lung cancer gave *inconsistent results among different ethnic groups* [14–17].

On the other hand, ERCC1 protein functions in nucleotide excision repair (NER) and DNA inter strand crosslinks (ICL) repair pathways; therefore, it was hypothesized that polymorphisms which alter the expression and/or function of ERCC1 may play a role in cancer pathogenesis [18–20].

Also, *cholinergic receptor nicotinic α3* (*CHRNA*3) gene coding for nicotinic acetylcholine receptor subunits (nAChRs) harbors another candidate variant, rs1051730 that has been associated with elevated risk of lung cancer in genome-wide association studies (GWAS) [21, 22].

In this study, we aim to examine the association of *XRCC1* rs25487, *ERCC1* rs735482, and *CHRNA3* rs1051730 variants with lung cancer and to assess the modulatory effect of the potential interaction between these variants on disease risk in Egyptian patients.

Methods

Subjects

This study is a case-control study that included 86 unrelated adult patients with primary lung cancer and 64 apparently healthy unrelated controls. Patients were presented to the Chest Diseases clinic of the National Research Center (NRC) from different governorates of Egypt. All subjects gave written informed consent and the study was approved by the local ethics committee. Medical history was obtained from all participants via questionnaire including demographic data, smoking and occupational history, as well as family history of malignancy. Thorough clinical examination and chest radiography were conducted.

Table 3 Association of studied SNPs with lung cancer under different genetic models of inheritance

SNP	Dominant	Co-dominant	Recessive	Over dominant
rs1051730				
Genotype	(A/G + A/A vs. G/G)	(A/G vs. G/G) or (A/G vs. AA)	(A/G + G/G vs. A/A)	A/G vs. G/G +A/A
OR (95%CI)	1.2(0.4-3.2)	0.8 (0.3–2.4)/1.3 (0.3–5.1)	0.7 (0.2–2.7)	1.0 (0.4–2.5)
p value	0.7	0.8/0.7	0.6	0.9
rs25487				
Genotype	(A/C + C/C vs. A/A)	(A/C vs. A/A or C/C)	A/C + A/A vs. C/C	A/C vs. A/A + C/C
OR (95%CI)	1.6 (0.5–4.4)	0.7 (0.2–2.0)	1.6 (0.5–4.4)	0.8 (0.2–2.2)
p value	0.3	0.5	0.3	0.6
rs735482				
Genotype	(A/G + GG vs. AA)	(A/G vs. A/A or G/G)	A/G + A/A vs. G/G	A/G vs. A/A + G/G
OR (95%CI)	1.8 (0.7–4.6)	2.0 (0.7–5.3)/1.3 (0.2–6.7)	1.0 (0.2–4.8)	0.5 (0.2–1.3)
p value	0.1	0.1/0.7	0.9	0.1

Exclusion criteria were pulmonary fibrosis, pneumonia, and any anti-cancer medication.

Genotyping analysis

Genomic DNA was extracted from whole peripheral blood using QIAamp DNA extraction kit (Qiagen Hilden, Germany, Cat No. 51304) according to the manufacturer's protocol. XRCC1 rs25487, *ERCC1* rs735482, and *CHRNA3* rs1051730 variants were genotyped using TaqMan® SNP Genotyping Assays. All primers and probes were designed by Applied Biosystems (Foster City, CA, USA) and genotyping analyses were performed on ABI 7500 real-time PCR system (Applied Biosystems) according to the manufacturer's protocol. Negative controls were included in all assays and 10% of samples were randomly selected and analyzed in duplicates and the concordance rate was 100%.

Statistical analysis

Data were analyzed using IBM SPSS version 20.0 software (Statistical Package for Social Science). Quantitative data were expressed as mean values ± standard deviation (SD) and qualitative data were expressed as frequency (%). Normally distributed data were compared using Student's *t* test. The significance of differences between proportions was tested by the Chi-square test (χ^2). Differences were considered significant with p value < 0.05. Genotype and allele frequencies between groups were compared by Chi-square test. Univariate logistic regression analysis was used to test the association between studied polymorphisms and diseases and were presented as unadjusted odds ratios (OR) with confidence interval (95% CI).

Results

Both patients and control groups were age matched (p = 0.08). Male gender was more frequent among lung cancer patients (81.4%) and associated with 6.4 times higher risk of lung cancer occurrence than female gender (p < 0.001). The frequency of smokers was significantly higher among patients than among control subjects (69.7% vs. 21.8%, p < 0.0001), and were at 8.2 times higher risk to develop lung cancer than nonsmokers. There was a significant association between the number of pack-year and the occurrence of lung cancer among smokers (p = 0.03). General characteristics of patients and control subjects are shown in Table 1.

The frequency of the three studied variants was higher in lung cancer patients than in control subjects, but none was of statistical significance under any genetic model (Tables 2 and 3). All studied genotypes were in agreement with Hardy–Weinberg equilibrium in both lung cancer patients and control groups (p > 0.05) (Figs. 1, 2, and 3).

Analysis of genotypes and variant alleles frequency in respect to histological types showed that the frequency of variant alleles was higher in non-small cell lung cancer (NSCLC) than in small cell lung cancer (SCLC) but of no statistical significance (Table 4). In respect to smoking status, *ERCC1* rs735482 variant (*G* allele) associated with 6.9 times higher risk to develop lung cancer among smokers compared to non-smokers (p = 0.03) (Table 5).

Only 5% of lung cancer patients carried the wild alleles of the three studied genes together, while 95% carried at least one of the three variants. Studying the synergistic effect of XRCC1 rs25487, *ERCC1* rs735482, and *CHRNA3* rs1051730 variants on the risk of lung cancer showed that concomitant presence of *CHRNA3* and *ERCC1* wild alleles was associated with 2.7-fold increased risk (p < 0.0001). While concomitant presence of *CHRNA3* rs1051730 variant with *ERCC1* wild allele was associated with 20-fold elevated risk (p < 0.0001). Meanwhile, concomitant presence of both variants, *ERCC1* rs735482 and *CHRNA3* rs1051730, elevated the risk by 9.9-fold (p < 0.0001). However, concomitant presence of *XRCC1* rs25487 with either *ERCC1* rs735482 or *CHRNA3* rs1051730 or both was not associated with increased risk of the disease (Table 6).

Discussion

In this work, we studied the association of *XRCC1* rs25487, *ERCC1* rs735482, and *CHRNA3* rs1051730 variants with lung cancer and assessed the modulatory effect

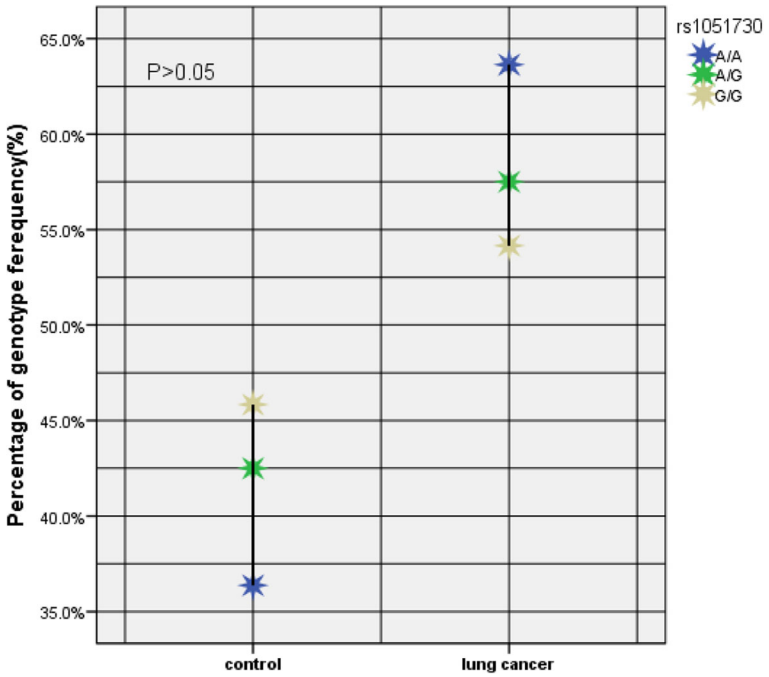

Fig. 1 Percentage of *rs1051730* genotypes frequency in lung cancer patients and controls

of the potential interaction between these variants on disease risk.

To our knowledge, this is the first work to study the three variants together in lung cancer patients. Our results showed higher frequency of the three studied variants among lung cancer patients but with no statistical significance. *ERCC1* rs735482 variant was associated with 6.9-fold increased risk to develop lung cancer among smokers emphasizing the role of gene-environment interaction. We demonstrated for the first time that concomitant presence of *CHRNA3* and *ERCC1* wild alleles was associated with 2.7-fold elevated risk of lung cancer, while concomitant presence of *CHRNA3* rs1051730 variant allele with *ERCC1* wild allele was associated with 20-fold elevated risk. In addition, concomitant presence of both variants, *ERCC1* rs735482 and *CHRNA3* rs1051730, was associated with 9.9-fold increased disease risk. Our results confirming the role of

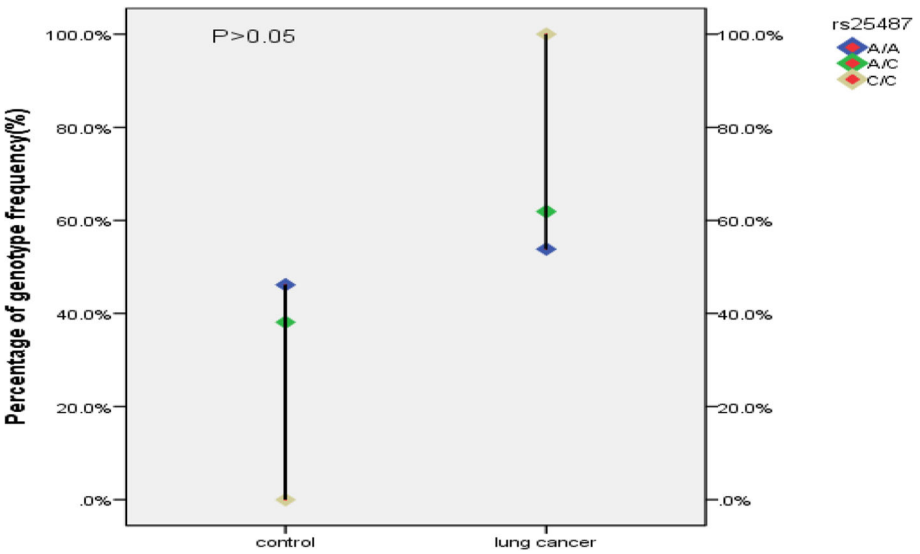

Fig. 2 Percentage of *rs25487* genotypes frequency in lung cancer patients and controls

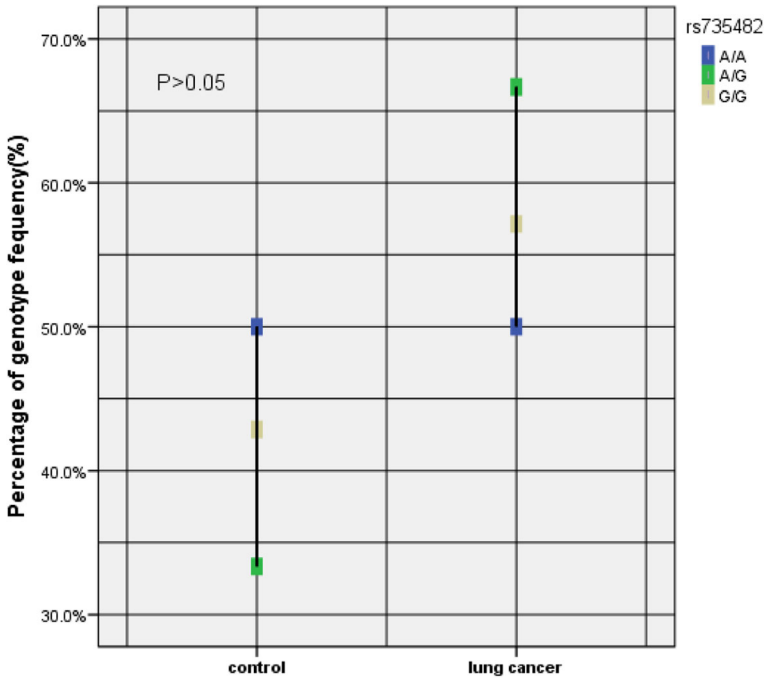

Fig. 3 Percentage of *rs735482* genotypes frequency in lung cancer patients and controls

gene-gene interaction and indicating variations in more than one gene may play a role in the susceptibility to lung cancer.

Our results support the results of previous studies that have reported lack of association between *CHRNA3* rs1051730 and lung cancer [23–28]. In contrast, *CHRNA3* rs1051730 has been reported to be significantly associated with elevated risk for lung cancer among Caucasians, Asians, Japanese, and in European ancestry [21, 29–35].

Mechanisms of elevated lung cancer risk independent of smoking in individuals with rs1051730 variant is not entirely clear. While David et al. found that *rs1051730* was associated with cigarette per day (CPD) and lung cancer in African-Americans [36], other studies have reported associations between *rs1051730* and lung cancer in nonsmokers [33, 37–39].

In our study, *XRCC1 rs25487* was not associated with lung cancer and concomitant presence with either *ERCC1* or *CHRNA3* variants was not associated with elevated risk for the disease in our population. The association of rs25487 with lung cancer in different ethnic groups gave inconsistent results [40–47], while some studies reported significant association between the variant allele and lung cancer [40–42], other studies reported lack of such association [43, 44].

In the present study, *ERCC1* rs735482 variant was associated with 6.9-fold elevated risk of lung cancer among

Table 4 Genotypes frequency in different histological types of lung cancer

		Histological type of lung cancer		*p* value
		Small cell lung cancer (*n* = 12) *n* (%)	Non-small cell lung cancer (*n* = 74) *n* (%)	
rs1051730	A/A	2 (16.6)	12 (16.2)	0.3
	A/G	4 (33.4)	42 (56.8)	
	G/G	6 (50.0)	20 (27.0)	
rs25487	A/A	8 (66.8)	48 (64.9)	0.4
	A/C	2 (16.6)	24 (32.4)	
	C/C	2 (16.6)	2 (2.7)	
rs735482	A/A	6 (50.0)	32 (43.2)	0.6
	A/G	4 (33.4)	36 (48.6)	
	G/G	2 (16.6)	6 (8.2)	

Table 5 Association between different genotypes and lung cancer in respect to smoking status

Genotype	OR(95% CI)/*P*
rs1051730	
A/G vs.GG	0.7 (0.1–5.8)/0.8
A/A vs. GG	1.8 (0.2–16.7)/0.6
rs25487	
A/C vs. A/A	1.07 (0.2–5.9)/0.9
C/C vs. A/A	3.4 (0.08–137.8)/0.5
rs735482	
A/G vs. A/A	6.9 (1.1–42.0)/0.036*
G/G vs. A/A	5.5 (0.4–77.6)/0.2

smokers. In Chinese population, *rs735482* was associated with lung cancer risk [48]. In contrast, Azad et al. reported lack of association with squamous cell carcinoma, the overall survival (OS), or the disease-free survival (DFS) [49]; however, in a Korean study, *rs735482* was associated with poor survival in NSCLC patients [50]. In contrast, better prognosis was associated with the variant allele in lung adenocarcinoma patients [20]. The inconsistent results were attributed to the inconformity to Hardy–Weinberg equilibrium or to the small sample size.

Conclusion

Gene-environment interaction involving *ERCC1* rs735482 variant elevates the risk of lung cancer among smokers. Concomitant presence of *CHRNA3* rs1051730 and *ERCC1* rs735482 variants augments the risk of lung cancer. Our results emphasize the role of gene-gene interaction in the pathogenesis of lung cancer and the underlying mechanisms need to be clarified in future studies.

Table 6 Gene-gene interaction in lung cancer patients

Haplotype	*p* value	OR (95% CI)
rs1051730 with *rs735482*		
A A	Reference	
G G	<0.0001*	20.8 (10.5–41.3)
A G	<0.0001*	9.9(4.8–20.2)
G A	<0.0001*	2.7 (1.5–4.8)
rs1051730 with *rs25487*		
AA	Reference	
G A	0.5	1.1 (0.7–1.9)
A C	0.1	2.1 (0.8–5.3)
G C	0.2	1.6 (0.7–3.8)
rs25487 with rs735482		
A A	Reference	
A G	0.1	1.5 (0.8–2.7)
C A	0.09	2.0 (0.8–4.7)
C G	0.2	1.8 (1.8–4.7)

The underline indicates the variant allele of the specific gene

Abbreviations

Arg: Arginine; BER: Base excision repair; CHRNA3: Cholinergic receptor nicotinicα3; CPD: Cigarette per day; DFS: Disease-free survival; DSB: Double strand breaks; ERCC1: Excision repair cross complementing group 1; Gln: Glutamine; GWAS: Genome-wide association studies; ICL: Inter strand crosslinks; nAChRs: Nicotinic acetylcholine receptor subunits; NER: Nucleotide excision repair; NSCLC: Non-small cell lung cancer; OS: Overall survival; SCLC: Small cell lung cancer; SNPs: Single-nucleotide polymorphisms; SSBR: Single-stranded break repair; UV: Ultraviolet; XRCC1: X-ray repair cross-complementing group 1

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None to declare.

Authors' contributions

All authors contributed to the present study. NE and DE designed the study, NE collected the samples and clinic pathological data, DE performed the molecular analysis, and AM analyzed the data. NE and DE wrote the manuscript. All authors have read, revised, and approved the final version of the manuscript.

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None to declare.

Availability of data and materials

All data generated and/or analyzed during this study are available from the corresponding author upon reasonable request.

Ethics approval and consent to participate

The study protocol was approved by Medical Research Ethics Committee (MREC) of the National Research Center of Egypt prior to the study commencement (Ref. no. 14008). All subjects were aware of the study protocol and gave written informed consent.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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