Cancer Letters 273 (2009) 172–176

Contents lists available at ScienceDirect

Cancer Letters

journal homepage: www.elsevier.com/locate/canlet

ERCC6/CSB gene polymorphisms and lung cancer risk ☆

Hongxia Ma [a], Zhibin Hu [a], Haifeng Wang [b], Guangfu Jin [a], Ying Wang [b], Weiwei Sun [b], Dan Chen [c], Tian Tian [a], Li Jin [b,c], Qingyi Wei [d], Daru Lu [c], Wei Huang [b], Hongbing Shen [a,*]

[a] *Department of Epidemiology and Biostatistics, Cancer Research Center of Nanjing Medical University, School of Public Health, 140 Han-Zhong Road, Nanjing, Jiangsu 210029, China*
[b] *Department of Genetics, Shanghai-MOST Key Laboratory of Health and Disease Genomics, Chinese National Human Genome Center, Shanghai 201203, China*
[c] *State Key Laboratory of Genetic Engineering, School of Life Sciences, Fudan University, Shanghai 200433, China*
[d] *Department of Epidemiology, The University of Texas, M.D. Anderson Cancer Center, Houston, TX 77030, USA*

ARTICLE INFO

Article history:
Received 31 March 2008
Received in revised form 31 March 2008
Accepted 4 August 2008

Keywords:
ERCC6
Single nucleotide polymorphism
Lung cancer
Molecular epidemiology

ABSTRACT

Nucleotide excision repair (NER) enzymes are critical for the removal of bulky DNA adducts caused by environmental carcinogens such as smoking. Of them, Cockayne syndrome complementation group B (CSB), coded by *ERCC6*, recruits NER repair factors to the DNA damage site and plays an important role in the repair process. Genetic variants of *ERCC6* may alter the regulation of DNA repair and therefore were hypothesized to be associated with altered risk of smoking-related lung cancer. To test this hypothesis, we genotyped eight tagging single nucleotide polymorphisms (tSNPs) and three potentially functional SNPs of *ERCC6* in 500 incident lung cancer cases and 517 controls in a Chinese population. Single locus analyses showed that none of the single SNP alone had the significant main affect on the risk of lung cancer. However, the combined variant genotypes of the four loci with P_{trend} approaching to 0.10 (rs2228526, rs4253160, rs12571445 and rs3793784) were associated with a significantly increased lung cancer risk (adjusted OR 1.35, 95% CI, 1.04–1.75 among subjects carrying three or more variant alleles), indicating that multiple loci in *ERCC6* may jointly contribute to the susceptibility of lung cancer. These findings, if validated, may contribute to identify at-risk subjects in the general population for smoking-related lung cancer.

© 2008 Elsevier Ireland Ltd. All rights reserved.

1. Introduction

Cigarette smoking is the established risk factor for lung cancer. Nucleotide excision repair (NER) plays a critical role in protecting the genome of our cell from insults of cancer-causing agents, such as smoking-related bulky adducts induced by benzo[α]pyrene [1,2]. Approximately 30 different proteins are involved in NER, which can be divided into two subpathways, global genome repair (GGR) and transcription-coupled repair (TCR), only differed in lesion recognition [3]. Studies have identified that genetic variant in DNA repair genes may modulate DNA repair capacity and consequently be associated with cancer risk [4].

Cockayne syndrome complementation group B (CSB), an enzyme encodes by excision repair cross-complementation group 6 (*ERCC6*), is necessary for TCR recognition and also plays a role in base excision DNA repair [5]. *ERCC6* defect was first described in Cockayne syndrome (CS), a human autosomal, recessive disorder, characterized as hypersensitivity to UV light and associated with different clinical features including poor growth, neurological abnormalities and cutaneous photosensitivity [6]. It was found that CS patients were specially defective in TCR

☆ Grant support: This work was supported in part by National Outstanding Youth Science Foundation of China 30425001 (to H. Shen) and 30625019 (to W. Huang), the China National Key Basic Research Program Grants 2002CB512902 (to D. Lu and H. Shen), 2006AA020706, 2004CB518605, 06XD14015 and 05DZ22201 (to W. Huang), and National "211" Environmental Genomics Grant (to D. Lu).

* Corresponding author. Tel.: +86 25 868 62747; fax: +86 25 868 62756.
E-mail address: hbshen@njmu.edu.cn (H. Shen).

0304-3835/$ - see front matter © 2008 Elsevier Ireland Ltd. All rights reserved.
doi:10.1016/j.canlet.2008.08.002

repair pathway involved in removing bulky adducts and ionizing radiation-reduced DNA damage [7], and CSB −/− mice were more susceptible to chemically induced skin cancer than were wild-type and heterozygous mice [8]. Up to date, it is controversial for the link between CSB and human cancer. In some studies, it was shown that CS patients were rarely to develop cancer of skin and/or internal organs [3,9,10]. However, some population-based studies revealed that polymorphisms of *ERCC6* had a significant impact on risk of some human cancers including lung cancer [11–13] and recurrence of superficial bladder cancer [14]. Furthermore, *in vitro* evidence showed that the polymorphisms of *ERCC6* may alter the function of the protein [13,15] and the reduced expression levels of *ERCC6* were associated with increased risk of lung cancer and squamous cell carcinoma of the head and neck [16,17]. Taken together, these evidence generated the hypothesis that genetic variants of *ERCC6* may affect the function of CSB, and consequently modulate DNA repair capacity and the risk of human cancers.

Therefore, to achieve an overall acquaintance of genetic variants of *ERCC6* in the susceptibility of lung cancer, we conducted an association study with both the tagging and potentially functional SNPs to test its modification effect on smoking-related lung cancer risk in a Chinese population.

2. Materials and methods

2.1. Study participants

The study was approved by the Institutional Review Boards of Nanjing Medical University, Nanjing, China. The recruitment of the study subjects was described previously [18]. Briefly, 500 cases with histopathologically confirmed incident lung cancer were recruited between July 2002 and December 2004 from the Cancer Hospital of Jiangsu Province (Nanjing) and the First Affiliated Hospital of Nanjing Medical University, Nanjing, China, without the restrictions of age, sex, and histology. The 517 cancer-free controls were randomly selected from a community-based screening program consisted of 10,500 individuals for non-infectious diseases conducted in Jiangsu Province during the same time period when the cases were recruited and frequency matched to the patients on sex, age, and residential area. A structured questionnaire was administered by interviewers to collect information on demographic data and environmental exposure history including tobacco smoking.

2.2. SNP selection and genotyping

We used the HapMap public SNP database (http://www.hapmap.org/) to identify tSNPs on the basis of their pairwise linkage disequilibrium (LD) (r^2 threshold: 0.8). As a result, eight SNPs with a minor allele frequency (MAF) > 0.05 were selected. Then, we used Pupasview software (http://pupasview.bioinfo.ochoa.fib.es/) to find potentially functional SNPs (influence protein function, mRNA splicing or promoter activity) and identified two additional SNPs: rs2228524 (synonymous SNPs, located on exonic splicing enhancer), rs3793784 (located on exonic splicing enhancer). Furthermore, we included all the common non-synonymous SNPs (nsSNP) in *ERCC6*. Among them, rs2228526 and rs2228528 were already selected as tSNPs; rs2228527 and rs2228529 were excluded because they were in highly linkage disequilibrium with rs2228526. Therefore, only rs4253211 (G > C, Arg1230Pro) was chosen. All these 11 SNPs (Table 1) were genotyped by using the Illumina SNP genotyping BeadLab platform and the information on assay conditions and the primers and probes is available upon request. The quality control for the Illumina high-throughput genotyping platform was described previously [18]. In brief, one blank well and three repeated samples were assigned into each 96-well assay plate to prevent contamination and to judge the clusters of genotype. The assay products were hybridized to high-density, bead-based microarrays and imaged on the Sherlock scanner (Illumina Inc. San Diego, CA). 'GenCall' software was used to run clustering and calling algorithms with the genotyping result output.

2.3. Statistical analysis

Differences in select demographic variables, smoking status, pack-years smoked, and the frequency of *ERCC6* genotypes between the cases and the controls were evaluated by using the χ^2 test. The associations between *ERCC6* genotypes and lung cancer risk were estimated by computing the odds ratios (ORs) and 95% confidence intervals (CIs) from both univariate and multivariate logistic regression analyses with adjustment for age, sex,

Table 1
Primary information of genotyped SNPs of *ERCC6*

Gene and locus	NCBI rs #	Contig position	Location	Base change	MAF for Chinese in database	*p* for HWE test	Genotyping rate (%)
ERCC6 10q11	rs3793784	1375787	5′ near gene	C → G	0.319	0.40	100
	rs2228524	1369125	L45L	G → C	0.423	0.65	100
	rs2228528	1360557	G399D	G → A	0.398	0.65	100
	rs4253079	1351102	Intron	A → C	0.174	0.09	99.9
	rs12571445	1350460	Intron	A → G	0.136	0.27	99.0
	rs4253160	1322284	Intron	A → T	0.311	0.37	100
	rs2274097	1307399	L1004L	C → T	0.089	0.72	97.1
	rs2228526	1307035	M1097V	A → G	0.100	0.67	98.7
	rs4253211	1306635	R1230P	G → C	0.083	0.11	99.6
	rs4253212	1306530	Intron	C → T	0.058	0.25	99.6
	rs4240505	1306384	Intron	C → T	0.488	0.97	99.9

Download English Version:

https://daneshyari.com/en/article/2114666

Download Persian Version:

https://daneshyari.com/article/2114666

Daneshyari.com