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# Cystic fibrosis transmembrane conductance regulator gene mutation and lung cancer risk

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ABSTRACT

The cystic fibrosis transmembrane conductance regulator (CFTR) holds an important role in retaining lung function, but its association with lung cancer is unclear. A case-control study was conducted to determine the possible associations of the genetic variants in the CFTR gene with lung cancer risk. Genotypes of the most common deletion ΔF508, one functional SNP, and eight tag SNPs in the CFTR gene were determined in 574 lung cancer patients and 679 controls. A logistic regression model, adjusting for known risk factors, was used to evaluate the association of each variant with lung cancer risk, as confirmation haplotype and sub-haplotype analyses were performed. ΔF508 deletion and genotypes with minor alleles in one tag SNP, rs10487372, and one functional SNP, rs213950, were inversely associated with lung cancer risk. The results of haplotype and sub-haplotype analyses were consistent with single variant analysis, all pointing to deletion ΔF508 being the key variant for significant haplotypes and sub-haplotypes. Individuals with 'deletion-T' (ΔF508/rs10487372) haplotype had a 68% reduced risk for lung cancer compared to common haplotype 'no-deletion-C' (OR = 0.32; 95% CI = 0.15–0.68; $p = 0.01$). Genetic variations in the CFTR gene might modulate the risk of lung cancer. This study, for the first time, provides evidence of a protective role of the CFTR deletion carrier in the etiology of lung cancer.



## 1. Introduction

Despite increasing knowledge of individual susceptibility, the genetic etiology of lung cancer remains ambiguous. Cystic fibrosis (CF) is a life-limiting autosomal recessive disorder in which progressive lung disease is common and early in life. The cystic fibrosis transmembrane conductance regulator (CFTR) functions as a chloride channel and controls the regulation of other transport pathways. CFTR gene mutations, resulting in severe dysfunction of the CFTR, are well known to be responsible for CF [1,2]. Although CF is rare, about 5% of the Caucasian populations are heterozygous mutation carriers of the CFTR gene. One theory for this high incidence of CFTR mutation carriers in the population is that these carriers may have a certain biological advantage [3].

The relationship between the CFTR gene and cancer risk has been investigated. A large cohort study in North American and European patients with CF found that while the overall risk of cancer was similar to that of the general population, there was an increased risk of digestive tract cancers in CF patients [4]. Individuals who were CFTR mutation carriers were found to be at an increased risk for young onset of pancreatic cancer [5]. An inverse association between CF gene mutations and incidence of several cancers, such as melanoma [3,6], breast cancer [6–8], colon cancer [6] and prostate cancer [9], was also reported. However, no studies have been reported on the association between CFTR and lung cancer risk. Because of the important role of the CFTR in maintaining lung function, we hypothesize that the CFTR gene mutation may alter lung cancer susceptibility. In our case-control study, the genetic variations of the CFTR gene were systematically investigated by analyzing the ΔF508 deletion, one functional single nucleotide polymorphism (SNP), and eight tag SNPs. Our goal was to determine the possible association of CFTR gene alterations and lung cancer risk.

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**Table 1**
Information of genotyped variants.

| SNP rs number[a] | Contig position (bp) [b] | Gene position | Minor allele frequency | | | *p* value for HWE[d] |
|---|---|---|---|---|---|---|
| | | | In database[c] | Cases | Controls | |
| ΔF508 (rs332) | 42383223 TCT > – | Exon_11 | – | – | – | – |
| SNP1: rs17139943 | 42313067 A > G | Intron_1 | 0.33 | 0.21 | 0.23 | 0.05 |
| SNP2: rs17449197 | 42362330 A > G | Intron_7 | 0.18 | 0.13 | 0.14 | 0.43 |
| SNP3: rs213950 | 42383109 G > A (470 Met > Val) | Exon_11 | 0.49 | 0.39 | 0.43 | 0.49 |
| SNP4: rs10487372 | 42384475 C > T | Intron_11 | 0.13 | 0.10 | 0.14 | 0.82 |
| SNP5: rs1469486 | 42403411 C > T | Intron_11 | 0.11 | 0.10 | 0.10 | 0.21 |
| SNP6: rs17547853 | 42410480 G > A | Intron_11 | 0.23 | 0.15 | 0.17 | 0.11 |
| SNP7: rs213968 | 42413569 C > T | Intron_12 | 0.48 | 0.39 | 0.43 | 0.43 |
| SNP8: rs11978434 | 42415428 T > C | Intron_13 | 0.33 | 0.23 | 0.24 | 0.09 |
| SNP9: rs213988 | 42445880 C > T | Intron_21 | 0.24 | 0.20 | 0.20 | 0.24 |

–, Information is not available.
[a] The *rs* number shown is the NCBI dbSNP cluster ID for each SNP and deletion.
[b] The number indicates the location of the SNP relative to the start codon ATG according to the NCBI genomic contig NT_007933.
[c] Minor allele frequency in the Hapmap database for Caucasian (CEU) population.
[d] The Hardy–Weinberg equilibrium (HWE) in the control group was tested using a goodness-of-fit chi-square test.

## 2. Materials and methods

### 2.1. Study subjects

Lung cancer patients were identified and enrolled at Mayo Clinic between 1997 and 2007. The detailed study design and the subject enrollment process were reported previously [10–12]. Briefly, new cases diagnosed with lung cancer are identified by a daily electronic pathology reporting system. Once identified, study consent was obtained from the patients for enrollment, their medical records abstracted, and interviews conducted. Controls were selected from community residents who were identified by having had a general medical examination and a leftover blood sample from routine clinical tests [10,13]. Excluded were individuals who had been diagnosed with major organ failure (e.g., heart, brain, lung, kidney, or liver) on or prior to this visit. The controls were frequency matched to patients on age, sex, and race/ethnicity. A self-administered questionnaire with the same questions as obtained from patients with lung cancer was completed by the controls. The research protocol and consent form were approved by the Mayo Clinic Institutional Review Board.

### 2.2. Data collection

Demographic and other risk information was obtained from all study subjects via a combination of a structured subject interview, self-administered questionnaire, and medical records [10–13]. Never smokers were defined as having smoked fewer than 100 cigarettes during their lifetimes. Detailed information on second hand smoking (SHS) history was collected on the source, amount, and duration of exposure. SHS was modeled as a dichotomized covariate (yes versus no). History of chronic obstructive pulmonary disease (COPD) was determined based on explicit diagnosis recorded in the medical history. Family history of lung cancer in first-degree relatives was also collected.

### 2.3. SNP selection and genotyping

The most common deletion, ΔF508 (rs332), was the primary target alteration under evaluation. Tag SNPs for the CFTR were selected using Haploview software. Genotyping data of the CFTR gene for Caucasian (CEU) Hapmap samples were downloaded from HapMap (http://www.hapmap.org). Tag SNPs were identified using the following criteria: aggressive tagging using 2 and 3 marker haplotypes; a minor allele frequency ≥0.1; $r^2 \geq 0.8$; and LOD, 3.0. Nine tag SNPs were selected to capture 103 of 103 (100%) alleles. One tag SNP, rs1800089, failed the test. Table 1 lists nine SNPs successfully genotyped and their genomic information; one of the SNPs was a functional SNP (rs213950, 470 Met > Val), and the other eight SNPs were haplotype tag SNPs.

Each subject's blood sample was assigned a blind identification number and tested at the Mayo Clinic Genomics Shared Resource laboratory. ΔF508 three-nucleotide deletion was assayed by fragment analysis using fluorescent primers tagged with 6-FAM and detected on the ABI 3730 Genetic Analyzer

**Table 2**
General characteristics of cases and controls: a Mayo Clinic case-control study of lung cancer, 1998–2007.

| Characteristics | Cases (574) | Controls (679) | *p*[a] |
|---|---|---|---|
| | *N* (%) | *N* (%) | |
| Race | | | |
| Caucasian | 574 (100) | 679 (100) | |
| Gender | | | 0.327 |
| Female | 300 (52.3) | 336 (49.5) | |
| Male | 274 (47.7) | 343 (50.5) | |
| Age (years) | | | 0.771 |
| ≤50 | 143 (24.9) | 159 (23.4) | |
| 50–79 | 360 (62.7) | 439 (64.7) | |
| >79 | 71 (12.4) | 81 (11.9) | |
| Cigarette smoking | | | <0.001 |
| Never | 202 (35.2) | 304 (44.8) | |
| Ever | 372 (64.8) | 375 (55.2) | |
| Second hand smoking | | | <0.001 |
| No | 76 (13.2) | 134 (19.7) | |
| Yes | 498 (86.8) | 545 (80.3) | |
| History of COPD | | | <0.0001 |
| No | 382 (66.6) | 659 (97.1) | |
| Yes | 192 (33.4) | 20 (2.9) | |
| Family history of lung cancer | | | <0.0001 |
| No | 503 (87.6) | 656 (96.6) | |
| Yes | 71 (12.4) | 23 (3.4) | |
| Histological types | | | |
| Adenocarcinoma | 266 (46.3) | – | |
| Squamous cell carcinoma | 115 (20.0) | – | |
| Non-small cell carcinoma | 45 (7.8) | – | |
| Small-cell carcinoma | 17 (3.0) | – | |
| Large-cell carcinoma | 11 (1.9) | – | |
| Bronchoalveolar carcinoma | 26 (4.5) | – | |
| Carcinoid carcinoma | 40 (7.0) | – | |
| Mixed histology/other | 54 (9.5) | – | |
| Tumor stages | | | |
| I + II | 255 (44.4%) | – | |
| III + IV | 319 (55.6%) | – | |

[a] Pearson's chi-square test.