Identification of D19S246 as a Novel Lung Adenocarcinoma Susceptibility Locus by Genome Survey with 10-cM Resolution Microsatellite Markers

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Abstract

Adenocarcinoma is now the most common histological subtype of lung cancer; however, genetic factors that affect cancer susceptibility are largely unknown. In this study, we performed a systematic survey of the human genome with an average resolution of 10 cM to identify loci that could help us target novel risk genes for lung adenocarcinoma using linkage disequilibrium. Genotyping of DNA “pools” from 100 lung adenocarcinoma cases and 100 controls, respectively, for 322 microsatellite loci dispersed in the human genome led us to identify 5 loci at which allele distribution was significantly (P < 0.05) or marginally (0.05 ≤ P < 0.1) different between the cases and controls. One of the 5 loci, D19S246 at chromosome 19q13.3, showed significant differences both in the allele and genotype distributions in the subsequent analysis in which 239 lung adenocarcinoma cases and 63 controls were added to the 100 cases and 100 controls used for the initial screening (P = 0.037 and P = 0.026, respectively), whereas the remaining 4 loci did not. These results suggest that the chromosome 19q13.3 region encompassing D19S246 contains a gene(s) of which the genetic polymorphisms are associated with lung adenocarcinoma risk and are in linkage disequilibrium with the D19S246 locus.

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Introduction

Lung cancer is a common cause of cancer death, and consists of three major histological subtypes: adenocarcinoma, squamous cell carcinoma, and small cell carcinoma (1–3). It is well known that the development of squamous and small cell carcinomas is strongly associated with smoking. Up to the present, genes responsible for susceptibility to lung cancer have been searched for by candidate gene approaches. The association of cancer risk with polymorphisms in genes that encode enzymes involved in the metabolism of tobacco carcinogens has been extensively studied, and several genes, such as CYP1A1-encoding cytochrome P450-1A1, CYP2A6-encoding cytochrome P450-2A6, and GSTM1 encoding glutathione S-transferase M1 have been recognized as being involved in susceptibility to squamous cell lung carcinoma (4–7).

Of the three types of lung cancer, adenocarcinoma is now the most common, and its proportion to the other two is increasing (8). Thus, identification of genetic factors responsible for susceptibility to lung adenocarcinoma is indispensable to establishing novel and efficient ways of preventing the disease. Smoking is considered to be responsible for the majority of lung adenocarcinomas; however, its development is less associated with smoking compared with squamous cell lung carcinoma and small cell carcinoma (2, 3, 8). In addition, genetic polymorphisms associated with the risk of squamous cell lung carcinoma have not been clearly associated with the risk of lung adenocarcinoma (4, 5, 7, 9, 10). These facts lead us to think that genetic factors involved in susceptibility are different among the histological subtypes of lung cancer.

Recent candidate gene studies by us and others have identified several candidates for lung adenocarcinoma susceptibility genes. They are drug/carcinogen metabolism genes, such as NQO1 (NAD(P)H:quinone oxidoreductase) and GSTTI (glutathione S-transferase T1), and DNA repair genes, such as XRCCI (X-ray cross-complementary group 1; Ref. 11–13). However, an alternative approach, such as genome scanning using LD3 in the human genome (14), will be also effective in identifying genes associated with the risk of lung adenocarcinoma, considering that a number of such genes is predicted to be harbored in the human genome (15, 16). We conducted a case-control study of lung adenocarcinoma recently using 20 highly polymorphic microsatellite markers dispersed in a 13-cM region of chromosome 12p12-q12 containing the region syntenic to the mouse Pas1 region (17). Microsatellite markers were used because they usually show high frequencies of heterozygosity, which enhance the sensitivity to detect allelic associations, and have been shown to be powerful tools in

3 The abbreviations used are: LD, linkage disequilibrium; Pas1, pulmonary adenoma susceptibility 1; OR, odds ratio.
case-control studies to detect and map the loci associated with susceptibility to several common diseases (18–24). The D12S1034 locus mapped in the region syntenic to the core PAS1 region of ~1.5-Mb in size was found to be associated with lung adenocarcinoma risk, indicating that the human PAS1 mutation is located in the vicinity of the D12S1034 locus and in LD with D12S1034 polymorphisms. This result indicated that a genome survey using microsatellite markers is useful for the identification of loci responsible for lung adenocarcinoma susceptibility.

Here, we performed a systematic survey of the human genome to find novel lung adenocarcinoma susceptibility loci by genotyping 322 microsatellite loci that span 22 autosomes at an average intermarker distance of 10 cM (Research Genetics, Inc., Huntsville, AL). A unilateral primer of each primer set was labeled with the ABI dyes, 6-FAM, HEX, or TED.

**Materials and Methods**

**Subjects.** The study population consisted of 339 lung adenocarcinoma cases and 163 control subjects recruited from the National Nishigunma Hospital and the National Cancer Center Hospital from 1999 to 2001 (Table 1). These 339 cases and 163 controls were the same as the ones used in our previous study (17). All of the cases and control subjects were Japanese. All of the lung adenocarcinoma cases, from whom informed consent as well as blood samples were obtained, were consecutively included in this study without any particular exclusion criteria.

The participation rate was nearly 80%. All of the cases were diagnosed by cytological and/or histological examinations according to the WHO classification (29). Diagnoses of primary lung cancers but not of metastases of other cancers were made by pathological examinations for these cases. Controls were randomly selected from inpatients and outpatients with no history of cancer at the hospitals during the study periods. The case distribution of clinical diagnoses among the controls was as follows: chronic obstructive pulmonary disease (21), pulmonary tuberculosis (17), bronchiectasis or pneumonia (16), pulmonary nontuberculous mycobacterioses (10), pneumoconiosis (9), old pulmonary tuberculosis (9), pulmonary abscess (9), interstitial pneumonia (6), pulmonary aspergillosis (5), diabetes mellitus (3), sarcoidosis (3), other respiratory disease (21), pancreaticitis (2), gastric ulcer (2), uterine myoma (1), hypertension (1), angina pectoris (1), pericarditis (1), rheumatoid arthritis (1), posterior mediastinal tumor (1), and 24 healthy individuals. The ages of the participants were computed from their date of birth. Smoking history was obtained via interview using a questionnaire. Smoking habit was represented by cigarette-years, which was defined as the number of cigarettes smoked daily multiplied by years of smoking, both in current smokers and former smokers. Nonsmokers were defined as those who had never smoked. Smokers were defined as those who had smoked at least 1 cigarette a day for ≥1 year. Informed consent was obtained from all of the participants before blood sampling, and the study was approved by the ethical committees of the Nishigunma Hospital and the National Cancer Center. From each subject, 10 mL of whole-blood sample was obtained. Genomic DNA was isolated using a Blood Maxi kit (Qiagen, Tokyo, Japan) according to the supplier’s instructions.

**Microsatellite Markers.** A genome-wide scan was performed using the human genome-wide screening set version 9 consisting of 387 microsatellite markers placed at an average intermarker distance of 10 cM (Research Genetics, Inc., Huntsville, AL). A unilateral primer of each primer set was labeled with the ABI dyes, 6-FAM, HEX, or TED.

To identify polymorphic microsatellite loci near the D19S246 locus, the genomic sequence of 200-kb containing the D19S246 sequence was obtained from the Celera Genome Database. Microsatellite loci in the 200-kb sequence was searched for using the RepeatMasker program. Three sets of primer pairs, used to amplify three novel microsatellite loci, were as follows: NY-246-2B, 5'-TGTGCTTCACTGCAAGTCTAAGA-3' and 5'-AAAACAAAAAAAGACGTTGCTTT-3'; NY-246-4A, 5'-TGTGCTTCACTGCAAGTCTAAGA-3' and 5'-ATGCTAGATGGCACAACCTAAA-3'; and NY-246-2G, 5'-TGCTAGAAAGGCTCTTCC-3' and 5'-GGACCCATCAGCTTTCTAAA-3'.

**Inference of the Allele Frequency in the DNA Pools.** Equal amounts of genomic DNA from 100 cases and 100 controls, respectively, were combined to create two individual “pools” of DNA representing each group. Ten ng of genomic DNA of each pool was suspended in a total volume of 15 μL PCR buffer, containing 1.5 mM MgCl2, 8 pmol specific primer pairs, including one labeled with a fluorescent reagent, 200 μM deoxyribonucleotide triphosphates, and 0.5 unit of Taq polymerase (Takara, Japan). The reactions were carried out in a thermal cycler for 10 cycles under the conditions of 94°C for 15 s, 55°C for 15 s, and 72°C for 30 s, followed by 25 cycles under the conditions of 94°C for 15 s, 55°C for 15 s, and 30 s

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at 72°C with a final extension of 10 min at 72°C. Amplified products were denatured for 2 min at 95°C, mixed with deionized-formamide dye, applied with a size standard marker of 500TAMRA (PE Biosystems) to each lane, and run on a GeneScan Polymer (POP4) in an ABI Prism 310 DNA Sequencer (PE Biosystems). Peak areas for each allele of microsatellite loci were calculated by the GeneScan software Version 2.1 (PE Biosystems). The peak area of each allele for a microsatellite locus in each pool was summed to obtain the total area of all of the alleles. The area of each allele was divided by the total area and multiplied by 200 to obtain the inferred number of each allele for the locus in each group.

Statistical Analysis of Allele and Genotype Differentiation. Differences in the allele distributions for each locus between the cases and controls were analyzed by the \( \chi^2 \) test (n is the number of alleles) using StatView software Version 5.0 (SAS Institute Inc., Cary, NC). The exact test of Hardy-Weinberg proportion and the genotypic differentiation test were performed by the Markov chain method with the Genepop program with the following parameters: dememorization number = 1000; no. of batches = 400; iteration per batch = 8000 (17, 20–22, 30, 31).\(^5\) Levels of \( P < 0.05 \) and \( 0.05 \leq P < 0.1 \) were considered as statistically significant and marginal, respectively.

Estimation of Risk-associated Alleles and Genotypes. Differences in the allele frequencies for the D19S246 locus between the cases and controls were analyzed by the “one to others” \( 2 \times 2 \chi^2 \) test using StatView software Version 5.0 (SAS Institute Inc.). The strength of association between lung adenocarcinoma risk and D19S246 genotypes was measured as ORs. ORs adjusted for age, gender, and smoking habit with 95% confidence intervals were calculated using an unconditional logistic regression analysis (32).

Results

A total of 339 pathologically documented lung adenocarcinoma cases and 163 unrelated control subjects were enrolled in this study (Table 1). The distributions of gender, age, and smoking habit were significantly or marginally different between the total cases and controls (\( P = 0.057, P = 0.024, \) and \( P = 0.069, \) respectively, by the \( \chi^2 \) test). We first selected 100 lung adenocarcinoma cases and 100 control subjects, matching the distributions of gender, age, and smoking habit to each other, from the total cases and controls (\( P = 0.655, P = 0.889, \) and \( P = 0.271, \) respectively, by the \( 2 \times 2 \chi^2 \) test). We first selected 100 lung adenocarcinoma cases and 100 control subjects, matching the distributions of gender, age, and smoking habit to each other, from the total cases and controls (\( P = 0.655, P = 0.889, \) and \( P = 0.271, \) respectively, by the \( 2 \times 2 \chi^2 \) test). Equal amounts of genomic DNA from each of the 100 cases and the 100 controls were combined respectively to create two individual pools of DNA representing each group. These DNA pools were subjected to the typing of 387 microsatellite markers to efficiently identify loci of which the allele distributions were different between the 100 cases and 100 controls. The 387 markers were mostly tetra-nucleotide repeats. Three hundred and twenty-two (83.2%) of the 387 microsatellite markers were successfully amplified, and the polymorphic bands were easily discriminated (a representative result is shown in Fig. 1A).

Thus, the allele distribution in each group was deduced for

these 322 loci based on the proportion of the area of each allele peak in the sum of all of the allele peaks as described in “Materials and Methods.” The remaining 65 (16.8%) markers were excluded because of weaknesses in PCR amplification or difficulties in allele discrimination. Deduced allele distributions among 100 cases and 100 controls were significantly (*P* < 0.05) different at 22 (6.8%) of the 322 microsatellite loci. Thus, we examined whether these 22 loci are polymorphic in the Japanese population by determining the length of the 15 microsatellites in DNAs from 8 individuals of the 163 controls. Fourteen loci were successfully amplified by PCR, whereas the remaining 1 locus was not amplified by PCR, probably because it was surrounded by interspersed repetitive sequences. Three of the 14 loci were considered to be highly polymorphic because >5 different sizes of alleles were detected among the 8 individuals. For the other 11 loci, <4 different sizes of alleles were detected among them. Thus, the 3 microsatellite markers with >5 different sizes of alleles were used for the individual typing of 339 cases and 163 controls. These loci, named as D19S246 at chromosome 19q13.3, showed significant differences both in allele and genotype distributions (*P* = 0.037 and *P* = 0.026, respectively). The remaining 3 loci did not show significant or marginal differences in either allele or genotype distribution among the cases and controls (*P* > 0.1).

A systematic survey of the whole human genome with 322 microsatellite markers defined D19S246 as the strongest candidate locus related to the risk for lung adenocarcinoma. Thus, to define the microsatellite locus showing the greatest difference in the allele and/or genotype distributions in the region surrounding this locus, we examined additional microsatellite loci in the vicinity of the D19S246 locus in the same cases and controls. By RepeatMasker computer program analysis of a 200-kb region surrounding the D19S246 locus, 15 microsatellite loci with uninterrupted di- to tetra-nucleotide runs with >5 repeat units were identified. Thus, we examined whether these 15 loci are polymorphic in the Japanese population by determining the length of the 15 microsatellites in DNAs from 8 individuals of the 163 controls. Fourteen loci were successfully amplified by PCR, whereas the remaining 1 locus was not amplified by PCR, probably because it was surrounded by interspersed repetitive sequences. Three of the 14 loci were considered to be highly polymorphic because >5 different sizes of alleles were detected among the 8 individuals. For the other 11 loci, <4 different sizes of alleles were detected among them. Thus, the 3 microsatellite markers with >5 different sizes of alleles were used for the individual typing of 339 cases and 163 controls. These loci, named as D19S246 at chromosome 19q13.3, showed significant differences both in allele and genotype distributions (*P* = 0.037 and *P* = 0.026, respectively). The remaining 3 loci did not show significant or marginal differences in either allele or genotype distribution among the cases and controls (*P* > 0.1).

### Table 2 Microsatellite markers showing different allele and genotype distributions between lung adenocarcinoma cases and controls

<table>
<thead>
<tr>
<th>Marker</th>
<th>Chromosomal location</th>
<th>DNA pool</th>
<th>Screening seta</th>
<th>Total subjectsb</th>
<th>Total subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td>D1S552</td>
<td>1p36</td>
<td>0.048</td>
<td>0.076</td>
<td>0.184</td>
<td>0.272 (0.002)</td>
</tr>
<tr>
<td>GATAA178G09</td>
<td>2q37</td>
<td>0.030</td>
<td>0.065</td>
<td>0.845</td>
<td>0.784 (0.002)</td>
</tr>
<tr>
<td>D3S3045</td>
<td>3q13</td>
<td>0.002</td>
<td>0.027</td>
<td>0.121</td>
<td>0.136 (0.002)</td>
</tr>
<tr>
<td>D6S474</td>
<td>6q22</td>
<td>&lt;0.001</td>
<td>0.056</td>
<td>0.061</td>
<td>0.066 (0.001)</td>
</tr>
<tr>
<td>D19S246</td>
<td>19q13.3</td>
<td>&lt;0.001</td>
<td>0.030</td>
<td>0.037</td>
<td>0.026 (0.001)</td>
</tr>
</tbody>
</table>

*a* *P* for the analysis of 100 cases and 100 controls.  
*b* *P* for the analysis of 339 cases and 163 controls.

### Table 3 Allele distribution of the D19S246 locus in lung adenocarcinoma cases and controls

<table>
<thead>
<tr>
<th>Allele</th>
<th>Size (bp)</th>
<th>Controls (%)</th>
<th>Cases (%)</th>
<th><em>P</em></th>
</tr>
</thead>
<tbody>
<tr>
<td>A1</td>
<td>179</td>
<td>92 (28.2)</td>
<td>236 (34.8)</td>
<td>0.037</td>
</tr>
<tr>
<td>A2</td>
<td>191</td>
<td>0 (0.0)</td>
<td>1 (0.1)</td>
<td>0.488</td>
</tr>
<tr>
<td>A3</td>
<td>195</td>
<td>0 (0.0)</td>
<td>1 (0.1)</td>
<td>0.488</td>
</tr>
<tr>
<td>A4</td>
<td>199</td>
<td>13 (4.0)</td>
<td>22 (3.2)</td>
<td>0.548</td>
</tr>
<tr>
<td>A5</td>
<td>203</td>
<td>122 (37.4)</td>
<td>219 (32.3)</td>
<td>0.109</td>
</tr>
<tr>
<td>A6</td>
<td>207</td>
<td>25 (7.7)</td>
<td>65 (9.6)</td>
<td>0.332</td>
</tr>
<tr>
<td>A7</td>
<td>211</td>
<td>27 (8.3)</td>
<td>43 (6.3)</td>
<td>0.258</td>
</tr>
<tr>
<td>A8</td>
<td>215</td>
<td>38 (11.7)</td>
<td>48 (7.1)</td>
<td>0.015</td>
</tr>
<tr>
<td>A9</td>
<td>219</td>
<td>7 (2.1)</td>
<td>37 (5.5)</td>
<td>0.016</td>
</tr>
<tr>
<td>A10</td>
<td>223</td>
<td>1 (0.3)</td>
<td>2 (0.3)</td>
<td>0.974</td>
</tr>
<tr>
<td>A11</td>
<td>227</td>
<td>1 (0.3)</td>
<td>4 (0.6)</td>
<td>0.551</td>
</tr>
</tbody>
</table>

*a* Obtained by the one to other chi^2* test.

### Table 4 Genotype distribution of the D19S246 locus in lung adenocarcinoma cases and controls

<table>
<thead>
<tr>
<th>Genotype</th>
<th>No. of cases (%)</th>
<th>OR 95% Confidence intervals</th>
<th><em>P</em></th>
</tr>
</thead>
<tbody>
<tr>
<td>Others/others</td>
<td>136 (40.1)/84 (51.5)</td>
<td>1.00</td>
<td>1.04–2.34</td>
</tr>
<tr>
<td>A1/others</td>
<td>170 (50.1)/66 (40.5)</td>
<td>1.56</td>
<td>1.04–2.34</td>
</tr>
<tr>
<td>A1/A1</td>
<td>33 (9.7)/13 (8.0)</td>
<td>1.43</td>
<td>0.70–2.96</td>
</tr>
<tr>
<td>Others/others</td>
<td>292 (86.1)/130 (79.8)</td>
<td>1.00</td>
<td>1.00–1.01</td>
</tr>
<tr>
<td>A8/others</td>
<td>46 (13.6)/28 (17.2)</td>
<td>0.72</td>
<td>0.42–1.21</td>
</tr>
<tr>
<td>A8/A8</td>
<td>1 (0.3)/5 (3.1)</td>
<td>0.10</td>
<td>0.01–0.91</td>
</tr>
<tr>
<td>Others/others</td>
<td>302 (89.1)/156 (95.7)</td>
<td>1.00</td>
<td>1.00–1.01</td>
</tr>
<tr>
<td>A9/others</td>
<td>37 (10.9)/7 (4.3)</td>
<td>1.21</td>
<td>0.39–7.79</td>
</tr>
<tr>
<td>A9/A9</td>
<td>0 (0.0)/0 (0.0)</td>
<td>N.D</td>
<td>N.D</td>
</tr>
</tbody>
</table>

*a* Adjusted for gender, age, and smoking habit. 
*b* N.D, not determined.
observed. Heterozygotes for the A1 or A9 alleles and homozygotes for the A8 allele were defined as genotypes associated significantly with lung adenocarcinoma risk \((P < 0.05)\).

To assess the relationship between smoking and the D19S246 polymorphism in the contribution to lung adenocarcinoma risk, allele distribution for the D19S246 locus was re-examined after dividing the study population into smokers and nonsmokers (data not shown). Allele distribution between the cases and controls was significantly different in nonsmokers, but not in smokers (by the \(2 \times n \chi^2\) test, \(P = 0.049\) and 0.340, respectively). However, the frequencies of the A5 and A6 alleles, but not of A1, A8, and A9, were significantly different between the cases and controls in smokers \((P > 0.05)\). ORs for the genotypes containing the A1, A8, or A9 allele were also re-examined after dividing the study population into smokers and nonsmokers. Increased ORs for genotypes containing the A1 or A9 allele and a decreased OR for those containing the A8 allele were observed both in smokers and nonsmokers. In particular, heterozygotes for the A1 allele and homozygotes for the A8 allele were significantly associated with lung adenocarcinoma risk in smokers \((P < 0.05)\), although none of the genotypes containing the A1, A8, or A9 allele were significantly associated in nonsmokers \((P > 0.05)\).

Discussion

We performed a genome survey with 322 microsatellite markers to identify chromosomal loci associated with lung adenocarcinoma risk. For this purpose, we genotyped two DNA pools representing 100 cases and 100 controls, matching the distributions of gender, age, and smoking habit to each other, and compared the allele distributions inferred for the two groups, respectively. Among the 322 loci, 22 were identified as loci showing differences in the inferred allele distributions between the cases and controls. Individual typing of the 22 loci revealed that actual allele distributions were significantly or marginally different at 5 of the 22 loci. Differences in the allele and genotype distributions remained significant at 1 of the 5 loci, which was D19S246 at chromosome 19q13.3, in a subsequent analysis with a larger number of cases and controls. Thus, it was suggested that a lung adenocarcinoma susceptibility gene is present in the vicinity of the D19S246 locus. The next study to be undertaken is to identify the gene of which the polymorphic alleles are in LD with those of D19S246. As an initial step, we defined D19S246 alleles significantly over- or under-represented in the cases. Three alleles, A1, A8, and A9, and genotypes containing these alleles showed association with lung adenocarcinoma risk. Therefore, it is possible that polymorphic alleles of the putative susceptibility gene constitute risk-associated haplotypes with the three alleles of D19S246. As we previously defined NQO1 and GSTT1 as genes showing association with lung adenocarcinoma risk \((13)\), the association of the D12S1034 locus with lung adenocarcinoma is also observed in the same subjects. These results indicate that the human genome
contains multiple loci associated with lung adenocarcinoma risk. It is to be noted that the control subjects in this study included many individuals with respiratory and other diseases associated with smoking. Therefore, the use of these control subjects could lead to underestimation or overestimation of $D19S246$ polymorphism, if these polymorphisms were related to the risks for diseases observed in the control subjects. Thus, associations of the $D19S246$ polymorphisms with lung adenocarcinoma should be additionally examined in different populations of adenocarcinoma cases and controls to strengthen the candidacy of $D19S246$ as a lung adenocarcinoma susceptibility locus. Analysis of populations of different ethnicities would also be worth undertaking. In addition, the survey at a 10-cM resolution is not dense enough for the comprehensive identification of susceptibility loci based on the length of LD in the human genome (33). Thus, a genome survey at a resolution of $<100$ kb is in progress in our laboratory for the comprehensive identification of lung adenocarcinoma susceptibility loci.

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References

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