Association between DNA repair gene ATM -111G/A (rs189037) polymorphism and NSCLC susceptibility in a Chinese population

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Abstract: Background: Since the identification of ATM in 1995, several population-based studies have revealed the association between specific ATM alleles and some common cancers. However, there were few studies investigating the association between ATM -111G/A (rs189037) polymorphism and NSCLC susceptibility. Methods: This case-control study consisted of 267 NSCLC patients and 280 cancer-free controls. The allele frequencies within the case and control groups were assessed by the χ² test. Using unconditional logistic regression, we calculated ORs, and 95% CIs to estimate the relative risks of NSCLC associated with the SNP genotypes. Results: The genotype frequencies of ATM -111G/A polymorphism were 20.22% GG, 50.94% GA, and 28.84% AA in cases and 30.71% GG, 51.07% GA, and 18.21% AA in controls, and the frequencies was significantly different (P = 0.002). The -111A allele revealed significantly increased frequency in NSCLC patients compared to healthy controls (54.31% vs. 43.75%, P = 0.001). We found that the AA genotype was significantly associated with increased NSCLC risk (OR = 1.78; 95% CI: 1.21-5.18; P = 0.009), and that -111A carriers were at increased risk of NSCLC (OR = 1.53, CI: 1.08-4.29, P = 0.025). In the recessive model, the GG/GA genotype was associated with a significantly increased risk of NSCLC compared with AA genotype (OR = 1.26, 95% CI = 1.03-2.91, P = 0.025). Conclusions: The ATM -111G/A polymorphism is correlated with NSCLC susceptibility, and this polymorphism may be a useful marker for NSCLC prevention and early detection.

Keywords: ATM, polymorphism, NSCLC, risk, susceptibility

Introduction

Non-small cell lung cancer (NSCLC) is the main type of lung cancer, one of the most common malignant tumors of the world [1]. It is a major health concern in China, and more research focus is needed for its prevention and control. The research of the correlation between gene polymorphism and NSCLC will help to clarify the pathogenesis of NSCLC, including its formation and development, and play an important part of the diagnosis and prognosis of patients with NSCLC [2].

The ATM gene is mapped to chromosome 11q22-23; it spans almost 150 kb and contains 66 exons [3]. The gene encodes a 350-kDa protein belonging to the phosphatidylinositol 3-kinase related protein kinases, which plays a key role in the detection and the repair of DNA double strand breaks [4, 5]. The frequency of ATM mutations in the general population has been estimated to be around 1-3% [6]. Since the identification of ATM in 1995, several population-based studies have revealed the association between specific ATM alleles and some common cancers, such as breast, thyroid, and prostate cancer [7-9]. However, there were few studies investigating the association between ATM -111G/A (rs189037) polymorphism and NSCLC susceptibility.

Materials and methods

Study subjects and samples

The present research was approved by the institutional Review Board of The Affiliated Hospital of Qingdao University. This case-control study consisted of 267 NSCLC patients and 280 can-
clic-free controls. All subjects were consecutively recruited between June 2011 and August 2014 in the Department of Thoracic Surgery, the Affiliated Hospital of Qingdao University. All patients were histopathologically confirmed NSCLC and had no preoperative chemotherapy or radiotherapy. The cancer-free controls were randomly recruited from healthy individuals who underwent routine physical examination in the same regions during the same period when the case patients were selected. At recruitment, written informed consents about the study were obtained from all subjects and each participant was interviewed to collect information regarding demographic factors and medical history.

**DNA extraction and genotyping**

Genomic DNA was extracted from peripheral blood samples by the conventional phenol-chloroform extraction method. Genotyping was performed on an Applied Biosystems 7500 FAST Real-Time PCR System using a TaqMan SNP genotyping assay. Amplification was done under the following conditions: 95°C for 10 min followed by 47 cycles of 92°C for 30 s and 60°C for 1 min. To confirm the genotyping results and assess the reproducibility, 10% duplicated samples were sequenced randomly, and these results were 100% concordant.

**Statistical analysis**

Hardy-Weinberg equilibrium (HWE) testing was carried out for all selected SNPs by the \( \chi^2 \) test in the control group. The allele frequencies within the case and control groups were assessed by the \( \chi^2 \) test. Using unconditional logistic regression, we calculated ORs, and 95% CIs to estimate the relative risks of NSCLC associated with the SNP genotypes. The SPSS 18.0 (SPSS, Chicago, IL) was used for statistical analysis. All \( P \) values presented in this study were two-sided, and we used \( P < 0.05 \) as the cut-off for statistical significance.

**Results**

**Subject characteristics**

In this case-control study, 267 NSCLC cases and 280 cancer-free controls were recruited, the selected characteristics of the subjects were summarized in **Table 1**. There were no significant difference in the distributions of age (\( P = 0.266 \)) and sex (\( P = 0.356 \)) between NSCLC cases and controls. However, compared to control subjects, the NSCLC cases were more likely to be smokers (75.28 vs. 63.57, \( P = 0.003 \)) and drinkers (83.52 vs. 71.07, \( P = 0.014 \)).

**Genotype and allele frequencies of ATM-111G/A polymorphism among NSCLC cases and controls**

The genotype and allele frequencies of the ATM-111G/A polymorphism among NSCLC cases and controls are shown in **Table 2**. The observed genotype frequencies for the ATM-111G/A polymorphism were in Hardy-Weinberg equilibrium in both cases and controls (\( P > 0.05 \)). The genotype frequencies of ATM-111G/A polymorphism were 20.22% GG, 50.94% GA, and 29.84% AA in the NSCLC cases and 20.71% GG, 50.71% GA, and 28.58% AA in the cancer-free controls.
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28.84% AA in cases and 30.71% GG, 51.07% GA, and 18.21% AA in controls, and the frequencies was significantly different (P = 0.002). The -111A allele revealed significantly increased frequency in NSCLC patients compared to healthy controls (54.31% vs. 43.75%, P = 0.001).

The association of ATM -111G/A (rs189037) polymorphism with NSCLC risk

We examined the association between ATM-111G/A polymorphism and the susceptibility to NSCLC. Multivariate logistic regression analysis was conducted after adjustment by age, sex, smoking status, and drinking status, the results were shown in Table 3. We found that the AA genotype was significantly associated with increased NSCLC risk (OR = 1.78; 95% CI, 1.21-5.18; P = 0.009). However, the GA genotype was not significantly associated with NSCLC risk (OR = 1.19; 95% CI, 0.92-2.89; P = 0.121). We found that -111A carriers were at increased risk of NSCLC (OR = 1.53, CI: 1.08-4.29, P = 0.025). In the recessive model, the GG/GA genotype was associated with a significantly increased risk of NSCLC compared with AA genotype (OR = 1.26, 95% CI = 1.03-2.91, P = 0.025).

Discussion

The 5-year survival rate of NSCLC after surgery can be up to 50% before occurring lymph node metastasis. However, most patients were diagnosed with advanced NSCLC in their first surgical treatment losing the opportunity for radical resection. Therefore, early diagnosis and early treatment still play a pivotal role in the treatment of lung cancer. Genetic variations are thought to lead to different susceptibilities to NSCLC for individuals [10]. So, finding available molecular genetic markers are important for early diagnosis and treatment.

Cancer is a multifactorial disease that results from complex interactions between environmental and genetic factors [11]. The genetic factors contribute more to the causation of cancer than lifestyle or environmental factors. In terms of genetic factors, the road to cancer is paved with alterations in the sequence and organization of the cellular genome that range from single nucleotide substitutions to gross chromosomal aberrations [12]. In recent years, studies based on the candidate-polymorphism approach markedly increased the number of associations between polymorphism and cancer risk that could be tested.

Carcinogens may induce various types of DNA damage, including DNA adducts and single- and double strand breaks (DSBs). Among the different types of DNA damage and their associated DNA repair proteins, ATM plays a critical role in the recognition, signaling, and repairing of DNA DSBs [13]. ATM is the product that mutated in autosomal recessive disease ataxia-telangiectasia (AT) and a member of the phosphoinositide 3-kinase family [14, 15]. In response to DSBs induction, ATM is rapidly activated and can phosphorylate various downstream substrates, some of which are key factors in the regulation of cell cycle arrest, DNA repair, and apoptosis. For example, ATM is an upstream factor of tumor-suppressor protein TP53 and regulates progression of the cell cycle and apoptosis by activation and stabilization of p53 [16, 17]. ATM can also interact with and phosphorylate oncogenic protein MDM2, checkpoint kinase CHK2, tumor suppressor protein BRCA1, and DNA-repair protein NBS1 [18-21].

Table 3. The association of ATM -111G/A (rs189037) polymorphism with NSCLC risk

<table>
<thead>
<tr>
<th>General genotype</th>
<th>Patients</th>
<th>Controls</th>
<th>OR (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>GG</td>
<td>54</td>
<td>86</td>
<td>1.00 (Reference)</td>
<td></td>
</tr>
<tr>
<td>GA</td>
<td>136</td>
<td>143</td>
<td>1.19 (0.92-2.89)</td>
<td>0.121</td>
</tr>
<tr>
<td>AA</td>
<td>77</td>
<td>51</td>
<td>1.78 (1.21-5.18)</td>
<td>0.009</td>
</tr>
<tr>
<td>Dominant genotype</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GG</td>
<td>54</td>
<td>86</td>
<td>1.00 (Reference)</td>
<td></td>
</tr>
<tr>
<td>GA+AA</td>
<td>213</td>
<td>194</td>
<td>1.67 (0.83-3.33)</td>
<td>0.243</td>
</tr>
<tr>
<td>recessive genotype</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GG+GA</td>
<td>190</td>
<td>229</td>
<td>1.00 (Reference)</td>
<td></td>
</tr>
<tr>
<td>AA</td>
<td>77</td>
<td>51</td>
<td>1.26 (1.03-2.91)</td>
<td>0.025</td>
</tr>
<tr>
<td>Allele frequency</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>G</td>
<td>244</td>
<td>315</td>
<td>1.00 (Reference)</td>
<td></td>
</tr>
<tr>
<td>A</td>
<td>290</td>
<td>245</td>
<td>1.53 (1.08-4.29)</td>
<td>0.017</td>
</tr>
</tbody>
</table>

1Adjusted for sex, age, smoking status, and drinking status.
The frequency of ATM mutations in the general population has been estimated to be around 1-3% [6]. Since the identification of ATM in 1995, several population-based studies have revealed the association between specific ATM alleles and some common cancers, such as breast, thyroid, and prostate cancer [7-9]. However, there were few studies investigating the association between ATM -111G/A (rs189037) polymorphism and NSCLC susceptibility. In the present study, we found that the genotype frequencies of ATM -111G/A polymorphism were 20.22% GG, 50.94% GA, and 28.84% AA in cases and 30.71% GG, 51.07% GA, and 18.21% AA in controls, and the frequencies was significantly different. The -111A allele revealed significantly increased frequency in NSCLC patients compared to healthy controls. We then examined the association between ATM -111G/A polymorphism and the susceptibility to NSCLC. Multivariate logistic regression analysis was conducted after adjustment by age, sex, smoking status, and drinking status. We found that the AA genotype was significantly associated with increased NSCLC risk, and that -111A carriers were at increased risk of NSCLC. In the recessive model, the GG/GA genotype was associated with a significantly increased risk of NSCLC compared with AA genotype.

In conclusion, the ATM -111G/A polymorphism is correlated with NSCLC susceptibility in Chinese population, and this polymorphism may be a useful marker for NSCLC prevention and early detection.

Disclosure of conflict of interest

None.

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References

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