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*MDM*2 309T>G polymorphism and risk of lung cancer in a Korean population

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Summary
Background: The MDM2 protein plays an important role in regulating cell proliferation and apoptosis by interaction with multiple proteins including p53 and Rb. A polymorphism (309T>G) in the MDM2 promoter has been shown to result in higher levels of MDM2 RNA and protein. In order to evaluate the association of the MDM2 309T>G polymorphism and lung cancer risk, we carried out a case—control study in a Korean population.
Methods: The *MDM*2 genotypes were determined in 582 lung cancer patients and in 582 healthy control subjects who were frequency matched for age and gender.
Results: The distribution of the *MDM*2 309T>G genotypes was not significantly different between overall lung cancer cases and controls. However, when the cases were categorized by tumor histology, the 309GG genotype was associated with a significantly increased risk of adenocarcinoma (adjusted OR = 1.91, 95% CI = 1.16—3.14, $P = 0.01$) compared to the 309TT genotype. In addition, the risk of adenocarcinoma increased as the number of 309G alleles increased ($P_{trend} = 0.01$).
Conclusion: Our findings suggest that the *MDM*2 309T>G polymorphism may be used as a marker for genetic susceptibility to adenocarcinoma of the lung.

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1. Introduction

Although cigarette smoking is the major cause of lung cancer, only a fraction of smokers develop lung cancer during their lifetime; this suggests that genetic constitution plays an important role in determining individual susceptibility to lung cancer [1,2]. Genetic susceptibility may result from inherited polymorphisms in the genes involved in carcinogen metabolism, cell-cycle control, repair of DNA damage and apoptosis [3—6].

MDM2 functions as a key negative regulator of p53. MDM2 binds to the N-terminal transactivation domain of p53, thereby inhibiting its transcriptional activity. MDM2 also functions as ubiquitin ligase for the p53, thereby promoting degradation of p53 [7—9]. In addition to its role in the regulation of p53, MDM2 has also been shown to promote tumorigenesis by interacting with Rb and to inhibit its growth regulatory function [10—13]. In addition, aberrant overexpression of MDM2 has been observed in a variety of human tumors, including lung cancers [14—17]. These results suggest that MDM2 plays an important role in the development of lung cancer.

The *MDM2* gene comprises two promoters, a constitutive promoter and a p53-responsive intronic promoter [13]. Recently, the 309T>G polymorphism (rs2279744), in the intronic p53-responsive promoter of the *MDM2* gene, was shown to increase the affinity of the transcriptional activator Sp1, resulting in higher levels of MDM2 RNA and protein [18]. Moreover, this polymorphism has been shown to be associated with an increased risk of lung cancer in Chinese and Norwegian populations [19,20]. Therefore, to further verify the role of the *MDM2* 309T>G polymorphism on the risk of lung cancer, we have carried out a case—control study in a Korean population.

2. Materials and methods

2.1. Study population

This present study was a hospital-based case—control study that included 582 lung cancer patients and 582 healthy controls. The details of the study population have been described elsewhere [6,21,22]. In brief, the eligible cases included all the patients who were newly diagnosed with primary lung cancer between January 2001 and June 2002 at Kyungpook National University Hospital, Daegu, Korea. There were no age, gender, histological or stage restrictions, but patients with a prior history of cancers were excluded from this study. Authors and a trained coordinator explained the objective and importance of this study, and we could include all patients with histologically confirmed primary lung cancer. All of patients signed an informed consent for blood sample collection. The cases included 270 (46.4%) squamous cell carcinomas (SCCs), 205 (35.2%) adenocarcinomas (ACs), 97 (16.7%) small cell carcinomas, and 10 (1.7%) large cell carcinomas. The control subjects were randomly selected from a pool of healthy volunteers who visited the general health check-up center at Kyungpook National University Hospital during the same period. A total of 3065 (1598 males and 1467 females) of 5578 healthy subjects agreed to this study (participation rate, 54.9%). Compared with refused subjects, participated subjects were similar in the distribution of sex (% of male, 52.5% versus 52.1%; $P = 0.80$) and age (52.2 ± 11.4 versus 52.1 ± 11.3; $P = 0.80$). From 3065 healthy volunteers, we randomly selected 582 control subjects frequency matched (1:1) to the cases based on sex and age (± 5 years). All cases and controls were ethnic Koreans who resided in Daegu City or in the surrounding regions. A trained interviewer completed a detailed questionnaire for each patient and control. The questionnaire included information on the average number of cigarettes smoked per day and the number of years the subjects had been smoking. For the smoking status of the subjects, a person who had smoked at least once a day for more than 1 year during his or her lifetime was regarded as a smoker. A former smoker was defined as one who had stopped smoking at least 1 year before either the diagnosis of lung cancer (cases) or the date that the informed consent form was signed (controls). The cumulative cigarette dose (pack-years) was calculated using the following formula: pack-years = (packs per day) $\times$ (years smoked). This study was approved by the institutional review board of the Kyungpook National University Hospital, and written informed consent was obtained from each participant.

2.2. Genotyping

The *MDM2* 309T>G genotypes were determined using the PCR—RFLP assay as described previously [23]. To ensure quality control, the genotyping analysis was performed ''blind'' with respect to case/control status. About 10% of the samples were randomly selected to be genotyped again by a different author, and the results were 100% concordant. To confirm the genotyping results, selected PCR-amplified DNA samples ($n = 2$, respectively, for each genotype) were examined by DNA sequencing, and the results were also 100% concordant.

2.3. Statistical analysis

The cases and controls were compared using the Student's t-test for continuous variables and a χ^2 test for categorical variables. Hardy—Weinberg equilibrium was tested for using a goodness-of-fit χ^2 test with one degree of freedom to compare observed genotype frequencies with expected genotype frequencies among the subjects. The cancer risk associated with the genotypes was estimated as an odds ratio (OR) and 95% confidence interval (CI) using conditional or unconditional logistic regression where it was appropriate. Crude ORs and ORs adjusted for possible confounders (gender as a nominal variable; age and pack-years smoked, as continuous variables) were calculated. Multivariate logistic regression analyses were performed to analyze the association between the genotypes and the risk of lung cancer after stratifying the subjects according to age (median years), gender, smoking status (current, former and never), cigarette consumption (median pack-years of smoking) and the histological types of lung cancer. All analyses were performed using Statistical Analysis Software for Windows, Version 8.12 (SAS Institute, Gary, NC, USA).