

Effects of Ataxia Telangiectasia Mutated (*ATM*) Genotypes and Smoking Habits on Lung Cancer Risk in Taiwan

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Abstract. *Aim: The study aimed to evaluate the association and interaction of ataxia telangiectasia mutated (ATM) genetic polymorphisms with lung cancer risk in Taiwan, where lung cancer is the primary cause of cancer-related death. Materials and Methods: In this hospital-based matched case-control study, associations of up to seven ATM single nucleotide polymorphisms (rs600931, rs652311, rs227060, rs228589, rs227092, rs624366 and rs189037) with lung cancer risk were investigated among Taiwanese. In this study, 358 lung cancer patients and 716 age- and gender-matched healthy controls were genotyped and the genetic-lifestyle interaction were analyzed. Results: The results showed that the percentages of GG, AG and AA for ATM rs652311 genotypes were significantly different at 34.6%, 48.9% and 16.5% in the lung cancer patient group and 39.9%, 51.0% and 9.1% in non-cancer control group, respectively. We further analyzed the genetic-lifestyle effects on lung cancer risk and found that the contribution of ATM rs652311 A allele-bearing genotypes to lung cancer susceptibility was enhanced in the cigarette smokers and not enhanced in the non-smokers ($p=0.0045$ and 0.2758 , respectively). Conclusion: Our results provide evidence that the A allele of ATM rs652311 may be associated with lung cancer risk, and may enhance the effects of smoking habit on lung cancer development.*

Lung cancer is keeping its throne as the leading cause of cancer death, both worldwide and in Taiwan (1). In literature,

it is reported that various carcinogens contained in cigarette smoke may produce reactive oxygen species that can induce DNA adducts and strand breaks in the genome (2). However, there are also some studies which show that only 10-15% of all smokers actually develop lung cancer during their life, suggesting that individual susceptibility to carcinogens in cigarette smoke can vary among different populations (3, 4). From the twentieth century, mounting evidence has shown that individual differences in susceptibility may be inherited via genes encoding for DNA repair proteins, which may be closely associated with personal cancer risk (5-10).

Endogenous and exogenous carcinogens may induce direct DNA adducts, single- and double-strand breaks (DSBs). Among the various types of DNA damage and their responsible repair proteins, ataxia telangiectasia mutated (ATM) plays a critical role in the recognition, signaling, and repairing of DNA DSBs immediately after their formation (11). ATM is rapidly activated after the formation of DSBs and can phosphorylate various downstream substrates, some of which are key factors in the regulation of cell-cycle arrest, DNA repair, and apoptosis. For instance, ATM is an upstream factor of the well-known tumor-suppressor protein p53, and regulates the progression of the cell cycle and apoptosis by activation and stabilization of p53 (12, 13). In addition, ATM can also phosphorylate oncogenic protein (murine double minute 2; MDM2) (14), checkpoint kinase (cell-cycle-checkpoint kinase 2; CHK2) (15), tumor-suppressor protein Breast cancer 1 (BRCA1) (16), and DNA-repair protein Nijmegen breakage syndrome 1 (NBS1) (17). Moreover, recent epidemiological and molecular analyses of ATM indicate that *ATM* genetic variations are low-penetrance susceptibility alleles for breast cancer (18-21), and oral cancer (22). *ATM* polymorphisms may contribute to the susceptibility of lung cancer in Korea (23), France (24), USA (25) and Taiwan (26). However, some literature reported that *ATM* polymorphisms may not be associated with lung cancer risk (27-29).

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Table I. The reference sequencing numbers, functional variations, primer sequences, polymerase chain reaction and restriction fragment length polymorphism (PCR-RFLP) conditions for the seven ataxia telangiectasia mutated (ATM) gene polymorphisms.

Reference sequencing #	Function variation	Primer sequences	Restriction enzyme	SNP sequence	DNA fragment size (bp)
rs600931	Intron	F: 5'-CTGGCCTAAGAGAAAAATATTGC-3' R: 5'-AATGTGTCTTGGGAAAGATGAC-3'	<i>HpyCH4V</i>	G A	100 bp 78+22 bp
rs624366	Intron	F: 5'-TTTATTTTGCTAACTTTAACTCTGTA-3' R: 5'-TGTTCAACAAATATGAGATGC-3'	<i>RasI</i>	G C	119 bp 94+25 bp
rs228589	Promotor	F: 5'-TGTGGTTCCTGCTGTGGTTT-3' R: 5'-CCGCCAGTCTCAACTCGTAA-3'	<i>FokI</i>	A T	195 bp 104+91 bp
rs227092	3'UTR	F: 5'-AGTATGGTGAAACCCTGTC-3' R: 5'-AAGAAGCCCAATGGATAG-3'	<i>HpyCH4IV</i>	T G	481 bp 265+216 bp
rs227060	Intron	F: 5'-AGCCCTAAAATACTCAAAAGCTTCAC-3' R: 5'-AGCACACGGAAACTCTCCTTCT-3'	<i>BfuAI</i>	T C	128 bp 94+34 bp
rs189037	5'UTR	F: 5'-GCTGCTTGGCGTTGCTTC-3' R: 5'-CATGAGATTGGCGGTCTGG-3'	<i>MscI</i>	G A	287 bp 176+111 bp
rs652311	3'UTR	F: 5'-GTAGTGTTCCTTAGTCGCCTCCTGTC-3' R: 5'-ACCAGGATCTTGCACCTTGTCAT-3'	<i>TaqI</i>	A G	133 bp 108+25 bp

F and R indicate forward and reverse primers, respectively.

Table II. Distributions of selected demographic data of the 358 patients with lung cancer and the 716 matched controls.

Characteristic	Controls (n=716)			Patients (n=358)			p-Value ^a
	n	%	Mean (SD)	n	%	Mean (SD)	
Age (years)			64.8 (6.8)			64.0 (6.9)	0.58
Gender							0.36
Male	488	68.1%		254	70.9%		
Female	228	31.9%		104	29.1%		
Cigarette habit							0.23
Smokers	563	78.6%		293	81.8%		
Non-smokers	153	21.4%		65	18.2%		

^aBased on Chi-square test.

Interestingly, the haplotypes of the nine *ATM* polymorphisms investigated, rs189037, rs228597, rs228592, rs664677, rs609261, rs599558, rs609429, rs227062, rs664982, were significantly associated with lung cancer among never smokers, not ever smokers (26). Therefore, in this study, we aimed to reveal the genotypic frequencies of seven polymorphisms of the *ATM* gene at rs600931, rs652311, rs227060, rs227092, rs624366, rs189037 and rs228589, focusing on the association of *ATM* genotypes with lung cancer susceptibility among Taiwanese ever smokers.

Materials and Methods

Investigated population and sample collection. Three hundred and fifty-eight patients diagnosed with lung cancer were recruited at the Outpatient Clinics of General Surgery between 2005-2008 at the China Medical University Hospital, Taichung, Taiwan, R.O.C. The

clinical characteristics of patients, including histological details, were all graded and defined by expert surgeons. All participants voluntarily completed a self-administered questionnaire and provided their peripheral blood samples. Twice as many non-lung cancer healthy volunteers, used as controls, were selected by matching for age, gender and personal habits after initial random sampling from the Health Examination Cohort of our hospital. The exclusion criteria of the controls included previous malignancy, metastasized cancer from other or unknown origin, and any genetic or familial diseases. Our study was approved by the Institutional Review Board of the China Medical University Hospital (DMR100-IRB-284) and written-informed consent was obtained from all participants.

Single nucleotide polymorphism (SNP) selection and genotyping design and conditions. Five tagging polymorphisms were selected with $r^2 > 0.8$ and minor allelic frequency $> 5\%$ in the Chinese population from the HapMap project, namely rs600931, rs624366, rs228589, rs227092, and rs227060 (30). Since the variants in the 5'

Table III. Distribution of ataxia telangiectasia mutated (*ATM*) genotypes among the 358 patients with lung cancer and the 716 matched controls.

Genotype	Controls		Patients		<i>p</i> -Value ^a
	n	%	n	%	
rs600931					
GG	283	39.5%	134	37.4%	0.7025
AG	297	41.5%	158	44.1%	
AA	136	19.0%	66	18.5%	
rs624366					
GG	301	42.0%	153	42.7%	0.7645
CG	343	47.9%	174	48.6%	
CC	72	10.1%	31	8.7%	
rs228589					
TT	253	35.3%	138	38.5%	0.5171
AT	313	43.7%	153	42.7%	
AA	150	21.0%	67	18.7%	
rs227092					
GG	293	40.9%	139	38.8%	0.5138
GT	278	38.8%	152	42.5%	
TT	145	20.3%	67	18.7%	
rs227060					
CC	303	42.3%	155	43.3%	0.7779
CT	311	43.4%	148	41.3%	
TT	102	14.3%	55	15.4%	
rs189037					
GG	255	35.6%	118	33.0%	0.6891
AG	339	47.3%	176	49.1%	
AA	122	17.1%	64	17.9%	
rs652311					
GG	286	39.9%	124	34.6%	0.0013*
AG	365	51.0%	175	48.9%	
AA	65	9.1%	59	16.5%	

^aBased on chi-square test; **p*<0.05.

and 3' untranslated regions of the *ATM* gene may also play a role in modifying the encoded protein function, two SNPs (rs189037 and rs652311) with minor allelic frequencies >5% were also chosen for our investigation. Genomic DNA was prepared from peripheral blood leucocytes using a QIAamp Blood Mini Kit (Blossom, Taipei, Taiwan, R.O.C.). The primer sequences and polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) conditions for *ATM* genotyping analysis are summarized in Table I.

Statistical analyses. All 716 controls and 358 cases with genotypic and clinical data were analyzed. Pearson's Chi-square test was used to compare the distribution of the genotypes between cases and controls. Data were recognized as significant when the statistical *p*-value was less than 0.05.

Results

The investigated subjects of the current study included 358 patients with lung cancer and 716 non-cancer healthy controls. The frequency distributions of selected characteristics among the patients and controls are

Table IV. Allelic frequencies of ataxia telangiectasia mutated (*ATM*) alleles among the 358 patients with lung cancer and the 716 matched controls.

Allele	Controls		Patients		<i>p</i> -Value ^a
	n	%	n	%	
rs600931					
Allele G	863	60.3%	426	59.5%	0.7319
Allele A	569	39.7%	290	40.5%	
rs624366					
Allele G	945	66.0%	480	67.0%	0.6282
Allele C	487	34.0%	236	33.0%	
rs228589					
Allele A	819	57.2%	429	59.9%	0.2278
Allele T	613	42.8%	287	40.1%	
rs227092					
Allele G	864	60.3%	430	60.1%	0.9008
Allele T	568	39.7%	286	39.9%	
rs227060					
Allele C	917	64.0%	458	64.0%	0.9746
Allele T	515	36.0%	258	36.0%	
rs189037					
Allele G	849	59.3%	412	57.5%	0.4385
Allele A	583	40.7%	304	42.5%	
rs652311					
Allele G	937	65.4%	423	59.1%	0.0040*
Allele A	495	34.6%	293	40.9%	

^aBased on chi-square test; **p*<0.05.Table V. Distribution of ataxia telangiectasia mutated (*ATM*) rs652311 genotypes among patients with lung cancer after stratification by personal smoking habit.

Variable	<i>ATM</i> rs652311 genotype			<i>p</i> -Value ^a
	GG (%)	AG (%)	AA (%)	
Smokers				0.0045*
Controls	223 (39.6%)	289 (51.3%)	51 (9.1%)	
Cases	99 (33.9%)	145 (49.7%)	48 (16.4%)	0.2758
Non-smokers				
Controls	63 (41.2%)	76 (49.7%)	14 (9.2%)	
Cases	25 (37.9%)	30 (45.5%)	11 (16.6%)	

^aBased on Chi-square test. **p*<0.05.

summarized in Table II. Since we applied frequency matching to select the non-cancer healthy controls, there was no difference in age, gender and smoking habit between the case and control groups (Table II).

The frequencies of the *ATM* genotypes among controls and cancer patients are analyzed and presented in Table III. Among the seven investigated SNPs, the genotypes of *ATM* rs652311 were differently distributed between lung cancer and healthy control groups (*p*=0.0013), while those for

rs600931, rs624366, rs228589, rs227092, rs227060 and rs189037 were not significant ($p>0.05$) (Table III).

The frequencies of the alleles for the seven *ATM* SNPs among the controls and lung cancer patients are shown and compared in Table IV. The allelic frequency of the *ATM* rs652311 allele A was 34.6% and 40.9% in the control and lung cancer groups, respectively. Statistically speaking, the allelic distribution of *ATM* rs652311 A and G alleles were significantly different between the control and lung cancer groups ($p=0.0040$). From the results of Tables III and IV, the A allele at *ATM* rs189037 seems to be associated with a higher susceptibility for lung cancer among this Taiwanese population.

The interaction of the genotype of *ATM* rs652311 with the smoking habits of the participants was of great interest since lung cancer is known to be a smoking-related cancer. The genotypic distribution of the variant genotypes of *ATM* rs652311 was significantly different between lung cancer and control groups who had a smoking habit ($p=0.0045$), but not different among the non-smokers ($p=0.2758$) (Table V). The percentage of AA genotype was much higher in lung cancer (16.4%) than in the control group (9.1%) among the smokers. Overall, it seems that there may be an interaction between the *ATM* rs652311 genotype and smoking lifestyle for lung cancer susceptibility.

Discussion

ATM has been reported to play a role in cell-cycle regulation and double-strand repair pathways, which are ultimately involved in cancer susceptibility (31-33). It was reported that the *ATM* genotype may be associated with risk of lung cancer in the Western countries (24, 25) and Korea (23). Some other reports were negative regarding this observation (27-29). There is only one report regarding the role of *ATM* as a genetic marker for lung cancer in Taiwan (26), where lung cancer has high prevalence and high mortality. Therefore, the main purpose of the present study was to investigate the association between *ATM* polymorphisms, on lung cancer risk in Taiwan and their interaction with smoking lifestyle. All seven *ATM* polymorphisms are located in non-coding regions, and might influence the splicing process and RNA stability (34). In this study, the A allele of *ATM* rs652311 polymorphism was significantly associated with Taiwan lung cancer (Tables III and IV), while the other six polymorphisms investigated were not. Although the *ATM* rs652311 genetic variation has not been reported to directly result in an amino acid coding change, it might be reasonable to suspect alternative splicing, intervention, modification, determination or involvement of this SNP influences the expression level or stability of the ATM protein. People carrying the A allele in their genome may have a lower capacity in cell-cycle regulation and double-strand repair, leading to higher susceptibility to lung cancer development.

As for the investigation of the joint effects of genetic (the genotype of *ATM* rs652311) and lifestyle (personal smoking status) factors on lung cancer risk, it was found that the percentage of those with AA genotype was significantly higher in the lung cancer group than in the control group (16.5% and 9.1%, respectively) among smokers. However, there was no such differential genotypic distribution for the non-smokers. It is interesting that findings of a previous study reported that the haplotype of *ATM* was associated with an increased risk of lung cancer among non-smokers (26), while the current study finds that the genotype of *ATM* rs652311 was associated with increased risk of lung cancer among smokers. Consistently, the genotype of *ATM* rs189037 was not found to contribute to enhanced risk of lung cancer in smokers in both studies.

There are still many studies needed in order to reveal any contribution of *ATM* to lung carcinogenesis. One aspect is to investigate the expression alterations at mRNA and protein levels for *ATM* and other genes in tumor sites from patients with lung cancer, compared with the non-tumor site. For instance, Lo and colleagues provided evidence to suggest that the GG and GT genotypes of APEX nuclease (multifunctional DNA repair enzyme) 1 (*APEX1*) T-656G (rs1760944) are protective against lung cancer risk in Taiwan (17). They also showed that GG and GT variant promoter had higher transcriptional activity than that with the TT genotype in lung cancer cells. Another aspect is to investigate the contribution of individual SNPs of *ATM* to lung carcinogenesis in cellular or animal models.

In conclusion, our findings suggest that the A allele of *ATM* rs652311 appears to be associated with higher lung cancer susceptibility. The *ATM* rs652311 A allele might become a potential biomarker for early cancer prediction for lung cancer, especially in smokers.

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