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Association between *Ataxia Telangiectasia Mutated* Gene Polymorphisms and Childhood Leukemia in Taiwan

Chung-Hsing Wang[1, 4], Kang-Hsi Wu[1], Yung-Li Yang[2], Ching-Tien Peng[1], Fuu-Jen Tsai[1], Dong-Tsamn Lin[2], Chang-Fang Chiu[3], Cheng-Chieh Lin[3], and Da-Tian Bau[3, 4]

[1]*Department of Pediatrics, China Medical University Hospital, Taichung 40402*
[2]*Department of Pediatrics, National Taiwan University Hospital, College of Medicine, Taipei 10051*
[3]*Terry Fox Cancer Research Laboratory, China Medical University Hospital, Taichung 40447*
and
[4]*Graduate Institute of Clinical Medical Science, China Medical University*
Taichung 40402, Taiwan, Republic of China

Abstract

The *ataxia telangiectasia mutated* (*ATM*) gene plays a major role in repairing the double-strand breaks and maintaining the genome stability. In this case-control study, associations of seven *ATM* single-nucleotide polymorphisms (rs600931, rs189037, rs652311, rs624366, rs228589, rs227092 and rs227060) with risks in childhood leukemia in a Taiwanese population were investigated. Two hundred and sixty-six patients with childhood leukemia and 266 age-matched healthy controls recruited were genotyped and analyzed. The *P*-values of the distributions of the genotypic frequencies in the seven *ATM* polymorphisms were 0.8925, 0.2835, 0.5772, 0.8731, 0.3641, 0.9181 and 0.5071, respectively. The *P*-values of the distributions of the allelic frequencies in the seven *ATM* polymorphisms were 0.6158, 0.1179, 0.6971, 0.7944, 0.1887, 0.6605 and 0.2747, respectively. Although the results did not indicate that *ATM* polymorphism is directly associated with childhood leukemia, the gene-gene and gene-environment interactions of *ATM* with other factors is worthy of further investigation in the future.

Key Words: ataxia telangiectasia mutated, polymorphism, childhood leukemia

Introduction

Child leukemia is the most common child cancers worldwide and is a critical issue of every society. The initiation etiology and genomic contributing factors of leukemia in both adult and child leukemia are still largely unknown. Most possibly, ionizing radiation, chemicals (such as benzene), drugs (such as alkylating agents), genetic, single-gene disorders (such as ataxia telangiectasia, neurofibromatosis, Blackfan-Diamond syndrome) and chromosome abnormalities are involved in the cause of child leukemia; however, solid evidences are still lacking. It is commonly recognized that single environmental or genetic factors can only ambiguously explain a small part of subjects that developed child leukemia. Thereafter, the genetic factors may be more comprehensive and could not be ignored. The responses of the cell to genetic injury and its ability to maintain genomic stability by means of a variety of DNA repair mechanisms are essential in preventing tumor initiation and progression. Mutations or defects in the DNA repairing system are essential for tumorigenesis. It is, therefore, logical to suspect that some genetic variants of DNA repair genes, such as *Ataxia Telangiectasia Mutated (ATM*) gene, might contribute to child leukemia pathogenesis.

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 re-

Corresponding author: Dr. Da-Tian Bau, Terry Fox Cancer Research Lab., China Medical University Hospital, 2 Yuh-Der Road, Taichung 40402, Taiwan, R.O.C. Tel: +886-4-22053366 ext. 3312, Fax: +886-4-22053366, E-mail: datian@mail.cmuh.org.tw; artbau1@yahoo.com.tw
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pair proteins, the *ATM* gene plays a critical role in the recognition, signaling and repairing of DNA DSBs (1). In response to induction by DSBs, 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 the tumor-suppressor protein TP53 and regulates progression of the cell cycle and apoptosis by activation and stabilization of p53 (2, 9). ATM can also interact with and phosphorylate the oncogenic protein MDM2 (21), checkpoint kinase CHK2 (4), tumor-suppressor protein BRCA1 (15) and DNA repair protein NBS1 (20). Moreover, recent large epidemiological and molecular analyses of *ATM* indicated that heterozygous carriers of some specific *ATM* mutations were associated with increased cancer risks and mortality of breast cancer with low-penetrance susceptibility (23, 29). However, there is no literature investigating *ATM* polymorphisms that may directly contribute to susceptibility of childhood leukemia in Taiwan.

In this study, we aimed at revealing the genotypic frequencies of seven polymorphisms of the *ATM* gene at rs600931, rs652311, rs227060, rs227292, rs624366, rs189037 and rs228589. We also aimed at investigating the association of *ATM* genotypes with childhood leukemia susceptibility in Taiwan.

Materials and Methods

Study Population and Sample Collection

Two hundred and sixty-six patients diagnosed with childhood leukemia (which means the population was under 18 years old) were recruited at the outpatient clinics of general surgery between 2005-2010 at the Pediatric Departments at the China Medical University Hospital and the National Taiwan University Hospital, Taiwan, Republic of China. The clinical characteristics of the patients including histological details were all defined by expert surgeons. All patients voluntarily participated, completed a self-administered questionnaire and provided peripheral blood samples. The same amounts of age-matched non-cancer healthy volunteers as controls were selected after initial random sampling from the Health Examination Cohort of the two hospitals. The successful rate of PCR-RFLP is 100%, and ten percent of the samples both in control and patient groups were analyzed for their genotypes by PCR direct sequencing (Genomics BioSci & Tech Co., Taipei, Taiwan, ROC).

Single Nuclestide Polymorphism (SNP) Selection and Genotyping Conditions

Five tagging polymorphisms were selected with r^2 >0.8 and minor allele frequency >5% in a Chinese population from the HapMap project including rs600931, rs624366, rs228589, rs227092 and rs227060 (3). Because the variants in 5'- and 3'-untranslated regions of the *ATM* gene may also play roles in modifying its functions, two SNPs (rs189037 and rs652311) with minor allele frequencies >5% were also selected for investigation. Genomic DNA was prepared from peripheral blood leucocytes using a QIAamp Blood Mini Kit (Blossom, Taipei, Taiwan) and further processed according to previous papers (5-7, 10-14, 19, 30). The polymerase chain reaction (PCR) cycling conditions were performed as follows: one cycle at 94°C for 5 min; 35 cycles of 94°C for 30 s, 55°C for 30 s, and 72°C for 30 s; and a final extension at 72°C for 10 min. Sequences of pairs of PCR primer and the enzyme recognition sites for each PCR product are listed in Table 1.

Statistical Analyses

Only those matches with all SNPs data (case/control = 266/266) were selected for the final analysis. To ensure that the controls used were representative of the general population and to exclude the possibility of genotyping error, deviation of the genotype frequencies of *ATM* SNPs in the control subjects from those expected under the Hardy-Weinberg equilibrium was assessed using the goodness-of-fit test. Pearson's *Chi*-square test was used to compare the distribution of the *ATM* genotypes between cases and controls. Data were recognized as significant when the statistical *P*-value was less than 0.05.

Results

The demographic data of the 268 cases and 268 controls are shown in Table 2. There was no difference in the distribution of age and gender between the two groups ($P > 0.05$) (Table 2).

The frequencies of the *ATM* genotypes between controls and the childhood leukemia patients are shown in Table 3. The distributions of the genotypes of *ATM* rs189037, rs600931, rs652311, rs624366, rs228589, rs227092 and rs227060 were not significantly different between the patient and control groups ($P > 0.05$) (Table 3).

The frequencies of the alleles for the seven *ATM* SNPs between controls and the childhood leukemia patients are shown in Table 4. The allele frequency distributions of *ATM* rs189037, rs600931, rs652311, rs624366, rs228589, rs227092 and rs227060 were not significantly different between the patient and control groups ($P > 0.05$) (Table 4).

Discussion

The *ATM* gene has been reported to play a role

Table 1. The primer sequences, polymerase chain reaction and restriction fragment length polymorphism (PCR-RFLP) conditions for *ATM* gene polymorphisms

Reference Sequencing	Function Variation	Primers Sequences	Restriction Enzyme	SNP Sequence	DNA Fragment Size (bp)
rs600931	Intron	F: 5'-CTGGCCTAAGAGAAAAATATTGC-3'	*HpyCH4V*	G	100 bp
		R: 5'-AATGTGTCTTGGGAAAGATGAC-3'		A	78 + 22 bp
rs189037	5'UTR	F: 5'-GCTGCTTGGCGTTGCTTC-3'	*MscI*	G	287 bp
		R: 5'-CATGAGATTGGCGGTCTGG-3'		A	176 + 111 bp
rs652311	3'UTR	F: 5'-GTAGTGTTTCTTAGTCGCCTCCTGTC-3'	*Taqa*	A	133 bp
		R: 5'-ACCAGGATCTTTGCACTTGTCAT-3'		G	108 + 25 bp
rs624366	Intron	F: 5'-TTTATTTTGCTAACTTTAACTCTGTA-3'	*RasI*	G	119 bp
		R: 5'-TGTTCAACAAATATGAGATGC-3'		C	94 + 25 bp
rs228589	Promoter	F: 5'-TGTGGTTCCTGCTGTGGTTT-3'	*FokI*	A	195 bp
		R: 5'-CCGCCAGTCTCAACTCGTAA-3'		T	104 + 91 bp
rs227092	3'UTR	F: 5'- AGTATGGTGAAACCCTGTC-3'	*HpyCH4IV*	T	481 bp
		R: 5'- AAGAAGCCCAATGGATAG-3'		G	265 + 216 bp
rs227060	Intron	F: 5'- AGCCCTAAAATACTCAAAAGCTTCAC-3'	*BfuAI*	T	128 bp
		R: 5'- AGCACACGGAAACTCTCCTTCT-3'		C	94 + 34 bp

*F and R indicate forward and reverse primers, respectively.

Table 2. Demographic data of 266 childhood ALL patients and 266 controls

Characteristic	Controls (n = 266)			Patients (n = 266)			*P-value*[a]
	n	%	Mean (SD)	n	%	Mean (SD)	
Age (years)			8.3 (4.8)			7.0 (4.4)	0.64
Gender							1.00
Male	148	55.6		148	55.6		
Female	118	44.4		118	44.4		

[a]Based on *Chi*-square test.

in DNA-damage repair pathways and cell-cycle control checkpoints, which are eventually involved in cancer susceptibility (16, 24, 25). Although a high frequency of *ATM* missense mutations in sporadic T-cell prolymphocytic leukemia has been reported (31), there is no evidence regarding the role of *ATM* as a genetic marker for childhood leukemia. Epidemiologic reports support that abnormal *ATM* genotype was associated with an increased risk for other cancers such as breast cancer (23, 26-28). However, screening cancer cases for truncating mutations in *ATM* has largely failed to reveal an increased incidence in any group of patients. Though some evidence supports the implication of *ATM* missense mutations in cancers, the presence of a large variety of rare missense variants in addition to common polymorphisms in *ATM* has made it difficult to establish such a relationship by association studies.

In this study, we have investigated the association between *ATM* polymorphisms and childhood leukemia risk in Taiwan. All the seven polymorphisms of *ATM* are located in the non-coding region of the gene and might influence the pre-mRNA splicing process and RNA stability as the IVS10-6 T>G, the variant G of which was shown to lead to incorrect splicing of exon 11 and exon skipping, resulting in frameshift and subsequent truncation of the protein at amino acid residue 419 (8). The results of the present study showed that none of the alleles of *ATM* among these seven tested polymorphisms was associated with childhood leukemia in a Taiwanese population (Tables 3 and 4). Although none of the *ATM* genetic variations directly resulted in amino acid change, it is reasonable to suspect alternative splicing, intervention, modification, determination or involvement of these SNPs may influence the expression level or stability of the ATM protein. In 1998, Takeuchi and his colleagues investigated the *ATM* mutations and loss of heterozygosity (LOH) at the *ATM* locus of patients with childhood T-cell acute lymphoblastic leukemia (ALL) and found that the *ATM* gene appeared

Table 3. Distribution of *ATM* genotypes among the childhood leukemia patients and the controls

Genotype	Controls	%	Patients	%	P^a
rs600931					
GG	103	38.7	108	40.6	0.8925
AG	112	42.1	110	41.4	
AA	51	19.2	48	18.0	
rs189037					
GG	106	39.9	89	33.5	0.2835
AG	119	44.7	128	48.1	
AA	41	15.4	49	18.4	
rs652311					
GG	108	40.6	117	44.0	0.5772
AG	134	50.4	122	45.9	
AA	24	9.0	27	10.1	
rs624366					
GG	112	42.1	117	44.0	0.8731
CG	130	48.9	124	46.6	
CC	24	9.0	25	9.4	
rs228589					
TT	96	36.1	112	42.1	0.3641
AT	117	44.0	106	39.9	
AA	53	19.9	48	18.0	
rs227092					
GG	104	39.1	108	40.6	0.9181
GT	111	41.7	110	41.4	
TT	51	19.2	48	18.0	
rs227060					
CC	113	42.5	121	45.5	0.5071
CT	111	41.7	112	42.1	
TT	42	15.8	33	12.4	

[a]*P* based on *Chi*-square test.

to be an infrequently altered tumor suppressor gene in childhood T-cell ALL (28). However, their sample size was only 18 and was not as comprehensive as ours. In 2003, Gumy Pause and his colleagues found a very high prevalence of genomic *ATM* alterations in 57 sporadic ALL cases. Their findings provided a further support that *ATM* played an important role in lymphomagenesis (18). In 2005, Meier and his colleagues performed the first whole-gene sequencing study of the *ATM* gene in a childhood T-cell ALL population in German and studied their relationships with cellular drug resistance, prognostic factors and long-term clinical outcome (22). They proposed that when the *ATM* gene carried some alterations such as mutation or loss of heterozygosity (LOH), the subjects might be predisposed to the development of childhood T-cell ALL and contributed to more unfavorable clinical outcomes such as shorter survival time (22). But their sample size was still small (control/case = 99/103), and the data were challenged by a report in 2006 for lack of reproductivity, and that the genetic variant should not interfere with normal splicing and was just a polymorphic marker unlikely to carry biological significance (17). The inconsistency of the reports may be partially due to different populations being investigated for the later study involved a Switzerland population.

The distributions of *ATM* genotypes at the seven loci were in Hardy-Weinberg equilibrium, which suggest not much selection bias for the subjects enrolled in terms of genotypes existed in this study. Therefore, the need for the present results to be verified in further larger studies is not so urgent. However, the interactions of *ATM* genotypes with environmental factors, such as second-hand smoking or radiation exposure, may be further investigated. Also, the in-

Table 4. Distribution of *ATM* alleles among the childhood leukemia patients and the controls

Allele	Controls	%	Patients	%	P^a
rs600931					
Allele G	318	59.8	326	61.3	0.6158
Allele A	214	40.2	206	38.7	
rs189037					
Allele G	331	62.2	306	57.5	0.1179
Allele A	201	37.8	226	42.5	
rs652311					
Allele G	350	65.8	356	66.9	0.6971
Allele A	182	34.2	176	33.1	
rs624366					
Allele G	354	66.5	358	67.3	0.7944
Allele C	178	33.5	174	32.7	
rs228589					
Allele A	309	58.1	330	62.0	0.1887
Allele T	223	41.9	202	38.0	
rs227092					
Allele G	319	60.0	326	61.3	0.6605
Allele T	213	40.0	206	38.7	
rs227060					
Allele C	337	63.3	354	66.5	0.2747
Allele T	195	36.7	178	33.5	

[a]*P* based on *Chi*-square test.

teraction of *ATM* with other genes, such as *CHK2*, *MDM2*, *NBS1* and *BRCA1*, is of interest. We have also performed the stratification analysis for both gender and age. The results showed that there was no association between the *ATM* genotypes and childhood leukemia in either boys or girls. Likewise, there was no association between the *ATM* genotypes and childhood leukemia among children younger than 8 versus equal or elder than 8 (data not shown).

In conclusion, this is the first report to investigate the association between *ATM* gene polymorphisms and childhood leukemia in Taiwan. Our findings suggested that the *ATM* genotypes we had examined were not associated with childhood leukemia susceptibility. The ATM may affect the initiation or progression of childhood leukemia at the post-transcription and post-translation levels. The gene-gene and gene-environment interactions could also be further investigated on the basis of this study.

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