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Association of *Matrix Metallopeptidase-2* Promoter Polymorphisms With the Risk of Childhood Leukemia

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Abstract. *Background/Aim: The association of matrix metalloproteinase-2 (MMP-2) genotypes with adult leukemia has been reported only once, but never for childhood leukemia. This study aimed to determine the role of MMP-2 promoter -1306 (rs243865) and -735 (rs2285053) genotypes in childhood leukemia risk. Materials and Methods: This case–control study included 266 patients and 266 age- and gender-matched healthy controls. The polymorphic sites of MMP-2 were genotyped by typical polymerase chain reaction-restriction fragment length polymorphism. Results: The CC, CT and TT of rs243865 genotype were 75.2, 23.7 and 1.1% in the case group and 69.2, 28.9 and 1.9% in the control group, respectively. The CT and TT genotypes caused a 0.75- and 0.55-fold increase in the risk of childhood leukemia, respectively. There was no differential distribution of rs2285053 genotypes. Allelic frequency analysis showed that the T allele of MMP-2 promoter -1306 and -735 conferred lower susceptibility than the C allele. Conclusion: The MMP-2 promoter genotypes play a minor role in determining personal susceptibility to childhood leukemia among the Taiwanese.*

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According to epidemiology, leukemia is the most common type of childhood cancer (1, 2), and accounts for 25-35% of cases of childhood cancer among most populations investigated (1, 3). There are two major subtypes of childhood leukemia, acute myeloid leukemia (AML) and acute lymphocytic leukemia (ALL), with the former accounting for about 76% of childhood leukemia cases (4, 5). In the recent two decades, accumulating evidence has suggested that genomic factors play a critical role in the development and therapeutic responses of childhood ALL. For instance, down syndrome and Fanconi anemia, which are identified as typical inherited genetic human diseases, are associated with an elevated risk of ALL (6, 7). In addition, genetic variations on several cancer-associated genes, such as *p53, N-ras,* and *PHF6*, have also been frequently identified among ALL cases (8). Furthermore, only a small proportion of children exposed to environmental risk factors were reported to have childhood ALL, indicating the potential for a genetic predisposition to the development of childhood ALL (1). Hence, the genomic biomarkers of childhood ALL risk, especially those useful for prediction of recurrence are of great interest among oncogenomic scientists and in urgent need.

The extracellular matrix (ECM) regulates the development and homeostasis of micro-environment, and its imbalance contributes significantly to cancer progression (9). ECM not only serves as the scaffold upon which tissues and cells are docked, but also regulates cell growth, proliferation, differentiation, death, invasion, migration in addition to modulating angiogenesis and immune function (10). The matrix

metalloproteinases (MMPs) are invariably up-regulated in the stromal compartment of epithelial cancers and appear to promote cancer cell metastasis *via* controlling the degradation of the ECM components such as connective tissue matrices (10-12). In recent years, the role of MMPs in the process of tumor metastasis has received continuous attention (13) and mounting evidence showed that MMP-2 plays an important role in the degradation of ECM and activation of metastasis capacity of solid tumor cells (14-17). However, the influence of MMP on the etiology of non-solid tumor leukemia is largely unrevealed.

The human *MMP-2* gene is located on chromosome 16q21, and its encoded protein belongs to the zinc ion-dependent endopeptidase family and is found in a wide variety of tissues (18-20). At least two promoter polymorphisms, -1306 (rs243865) and -735 (rs2285053) of *MMP-2*, can team up to affect *MMP-2* mRNA and protein expression levels by modulating the transcription of *MMP-2*, and eventually affecting tumor metastatic behavior and development of several types of solid cancers, including breast, lung, esophageal and colon cancer (21-24). In addition, it was reported that MMP-2 is up-regulated among oral cancer patients, particularly those with lymph node metastases (25). Regarding leukemia and *MMP-2* genotypes, it has been reported that the variant genotypes of CT and TT at *MMP-2* -1306 position were higher in the ALL group than in the control group and can serve as a risk biomarker for ALL (26). This is the only study that has investigated the association of *MMP-2* genotypes with leukemia, and its findings are in urgent need to be validated in other populations. Their population was composed of 376 ALL patients and 352 healthy subjects. However, they did not investigate the influence of *MMP-2* -735 (rs2285053) on leukemia risk. In addition, their investigated population included adults with an average age of 47.3 and 48.7 years for the control and case groups, respectively. Thus the present genotyping study was conducted to examine the contributions of *MMP-2* promoter -1306 (rs243865) and -735 (rs2285053) polymorphisms to the susceptibility of childhood ALL in Taiwan.

Materials and Methods

Collection of childhood leukemia patients and control subjects. The current study has been approved by the China Medical University Hospital Institutional Review Board (DMR103-IRB-153). During 2005 to 2010, 266 patients diagnosed with childhood (defined as those under 18 years of onset age) ALL were collected from the Pediatric Departments at China Medical University Hospital and National Taiwan University Hospital in Taiwan. Written informed consent was obtained with the help of one or both parents of all participants. All of the clinical characteristics of collected childhood ALL cases, including their histological details, were identified and recorded by expert surgeons. All children were asked to complete a questionnaire with the help of their parents or guardians, and provided 3-3.5 ml of their peripheral blood samples. The questionnaire well recorded the disease history, diet and sleeping habits of the child in addition to the disease history, diet, behavioral lifestyle and socioeconomic status of the parents. Then, 266 age- and gender-matched healthy participants were chosen as the control group following initial random sampling from the Health Examination Cohort established as we have previously published (27-29). Most of the volunteers underwent health examinations every 5 to 6 months with no gap longer than one year. Originally, a total of 457 volunteers fitted the criteria and were recruited into this study. They were cancer free by the age at diagnosis according to the International Classification of Disease, ninth revision (ICD-9) codes (defined by World Health Organization). At last, 266 participants were recruited into the current study to match the population structure with respect to number, age and gender with the 266 childhood ALL population. The overall agreement rate in the study was higher than 85%. Age and gender of all the participants in case and control groups are summarized in Table I.

Genotyping processes. The genomic DNA was extracted from the peripheral blood leucocytes of each participant within 24 h after their donation, and stored at −80˚C until processed as per our previous studies (30-32). In this study, the genotypes at -1306 and -735 polymorphic sites in the *MMP-2* promoter region were determined for all the subjects in both the control and oral cancer patient groups. In brief, the polymorphic sites were genotyped by typical polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) methodologies using the BioRad Mycycler (BioRad, Hercules, CA, USA). Each PCR reaction consisted of 5 min initial cycle at 94˚C; 40 cycles of 94˚C for 30 sec, 55˚C for 30 sec, and 72˚C for 30 sec; and a final extension at 72˚C for 10 min. After PCR, the SNP-containing DNA fragments were subjected to overnight digestion with restriction endonucleases. Following digestion, each sample was immediately analyzed by agarose gel electrophoresis. All the genotypic processing was repeated by two researchers independently, and blindly, and the results were 100% concordant. The details of primer sequences and the restriction enzymes are provided in Table II.

Statistical analysis. The Student's *t*-test was used for comparing the distribution of ages between the two groups. Pearson's Chi-square test was applied to compare the distribution of the *MMP-2* -1306 and -735 genotypes among subgroups. The associations between the *MMP-2* -1306 and -735 polymorphic genotypes and childhood ALL risk were estimated by computing odds ratios (ORs) and counterpart 95% confidence intervals (CIs) under logistic regression analysis. Any difference with $p<0.05$ was identified statistically significant.

Results

The distribution frequencies of age at onset and gender of the investigated 266 childhood ALL cases and 266 non-cancer age- and gender-matched controls are summarized in Table I. Since, the frequency matching for age and gender was applied to recruit the non-cancer healthy controls, there was no difference in the distributions of age and gender between the control and case groups (Table I). The distributions of the *MMP-2* promoter -1306 and -735 genotypes among the non-cancer controls and the childhood ALL cases are presented and statistically compared in Table II. First, for the two *MMP-2* genotypes in the control group, a goodness-of-fit test

Table I. *Distribution of selected demographics among the 266 childhood ALL patients and the 266 matched controls.*

Characteristics	Controls (n=266)			Patients (n=266)			*p*-Value
	n	%	Mean (SD)	n	%	Mean (SD)	
Age at onset (years old)			8.3 (4.8)			7.0 (4.4)	0.6483[a]
Gender							1.0000[b]
Male	148	55.6%		148	55.6%		
Female	118	44.4%		118	44.4%		

[a]Based on Student's *t*-test; [b]Based on Chi-square test; SD: standard deviation.

Table II. *Summary of the primer sequences, restriction enzymes and amplicons used for genotyping matrix metalloproteinase-2 (MMP-2) by PCR-RFLP methodology.*

Polymorphic site	Primer sequences	Restriction endonuclease	Amplicon size after cutting, bp
MMP-2 -1306	Forward 5'-CTTCCTAGGCTGGTCCTTACTGA-3'	*XspI*	C: 188+5
	Reverse 5'-CTGAGACCTGAAGAGCTAAAGAGCT-3'		T: 162+26+5
MMP-2 -735	Forward 5'-GGATTCTTGGCTTGGCGCAGGA-3'	*HinfI*	C: 391
	Reverse 5'-GGGGGCTGGGTAAAATGAGGCTG-3'		T: 338+53

was carried out for the examination of Hardy-Weinberg equilibrium. The results indicated that the frequency distributions of the *MMP-2* -1306 and -735 genotypes in the control group were consistent with the Hardy-Weinberg equilibrium ($p>0.05$). Therefore, the control samples in this study were indeed random samples and could represent the Taiwanese childhood population. The variant genotype frequencies for *MMP-2* -1306, CT and TT, were lower in the childhood ALL case group than those in the non-cancer control group (p for trend=0.2771, ORs=0.75 and 0.55, 95%CI=0.51-1.11 and 0.13-2.34, respectively). However, the differences were not significant (Table III, top). The distributions of *MMP-2* promoter 735 genotypes were not significant between childhood ALL and the non-cancer control groups (*p* for trend=0.6731) (Table III, bottom).

To confirm the findings in Table III, allelic frequency distribution analysis for the *MMP-2* promoter -1306 and -735 genotypes was performed and the results are summarized in Table IV. The minor allele frequencies at the *MMP-2* -1306 site were 13.0% and 16.4% in case and control groups, respectively. The *p*-value was 0.1187, showing no statistically significant difference between the case and control groups (ORs=0.76, 95%CI=0.54-1.07) (Table IV, top). Similarly, the minor allele frequencies at the *MMP-2* -735 site were 21.4% and 19.2% in case and control groups, respectively. The *p*-value was 0.3604, showing no statistical significance between the case and control groups (ORs=1.15, 95%CI=0.85-1.55) (Table IV, bottom). Therefore, there was no statistically significant difference in the allelic frequencies of *MMP-2* promoter at the sites -1306 or -735.

Last, the potential of the *MMP-2* promoter -1306 and/or -735 genotypes to serve as predictors for the prognosis for childhood ALL patients were examined. Therefore, the distributions of the *MMP-2* promoter -1306 and -735 genotypes among the patients stratified by age and gender status were investigated. However, there was no differential distribution of the *MMP-2* promoter -1306 or -735 genotypes between the patients according to age or gender (data not shown).

Discussion

In the current hospital-based case–control study, the contribution of *MMP-2* promoter -1306 and -735 genotypes to Taiwanese childhood ALL risk was evaluated among 266 childhood ALL patients and 266 age- and gender-matched controls. The variation in the two SNP locus, -1306 and -735, might destroy the binding site of Sp1, resulting in the decrement of its transcription, and eventually in a decrease in the expression of MMP-2 (33). The results in Tables III and IV indicated that none of the genotypic or the allelic frequencies of *MMP-2* -1306 or -735 were differentially distributed among the 266 childhood ALL patients and the 266 non-cancer healthy controls (Tables III and IV). Our finding is different from that of a previous study, reporting that the frequency of *MMP-2* -1306C/T genotypes and alleles were significantly different between the adult ALL case and

Table III. *Distribution of matrix metalloproteinase-2 (MMP-2) genotypes among patients with childhood ALL and non-cancer controls.*

	Controls		Patients		OR (95%CI)	*p*-Value[a]
	n	%	n	%		
MMP-2 -1306						
CC	184	69.2%	200	75.2%	1.00 (Reference)	
CT	77	28.9%	63	23.7%	0.75 (0.51-1.11)	0.1513
TT	5	1.9%	3	1.1%	0.55 (0.13-2.34)	0.4139
P_{trend}						0.2771
MMP-2 -735						
CC	176	66.2%	167	62.8%	1.00 (Reference)	
CT	78	29.3%	84	31.6%	1.14 (0.78-1.65)	0.5068
TT	12	4.5%	15	5.6%	1.32 (0.60-2.90)	0.4919
P_{trend}						0.6731

[a]Based on Chi-square test without Yates' correction;

Table IV. *Distribution of allelic frequencies for matrix metalloproteinase-2 (MMP-2) among patients with childhood ALL and non-cancer controls.*

	Controls, n	%	Patients, n	%	OR (95%CI)	*p*-Value[a]
MMP-2 -1306						
C	445	83.6%	463	87.0%	1.00 (Reference)	
T	87	16.4%	69	13.0%	0.76 (0.54-1.07)	0.1187
MMP-2 -735						
C	430	80.8%	418	78.6%	1.00 (Reference)	
T	102	19.2%	114	21.4%	1.15 (0.85-1.55)	0.3604

[a]Based on Chi-square test without Yates' correction.

control groups. In addition, none of the variant CT or TT genotypes at MMP-2 promoter -1306 or -735 may in combination with age or gender, influence the childhood ALL susceptibility (data not shown). There are two explanations for the different findings. One is the different populations examined, and the other is that the influence of *MMP-2* on the development of leukemia may be somehow different between adult and childhood leukemia.

The MMP-2 protein is in charge of the degradation of the intact fibrillar collagen, elastin, endothelin, fibroblast growth factor, MMP-9, MMP-13, plasminogen, and TGF-β (34), and MMP-2-mediated ECM degradation is essential for the processes of epithelial-mesenchymal transition (EMT) and the metastatic tumor cells to undergo invasion and migration (35, 36). It has been shown that activated MMP-2 is frequently observed in tumor sites, and is associated with poor prognosis of many types of cancer including melanoma, colorectal, breast, ovarian, lung and prostate cancer (37). The -1306 polymorphic site of *MMP-2* is located upstream of the *MMP-2* gene and may affect the protein expression by modulating its transcription, hence leading to the occurrence of human diseases, such as bladder cancer and sclerosing cholangitis (38, 39); A variety of transcription factors, such as activator protein-1 (AP-1), specificity protein-1 (SP-1) and activator protein-2 (AP-2), have binding sites at the *MMP-2* promoter region to regulate transcription of the *MMP-2* gene (40, 41). For instance, when the C nucleotide is substituted by T at *MMP-2* -1306, the SP-1 binding region is inactivated, thus inhibiting the transcription and as a result the translation of MMP-2 (42). Thus, there is a possibility that the *MMP-2* genotypes, especially those at -1306 and -735, are associated with the metastatic capacity of cancer cells. However, taken together, our results and those from the literature indicate that the contribution of *MMP-2* promoter -1306 and -735 polymorphic sites to childhood ALL is not conclusive yet. Because of the limited number of studies, the temporary inconsistence should be interpreted with caution and further studies in multiple populations are needed to reveal the role of *MMP-2* promoter genotypes in ALL.

Another important issue is that the contribution of other MMPs together with their modulators should not be disregarded, since the complicated interactions among ECM and *MMPs* are all essential to the development of childhood ALL. In the recent years, we have investigated the contribution of genomic variants of other *MMPs* to childhood ALL susceptibility among Taiwanese. For instance, the G

genotype at *MMP-1* promoter -1607 (rs1799750) was found to reduce childhood ALL risk (43). In addition, *MMP-8* C-799T, Val436Ala, or Lys460Thr may play a minor role in determining personal susceptibility of childhood ALL (27). As for *MMP-7*, variant genotypes at A-181G but not C-153T were associated with a higher risk of childhood ALL, especially among boys and those aged less than 3.5 years at onset (29). In the future, the contribution of the genotypes of other *MMPs*, especially those whose proteins were identified to be differentially expressed among ALL patients and healthy controls, will be helpful to reveal the role of ECM dysregulation in ALL etiology. In addition, an overall genotypic/phenotypic analysis of *MMP-2* and of its inhibitor, *tissue inhibitors of metalloproteinase-2* (*TIMP-2*) (11) may provide further evidence for evaluating the contribution of these genotypes to childhood ALL.

In conclusion, our results provide evidence showing that the variant CT and TT genotypes at *MMP-2* promoter -1306 or -735 may play a minor role in determining the susceptibility to childhood ALL in Taiwan.

Conflicts of Interest

All the Authors declare no conflict of interest.

Authors' Contributions

Research Design: Gong CL and Bau DT; Patient and Questionnaire Summarize: Hsu PC, Pei JS and Chen CC; Experiment Performance: Chang WS and Tsai CW; Statistical analysis: Kuo CC; Manuscript Writing: Hsu PC, Gong CL and Bau DT; Reviewing and Revising: Cheng SP.

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