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Matrix Metalloproteinase-1 Genotype Contributes to the Risk of Non-solid Tumor in Childhood Leukemia

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Abstract. *Aim: Up-regulation of metalloproteinase (MMPs) proteins have been shown in various types of solid cancers and the genotype of MMP1 has been associated with the risk of solid cancers. However, the contribution of MMP1 genotype to leukemia has never been investigated to our knowledge. Therefore, in this study we aimed to evaluate the contribution of the genotypic variants in the promoter region of MMP1 to childhood acute lymphoblastic leukemia (ALL) risk in Taiwan. Materials and Methods: In this case–control study, 266 patients with childhood ALL and 266 non-cancer controls were genotyped by polymerase chain reaction-restriction fragment length polymorphism methodology. Results: The distribution of 2G/2G, 1G/2G and 1G/1G for MMP1 promoter rs1799750 genotype was 49.2%, 39.5% and 11.3% in the childhood ALL group and 36.8%, 43.6% and 19.5% in the non-cancer control group, respectively (p for trend=0.0046), significantly differentially distributed between childhood ALL and control groups. The carrier comparisons in dominant and recessive models also support the findings that 1G appears to be the protective allele in childhood ALL. In genotype and gender interaction analysis, it was found that boys carrying the MMP1 rs1799750 1G/2G or 1G/1G genotypes had lower odds ratios(ORs) of 0.68 and 0.43 [95% confidence intervals (CI)=0.47-0.98 and 0.26-0.73, p=0.0395 and 0.0013, respectively] for childhood ALL than those carrying the 2G/2G genotype. Analysis of genotype inaction with age of onset age showed those aged less than 3.5 years at onset carrying the 1G/2G or 1G/1G genotypes had lower ORs (0.0183 and 0.0004, respectively) for childhood ALL, but there was no such difference for those having an age at onset of 3.5 years or more. Conclusion: Our results indicate that the MMP1 rs1799750 1G allele is a protective biomarker for childhood ALL.*

Globally, acute lymphoblastic leukemia (ALL) is the most common pediatric leukemia and accounts for 25-30% of childhood malignancies (1, 2). Statistically, the annual worldwide incidence rate of childhood ALL is approximately 10 newly diagnosed cases per 100,000, with a peak incidence occurring at the age of 2 to 5 years (3). Although the clinical, pathological and immunophenotypic features of ALL are well documented, its etiology has not been fully clarified. From the epidemiological viewpoint, several factors, such as ionizing radiation, parental use of alcohol and tobacco, and viral exposure, have been identified as potential risk factors for the development of childhood ALL. But among these factors, only ionizing radiation has been confirmed regarding its mechanism of action in the etiology of leukemia (4). In recent years, more and more reports have supported the concept that genomic factors may play a role in the initiation and development of childhood ALL. Firstly, Down syndrome and Fanconi anemia, two well-known inherited genetic disorders, have been associated with an elevated risk for ALL (5, 6). Secondly, genetic mutations in several typical cancer-related genes, such as *p53*, neuroblastoma RAS viral oncogene homolog (*NRAS*), and PHD finger protein 6 (*PHF6*), have frequently been identified in patients with ALL (7). Thirdly, only a small proportition of children with

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ALL have a history of been exposed to these factors, indicating the potential role for a genetic predisposition in the etiology of ALL, especially childhood ALL (2).

The matrix metalloproteinases (MMPs), also known as matrixins, are a family of proteases that play a key role in extracellular matrix component regulation by their action in degradation of various connective tissue matrices (8, 9). Homeostasis of each MMP is also a dynamic balance of a complicated network through interactions with other members and their specific inhibitors, *e.g.* the tissue inhibitors of metalloproteinases (TIMPs) (9). MMP1, also known as collagenase-1, is most abundant among the MMPs and under the control of activator protein-1 (AP1), which binds to the promoter region of mitogen-activated kinase through polyomavirus-enhancing activity-3 (10, 11). In 2016, a polymorphic variation was found in the *MMP1* promoter region at upstream position 1,607 bp (rs1799750, also known as rs11292517, rs17886084, rs61633513, rs139258005, rs375359915 and rs368625565), which controls the transcriptional activity of *MMP1* and was associated with the incidence and progression of several types of cancer, including oral (12), breast (13), ovarian (14), lung (15), esophageal (16, 17), gastric (18) and colorectal (19).

The genomic contribution of *MMP1* to ALL has not been well elucidated. The purpose of this study was to reveal the contribution of *MMP1* genotype at the promoter -1607 site to the risk of ALL in a representative pediatric population sample (controls/cases=266/266) of Taiwanese children.

Materials and Methods

Study population and sample collection. Our study was approved by the Institutional Review Board of China Medical University Hospital, and written informed consent was obtained from one or both parents of all participants. Two hundred and sixty-six patients diagnosed with childhood ALL (all patients under 18 years of age) were recruited between 2005-2010 from the General Surgery outpatient clinics within the Pediatric Departments at the China Medical University Hospital and the National Taiwan University Hospital, Taiwan, Republic of China. All of the clinical characteristics of these patients, including their histological details, were identified by expert surgeons. All children voluntarily participated, completed a questionnaire with the help of parents or guardians, and provided peripheral blood samples. The questionnaire recorded their disease history, diet and sleeping habit, and the disease history, diet, behavioral lifestyle and social-economic status of the parents. An equal number of age-matched non-cancer healthy volunteers were selected for use as a control group following initial random sampling from the Health Examination Cohort established from 2005 to 2010 as previously published (20-22). The registered health practitioners in the hospital provide a multidisciplinary team approach of health assessment for the volunteers. Most of the volunteers underwent health examinations every 5 to 6 months. A total of 457 volunteers age under 18 years were recruited into this study and chosen were cancer free by the age at diagnosis of the case child with the International Classification of Disease, ninth revision (ICD-9) codes (defined by World Health Organization). Finally, 266 participants were included for analysis in the study since to match the population structure (number, age and gender) with our case population. The overall agreement rate in the study was above 85%.

Genotyping assays. Genomic DNA was prepared from peripheral blood leukocytes using a QIAamp Blood Mini Kit (Blossom, Taipei, Taiwan), stored long-term at −80˚C, diluted and aliquoted for genotyping as a working stock at −20˚C (23, 24). The sequences of primers and the restriction enzymes for *MMP1* promoter -1607 genotyping are the same as our recently published *MMP1* rs1799750 genotyping methodology (12, 13). The forward and reverse primers were 5'-TGACTTTTAAAACATAGTCTATGT-3' and 5'-GATTGATTTGAGATAAGTCATAGC-3', respectively. The polymerase chain reaction (PCR) cycling conditions were: one cycle at 94˚C for 5 min; 35 cycles of 94˚C for 30 s, 58˚C for 30 s, and 72˚C for 30 s; and a final extension at 72˚C for 10 min. After amplification, the PCR products were subject todigestion by *Alu*I restriction endonuclease for 2 h at 37˚C and separation using 3% agarose gel electrophoresis. The genotypes were identified as homozygous 2G/2G with 269-bp product, heterozygous 1G/2G with 269-, 241- and 28-bp products, and homozygous 1G/1G with 241- and 28-bp products. All the genotypic processing was repeated by two researchers independently, and blindly, and the results were 100% concordant. In addition, the success rate of PCR-restrictive fragment length polymorphism (RFLP) is 100%, and the genotypes of 5% of the participants in both the control and patient groups were analyzed by PCR direct sequencing (Genomics BioSci & Tech Co., Taipei, Taiwan). The concordance between direct sequencing and PCR-RFLP was 100%.

Statistical analyses. Those participants having both genotypic and clinical data (controsl/cases=266/266) were selected for final analysis. The descriptive statistics of patients and controls are presented as the mean and standard deviation (SD) or as percentages. The Pearson's chi-square test or Fisher's exact test (when any cell was less than five) was used to compare the distribution of the genotypes. Associations were evaluated as odds ratios (ORs) with 95% confidence intervals (CIs). Statistical tests were deemed significant when the *p*-value was less than 0.05.

Results

The frequency distributions for the age and gender of 266 patients with childhood ALL and 266 non-cancer healthy controls are shown in Table I. The data showed that the age and gender of the cases and controls were indeed both well matched in these two groups ($p>0.05$) (Table I).

The genotypic analysis for the *MMP1* rs1799750 among the controls and patients are shown in Table II. The genotypic frequency distributions for *MMP1* rs1799750 were significantly different between childhood ALL and control groups (p for trend=0.0046) (Table II). In detail, the *MMP1* rs1799750 heterozygous 1G/2G and homozygous 1G/1G were associated with decreased risk of childhood ALL ($p=0.0395$ and 0.0013, OR=0.68 and 0.43, 95% CI=0.47-0.98 and 0.26-0.73, respectively; Table II). In the recessive and dominant

Table I. *Selective demographic information of 266 childhood acute lymphoblastic leukemia cases and 266 matched controls.*

Characteristic	Controls (n=266)			Cases (n=266)			*p*-Value
	n	%	Mean (SD)	n	%	Mean (SD)	
Age at onset			8.3 (4.8)			7.0 (4.4)	0.64[a]
<3.5 years	133	50.0%		133	50.0%		
≥3.5 years	133	50.0%		133	50.0%		1.00[b]
Gender							
Male	148	55.6%		148	55.6%		
Female	118	44.4%		118	44.4%		1.00[b]

[a]Based on Student's *t*-test; bbased on Chi-square test.

Table II. *Analysis of the metalloproteinase 1 rs1799750 genotypic and allelic frequencies among 266 childhood acute lymphoblastic leukemia cases and 266 healthy controls.*

Genotype	Controls	%	Cases	%	*p*-Value[a]	OR (95% CI)
Genotype analysis						
2G/2G	98	36.8%	131	49.2%		1.00 (Reference)
1G/2G	116	43.6%	105	39.5%	**0.0395**	**0.68 (0.47-0.98)**
1G/1G	52	19.5%	30	11.3%	**0.0013**	**0.43 (0.26-0.73)**
p_{trend}					**0.0046**	
Carrier comparison						
2G/2G +1G/2G	214	80.5%	236	88.6%		1.00 (Reference)
1G/1G	52	19.5%	30	11.3%	**0.0083**	**0.52 (0.32-0.85)**
2G/2G	98	36.8%	131	49.2%		1.00 (Reference)
1G/1G+1G/2G	168	63.2%	135	50.8%	**0.0039**	**0.60 (0.43-0.85)**

OR: Odds ratio; CI: confidence interval. [a]Based on Pearson's Chi-square test. Statistically significant differences are shown in bold.

models, there was still significant association between the genotype of *MMP1* rs1799750 and childhood ALL risk (p=0.0083 and 0.0039, OR=0.53 and 0.60, 95% CI=0.32-0.85 and 0.43-0.85, respectively; Table II). The conclusion that can be deduced from Table II is that the *MMP1* rs1799750 1G/2G and 1G/1G genotypes (1G allele) seemed to be a protective factor for childhood ALL in Taiwanese.

Because age and gender are the predominant risk factors for developing childhood ALL, the contribution of the *MMP1* rs1799750 genotype to childhood ALL stratified by age and gender were further analyzed and the results or presented in Table III. The average median age of onset of ALL in the control and patient groups was 3.5 years; thus, we further stratified the groups into subgroups of those <3.5 and ≥3.5 year-old. Notably, in the younger sub-group, those with heterozygous1G/2G or homozygous 1G/1G genotype for *MMP1* rs1799750 had lower risk for developing childhood ALL than those with the wild-type 2G/2G genotype (p for trend=0.0008, p=0.0183 and 0.0004; OR=0.53 and 0.25, 95% CI=0.31-0.90 and 0.12-0.56 for 1G/2G and 1G/1G, respectively), and the combined group of those carrying 1G *MMP1* rs1799750 genotypes also gave similar results (OR=0.44, 95% CI=0.27-0.72; p=0.0009); however, there was no any significant association found in the analysis of the older sub-group (Table III).

For gender, males with 1G/2G or 1G/1G genotypes for *MMP1* rs1799750 were less likely to develop childhood ALL than those with the homozygous 2G/2G genotype (p for trend=0.0014; OR=0.57 and 0.24, 95% CI=0.34-0.95 and 0.10-0.56; p=0.0318 and 0.0005 for 1G/2G and 1G/1G, respectively), and the combined group of those carrying 1G *MMP1* rs1799750 genotypes also gave similar results (OR=0.47, 95% CI=0.29-0.76; p=0.0021). However, there was no significant association found in the analysis of the female sub-group (Table III).

In summary, the results of stratification analysis revealed an interaction between a younger age at onset and being male with *MMP1* rs1799750 genotype in susceptibility to childhood ALL.

Table III. *Distribution of the metalloproteinase 1 (MMP1) rs1799750 genotypes stratified by age and gender among 266 childhood acute lymphoblastic leukemia cases and 266 healthy controls.*

	MMP1 rs1799750				
Characteristic	Controls n (%)	Cases n (%)	p_{trend}[a]	*p*-Value[a]	OR (95% CI)
Age at onset					
<3.5 years			**0.0008**		
2G/2G	49 (36.8)	76 (57.1)			1.00 (Reference)
1G/2G	56 (42.1)	46 (34.6)		**0.0183**	**0.53 (0.31-0.90)**
1G/1G	28 (21.1)	11 (8.3)		**0.0004**	**0.25 (0.12-0.56)**
1G/2G + 1G/1G	84 (63.2)	57 (42.9)		**0.0009**	**0.44 (0.27-0.72)**
≥3.5 years			0.6263		
2G/2G	49 (36.8)	55 (41.3)			1.00 (Reference)
1G/2G	60 (45.1)	59 (44.4)		0.6224	0.88 (0.52-1.48)
1G/1G	24 (18.1)	19 (14.3)		0.3373	0.71 (0.35-1.44)
1G/2G + 1G/1G	84 (63.2)	78 (58.7)		0.4509	0.83 (0.51-1.35)
Gender					
Male			**0.0014**		
2G/2G	51 (38.3)	76 (57.1)			1.00 (Reference)
1G/2G	57 (42.9)	48 (36.1)		**0.0318**	**0.57 (0.34-0.95)**
1G/1G	25 (18.8)	9 (6.8)		**0.0005**	**0.24 (0.10-0.56)**
1G/2G + 1G/1G	82 (61.7)	57 (42.9)		**0.0021**	**0.47 (0.29-0.76)**
Female			0.4936		
2G/2G	47 (35.3)	55 (41.3)			1.00 (Reference)
1G/2G	59 (44.4)	57 (42.9)		0.4807	0.83 (0.48-1.41)
1G/1G	27 (20.3)	21 (15.8)		0.2451	0.66 (0.33-1.33)
1G/2G + 1G/1G	86 (64.7)	78 (55.93)		0.3131	0.78 (0.47-1.27)

OR, Odds ratio; CI, confidence interval. [a]Based on Chi-square test. Statistically significant differences are shown in bold.

Discussion

In the current study, we firstly examined the contribution of *MMP1* genotype to childhood ALL susceptibility. Since MMP1 plays an essential role in angiogenesis and metastasis *via* its regulatory function in the extracellular matrix, it is very possible that hereditary genomic variations may determine personal susceptibility to carcinogenesis. In literature, the polymorphic *MMP1* genotype at -1,603 (rs1799750) may determine the *MMP1* mRNA and protein levels, and the susceptibility to cancer (25). Head and neck squamous carcinoma cells with the 2G/2G genotype were found to express significantly more *MMP1* mRNA than those with 1G/2G or 1G/1G *MMP1* rs1799750 genotypes. Moreover, the 2G allele of *MMP1* rs1799750 is associated with the risk of several types of cancer, including oral (12), breast (13), gastric (18), colorectal (26) and bladder (27). In addition, a negative association was also found in ovarian (14) and lung (15) cancer. However, little is known about the association between *MMP1* genotype and the risk of leukemia, which is a non-solid type of cancer.

In the current study, we found that the 1G/1G homozygous and 1G/2G heterozygous genotypes of *MMP1* rs1799750 were significantly associated with a lower susceptibility to childhood ALL (Table II). As far as we are aware of, the current study is the first to reveal the genotypic contribution of *MMP1* genotypes to (childhood) ALL, with the novel findings that *MMP1* rs1799750 may be a potential marker for prediction of childhood ALL (Table II).

The MMP1 protein is involved in the degradation of the native collagens in extracellular matrix (ECM). Under normal conditions, MMP1 is expressed at a relatively low level under the see-saw regulation of TIMP1 protein (28, 29). In addition, MMP1 has been reported to play a critical role in the invasion and migration processes of solid tumors (30, 31). Furthermore, mounting evidence indicates that up-regulation of MMP1 is observed in the borders of solid tumors, such as in breast and oral cancer (32-34). In 2010, Scrideli and colleagues collected bone marrow samples from 134 children with ALL and evaluated the mRNA expression profile of *TIMP1, TIMP2, MMP2* and *MMP9*. They found that *TIMP1* gene expression values higher than the median were associated with a significantly lower 5-year event free-survival, indicating that a high *TIMP1* level may be a potential marker for poor prognosis of ALL (35). It is still controversial whether MMP1 expression is lower in those tissues with higher TIMP1 expression, and is likely to be associated with significantly

lower 5-year event free-survival and poorer prognosis. Moreover, revealing the contribution of *TIMP1* genotypes to childhood ALL and the detail mechanisms and crosstalk between TIMP1 and MMP1 may help our further understanding of the tissue microenvironmental alterations during ALL progression.

In the current study, we further analyzed the influence of *MMP1* rs1799750 genotype on childhood ALL susceptibility according to the age of onset and gender of the investigated children. Children in the early onset subgroup, aged less than 3.5 years, had a lower risk of childhood ALL with 1G/2G or 1G/1G *MMP1* rs1799750 genotypes than those with wild-type 2G/2G genotype. However, this difference was not found for the older subgroup of children (Table III). We also found that boys with 1G/2G or 1G/1G *MMP1* rs1799750 genotypes had a lower risk of childhood ALL than those with the wild-type 2G/2G genotype. At the same time, although no statistically significant association was found in the analysis of *MMP1* rs1799750 genotypes among girls, there was a similar protective role of 1G-carrying *MMP1* rs1799750 genotypes (Table III). Future investigation with a larger sample size may confirm the findings for the gender difference in the contribution of *MMP1* rs1799750 genotype to ALL susceptibility among boys and girls. In the current study, it seems that the protective impact of the 1G allele at *MMP1* rs1799750 with respect to ALL risk was more obvious for Taiwanese boys than girls (Table III). Similarly in our previous findings, the A allele for flap endonuclease 1 rs174538 was also protective against childhood ALL, and the association was again only significant in boys but not girls (22). In searching for the different effects of sex hormones on leukemia cells, it was found that 17-β estrogen induced a significant increase of apoptosis in macrophage-like U937 cells, but testosterone did not (36). On the contrary, progesterone, but not 17-β-estradiol, increases the secretion of tumor necrosis factor α in U937 cells, inducing the death of the cells by another pathway (37). The different roles of sexual hormones in childhood ALL need more investigation.

In conclusion, this study documented the evidence of a positive association between the genotype of *MMP1* rs1799750 and childhood ALL in addition to age and gender interactions with the *MMP1* rs1799750 genotype in determining childhood ALL susceptibility. The presence of the 1G allele at *MMP1* rs1799750 was not only a novel predictive biomarker for childhood ALL but also a protective determinant for boys and patients younger than 3.5 years.

Conflicts of Interest

The Authors declare no interest conflict with any person or company.

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