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Contribution of Cyclin-dependent Kinase Inhibitor 1B Genotypes to Childhood Leukemia Risk

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Abstract. *Background/Aim: Although genetic differences in cell-cycle control genes have been associated with cancer risk, to our knowledge, no report has specifically examined the role of gene variants in childhood acute lymphoblastic leukemia (ALL). Cyclin-dependent kinase inhibitor 1B (CDKN1B; also known as p27/KIP1) is a cell-cycle regulating gene. This study aimed at investigating the association between CDKN1B genotypes and childhood ALL risk. Materials and Methods: In 266 childhood ALL cases and 266 healthy controls, the CDKN1B rs34330 and 2066827 polymorphisms were genotyped, and the association of CDKN1B genotypes with childhood ALL risk were analyzed. Results: The genotypes of CDKN1B rs34330 and 2066827 were similarly distributed between the control and case groups (p for trend=0.8718 and 0.4030, respectively). The allelic frequency also exhibited no statistical difference (p=1.0000 and 0.6666, respectively). There was no significant interaction between CDKN1B genotypes and age or sex. Conclusion: CDKN1B genotypes were not found to be minor contributors to childhood ALL susceptibility in Taiwan.*

Acute lymphoblastic leukemia (ALL), the most common cause of cancer-related death among children, still presents a poor prognosis (1). The pathogenesis of childhood ALL remains largely unknown, and genetic variations and some risk factors, such as advanced parental age, have been reported to be the cause of childhood ALL (2-4). In recent years, a few novel polymorphic biomarkers have been reported to play a role in childhood ALL risk (5-8). Interestingly, there are still many more genomic factors waiting to be explored for the contribution of their genotypic and phenotypic patterns to the etiology of childhood ALL.

The *CDKN1B* gene (also known as *p27/KIP1*), located on chromosome 12p13, encodes for cyclin-dependent kinase (CDK) inhibitor 1B, which plays a role in the suppressive regulation of the cell cycle (9-11), and may also play critical roles in leukemia (12). Under normal conditions, DNA can be affected by numerous DNA-damaging agents exogenous and endogenous, and such damaged cells undergo cell-cycle arrest to allow DNA adducts and errors to be removed. Therefore, dysregulation of cell-cycle arrest, or normal control, may result in the initiation of carcinogenesis (13, 14). There are at least two well-known polymorphic sites of

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Key Words: CDKN1B, childhood leukemia, genotype, polymorphism, Taiwan.

Table I. *Basic and clinical indices for the 266 childhood acute lymphoblastic leukemia (ALL) cases and the 266 healthy controls of this study.*

Characteristic		Controls (n=266)	Cases (n=266)	*p*-Value
Age at ALL onset, years	Mean±SD	8.3±4.8	7.0±4.4	0.6483[a]
Sex, n (%)	Male	148 (55.6%)	148 (55.6%)	
	Female	118 (44.4%)	118 (44.4%)	1.0000[b]
White blood cell count, $\times 10^9$/l	Mean±SD	7.5±2.0	54.3±75.9	<0.0001
Immunophenotype, n (%)	B Subtype		227 (85.3%)	
	T Subtype		39 (14.7%)	
Risk classification, n (%)	Standard		130 (48.9%)	
	High		67 (25.2%)	
	Very high		69 (25.9%)	
Survival, n (%)	<5 Years		69 (25.9%)	
	≥5 Years		197 (74.1%)	

SD: Standard deviation. [a]Student's *t*-test; [b]chi-square test without Yates' correction.

the *CDKN1B* gene, one is rs2066827 (109T/G), and the other is rs34330 (-79 C/T). The former is located in intron 1, while the latter is located in promoter region. They are most frequently studied for their association with cancer. For instance, in 2012, a meta-analysis was conducted to investigate the association between *CDKN1B* gene rs2066827 polymorphism and cancer susceptibility (15). However, ALL has not yet been investigated, let alone childhood ALL. Therefore, we aimed to examine the contribution of *CDKN1B* rs34330 and rs2066827 genotypes to childhood ALL susceptibility in a representative Taiwanese population.

Materials and Methods

Collection of childhood leukemia cases and matched healthy controls. We recruited all the childhood ALL cases from pediatric oncologists and all cases were confirmed by pathology. Each case completed a questionnaire with the help from their parents or guardians and donated 3-5 ml of blood for genotyping. Healthy controls, identified as never having had any type of tumor, were matched to each case by age (±2 years) and sex. All the participants were definitively Taiwanese. Their demographic characteristics are summarized in Table I. This study was approved by the Institutional Review Board of China Medical University Hospital (approval number DMR103-IRB-153).

Genotyping methodology for CDKN1B polymorphisms. Genomic DNA was extracted from blood leukocytes within 24 h of sampling. The genotypes of *CDKN1B* rs34330 and rs2066827 were determined by polymerase chain reaction (PCR)-based restriction fragment length polymorphism methodology. The PCR conditions set for both *CDKN1B* rs34330 and rs2066827 genotyping was a starting cycle at 94˚C for 5 min; repeated 35 cycles at 94˚C for 30 s, one cycle at annealing 55˚C for 30 s, one cycle at 72˚C for 30 s and a final step at 72˚C for 10 min. The sequences of forward and reverse primers together with their PCR products, corresponding restriction enzymes, and cutting adducts for *CDKN1B* rs34330 and rs2066827 are summarized in Table II.

Statistical methodology for examining the association of CDKN1B rs34330 and rs2066827 with childhood ALL risk. The good-of-fit chi-square test was used to examine for fitness of Hardy-Weinberg equilibrium of *CDKN1B* rs34330 and rs2066827 in the control group. Unpaired Student's *t*-test was used to investigate the distributions of ages. Pearson's chi-square methodology was used to check the distribution pattern of *CDKN1B* rs34330 and rs2066827 genotypes. The association of *CDKN1B* rs34330 and rs2066827 genotypes with childhood ALL were also examined by odds ratios (ORs) with their 95% confidence intervals (CIs). Associations with a *p*-value of 0.05 or less were taken as being statistically significant.

Results

Comparison of basic and clinical parameters. The information of age at ALL onset, sex, and white blood cell counts of the childhood ALL cases and matched healthy controls are recorded in Table I. In addition, the immunophenotype, risk classification and survival time for the cases are also shown (Table I). Since we matched each case to a control based on age and sex, there was no difference in distributions of the two indices between the two groups (both *p*-values>0.05, Table I). The childhood ALL cases had significantly higher white blood cell counts (54.3×10^9/l) than those of healthy controls (7.5×10^9/l) ($p<0.0001$). Among the patients, 48.9% (130 cases) were at standard risk, 25.2% (67 cases) were at high risk, and 25.9% (69 cases) were at very high risk. Lastly, 25.9% of the cases survived less than 5 years (Table I).

Association between CDKN1B rs34330 genotypes and childhood ALL. The genotypic distributions of *CDKN1B* rs34330 among the controls and the patients with childhood ALL are presented in Table III. Firstly, the frequencies of *CDKN1B* rs34330 genotypes among the controls fit well with the Hardy-Weinberg equilibrium ($p=0.0606$). Secondly, the genotypes of *CDKN1B* rs34330 were not significantly

Table II. *Sequences of primer pairs, polymerase chain reaction (PCR) products, restriction enzymes, and cutting adducts for cyclin-dependent kinase inhibitor 1B polymorphisms rs34330 and rs2066827.*

Polymorphic sites	Primers	PCR product length, base pairs	Restriction enzyme	Cutting adducts, base pairs
rs34330	F: 5'- TGGCTCGTCGGGGTCT-3') R: 5'-CCATCCGCTCCAGGCT-3'	195	Hae III	C: 129+66 T: 195
rs2066827	F: 5'-TAGAGGGCAAGTACGAGTGG-3') R: 5'-TGGTTGGGAAAGGGTCAT-3'	288	Bgl I	T: 288 G: 173+115

F: Forward; R: reverse.

Table III. *Genotypes of cyclin-dependent kinase inhibitor 1B rs34330 polymorphism among the 266 childhood acute lymphoblastic leukemia cases and the 266 healthy controls.*

Genotype	Controls, n (%)	Cases, n (%)	OR (95% CI)	*p*-Value[a]
rs34330				
CC	53 (19.9%)	56 (21.0%)	1.00 (Reference)	
CT	148 (55.6%)		0.91 (0.58-1.41)	0.6678
TT	65 (24.5%)	68 (25.6%)	0.99 (0.60-1.64)	0.9693
p_{trend}				0.8718
p_{HWE}				0.0606
Carrier comparison				
CC+CT	201 (75.5%)		1.00 (Reference)	
TT	65 (24.5%)	68 (25.6%)	1.06 (0.72-1.57)	0.7639
CC	53 (19.9%)	56 (21.0%)	1.00 (Reference)	
CT+TT	213 (80.1%)	210 (79.0%)	0.93 (0.61-1.42)	0.7473

CI: Confidence interval; OR: odds ratio. [a]Chi-square test without Yates's correction; p_{trend}: *p*-value for trend analysis; p_{HWE}: *p*-value for Hardy-Weinberg equilibrium analysis.

differently distributed between the two groups (*p* for trend=0.8718) (Table III). In detail, the *CDKN1B* rs34330 heterozygous CT and homozygous variant TT genotypes were not associated with an altered childhood ALL risk, compared with the wild-type CC genotype (OR=0.91 and 0.99, 95% CI=0.58-1.41 and 0.60-1.64, *p*=0.6678 and 0.9693, respectively). Thirdly, in the recessive and model, there was no association variant genotypes of *CDKN1B* rs34330 with childhood ALL risk (OR=1.06 and 0.93, 95% CI=0.72-1.57 and 0.61-1.42, *p*=0.7639 and 0.7473, respectively) (Table III).

Association between CDKN1B rs2066827 genotypes and childhood ALL. The genotypic distributions of *CDKN1B* rs2066827 are presented in Table IV. Firstly, the genotypic frequencies of *CDKN1B* rs2066827 among the controls fit well with the Hardy-Weinberg equilibrium (*p*=0.7066). Secondly, none of the *CDKN1B* rs2066827 genotypes seemed to be significantly associated with childhood ALL risk in any model (all *p*-values>0.05).

Allelic frequency distribution analysis. To validate the results in Table III and Table IV, an allelic frequency distribution analysis for *CDKN1B* rs34330 and rs2066827 was conducted, and the results are shown in Table V. The results showed that the variant alleles at *CDKN1B* rs34330 and rs2066827 were not associated with childhood ALL risk at all (OR=1.00 and 0.83, 95% CI=1.00-1.00 and 0.36-1.94, *p*=1.0000 and 0.6666, respectively; Table V), supporting the findings above.

Discussion

Generally speaking, it is thought that cancer is closely associated with the dysregulation of cell division. In mammalian cells, cell division is under the controlling system comprising cyclins, CDKs, essential coenzymes of CDK, and CDK inhibitors (16, 17). Typically, CDKs and cyclins are precisely regulated to guarantee accurate cell-cycle progression. For instance, a subtle dysregulation in the G_1 to S phase transition due to cell cycle-related genes or proteins may be associated with various types of cancer (18-23). In particular, cyclin D1 (*CCND1*) genotypes were found to be significantly associated with non-solid tumor childhood ALL risk (5). Thus, we intended to investigate the contribution of *CDKN1B* genotypes to childhood ALL risk.

Table IV. *Genotypes of cyclin-dependent kinase inhibitor 1B rs2066827 polymorphism among the 266 childhood acute lymphoblastic leukemia cases and the 266 healthy controls.*

Genotype	Controls, n (%)	Cases, n (%)	OR (95% CI)	*p*-Value[a]
rs2066827				
TT	254 (95.5%)	257 (96.6%)	1.00 (Reference)	
GT	12 (4.5%)	8 (3.0%)	0.66 (0.26-1.64)	0.3664
GG	0 (0.0%)	1 (0.4%)	1.00 (1.00-1.00)	1.0000
p_{trend}				0.4030
p_{HWE}				0.7066
Carrier comparison				
TT+GT	266 (100.0%)	265 (99.6%)	1.00 (Reference)	
GG	0 (0.0%)	1 (0.4%)	1.00 (1.00-1.00)	1.0000
TT	254 (95.5%)	257 (96.6%)	1.00 (Reference)	
GT+GG	12 (4.5%)	9 (3.4%)	0.74 (0.31-1.79)	0.5042

CI: Confidence interval; OR: odds ratio. [a]Chi-square test without Yates's correction (n≥5), or Fisher's exact test (n<5); p_{trend}: *p*-value for trend analysis; p_{HWE}: *p*-value for Hardy-Weinberg equilibrium analysis.

Table V. *Distribution of allelic frequencies for cyclin-dependent kinase inhibitor 1B rs34330 and rs2066827 polymorphisms among the 266 childhood acute lymphoblastic leukemia cases and the 266 healthy controls.*

Allele	Controls, n (%)	Cases, n (%)	OR (95% CI)	*p*-Value[a]
rs34330				
C	254 (47.7%)	254 (47.7%)	1.00 (Reference)	
T	278 (52.3%)	278 (52.3%)	1.00 (1.00-1.00)	1.0000
rs2066827				
T	520 (97.7%)	522 (98.1%)	1.00 (Reference)	
G	12 (2.3%)	10 (1.9%)	0.83 (0.36-1.94)	0.6666

CI: Confidence interval; OR: odds ratio. [a]Chi-square test without Yates's correction.

CDKN1B genotypes have been investigated for their association with cancer susceptibility in a panel of cancer types, including ovarian, breast and prostate cancer (24-27). However, childhood ALL is not on that list. To the best of our knowledge, the current study is the first to investigate the association of *CDKN1B* genotypes with childhood ALL. As recorded in literature, down-regulation of *CDKN1B* expression is a common event in breast carcinogenesis and associated with higher tumor grade and poorer prognosis (28). The *CDKN1B* rs2066827 genotype was associated with shortened survival among metastasis-free breast cancer patients (29), but we found no investigation of its contribution to childhood leukemia.

In the current study, we found that the genotypes of neither *CDKN1B* rs34330 nor rs2066827 were associated with childhood leukemia among Taiwanese children (Table III and Table IV). Furthermore, the allelic frequency analysis validated the findings that the neither the variant T allele of *CDKN1B* rs34330 nor the variant G allele of *CDKN1B* rs2066827 altered the risk of childhood ALL (Table V). Our study also demonstrated that older children (≥3.5 years) or younger children do not have different risk of suffering from childhood ALL (data not shown). Similarly, there was no sex difference in the susceptibility of childhood ALL (data not shown).

The cell cycle is mainly regulated by CDKs and CDK-cyclin complexes (30-32), which result in retinoblastoma phosphorylation and inactivation (33-35). This complicated procedure is governed by inhibitors which are classified into two groups: Inhibitors of kinase 4 (INK4) and CDK-inhibitory protein/kinase inhibitor proteins. The former group is composed of CDKN2A (INK4A/p16 and ARF/p14), CDKN2B (INK4B/p15), CDKN2C (INK4C/p18) and CDKN2D (INK4D/p19), while the latter group is composed of CDKN1A (WAF1/p21/CIP1) and CDKN1B (KIP1/p27). At the current time, we cannot rule out the possibility that CDK-inhibitory protein/kinase inhibitor proteins other than CDKN1B may contribute to the etiology of childhood ALL, and their genotypes may serve as markers for childhood ALL. This possibility remains to be investigated.

In conclusion, this study provides preliminary evidence for whether the *CDKN1B* genotype can serve as a biomarker for

childhood ALL. Our results showed that neither of *CDKN1B* rs34330 nor rs2066827 genotypes were associated with childhood leukemia among Taiwanese children. Further studies are needed to validate the clinical involvement of other cell-cycle regulation genes in this disease.

Conflicts of Interest

All the Authors declare no conflicts of interest in this study.

Authors' Contributions

Research design: Pei JS, Chang WS, Bau DT and Hsu PC; patient and questionnaire summary: Wang CH, Chen CC, Pei JS and Hsu PC; experimental data clearing and checking: Yang YC and Hsu SW; statistical analysis: Hsu YN and Wang YC; article writing: Chang WS, Tsai CW and Bau DT; article reviewing and revising: Bau DT, Wang CH and Tsai CW.

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