ANTICANCER RESEARCH *42*: 5283-5290 (2022)
doi:10.21873/anticanres.16035

Significant Contribution of Interleukin-18 Genotypes to Childhood Acute Lymphocytic Leukemia Risk in Taiwanese

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Abstract. *Background/Aim: Evidence has shown that interleukin-18 (IL-18) has both antitumor and pro-tumor effects in various types of leukemia. The current study aimed at investigating the contribution of IL-18 polymorphisms to the risk of childhood acute lymphocytic leukemia (ALL) in Taiwan. Materials and Methods: IL-18 promoter -656 (rs1946519), -607 (rs1946518), and -137 (rs187238) genotypes of 266 childhood ALL cases and 266 controls were determined by polymerase chain reaction-restriction fragment length polymorphism methodology. Results: The distributions of genotypic and allelic frequencies of IL-18 rs1946519, rs1946518 or rs187238, were not significantly different between childhood ALL cases and controls (all p>0.05). However, in the stratification analysis among the cases, IL-18 rs187238 GC and CC genotypes were associated with increased childhood ALL risk and shorter survival (OR=4.19 and 2.93, 95%CI=2.04-8.64 and 1.19-7.23, p=0.0001 and 0.0250, respectively). No association was found with rs1946519 and rs1946518 (all p>0.05). Conclusion: IL-18 rs187238 GC and CC genotypes can serve as predictors for childhood ALL prognosis among Taiwanese. Validation in larger and various populations can greatly extend the feasibility of this novel predictor.*

Acute lymphoblastic leukemia (ALL) is a disease that arises from the uncontrolled proliferation of lymphoid progenitors (1, 2). Typically, ALL is the most prevailing pediatric hematologic malignancy and mainly attacks children aged 2–5 years old (3-5). Although the pathogenesis and etiology of childhood ALL remain largely unknown, it is widely believed that childhood ALL is caused by genetic variations and environmental factors (6, 7). Recently, lots of studies reported that subtle alterations in the inherited genome, single nucleotide polymorphisms (SNPs), may play a critical role in determining the personal susceptibility to childhood ALL (8-13). The genetic factors associated with childhood ALL are largely undefined, and further explorations of the roles of these factors in relation to childhood ALL are beneficial for early detection and prediction of the disease.

Interleukin-18 (IL-18) was originally found in 1999 as a member of IL-1 cytokine family (14). It is secreted by various cells including T and B lymphocytes, monocytes,

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Key Words: Childhood ALL, genotype, IL-18, polymorphism, Taiwan.

macrophages, natural killer cells, and Langerhans cells (15-17). In literature, IL-18 is a double-edged knife, carrying both anti-tumor and pro-tumor effects (18, 19). On the anti-tumor side, IL-18 can activate natural killer cells, promoting primarily Th1 responses, resulting in the elimination of tumor cells (20-23). On the opposite side, IL-18 is capable of activating lots of behaviors of tumor cells, including angiogenesis, proliferation, migration, and immune escape ability (24). Higher expression levels of IL-18 have been reported in different solid cancer types, such as gastric, lung, and breast cancer (25-27). There is still no conclusive finding regarding IL-18 expression levels in childhood ALL.

In humans, *IL-18* gene is located on chromosome 11q22.2-q22.23 (28). In literature, IL-18 expression levels have been shown to be regulated by at least *IL-18,* -607 (A/C, rs1946518) and -137 (G/C, rs187238) (29). For instance, the *IL-18* gene promoter -137 (G/C, rs187238) polymorphism may change the binding site of histone 4 transcription factor-1 nuclear factor, thus altering IL-18 expression levels (29). Human hematopoietic cell lines, including U937, HL-60, KG-1, K562, J6-1, Jurkat, and HEL, express IL-18 and its receptor (30). In addition, although there is no evidence of IL-18 over-expression in childhood ALL patients, elevated levels of IL-18 have been reported in several types of leukemia patients, such as ALL, chronic myelogenous leukemia (CML) (31), T-cell large granular lymphocytic leukemia (32), and acute mixed lineage leukemia (33). However, IL-18 receptor expression has been mainly reported in CD19+ B cells and some CD8+ T cells (34). In 2005, Wu *et al*. examined the expression levels of cytokines and their receptors in childhood ALL (35), but no difference was found regarding IL-18.

In 2022, high circulating levels of IL-18 were suggested as a potential predictor for decreased risk of acute myeloid leukemia (AML) (36). In 2017, *IL-18* rs1946518 genotypes were reported to associate with prognosis and survival of AML (37), but to the best of our knowledge, there has been no study on *IL-18* genotypes in association with ALL. Based on these findings, the aim of this study was to investigate the potential association between *IL-18* -656 (rs1946519), -607 (rs1946518), -137 (rs187238) genotypes and susceptibility to ALL in the Taiwanese population. The genomic map of *IL-18* rs1946519, rs1946518, and rs187238 is shown in Figure 1.

Materials and Methods

Childhood leukemia cases and healthy controls. Childhood ALL cases were identified by expert pediatric oncologists. All the recruited 266 controls and 266 cases have completed a questionnaire with the help of their parents or guardians and donated their blood sample. Non-cancer healthy controls were matched to each case by age (within 2 years) and sex. The participants are all Taiwanese. This study was approved by the Institutional Review Board of China Medical University Hospital (CMUH111-REC1-038).

IL-18 genotyping design and settings. *IL-18* rs1946519, rs1946518, and rs187238 genotyping was conducted as previously published (38-41). Briefly, *IL-18* rs1946518 and rs187238 genotyping was carried out using Real-Time PCR (Applied Biosystems, Foster City, CA, USA). As for *IL-18* rs1946519, the polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) methodology was adapted (41). The restriction enzymes have been purchased from New England Biolabs (Ipswich, MA, USA).

Statistical analysis. Genotyping results from 266 childhood ALL patients and 266 healthy controls were finally analyzed. Student's *t*-test was adopted to evaluate the differential distribution of age in case and control groups. Pearson's Chi-square test was used to evaluate the possible differential distributions of various *IL-18* genotypes. The associations between specific *IL-18* genotypes and childhood ALL cancer risk were estimated by odds ratios (ORs) and corresponding 95% confidence intervals (CIs). A *p*-value less than 0.05 was considered statistically significant.

Results

Comparison of basic and clinical demographics. There was no difference in age and sex between the ALL case and control groups ($p>0.05$) since the two groups were well matched for these indices (Table I). As for white blood cell counts, childhood ALL cases had significantly higher levels compared to those of healthy controls ($p<0.0001$). Among childhood ALL patients, 85.3% (227) of them were of B subtype and 14.7% (39) were of T subtype. Furthermore, 48.9% (130) had standard risk for childhood ALL, 25.2% (67) had high risk for childhood ALL, and 25.9% (69) had very high risk for childhood ALL. Regarding survival, 25.9% of the patients survived for less than 5 years, whereas 74.1% survived for longer than 5 years (Table I).

Association between IL-18 genotypes and childhood ALL risk. The distributions of genotype frequencies of *IL-18* rs1946519, rs1946518, and rs187238 were 0.4521, 0.7066, and 0.2825, respectively, and fitted well with the Hardy-Weinberg equilibrium. There was no significant difference in the distribution of *IL-18* rs1946519, rs1946518, or rs187238 between childhood ALL and control groups *(p* for trend=0.8495, 0.7860, 0.8438, respectively) (Table II). In detail, variant GT and TT genotypes at *IL-18* rs1946519 did not associate with altered childhood ALL risk (OR=1.10 and 1.13, 95%CI=0.75-1.61 and 0.70-1.84, $p=0.7114$ and 0.7003, respectively). Variant AC and CC genotypes at *IL-18* rs1946518 did not associate with altered childhood ALL risk either (OR=0.89 and 1.01, 95%CI=0.59-1.34 and 0.62-1.62, $p=0.6465$ and 0.9825, respectively). Variant GC and CC genotypes at *IL-18* rs187238 also did not associate with altered childhood ALL risk (OR=0.90 and 0.78, 95%CI=0.57-1.40 and 0.21-2.95, $p=0.7173$ and 0.7494, respectively). We also conducted recessive and dominant model analysis, but no significant association was found (data not shown).

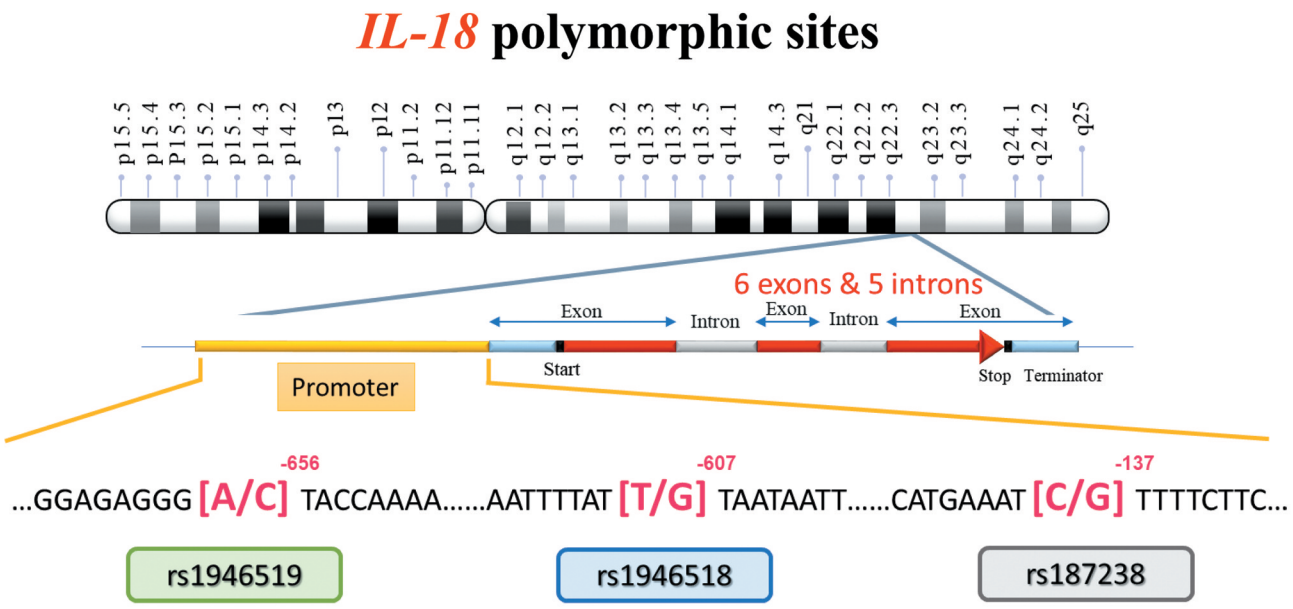

Figure 1. *The polymorphic sites of interleukin-18 (IL-18) rs1946519, rs1946518, and rs187238 on chromosome 11.*

Association between IL-18 rs1946519, rs1946518, and rs187238 alleles and childhood ALL risk. To further validate the findings shown in Table III, we performed statistical analysis on the allelic frequency distributions of the *IL-18* rs1946519, rs1946518, and rs187238, and the results showed that neither the T allele at *IL-18* rs1946519, nor the C allele at *IL-18* rs1946518 and the C allele at *IL-18* rs187238 was associated with a significantly altered risk of childhood ALL (OR=1.07, 1.00 and 0.89, 95%CI=0.84-1.37, 0.79-1.27 and 0.60-1.31, p=0.6206, 1.0000 and 0.6174) (Table III).

Association between IL-18 rs1946519, rs1946518, and rs187238 genotypes and childhood ALL immunophenotype, risk classification, and survival. We analyzed the potential contribution of *IL-18* rs1946519, rs1946518, and rs187238 genotypes to childhood ALL immunophenotype, risk classification, and survival, and no association with *IL-18* rs1946519 or rs1946518 was found (p>0.05) (Table IV and Table V). However, we found that *IL-18* rs187238 variant genotypes (GC+CC) were associated with higher (high or very high) childhood ALL risk, and shorter survival (OR=4.19 and 2.93, 95%CI=2.04-8.64 and 1.19-7.23, p=0.0001 and 0.0250, respectively) (Table VI).

Discussion

In this study, we evaluated the contribution of *IL-18* genotypes to ALL risk in a representative Taiwanese population, consisting of 266 childhood ALL patients and the same number of healthy controls (Table I). The data showed that *IL-18* rs1946519, rs1946518, and rs187238 genotypes were not associated with childhood ALL risk (Table II and Table III). Thus, these *IL-18* SNPs may not serve as useful biomarkers for early detection of childhood ALL in Taiwan. Noticeably, we have found that *IL-18* rs187238 GC+CC genotypes were associated with higher risk for childhood ALL, and shorter survival (Table VI). This is a novel finding and will be quite useful for prognosis prediction. The findings also support the concept that IL-18 somehow plays a critical role in the etiology of ALL, although the detail mechanisms need further investigation.

To the best of our knowledge, there is no report on the role of *IL-18* genotypes in ALL. In 2015, for a study was conducted on the role of *IL-18* genotypes in chronic lymphocytic leukemias (CLL) and CML among Turkish patients (42). However, the sample sizes for CLL, CML and healthy controls were only 20, 30, and 30, respectively. Although they provided promising data showing that *IL-18* rs187238 was associated with chronic leukemia in the Turkish population, large-scale studies are required to validate their findings. In 2017, Wang *et al*. reported that *IL-18* rs1946518 was not associated with the risk of AML, but the GT genotype of *IL-18* rs1946518 led to significantly poorer survival rates (37). The case and control sample sizes of their study were 383 and 300, which were more representative and reliable.

The genotypes of *IL-18* rs1946518 and rs187238 have been investigated for their association with the risk of various types of solid cancers. In esophageal, colorectal,

Table I. *Distribution of some basic and clinical demographics of the 266 patients with childhood acute lymphoblastic leukemia and 266 matched controls.*

Characteristic		Controls (n=266)	ALL patients (n=266)	*p*-Value
Onset age, 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%)	0.9999[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 risk		130 (48.9%)	
	High risk		67 (25.2%)	
	Very high risk		69 (25.9%)	
Survival, years	<5 Years		69 (25.9%)	
	≥5 Years		197 (74.1%)	

ALL: Acute lymphoblastic leukemia; SD: Standard deviation; [a]Based on Student's *t*-test; [b]based on chi-square test without Yates' correction; *Statistically significant *p*-value.

Table II. *Distribution of interleukin-18 (IL-18) genotypes among the 266 patients with childhood acute lymphoblastic leukemia and 266 healthy controls.*

Polymorphic site	Genotypes	Controls, n (%)	ALL patients, n (%)	OR (95%CI)	*p*-Value[a]
rs1946519	GG	91 (34.2%)	85 (32.0%)	1.00 (Reference)	
	GT	124 (46.6%)	127 (47.7%)	1.10 (0.75-1.61)	0.7114
	TT	51 (19.2%)	54 (20.3%)	1.13 (0.70-1.84)	0.7003
	p_{trend}				0.8495
	p_{HWE}				0.4521
rs1946518	AA	68 (25.6%)	72 (27.1%)	1.00 (Reference)	
	AC	136 (51.1%)	128 (48.1%)	0.89 (0.59-1.34)	0.6465
	CC	62 (23.3%)	66 (24.8%)	1.01 (0.62-1.62)	0.9825
	p_{trend}				0.7860
	p_{HWE}				0.7066
rs187238	GG	212 (79.7%)	217 (81.6%)	1.00 (Reference)	
	GC	49 (18.4%)	45 (16.9%)	0.90 (0.57-1.40)	0.7173
	CC	5 (1.9%)	4 (1.5%)	0.78 (0.21-2.95)	0.7494
	p_{trend}				0.8438
	p_{HWE}				0.2825

ALL: Acute lymphoblastic leukemia; CI: confidence interval; OR: odds ratio; p_{trend}: *p*-value for trend analysis; p_{HWE}: *p*-value for Hardy–Weinberg equilibrium analysis [a]Based on chi-square test without Yates' correction (n≥5) or Fisher's exact test (n<5).

Table III. *Distribution of interleukin-18 (IL-18) allelic frequencies among the 266 patients with childhood acute lymphoblastic leukemia and 266 healthy controls.*

Allele	Controls, N	%	Patients, N	%	OR (95%CI)	*p*-Value[a]
rs1946519						
G	306	57.5%	297	55.8%	1.00 (Reference)	
T	226	42.5%	235	44.2%	1.07 (0.84-1.37)	0.6206
rs1946518						
A	272	51.1%	272	51.1%	1.00 (Reference)	
C	260	48.9%	260	48.9%	1.00 (0.79-1.27)	1.0000
rs187238						
G	473	88.9%	479	90.0%	1.00 (Reference)	
C	59	11.1%	53	10.0%	0.89 (0.60-1.31)	0.6174

CI: Confidence interval; OR: odds ratio; [a]Based on chi-square test without Yates' correction.

Table IV. *Distribution of interleukin-18 (IL-18) rs1946519 genotypes among the 266 patients with childhood acute lymphoblastic leukemia stratified by immunophenotype, risk classification, and survival.*

Characteristics	*IL-18* rs1946519 genotypes		OR (95%CI)	*p*-Value[a]
	GG	GT+TT		
Immunophenotype				
B subtype, n (%)	70 (30.8%)	157 (69.2%)	1.00 (Reference)	
T subtype, n (%)	15 (38.5%)	24 (61.5%)	0.71 (0.35-1.44)	0.4488
Risk classification				
Standard risk	42 (32.3%)	88 (67.7%)	1.00 (Reference)	
High or very high risk	43 (31.6%)	93 (68.4%)	1.03 (0.62-1.73)	0.9040
Survival				
<5 years	25 (36.2%)	44 (63.8%)	1.00 (Reference)	
≥5 years	60 (30.5%)	137 (69.5%)	1.30 (0.73-2.31)	0.4621

CI: Confidence interval; OR: odds ratio; [a]Based on chi-square test without Yates' correction.

Table V. *Distribution of interleukin-18 (IL-18) rs1946518 genotypes among the 266 patients with childhood acute lymphoblastic leukemia stratified by immunophenotype, risk classification, and survival.*

Characteristics	*IL-18* rs1946518 genotypes		OR (95%CI)	*p*-Value[a]
	AA	AC+CC		
Immunophenotype				
B subtype, n (%)	58 (25.6%)	169 (74.4%)	1.00 (Reference)	
T subtype, n (%)	14 (35.9%)	25 (64.1%)	0.61 (0.30-1.26)	0.2508
Risk classification				
Standard risk	37 (28.5%)	93 (71.5%)	1.00 (Reference)	
High or very high risk	35 (25.7%)	101 (74.3%)	1.15 (0.67-1.97)	0.7172
Survival				
<5 years	21 (30.4%)	48 (69.6%)	1.00 (Reference)	
≥5 years	51 (25.9%)	146 (74.1%)	1.25 (0.68-2.29)	0.5659

CI: Confidence interval; OR: odds ratio; [a]Based on chi-square test without Yates' correction.

Table VI. *Distribution of interleukin-18 (IL-18) rs187238 genotypes among the 266 patients with childhood acute lymphoblastic leukemia stratified by immunophenotype, risk classification, and survival.*

Characteristics	*IL-18* rs187238 genotypes		OR (95% CI)	*p*-Value[a]
	GG	GC+CC		
Immunophenotype				
B subtype, n (%)	188 (82.8%)	39 (17.2%)	1.00 (Reference)	
T subtype, n (%)	29 (74.4%)	10 (25.6%)	1.66 (0.75-3.69)	0.3004
Risk classification				
Standard risk	119 (91.5%)	11 (8.5%)	1.00 (Reference)	
High or very high risk	98 (72.1%)	38 (27.9%)	4.19 (2.04-8.64)	0.0001*
Survival				
<5 years	63 (91.3%)	6 (8.7%)	1.00 (Reference)	
≥5 years	154 (78.2%)	43 (21.8%)	2.93 (1.19-7.23)	0.0250*

CI: Confidence interval; OR: odds ratio; [a]Based on chi-square test without Yates' correction; *Statistically significant *p*-values.

ovarian, bladder, prostate, breast and lung cancer, positive associations have been reported (27, 41, 43-48). However, there also studies reporting no association (49-52). Data have also shown that *IL-18* rs1946518/rs187238 haplotype was associated with an elevated nasopharyngeal carcinoma risk (53). These inconsistent conclusions might be explained not only by ethnic differences, but also by the type of cancer. These findings should be validated in various populations with large sample sizes.

Over-expression of IL-18 in serum has been reported to serve as a good marker for solid cancers, such as lung cancer (27); however, whether the serum level of IL-18 is a good marker for ALL is still unknow. There is evidence that high circulating levels of IL-18 associate with a decreased risk of AML (36). Dynamic alterations of IL-18 protein make it difficult to conclude whether IL-18 protein can serve as a good marker for ALL. However, the current results showed that the GG genotype of *IL-18* rs187238 can be a predictor of childhood ALL survival, although the detail mechanism needs more investigations (Table VI).

In conclusion, our pilot study showed that *IL-18* rs1946519, rs1946518, and rs187238 genotypes cannot serve as prognostic predictors for childhood ALL risk, as shown in other solid tumors. However, the variant GC and CC genotypes of *IL-18* rs187238 may serve as a predictor of higher risk and shorter survival.

Conflicts of Interest

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

Authors' Contributions

Research design: Chen CC, Tzeng HE, Kuo CC; patient and questionnaire summaries: Wang CH, Kuo CC, Lim SNS, Hsu PC; experimental work: Chang WS, Chin YT, Tsai CW; statistical analysis: Hsu YN, Chen CC; manuscript writing: Tsai CW, Pei JS, Bau DT; manuscript checking and discussing: Chen CC, Tzeng HE, Kuo CC, Lim SNS, Hsu PC, Chang WS, Chin YT, Tsai CW, Hsu YN, Pei JS, Bau DT.

Acknowledgements

The Authors are grateful to the Tissue-bank of China Medical University Hospital and doctors/nurses for their blood sample and questionnaire collection. This study was supported by research grants from China Medical University Hospital, Taichung, Taiwan (DMR-111-160), and Taoyuan General Hospital, Ministry of Health and Welfare, Taoyuan, Taiwan (PTH110039).

References

1 Terwilliger T and Abdul-Hay M: Acute lymphoblastic leukemia: a comprehensive review and 2017 update. Blood Cancer J *7(6)*: e577, 2017. PMID: 28665419. DOI: 10.1038/bcj.2017.53

2 Mrózek K, Harper DP and Aplan PD: Cytogenetics and molecular genetics of acute lymphoblastic leukemia. Hematol Oncol Clin North Am *23(5)*: 991-1010, v, 2009. PMID: 19825449. DOI: 10.1016/j.hoc.2009.07.001

3 Eden T: Aetiology of childhood leukaemia. Cancer Treat Rev *36(4)*: 286-297, 2010. PMID: 20223594. DOI: 10.1016/j.ctrv.2010.02.004

4 Terracini B: Epidemiology of childhood cancer. Environ Health *10(Suppl 1)*: S8, 2011. PMID: 21489218. DOI: 10.1186/1476-069X-10-S1-S8

5 Karathanasis NV, Choumerianou DM and Kalmanti M: Gene polymorphisms in childhood ALL. Pediatr Blood Cancer *52(3)*: 318-323, 2009. PMID: 18989891. DOI: 10.1002/pbc.21825

6 Bhojwani D, Yang JJ and Pui CH: Biology of childhood acute lymphoblastic leukemia. Pediatr Clin North Am *62(1)*: 47-60, 2015. PMID: 25435111. DOI: 10.1016/j.pcl.2014.09.004

7 Schüz J and Erdmann F: Environmental exposure and risk of childhood leukemia: an overview. Arch Med Res *47(8)*: 607-614, 2016. PMID: 28476188. DOI: 10.1016/j.arcmed.2016.11.017

8 Pei JS, Chang WS, Chen CC, Mong MC, Hsu SW, Hsu PC, Hsu YN, Wang YC, Tsai CW and Bau DT: Novel contribution of long non-coding RNA *MEG3* genotype to prediction of childhood leukemia risk. Cancer Genomics Proteomics *19(1)*: 27-34, 2022. PMID: 34949657. DOI: 10.21873/cgp.20301

9 Pei JS, Chang WS, Hsu PC, Chen CC, Yang YC, Hsu SW, Hsu YN, Wang YC, Wang CH, Tsai CW and Bau DT: Contribution of cyclin-dependent kinase inhibitor 1B genotypes to childhood leukemia risk. In Vivo *36(4)*: 1637-1642, 2022. PMID: 35738638. DOI: 10.21873/invivo.12874

10 Hsu PC, Pei JS, Chen CC, Chang WS, Chin YT, Huang TL, Yang JS, Wang YC, Chen JC, Hsu YN, Tsai CW and Bau DT: Significant association of *CCND1* genotypes with susceptibility to childhood acute lymphoblastic leukemia. Anticancer Res *41(10)*: 4801-4806, 2021. PMID: 34593429. DOI: 10.21873/anticanres.15295

11 Pei JS, Chen CC, Chang WS, Wang YC, Chen JC, Hsiau YC, Hsu PC, Hsu YN, Tsai CW and Bau DT: Significant associations of lncRNA H19 genotypes with susceptibility to childhood leukemia in Taiwan. Pharmaceuticals (Basel) *14(3)*: 235, 2021. PMID: 33800276. DOI: 10.3390/ph14030235

12 Chen CC, Hsu PC, Shih LC, Hsu YN, Kuo CC, Chao CY, Chang WS, Tsai CW, Bau DT and Pei JS: MiR-196a-2 genotypes determine the susceptibility and early onset of childhood acute lymphoblastic leukemia. Anticancer Res *40(8)*: 4465-4469, 2020. PMID: 32727776. DOI: 10.21873/anticanres.14451

13 Pei JS, Chang WS, Hsu PC, Chen CC, Chin YT, Huang TL, Hsu YN, Kuo CC, Wang YC, Tsai CW, Gong CL and Bau DT: Significant association between the MiR146a genotypes and susceptibility to childhood acute lymphoblastic leukemia in Taiwan. Cancer Genomics Proteomics *17(2)*: 175-180, 2020. PMID: 32108040. DOI: 10.21873/cgp.20178

14 Dinarello CA: Interleukin-18. Methods *19(1)*: 121-132, 1999. PMID: 10525448. DOI: 10.1006/meth.1999.0837

15 Baxevanis CN, Gritzapis AD and Papamichail M: In vivo antitumor activity of NKT cells activated by the combination of IL-12 and IL-18. J Immunol *171(6)*: 2953-2959, 2003. PMID: 12960319. DOI: 10.4049/jimmunol.171.6.2953

16 Lebel-Binay S, Berger A, Zinzindohoué F, Cugnenc P, Thiounn N, Fridman WH and Pagès F: Interleukin-18: biological properties and clinical implications. Eur Cytokine Netw *11(1)*: 15-26, 2000. PMID: 10705295.

17 Tschoeke SK, Oberholzer A and Moldawer LL: Interleukin-18: a novel prognostic cytokine in bacteria-induced sepsis. Crit Care Med *34(4)*: 1225-1233, 2006. PMID: 16540967. DOI: 10.1097/01.CCM.0000208356.05575.16

18 Liu JM, Liu JN, Wei MT, He YZ, Zhou Y, Song XB, Ying BW and Huang J: Effect of IL-18 gene promoter polymorphisms on prostate cancer occurrence and prognosis in Han Chinese population. Genet Mol Res *12(1)*: 820-829, 2013. PMID: 23546966. DOI: 10.4238/2013.March.15.2

19 Akamatsu S, Arai N, Hanaya T, Arai S, Tanimoto T, Fujii M, Kohno K, Micallef MJ, Ikeda M and Kurimoto M: Antitumor activity of interleukin-18 against the murine T-cell leukemia/lymphoma EL-4 in syngeneic mice. J Immunother *25(Suppl 1)*: S28-S34, 2002. PMID: 12048348. DOI: 10.1097/00002371-200203001-00005

20 Günel N, Coşkun U, Sancak B, Günel U, Hasdemir O and Bozkurt S: Clinical importance of serum interleukin-18 and nitric oxide activities in breast carcinoma patients. Cancer *95(3)*: 663-667, 2002. PMID: 12209760. DOI: 10.1002/cncr.10705

21 Dinarello CA: IL-18: A TH1-inducing, proinflammatory cytokine and new member of the IL-1 family. J Allergy Clin Immunol *103(1 Pt 1)*: 11-24, 1999. PMID: 9893178. DOI: 10.1016/s0091-6749(99)70518-x

22 Gillies SD, Young D, Lo KM and Roberts S: Biological activity and *in vivo* clearance of antitumor antibody/cytokine fusion proteins. Bioconjug Chem *4(3)*: 230-235, 1993. PMID: 8324014. DOI: 10.1021/bc00021a008

23 Okamura H, Tsutsi H, Komatsu T, Yutsudo M, Hakura A, Tanimoto T, Torigoe K, Okura T, Nukada Y and Hattori K: Cloning of a new cytokine that induces IFN-gamma production by T cells. Nature *378(6552)*: 88-91, 1995. PMID: 7477296. DOI: 10.1038/378088a0

24 Park S, Cheon S and Cho D: The dual effects of interleukin-18 in tumor progression. Cell Mol Immunol *4(5)*: 329-335, 2007. PMID: 17976312.

25 Ye ZB, Ma T, Li H, Jin XL and Xu HM: Expression and significance of intratumoral interleukin-12 and interleukin-18 in human gastric carcinoma. World J Gastroenterol *13(11)*: 1747-1751, 2007. PMID: 17461482. DOI: 10.3748/wjg.v13.i11.1747

26 Eissa SA, Zaki SA, El-Maghraby SM and Kadry DY: Importance of serum IL-18 and RANTES as markers for breast carcinoma progression. J Egypt Natl Canc Inst *17(1)*: 51-55, 2005. PMID: 16353083.

27 Jia Y, Zang A, Jiao S, Chen S and Yan F: The interleukin-18 gene promoter -607 A/C polymorphism contributes to non-small-cell lung cancer risk in a Chinese population. Onco Targets Ther *9*: 1715-1719, 2016. PMID: 27051306. DOI: 10.2147/OTT.S99581

28 Tsuboi K, Miyazaki T, Nakajima M, Fukai Y, Masuda N, Manda R, Fukuchi M, Kato H and Kuwano H: Serum interleukin-12 and interleukin-18 levels as a tumor marker in patients with esophageal carcinoma. Cancer Lett *205(2)*: 207-214, 2004. PMID: 15036653. DOI: 10.1016/j.canlet.2003.10.010

29 Giedraitis V, He B, Huang WX and Hillert J: Cloning and mutation analysis of the human IL-18 promoter: a possible role of polymorphisms in expression regulation. J Neuroimmunol *112(1-2)*: 146-152, 2001. PMID: 11108943. DOI: 10.1016/s0165-5728(00)00407-0

30 Zhang B, Ma XT, Zheng GG, Li G, Rao Q and Wu KF: Expression of IL-18 and its receptor in human leukemia cells. Leuk Res *27(9)*: 813-822, 2003. PMID: 12804640. DOI: 10.1016/s0145-2126(03)00005-5

31 Taniguchi M, Nagaoka K, Ushio S, Nukada Y, Okura T, Mori T, Yamauchi H, Ohta T, Ikegami H and Kurimoto M: Establishment of the cells useful for murine interleukin-18 bioassay by introducing murine interleukin-18 receptor cDNA into human myelomonocytic KG-1 cells. J Immunol Methods *217(1-2)*: 97-102, 1998. PMID: 9776579. DOI: 10.1016/s0022-1759(98)00098-2

32 Ogata A, Kitano M, Fukamizu M, Hamano T and Sano H: Increased serum interleukin-18 in a patient with systemic lupus erythematosus and T-cell large granular lymphocytic leukemia. Mod Rheumatol *14(3)*: 267-270, 2004. PMID: 17143689. DOI: 10.1007/s10165-004-0306-5

33 Takubo T, Kumura T, Nakao T, Nakamae H, Aoyama Y, Kinoshita Y, Koh KR, Ohta K, Yamane T, Hino M, Kamitani T and Tatsumi N: Expression of human interleukin-18 antigen in leukemia cells in a patient with acute mixed lineage leukemia. Haematologia (Budap) *31(1)*: 69-71, 2001. PMID: 11345407. DOI: 10.1163/15685590151092733

34 Kunikata T, Torigoe K, Ushio S, Okura T, Ushio C, Yamauchi H, Ikeda M, Ikegami H and Kurimoto M: Constitutive and induced IL-18 receptor expression by various peripheral blood cell subsets as determined by anti-hIL-18R monoclonal antibody. Cell Immunol *189(2)*: 135-143, 1998. PMID: 9790727. DOI: 10.1006/cimm.1998.1376

35 Wu S, Gessner R, von Stackelberg A, Kirchner R, Henze G and Seeger K: Cytokine/cytokine receptor gene expression in childhood acute lymphoblastic leukemia: correlation of expression and clinical outcome at first disease recurrence. Cancer *103(5)*: 1054-1063, 2005. PMID: 15651075. DOI: 10.1002/cncr.20869

36 Song J, Li A, Qian Y, Liu B, Lv L, Ye D, Sun X and Mao Y: Genetically predicted circulating levels of cytokines and the risk of cancer. Front Immunol *13*: 886144, 2022. PMID: 35865545. DOI: 10.3389/fimmu.2022.886144

37 Wang H, Hua M, Wang S, Yu J, Chen C, Zhao X, Zhang C, Zhong C, Wang R, He N, Hou M and Ma D: Genetic polymorphisms of IL-18 rs1946518 and IL-1β rs16944 are associated with prognosis and survival of acute myeloid leukemia. Inflamm Res *66(3)*: 249-258, 2017. PMID: 27928589. DOI: 10.1007/s00011-016-1012-4

38 Chang WS, Liu LC, Hsiao CL, Su CH, Wang HC, Ji HX, Tsai CW, Maa MC and Bau DT: The contributions of the tissue inhibitor of metalloproteinase-1 genotypes to triple negative breast cancer risk. Biomedicine (Taipei) *6(1)*: 4, 2016. PMID: 26872812. DOI: 10.7603/s40681-016-0004-6

39 Huang CY, Chang WS, Tsai CW, Hsia TC, Shen TC, Bau DT and Shui HA: Interleukin-18 promoter genotype is associated with the risk of nasopharyngeal carcinoma in Taiwan. Cancer Manag Res *10*: 5199-5207, 2018. PMID: 30464617. DOI: 10.2147/CMAR.S179367

40 Chang WS, Shen TC, Yeh WL, Yu CC, Lin HY, Wu HC, Tsai CW and Bau DT: Contribution of inflammatory cytokine interleukin-18 genotypes to renal cell carcinoma. Int J Mol Sci *20(7)*: 1563, 2019. PMID: 30925760. DOI: 10.3390/ijms20071563

41 Wu MF, Chen LH, Hsia NY, Shen YC, Shen TC, Wang ZH, Yang YC, Wang YC, Chang WS, Hsia TC, Bau DT and Tsai CW: Significant contribution of interleukin-18 genotypes to lung cancer risk in Taiwanese. Anticancer Res *42(7)*: 3381-3387, 2022. PMID: 35790262. DOI: 10.21873/anticanres.15825

42 Yalçın S, Mutlu P, Çetin T, Sarper M, Özgür G and Avcu F: The -137G/C polymorphism in interleukin-18 gene promoter contributes to chronic lymphocytic and chronic myelogenous leukemia risk in Turkish patients. Turk J Haematol *32(4)*: 311-316, 2015. PMID: 26376814. DOI: 10.4274/tjh.2014.0126

43 Wei YS, Lan Y, Liu YG, Tang H, Tang RG and Wang JC: Interleukin-18 gene promoter polymorphisms and the risk of esophageal squamous cell carcinoma. Acta Oncol *46(8)*: 1090-1096, 2007. PMID: 17851835. DOI: 10.1080/02841860701373595

44 Liu Y, Lin N, Huang L, Xu Q and Pang G: Genetic polymorphisms of the interleukin-18 gene and risk of prostate cancer. DNA Cell Biol *26(8)*: 613-618, 2007. PMID: 17688413. DOI: 10.1089/dna.2007.0600

45 Nikiteas N, Yannopoulos A, Chatzitheofylaktou A and Tsigris C: Heterozygosity for interleukin-18 -607 A/C polymorphism is associated with risk for colorectal cancer. Anticancer Res *27(6B)*: 3849-3853, 2007. PMID: 18225542.

46 Bushley AW, Ferrell R, McDuffie K, Terada KY, Carney ME, Thompson PJ, Wilkens LR, Tung KH, Ness RB and Goodman MT: Polymorphisms of interleukin (IL)-1alpha, IL-1beta, IL-6, IL-10, and IL-18 and the risk of ovarian cancer. Gynecol Oncol *95(3)*: 672-679, 2004. PMID: 15581980. DOI: 10.1016/j.ygyno.2004.08.024

47 Khalili-Azad T, Razmkhah M, Ghiam AF, Doroudchi M, Talei AR, Mojtahedi Z and Ghaderi A: Association of interleukin-18 gene promoter polymorphisms with breast cancer. Neoplasma *56(1)*: 22-25, 2009. PMID: 19152241. DOI: 10.4149/neo_2009_01_22

48 Jaiswal PK, Singh V, Srivastava P and Mittal RD: Association of IL-12, IL-18 variants and serum IL-18 with bladder cancer susceptibility in North Indian population. Gene *519(1)*: 128-134, 2013. PMID: 23403235. DOI: 10.1016/j.gene.2013.01.025

49 Vairaktaris E, Serefoglou ZC, Yapijakis C, Agapi C, Vassiliou S, Nkenke E, Antonis V, Sofia S, Neukam FW and Patsouris E: The interleukin-18 -607A/C polymorphism is not associated with risk for oral cancer. Anticancer Res *27(6B)*: 4011-4014, 2007. PMID: 18225563.

50 Asefi V, Mojtahedi Z, Khademi B, Naeimi S and Ghaderi A: Head and neck squamous cell carcinoma is not associated with interleukin-18 promoter gene polymorphisms: a case-control study. J Laryngol Otol *123(4)*: 444-448, 2009. PMID: 18940019. DOI: 10.1017/S0022215108003733

51 Pratesi C, Bortolin MT, Bidoli E, Tedeschi R, Vaccher E, Dolcetti R, Guidoboni M, Franchin G, Barzan L, Zanussi S, Caruso C and De Paoli P: Interleukin-10 and interleukin-18 promoter polymorphisms in an Italian cohort of patients with undifferentiated carcinoma of nasopharyngeal type. Cancer Immunol Immunother *55(1)*: 23-30, 2006. PMID: 16059673. DOI: 10.1007/s00262-005-0688-z

52 Farhat K, Hassen E, Bouzgarrou N, Gabbouj S, Bouaouina N and Chouchane L: Functional IL-18 promoter gene polymorphisms in Tunisian nasopharyngeal carcinoma patients. Cytokine *43(2)*: 132-137, 2008. PMID: 18555694. DOI: 10.1016/j.cyto.2008.05.004

53 Nong LG, Luo B, Zhang L and Nong HB: Interleukin-18 gene promoter polymorphism and the risk of nasopharyngeal carcinoma in a Chinese population. DNA Cell Biol *28(10)*: 507-513, 2009. PMID: 19622039. DOI: 10.1089/dna.2009.0912

Received August 12, 2022
Revised September 6, 2022
Accepted September 7, 2022