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Association Between *PIP4K2A* Polymorphisms and Acute Lymphoblastic Leukemia Susceptibility

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Abstract: Acute lymphoblastic leukemia (ALL) is one of the most common pediatric cancers in the world. Several single-nucleotide polymorphisms (SNPs) locating at *PIP4K2A* locus were identified to be associated with ALL susceptibility through genome-wide association studies, however, followed by inconsistent reports in replication studies. In this study, we conducted a meta-analysis to investigate the association status of the top independent SNPs (rs7088318 and rs4748793) with ALL susceptibility by combining the data from 6 independent studies, totally including 3508 cases and 12,446 controls with multi-ethnic populations. Consistent association with ALL risk of both SNPs were observed (odds ratio [OR] 1.28 and 1.29, 95% confidence interval [CI] 1.20–1.36 and 1.19–1.40, respectively). Considering clinic characteristics, rs7088318 is more related to patients with African ancestry (OR 1.48, 95% CI 1.21–1.80) and hyperdiploid subtype (OR 1.42, 95% CI 1.25–1.61). Moreover, several SNPs (eg, rs45469096) were identified to be in high linkage disequilibrium with rs7088318, and affected *PIP4K2A* expression in lymphocytes probably by altering the binding affinity of some transcriptional factors. In conclusion, we systematically investigated the relationship between SNPs at *PIP4K2A* locus and ALL susceptibility, and further found potential causal variant candidates, thus better elucidating the role of *PIP4K2A* gene in leukemogenesis.

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Abbreviations: 95% CI = 95% confidence interval, AFR = African Americans, ALL = acute lymphoblastic leukemia, ASI = Asians, CNKI = Chinese National Knowledge Infrastructure,

eQTL expression = quantitative trait loci, EUR = European and American Caucasians, GWAS = genome-wide association study, HIS = Hispanics, HWE = Hardy–Weinberg equilibrium, ICD = International Classification of Disease, LCL = lymphoblastoid cell line, LD = linkage disequilibrium, MAF = minor allele frequency, NA = not available, OR = odds ratio, SNP = single-nucleotide polymorphism.

INTRODUCTION

Acute lymphoblastic leukemia (ALL) (ICD: C91.01) is the most common pediatric cancer worldwide.^{1,2} Inherited genetic susceptibility basis of such deadly malignancy has been largely investigated through genome-wide association studies (GWAS), identifying common variants at 6 genetic loci: *ARID5B*, *IKZF1*, *CEBPE*, *CDKN2A*, *PIP4K2A-BMI1*, and *GATA3*.^{3–10} Multiple independent studies have been followed, and consistently replicated associations at some loci (eg, *ARID5B*), but not others (eg, *CDKN2A*).^{11–19} Patient characteristics (eg, ethnicities, age at diagnosis, and ALL subtypes) are considered to be important factors affecting the association status. For instance, risk allele of rs10821936 at *ARID5B* is enriched in patients with hyperdiploid subtype and Native American genetic ancestry,¹⁹ whereas genotype of rs3824662 at *GATA3* is more significantly associated with ALL risk in older patients and Ph-like subtype.^{6,9,10} Recently, we identified 2 independent signals at 10p12.31–12.2 locus, with the strongest signals at rs7088318 (intronic region of *PIP4K2A*) and rs4748793 (upstream of *COMMD3/BMI1*), respectively, indicating multiple causal variants are located within this region.⁵ Both SNPs are significantly associated with ALL susceptibility across ethnicities in our discovery cohort. Association of rs7088318 can be validated in 3 ethnic groups (ie, European Americans, African Americans, and Hispanics) with varied odds ratio (OR), whereas rs4748793 can only be validated in Caucasians.^{11,14,20} Independent Illumina platform-based GWAS also identified the association signal at 10p12.2, with the top SNP rs10828317, which is in high linkage disequilibrium (LD) with rs7088318 ($r^2 = 0.7$ in Caucasians).¹⁰ The effect of this SNP is varied on the major subtypes of ALL (ie, TEL-AML1 and hyperdiploidy), partially explaining the inconsistent findings in some of the follow-up studies.²¹

Both rs7088318 and rs4748793 are located in intronic or intergenic regions, and no coding variant within this region has been identified through a large scale of exome chip-based GWAS,⁸ raising the possibility that the causal variants tagged by the GWAS SNPs could be associated with ALL risk by affecting epigenetic regulation rather than inducing functional change of the nearby genes.²² Indeed, rs7088318 is considered to be a strong expression quantitative trait loci (eQTL) for *PIP4K2A* in both immortalized lymphoblastoid cell lines (LCLs) and primary leukemia cells from patients, with risk allele of rs7088318 positively related to higher expression of

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PIP4K2A.⁵ Moreover, suppression of *PIP4K2A* expression can prevent tumor cell growth and induce apoptosis in cell line and mouse models,²³ indicating causal variants on *PIP4K2A* could impact leukemogenesis through regulating its expression level.

In this study, we searched all the related publications and conducted a meta-analysis with a large sample size (3508 cases and 12,446 controls), to ascertain the effects of SNPs at 10p12.31–12.2 (including rs7088318 and rs4748793) on ALL risk in terms of ethnicities and subtypes, and further screened the potential causal variants accounting for the association.

METHODS

Literature and Study Acquisition

Systematically, literature searching carried out independently by 2 investigators from PubMed, Google Scholar, and the Chinese National Knowledge Infrastructure (CNKI) date to December 20, 2015, according to following search terms: “rs7088318” or “rs4748793,” or “acute lymphoblastic leukemia” and “polymorphisms” and “*PIP4K2A*,” or “genetic polymorphism” and “acute lymphoblastic leukemia” and “GWAS.” All papers were restricted to English (N=40). Initially, checking of the titles, and also the abstracts, was conducted to remove the duplicated articles, along with papers which do not meet our subject. Then, reading was conducted through every remaining studies and retained valuable papers which met the following criteria: used the case-control design, evaluated the association of SNPs at *PIP4K2A* and ALL susceptibility, providing the numbers of cases and controls, providing the genotype count or sufficient data to impute the genotypes, data without overlap (n = 4). When multiple publications were reported on the same or overlapping data, only the publication with the most updated or detailed data was included. The literature screening flow presented in Figure 1 and ethical approval, and also patient consent, were needless, because all the information was acquired from published studies.

Data Extraction and Verification

The following information from each publication was independently extracted by two authors: the first author; the

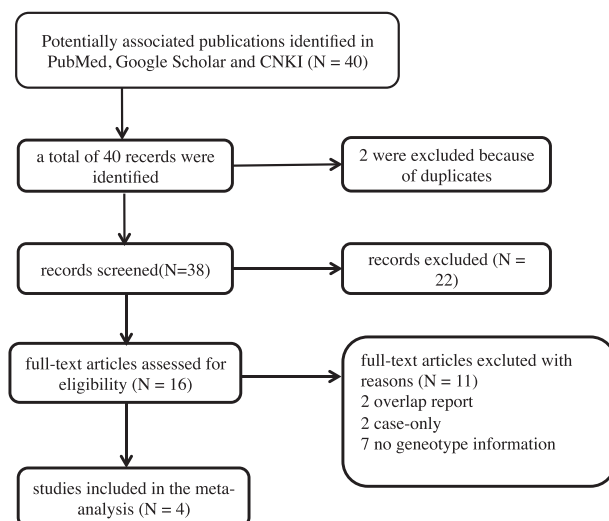


FIGURE 1. Flow chart of included studies for the meta-analysis.

publication date; the population and ethnicity of subjects enrolled in each study; the studying cohort; the genotyping platform; the country or institution of each publication; the sample size, and also genotype count or other available data; the study design; and the sex and age of study populations. When datasets were not accessible or incomplete for the required data, corresponding authors were contacted for additional information. For accuracy, all the information was double-checked and the third reviewer was in discussion once encountering controversy information. Detailed information on the included papers is listed in Table 1.

Choice of Genetic Model

The rs7088318 polymorphism has 2 alleles, with variant allele T and wild-type allele C. we intended to analyze the association between rs7088318 polymorphism and childhood ALL susceptibility by using the allele model (T allele vs C allele), the dominant model (TT + TC vs CC), and the recessive model (TT vs TC + CC). Equally, the rs4748793 polymorphism has wild-type C allele and variant T allele. We also adopted the similar genetic model to analyze the association between rs4748793 polymorphism and childhood ALL susceptibility.

Heterogeneity Test

Heterogeneity among studies was evaluated by the Q statistic and the I^2 statistic, of which Q approximately follows a chi-square distribution with $k - 1$ (k indicates the number of studies) degrees of freedom. P value was used to measure the significance level of heterogeneity. $I^2 = (Q - [k - 1]) / Q \times 100\%$, ranging from 0% to 100%. I^2 was considered as a critical value, when $I^2 < 50\%$ and P value > 0.1 , fixed-effect model was superior to random-effect model to calculate summary OR and 95% confidence interval (CI), whereas the random-effect model was employed if $I^2 > 50\%$ and P value < 0.1 because of high heterogeneity.

Lineage Disequilibrium Region Determination and Epigenomic Information Analyses

The r^2 value is used to determine the LD block around rs7088318 in 4 ethnic groups (ie, EUR [European and American Caucasians], AFR [African Americans], ASI [Asians], and HIS [Hispanics]). Chromosome positions were determined by using Haploreg (<http://www.broadinstitute.org/mammals/haploreg/haploreg.php>) in each ethnic group, respectively, and the overlapped region was determined at Chr10: 22805109 to 22857245. Further, epigenomics information from ENCODE was illustrated with Epigenome Browser (<http://epigenomegateway.wustl.edu/>).

Expression QTL Analyses

The *PIP4K2A* expression was obtained for HapMap CEU LCLs (GSE7851²⁴), and *PIP4K2A* SNP genotypes of HapMap CEU cell lines were obtained from the 1000 genome project web site (<http://browser.1000genomes.org/>). Genotype expression association was assessed using a linear regression model for the available individuals (n = 41).

RESULTS

Study Characteristics

Through literature searching with keywords (see “Methods” section), 6 independent studies demonstrated in 4 articles met the inclusion criteria and were selected for meta-

TABLE 1. Principle Characteristics of the Studies Included in the Meta-analysis for SNPs at PIP4K2A-BMI1 Locus

Publication Time	Author	SNP ID	Ethnicity	Sample Size		Study Design	Genotyping Platform
				Case	Control		
2013	Xu H	rs7088318 and rs4748793	Caucasian	1501	3987	GWAS and replication	Affymetrix Array
			African American	217	2438		
			Hispanic	448	1648		
2014	Deng J		Asian	570	673	replication	TaqMan Genotyping Assay
2013	Walsh KM		Hispanic	297	454	replication	Array
2013	Lopez-Lopez E	rs7088318	Caucasian	191	342	replication	Allelic specific PCR
2013	Gabriele M	rs10828317	Caucasian	3107	6211	GWAS and replication	Illumina Array

GWAS = genome-wide association study.

analyses (Figure 1). Characteristics of these studies in totality are summarized in Table 1.

Meta-analysis of the rs7088318 Polymorphism and ALL Susceptibility

Six studies assessed the association between rs7088318 and ALL susceptibility with a total of 3508 cases and 12,446 controls, and 3269 cases and 9542 controls were used for meta-analysis after excluding admixture populations (Table 1 and Supplementary Table 1, <http://links.lww.com/MD/A942>). Because no heterogeneity was observed in the allele model ($P = 0.63$, and $I^2 = 0\%$), we used fixed-effect model to conduct the meta-analysis, and found that T allele significantly exhibited a 1.28-fold (OR 1.28, 95% CI 1.20–1.36) increased risk to develop ALL ($P < 0.001$; Figure 2) compared with C allele. In addition, no heterogeneity was observed in the dominant model ($P = 0.45$, $I^2 = 0\%$) and recessive model ($P = 0.33$, $I^2 = 13\%$). T allele was consistently associated with higher ALL risk in dominant model ($P < 0.001$, OR 1.36, 95% CI 1.20–1.54) and recessive model ($P < 0.001$, OR 1.40, 95% CI 1.28–1.53) in fixed model. We next examined the effect of rs7088318 by patient characteristics (eg, ethnicity and ALL subtype). For ethnicities, rs7088318 was significantly related to ALL susceptibility in all ethnic groups with varied risk coefficients (OR 1.24 in Caucasians, OR 1.29 in Hispanics, OR 1.48 in African Americans, and OR 1.24 in Asians), whereas for subtypes, rs7088318 had a larger effect on hyperdiploidy

subtypes (OR 1.42, $P < 0.001$ in 657 cases/8527 controls). Detail information is summarized in Table 2.

Meta-analysis of the rs4748793 Polymorphism and ALL Susceptibility

Relatively fewer studies assessed the association between rs4748793 and ALL susceptibility with a total of 3317 cases and 12,104 controls from 5 studies, and 3068 cases and 9200 controls were used for meta-analysis after excluding admixture populations (Table 1 and Supplementary Table 1, <http://links.lww.com/MD/A942>). Because no significant heterogeneity was observed in the allele model ($P = 0.22$, and $I^2 = 30\%$), we used fixed-effect model to conduct the meta-analysis, and found that T allele significantly exhibited a 1.29-fold (95% CI 1.19–1.40) increased risk to develop ALL ($P < 0.001$; Figure 3) compared with C allele. Consistent association was observed in dominant model ($I^2 = 0\%$, $P = 0.003$, OR 1.45, 95% CI 1.44–1.84) and recessive model ($I^2 = 31\%$, $P < 0.001$, OR 1.36, 95% CI 1.23–1.49). Ethnicities could be an important factor, because significances were only observed in Caucasians ($P < 0.001$, OR 1.38, 95% CI 1.24–1.55) and Hispanics ($P = 0.008$, OR 1.23, 95% CI 1.06–1.43), rather than in African Americans ($P = 0.18$, OR 1.29, 95% CI 0.89–1.86) and Asians ($P = 0.44$, OR 1.08, 95% CI 0.88–1.32). Similar to rs7088318, rs4748793 also exhibited higher OR in hyperdiploid subtype ALL ($P < 0.001$, OR 1.58, 95% CI 1.35–1.86). Detailed information is summarized in Table 2.

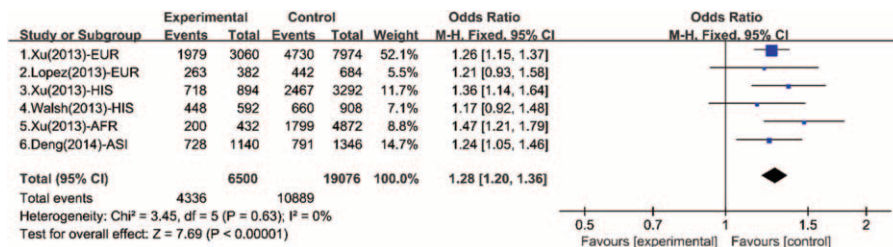


FIGURE 2. Forest plot of ALL susceptibility associated with rs7088318 of PIP4K2A locus with allele model. For each study, the estimates of OR and its 95% CI are plotted with square and a horizontal line. The area of the squares reflects the weight. The diamond represents the summary OR and 95% CI. Abbreviations: AFR = African Americans, ALL = acute lymphoblastic leukemia, ASI = Asians, CI = confidence interval, EUR = European and American Caucasians, HIS = Hispanics, MAF = minor allele frequency, OR = odds ratio.

TABLE 2. *PIP4K2A* Polymorphisms With ALL Susceptibility

SNP	Ethnicity	Case/Control	OR	95% CI	P
rs7088318	All	3250/9538	1.28	1.20–1.36	<0.001
	EUR	1721/4329	1.24	1.14–1.35	<0.001
	AFR	216/2436	1.48	1.21–1.80	<0.001
	HIS	743/2100	1.29	1.12–1.49	<0.001
	ASI	570/673	1.24	1.05–1.46	<0.001
rs4748793	Hyperdiploid	659/8523	1.42	1.25–1.61	<0.001
	All	3045/9195	1.29	1.19–1.40	<0.001
	EUR	1525/3983	1.38	1.24–1.55	<0.001
	AFR	215/2438	1.29	0.89–1.86	0.18
	HIS	735/2101	1.23	1.06–1.43	<0.001
	ASI	570/673	1.08	0.88–1.32	0.44
	Hyperdiploid	654/4261	1.58	1.35–1.86	<0.001

AFR = African Americans, ALL = acute lymphoblastic leukemia, ASI = Asians, CI = confidence interval, EUR = European and American Caucasians, HIS = Hispanics, OR = odds ratio.

Publication Bias and Sensitivity Analysis

We used Begg test and Egger test to measure the publication bias for all model; no evidence of obvious asymmetry was observed (Figure 4). Quality evaluation of the included studies was also estimated according to John P A Ioannidis’s guidelines proposed in 2007,²⁵ showing low risk of bias (Supplementary Table 2, <http://links.lww.com/MD/A942>). The result of sensitivity analysis showed that the association between rs7088318 (but not rs4748793) and ALL risk does not significantly change when removing each of the studies.

Causal Variant Candidate Determination

No coding region located SNP was significantly associated with ALL susceptibility according to the exome-based GWAS approach. Additionally, rs7088318 was considered as an eQTL locus, affecting the expression level of *PIP4K2A* in both cell line and clinic level. Therefore, we investigated the potential causal variant tagged by rs7088318 through webtools (Haploreg and Epigenome Browser),^{26,27} and summarized the moderate LD region ($r^2 > 0.6$) with rs7088318 in Table 3. Because rs7088318 was associated with ALL susceptibility in all ethnicities, we considered the causal variant tend to be in their overlapped region at Chr10: 22805109 to 22857245 (Table 3). Based on the chromatin state information from ENCODE database, a strong regulatory region (Chr10: 22839650–22840400) tagged by Dnase-sequencing signals

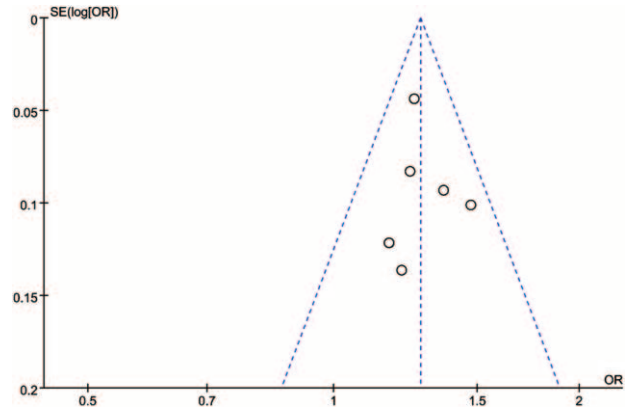


FIGURE 4. Funnel plot of publication bias test for rs7088318. Each point represents a separate study for the indicated association.

were observed in LCLs (Figure 5A). Several transcriptional factor-binding signals were detected by CHIP-sequencing assay, including CTCF, YY1, and RAD21 (Figure 5A and B). Moreover, this region was also conserved across species (Figure 5B), suggesting SNPs located at this enhancer could strongly impact gene regulation and thus be considered as potential causal variants. Therefore, 3 SNPs (ie, rs45469096, rs74587525, and rs7084761) within this region were listed in Table 4, and minor allele of these SNPs was associated with protect allele of rs7088318. We next investigated the effect of these SNPs on *PIP4K2A* expression in LCLs from Hapmap. Five and 2 individuals having variant alleles were found for rs45469096 and rs7084761, respectively. Minor allele of both SNPs were related to lower expression of *PIP4K2A* compared with the major allele according to eQTL analyses, with $P = 0.015$ and 0.09 , respectively (Figure 6 A and B). Interestingly, minor allele of rs45469096 and rs7084761 were mutually exclusively related, LCLs with either minor allele of these 2 SNPs would have significantly lower expression of *PIP4K2A* ($P = 0.001$) (Figure 6C), suggesting these 2 SNPs could account for the association of rs7088318 with ALL risk, and thus be considered as causal variant candidates for *PIP4K2A* locus.

Significant publication bias was detected for rs4748793, indicating more independent studies would be needed to confirm its association with ALL susceptibility. Therefore, we did not conduct epigenomic analyses and causal variant screening at this locus.

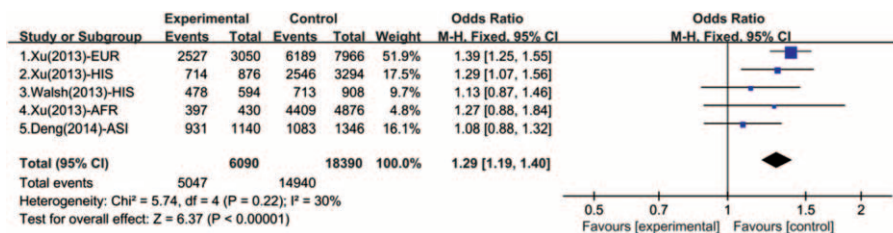
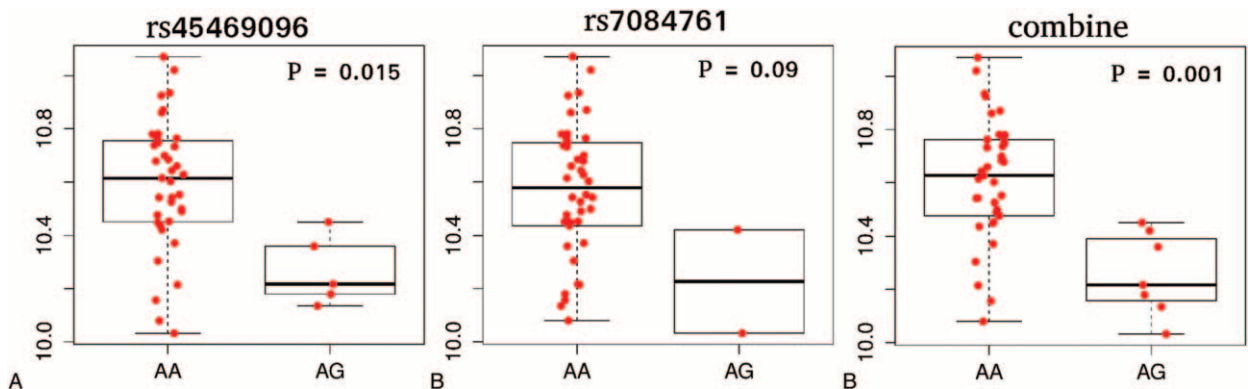


FIGURE 3. Forest plot of ALL susceptibility associated with rs4748793 of *PIP4K2A* locus with allele model. For each study, the estimates of OR and its 95% CI are plotted with square and a horizontal line. The area of the squares reflects the weight. The diamond represents the summary OR and 95% CI. Abbreviations: AFR = African Americans, ALL = acute lymphoblastic leukemia, ASI = Asians, CI = confidence interval, EUR = European and American Caucasians, HIS = Hispanics, MAF = minor allele frequency, OR = odds ratio.

TABLE 4. Characteristics of the Causal Variant Candidates

SNP ID	Position (Chr10)	Genotype (A/B allele)	MAF-EUR (n = 1006)	MAF-AFR (n = 1322)	MAF-HIS (n = 694)	MAF-ASI (n = 1008)	Conserved Region	Location	Binding Factor
rs115154973	22837527	A/C	1.49%	0.45%	0.72%	0	On	Intron	MAFK, MAFF
rs45469096	22839952	G/A	4.08%	0.45%	1.87%	0	Around	Intron	MAZ, CTCF, EGR1, YY1, SMC3, RAD21, ZBTB7A, TEAD4, ZNF263
rs74587525	22840293	A/G	0	5.45%	0.29%	0.10%	Around	Intron	TAL1, ZNF263
rs7084761	22840312	G/A	5.86%	0.15%	4.32%	0.20%	Around	Intron	TAL1, ZNF263

AFR = African Americans, ASI = Asians, EUR = European and American Caucasians, HIS = Hispanics, MAF = minor allele frequency, SNP = single-nucleotide polymorphism.

**FIGURE 6.** eQTL analyses of the causal variant candidates rs45469096 (A), rs7084761 (B), and their combination (C). eQTL = expression quantitative trait loci.

more evidences indicate that causal variants are located in the epigenomic regulatory regions (eg, promoter, enhancer, etc) and possibly affect the phenotypes by impacting the expression level of the nearby genes, such as rs1427407, which alters the TAL-binding motifs of *BCL11A* enhancer region and impacts *BCL11A* expression.²⁸ For *PIP4K2A*, this gene encodes PtdIns5P 4-kinaseII α , which is the major component of type II PtdIns5P 4-kinases, catalyzing the phosphorylation of phosphatidylinositol-5-phosphate on hydroxyl of the myo-inositol ring to form phosphatidylinositol-4,5-bisphosphate.²⁹ This gene is highly expressed in peripheral blood cells,³⁰ and is located in cytoplasm and nucleus. Functional studies indicate *PIP4K2A* could involve in TP53 and PI3K/AKT pathway,^{31,32} which play important roles on leukemogenesis. Interestingly, *PIP4K2A* expression is positively related to increased cell growth and decreased apoptosis rate in vitro.²³ Also, knockout of *PIP4K2A* abrogated TP53 deficiency-based tumor development in mice, and inhibition of *PIP4K2A* can be compelling target for anticancer therapeutics.³² These facts indicate the important role of *PIP4K2A* on leukemogenesis, and suggest the causal variant for ALL risk at this locus could impact on leukemogenesis through regulating gene expression. Indeed, rs7088318 is considered as an eQTL in blood cells with the risk allele associated with

higher *PIP4K2A* expression⁵; we therefore screened the epigenomic regulatory elements for potential causal variants through webtools (Haploreg²⁶ and Epigenome Browser²⁷) and found rs45469096 and rs7084761 as the strongest candidates. These 2 SNPs locate at binding sites of multiple regulatory factors and impact the *PIP4K2A* expression independently, indicating variant alleles of these SNPs could alter the binding affinity of the binding elements (eg, transcriptional factors), thus impacting ALL susceptibility. However, further functional experiments are needed to confirm their functional status.

In conclusion, our meta-analysis demonstrates the significant association of these 2 SNPs (ie, rs7088318 and rs4748793) at *PIP4K2A-BMI1* locus with ALL susceptibility, and the effect of these SNPs varied in terms of patient characteristics. Also, potential causal variants (eg, rs45469096 and rs7084761) accounting for rs7088318 were determined, and further population-based validation and functional experiments were needed.

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