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ORIGINAL ARTICLE – CANCER RESEARCH

Replication analysis confirms the association of several variants with acute myeloid leukemia in Chinese population

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Abstract

Purpose Two genome-wide association studies (GWASs) have identified several new acute leukemia susceptibility loci in populations of European descent. However, the roles of these loci in the development of acute leukemia in other populations are largely unknown.

Methods We genotyped 16 single-nucleotide polymorphisms selected from published GWASs in an independent case–control study with a total of 545 acute myeloid leukemia (AML) cases and 1034 cancer-free controls in a Chinese population. Multivariate logistic regression was used to analyze the associations between these variants and AML risk.

Results We found that with the similar effect to GWASs, risk alleles of rs2191566, rs9290663, rs11155133, rs2239633, rs10821936, and rs2242041 significantly increased the risk of AML in at least one genetic model [odds ratios (ORs) range from 1.26 to 4.34, P values range from <0.001 to 0.043]. However, the variant T allele of rs10873876 decreased the AML risk, which was in the opposite effect direction (OR 0.62, $P < 0.001$ in additive model). Besides, we found significant multiplicative interaction between rs9290663 and age (≤45 years old and >45 years old; $P = 0.009$).

Conclusion Our results indicated that genetic variants associated with acute leukemia risk in European populations may also play important roles in AML development in Chinese population.

Keywords Leukemia · Susceptibility · Polymorphism

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Introduction

Acute leukemia consists of a group of heterogeneous malignancies in which immature and dysfunctional hematopoietic progenitors proliferate and accumulate in the bone marrow (Huang et al. 2013). Acute leukemia is composed of acute lymphoblastic leukemia (ALL) and acute myeloid leukemia (AML), and there were 6020 and 18,860 new ALL and AML cases around the world in 2013 (Siegel et al. 2014). Both ALL and AML occur during all ages but with very different age distributions. ALL has a peak incidence during childhood and thereafter remains at a low incidence during adulthood (Redaelli et al. 2005), whereas AML is relatively uncommon in childhood and gradually increases with age (Deschler and Lübbert 2006), similar to most of other malignancies.

The etiology of acute leukemia is largely unknown. A few environmental risk factors have been described, such

as ionizing radiation, benzene, pesticides, and illicit drug use (Belson et al. 2007; Eden 2010; Schnatter et al. 1996); however, they can only account for a minor proportion of incident cases. The opinion that acute leukemia may have a genetic basis has long been pursued through candidate gene-based association studies, identifying genes involved in xenobiotic metabolism (Krajinovic et al. 1999), DNA repair (Bănescu et al. 2013), cell-cycle regulation (Li et al. 2013), and oxidative stress response (Krajinovic et al. 2002). Despite differences in the pathogenesis, AML and ALL sometimes share some genetic factors. For example, *XRCC1* (X-ray repair cross-complimenting group 1 gene) 399Gln allele could increase risk of both AML (Sorour et al. 2013) and ALL (Sorour et al. 2013; Pakakasama et al. 2007), and *MTR* (5-methyltetrahydrofolate-homocysteine methyltransferase) 2756GG genotype showed similar effect on both acute leukemia subtypes (Lightfoot et al. 2010).

So far, several GWASs have explored the association of genetic variations with acute leukemia risk, especially for ALL. However, some GWASs of ALL focused on specific subtypes, like B cell precursor (BCP) ALL, ETV6-RUNX1-rearranged ALL, and Ph-like ALL (Migliorini et al. 2013; Xu et al. 2013; Ellinghaus et al. 2012; Perez-Andreu et al. 2013), and one GWAS had a small sample size (50 cases and 50 controls) (Han et al. 2010). Only two GWASs focused on the risk of all subtypes of ALL with a relatively large sample size (Treviño et al. 2009; Papaemmanuil et al. 2009), which provided statistically robust evidence for the role of common genetic variants in the susceptibility to acute leukemia. Using the Affymetrix 500 K Mapping array and publicly available genotype data, Treviño et al. identified 18 single-nucleotide polymorphisms (SNPs) significantly associated with ALL risk among 317 European ALL patients and 17,958 European individuals without acute leukemia (Treviño et al. 2009). Papaemmanuil et al. conducted a GWAS of two European case–control series with a total of 907 ALL cases and 2398 controls using Illumina Infinium HD Human370 Duo BeadChips and performed a meta-analysis to derive joint effect of each SNP. Finally, three SNPs were found to be associated with ALL risk (Papaemmanuil et al. 2009). Subsequently, many replication studies confirmed that SNPs identified by these two GWASs could affect ALL susceptibility in different populations (Gutiérrez-Camino et al. 2013; Wang et al. 2013; Healy et al. 2010; Chokkalingam et al. 2013; Linabery et al. 2013); however, only one study focused on AML and found that some SNPs associated with ALL in previous GWASs were also associated with AML risk in European population (Rudant et al. 2013).

Here, we conducted a case–control study with 545 AML cases and 1,034 controls in a Chinese population to first evaluate whether these variants are associated with AML risk in Chinese population.

Materials and methods

Ethics statement

The present study was approved by the institutional review board of Nanjing Medical University. The design and performance of current study involving human subjects were clearly described in a research protocol. All participants were voluntary and would complete the informed consent in written before taking part in this research.

Study subjects

A total of 545 AML cases and 1034 cancer-free controls were included in the current study, and all of the cases and controls were unrelated ethnic Han Chinese. All of the AML patients were newly diagnosed according to French–American–British (FAB) diagnosis and typing standard and consecutively recruited between December 2007 and August 2011 from Wuxi People's Hospital Affiliated to Nanjing Medical University. There was no restriction in terms of age, stage of disease, or histology, but those who had a history of cancer, chemotherapy, or hematopoietic stem cell transplantation (HSCT) were excluded from the case group. All of the controls were randomly selected from more than 30,000 participants in a community screening of non-communicable disease conducted in Jiangsu Province during the same period as the cases were recruited. All of the controls had no self-reported cancer history, and those who had a history of hematological system diseases were excluded. At the time of recruitment, informed consent was obtained from each subject, and each subject provided 5 ml of venous blood. This study was approved by the institutional review board guidelines, according to the Declaration of Helsinki.

SNP selection

We first selected 18 SNPs identified by Treviño et al. (rs10821936, rs10994982, rs11978267, rs10849033, rs10873876, rs11155133, rs12621643, rs1881797, rs2089222, rs2191566, rs6428370, rs7554607, rs9290663, rs1879352, rs563507, rs2242041, rs6509133, and rs2167364) (Treviño et al. 2009), and 3 SNPs identified by Papaemmanuil et al. (rs7089424, rs4132601, and rs2239633) (Papaemmanuil et al. 2009). Of all 21 SNPs, 3 SNPs were, respectively, in high linkage disequilibrium (LD) with other 3 SNPs (rs11978267 vs. rs4132601, rs10821936 vs. rs7089424, and rs2191566 vs. rs6509133) in Chinese Han population (CHB) according to HapMap database (HapMap Data Rel 27 Phase II + III, Feb09, on NCBI B36 assembly, dbSNP b126). Thus, we selected either one of each pairs. Besides, rs1881797 and rs563507

were excluded because the minor allele frequencies (MAF) were less than 0.05 in CHB. Finally, 16 SNPs were kept for genotyping.

Genotyping

DNA was extracted from venous blood using phenol/chloroform extracting method and stored in an environment of minus 20 degree centigrade. Genotyping was performed using the TaqMan allelic discrimination assay on the platform of 7900HT Real-Time PCR System (Applied Biosystems, Foster City, CA) without knowing the subjects' status (case or control). Two negative controls included in each 384-well reaction plat were used for quality control, and the genotyping results were determined by using SDS 2.3 Allelic Discrimination software (Applied Biosystems).

Statistical analysis

Differences between the cases and controls on the demographic characteristics were analyzed by using the Student's test (for continuous variables) and Chi-squared test (for categorical variables). Hardy–Weinberg equilibrium (HWE) was tested by a goodness-of-fit Chi-squared test to compare the observed genotype frequencies to the expected ones among the control subjects. The associations between these SNPs and AML risks were estimated by computing the odds ratio (ORs) and their 95 % confidence intervals (CIs) from multivariate logistic regression analysis. Likelihood ratio test was used for stratification analysis. Power was calculated using Power and Sample Size Calculation (PS) software (http://biostat.mc.vanderbilt.edu/twiki/bin/view/Main/PowerSampleSize, accessed Dec 14, 2010), as the type I error probability was set as 0.05, and OR was set as 1.5. Other statistical analyses were performed with SAS 9.1.3 software (SAS Institute, Cary, NC). $P < 0.05$ was the criterion of statistical significance, and all statistical tests were two sided.

Results

Demographic and clinical characteristics of the study subjects are described in Table 1. The age (44.1 ± 17.2 vs. 45.4 ± 9.6) and gender (male 53.4 vs. 56.7 %) were comparable ($P > 0.05$) between cases and controls. For clinical and cytogenetic characteristics, most cases were M2 AML (32.1 %), of myeloid lineage (69.4 %), with aberrant karyotypes (45.1 %), and without common fusion gene transcripts (55.6 %).

The basic information of selected SNPs is presented in Table 2, including locations on chromosomes, genes, allele changes, genotype distributions in both cases and controls, MAF among all subjects, HWE test among controls, call rate of all samples, and power. Consistent with published

Table 1 Demographic and clinical characteristics of study subjects

Characteristics	AML (n = 545)		Controls (n = 1034)		P
	N	(%)	N	(%)	
Sex					
Male	291	53.4	586	56.7	0.213
Female	254	46.6	448	43.3	
Age at diagnosis, year					
Mean ± SD	44.1 ± 17.2		45.4 ± 9.6		0.102[a]
≤45	298	54.7	510	49.3	
>45	247	45.3	524	50.7	
Lineage					
Myeloid	378	69.4			
Myeloid and lymphoid	157	28.8			
Myeloid and monocytic	10	1.8			
Classification of diagnosis					
M0	3	0.6			
M1	103	18.9			
M2	175	32.1			
M3	90	16.5			
M4	58	10.6			
M5	89	16.3			
Unknown	27	5.0			
Karyotype					
Aberrant	246	45.1			
Normal	235	43.1			
Unknown	64	11.8			
Molecular subtype					
Common fusion gene transcripts	187	34.3			
PML/RARα	77	14.1			
BCR/ABL	13	2.4			
AML1/ETO	54	9.9			
CBFβ/MYH11	10	1.8			
MLL rearrangement	15	2.8			
WT1	11	2.0			
Others	7	1.3			
No common fusion gene transcripts	303	55.6			
Unknown	55	10.1			

[a] *P* value of independent-sample *T* test for age

GWASs (Treviño et al. 2009; Papaemmanuil et al. 2009), we set G allele of rs2239633 and rs2191566 as risk alleles, though rs2239633-A and rs2191566-T are variant alleles in Chinese population. When we assumed the OR as 1.5, the results of 13 SNPs achieved a statistical power of greater than 80 %, except for three SNPs (rs2242041, rs11155133, and rs1879352).

Then, we conducted the association analyses between selected SNPs and AML risk in additive model. As shown

Table 2 Basic information of 16 selected SNPs

Location	SNP	Gene	Allele	Genotype of case[b]	Genotype of control[c]	MAF[d]	HWE[e]	Call rate	Power (%)[f]
1p31.1	rs10873876	*ST6GALNAC3*	C>T	323/209/0	542/407/83	0.278	0.591	0.991	94.8
1q31.3	rs6428370	Between genes	A>G	323/178/33	645/332/53	0.213	0.231	0.991	91.0
1q43	rs7554607	*RYR2*	A>G	259/230/40	520/416/97	0.295	0.299	0.989	95.3
2q36.1	rs12621643	*KCNE4*	G>T	236/230/52	479/451/104	0.319	0.886	0.983	95.8
3q26.32	rs9290663	*KCNMB2*	A>T	306/190/34	655/335/42	0.203	0.919	0.989	90.2
6q24.1	rs11155133	Between genes	A>G	390/105/16	829/196/9	0.103	0.487	0.978	71.0
7p12.1	rs2242041	*DDC*	C>G	414/91/24	805/218/11	0.116	0.392	0.990	77.1
7p12.1	rs2167364	*DDC*	A>G	409/117/8	745/274/14	0.146	0.044	0.992	83.7
7p12.2	rs11978267	*IKZF1*	A>G	398/112/19	736/277/20	0.153	0.301	0.989	83.7
10q21.2	rs10821936	*ARID5B*	T>C	206/243/82	411/501/122	0.360	0.100	0.991	96.4
10q21.2	rs10994982	*ARID5B*	A>G	146/259/130	256/558/219	0.482	0.009	0.993	96.9
12p13.32	rs10849033	Between genes	A>G	166/246/118	312/507/212	0.452	0.818	0.989	96.9
12q24.22	rs2089222	*MAP1LC3B2*	G>A	352/158/21	692/302/39	0.184	0.401	0.991	88.1
14q11.2	rs2239633	*CEBPE*	G>A[a]	200/276/50	398/472/140	0.372	0.997	0.973	96.5
18p11.32	rs1879352	Between genes	A>G	470/61/4	925/106/3	0.054	0.984	0.994	46.7
19q13.31	rs2191566	*ZNF230*	G>T[a]	302/183/46	444/477/111	0.339	0.306	0.990	96.2

[a] To be consistent with the article of GWAS, we set rs2239633-G and rs2191566-G as risk alleles in association analysis

[b] Frequencies of three genotypes (wide-type homozygote/heterozygote/variant homozygote) among cases

[c] Frequencies of three genotypes (wide-type homozygote/heterozygote/variant homozygote) among controls

[d] Minor allele frequency among control group

[e] *P* value of Hardy–Weinberg equilibrium test among control subjects

[f] Power was calculated using Power and Sample Size Calculation software, as the type I error probability was set as 0.05, and OR was set as 1.5

in Table 3, four SNPs were associated with an altered risk of AML ($P < 0.05$). Similar to the findings of published GWASs, risk alleles of rs2191566, rs9290663, and rs11155133 significantly increased the risk of AML (rs2191566: adjusted OR 1.46, 95 % CI 1.24–1.72, $P < 0.001$; rs9290663: adjusted OR 1.26, 95 % CI 1.05–1.50, $P = 0.011$; rs11155133: adjusted OR 1.32, 95 % CI 1.05–1.65, $P = 0.017$). However, the variant T allele of rs10873876 decreased the AML risk, which was in the opposite effect direction (OR 0.62, 95 % CI 0.52–0.75, $P < 0.001$). We also explored the associations between these SNPs and AML risk in other genetic models and found that other three SNPs (rs2239633, rs10821936, and rs2242041) achieved statistical significance in dominant or recessive models (Supplementary Table 1).

Furthermore, we examined the association of above seven SNPs with risk of AML stratified by selected variables including age, gender, lineage, karyotype, and molecular subtype. We observed heterogeneities of ORs for rs9290663 among different age groups ($P = 0.048$, Table 4), and interaction analysis showed significant multiplicative interaction between rs9290663 and age (≤45 years old and >45 years old; $P_{int} = 0.009$;

Table 3 Association of selected SNPs and AML risk in additive model

SNP	OR (95 % CI)[a]	P^a	OR (95 % CI)[b]	P^b
rs2191566	1.46 (1.24–1.72)	<0.001	1.46 (1.24–1.72)	<0.001
rs10873876	0.62 (0.52–0.75)	<0.001	0.62 (0.52–0.75)	<0.001
rs9290663	1.26 (1.06–1.50)	0.010	1.26 (1.05–1.50)	0.011
rs11155133	1.33 (1.06–1.67)	0.014	1.32 (1.05–1.65)	0.017
rs2239633	1.08 (0.92–1.26)	0.368	1.08 (0.92–1.26)	0.369
rs10821936	1.11 (0.95–1.29)	0.202	1.11 (0.95–1.29)	0.199
rs2242041	1.14 (0.92–1.42)	0.231	1.14 (0.92–1.42)	0.225
rs11978267	0.91 (0.74–1.12)	0.392	0.91 (0.74–1.13)	0.398
rs10849033	1.01 (0.87–1.17)	0.866	1.01 (0.87–1.17)	0.863
rs2089222	1.03 (0.85–1.24)	0.767	1.04 (0.86–1.25)	0.709
rs1879352	1.20 (0.88–1.63)	0.245	1.19 (0.88–1.62)	0.262
rs6428370	1.09 (0.92–1.30)	0.319	1.10 (0.92–1.31)	0.302
rs7554607	0.99 (0.84–1.16)	0.896	0.99 (0.84–1.16)	0.871
rs12621643	1.02 (0.87–1.20)	0.833	1.02 (0.87–1.20)	0.822
rs2167364	0.82 (0.66–1.03)	0.090	0.83 (0.66–1.04)	0.100
rs10994982	1.01 (0.87–1.18)	0.872	1.01 (0.87–1.18)	0.864

[a] Crude results without adjusting

[b] Adjusting for age and gender

Table 4 Stratification analysis of rs9290663 associated with AML risk in additive model

Characteristics	OR (95 % CI)	P
Age		
≤45	0.99 (0.78–1.27)	0.048
>45	1.60 (1.24–2.06)	
Gender		
Male	1.25 (0.97–1.59)	0.243
Female	1.28 (0.99–1.65)	
Lineage		
Myeloid	1.37 (1.13–1.68)	0.144
Myeloid and lymphoid	0.99 (0.74–1.34)	
Myeloid and monocytic	1.34 (0.49–3.69)	
Karyotype		
Aberrant	1.27 (1.00–1.61)	0.873
Normal	1.28 (1.01–1.62)	
Molecular subtype		
PML/RARα	1.28 (0.85–1.91)	0.818
AML1/ETO	1.23 (0.78–1.96)	
Others	1.38 (0.86–2.16)	
No common fusion gene transcripts	1.17 (0.94–1.45)	

Supplementary Table 2). No heterogeneity was found for the other SNPs among any of these subgroups.

As the fusion gene AML1/ETO and PML/RARα, respectively, accounted for the majority of molecular subtypes of M2 AML and M3 AML, we then investigated the association of these two genes with the seven SNPs in M2 and M3 AML. As shown in Supplementary Table 3, rs2191566-G allele significantly increased the risk of M2 AML with AML1/ETO (OR 2.04, 95 % CI 1.20–3.48), but there was no such effect on M2 AML without common fusion gene transcripts (OR 1.06, 95 % CI 0.77–1.44; heterogeneity test: $P = 0.038$). Additionally, there is no heterogeneity for the other six SNPs in different groups.

Discussion

The two published GWASs have provided the unambiguous evidence that several common genetic variations influence the risk of ALL (Treviño et al. 2009; Papaemmanuil et al. 2009), although several replication studies in ALL were later reported; however, the role of these SNPs in the susceptibility to AML is rarely investigated (Sorour et al. 2013; Pakakasama et al. 2007; Lightfoot et al. 2010). In our study, we evaluated the association of these SNPs with AML risk in an independent case–control study with 545 AML cases and 1034 controls in a Chinese population and found that seven SNPs (rs2191566, rs10873876, rs9290663 and rs11155133 in additive model and rs2239633,

rs10821936 and rs2242041 in other genetic models) were significantly associated with altered risk of AML.

rs2191566 located at 19q13.31 is in the intron of *ZNF230* (zinc finger protein 230), which plays a role in mammalian spermatogenesis (Song et al. 2008; Xu et al. 2009; Qiu et al. 2003). However, no study has demonstrated the roles of *ZNF230* in tumorigenesis. In our study, we observed that rs2191566-G significantly altered the risk of AML from myeloid lineage, but not for AML from other two lineages (myeloid and lymphoid, myeloid and monocytic). Besides, rs2191566-G could increase the risk of M2 AML with AML1/ETO, but not for M2 AML without common fusion gene transcripts. These findings suggested that rs2191566 affects the susceptibility to AML, and the mechanisms are variable in different AML subtypes.

rs9290663 (A>T) located at 3q26.32 is in the intron of *KCNMB2* that encodes the β2 subunit of potassium large conductance calcium-activated channel. Our study found that rs9290663-T allele could increase AML risk, and there was interaction between rs9290663 and age, as people who are more than 45 years old and carry rs9290663-TT genotype will get the highest risk of AML; however, the reason is unclear so far.

rs2239633 (G>A) maps to the 5′ near region of *CEBPE* gene encoding CCAAT/enhancer-binding protein (C/EBP), epsilon. Interestingly, the Web-based tool of TFSEARCH 1.3 (http://www.cbrc.jp/research/db/TFSEARCH.html) showed that the A-to-G base change of another significant SNP (rs11155133) might affect the binding of C/EBP. We can infer that rs2239633 and rs11155133 alter the AML risk by affecting C/EBP binding, as C/EBP takes important roles in leukemogenesis (Papaemmanuil et al. 2009).

rs10821936 is in the intron of *ARID5B* gene, and s2242041 (C>G) at 7p12.1 is in the intron of *DDC* gene. Both *ARID5B* and *DDC* were found to be involved in some malignancies (Chang et al. 2008; Bourquin et al. 2006; Geomela et al. 2012; Avgeris et al. 2008). However, the exact mechanism of these SNPs in leukemogenesis was unknown.

Noteworthy, the variant T allele of rs10873876 showed a protective effect on AML risk, which was opposite to the result of GWAS (Treviño et al. 2009). There might be two reasons explaining this. First, the MAF of rs10873876-T allele in our control group was 0.278, while it was only 0.150 in European population, and such difference may lead to different associations. Second, the effects of rs10873876 and the relevant genes on ALL and AML may be different, because of different mechanisms of ALL and AML tumorigenesis, taking the different blood cell progenitors, for example (Mi et al. 2007). However, the detailed mechanism of such associations needs to be further explored.

There were two main limitations in our study. Firstly, the sample size might be relative small, as three SNPs

(rs2242041, rs11155133, and rs1879352) did not achieve a statistical power of greater than 80 % when we assumed that the OR was 1.5. Secondly, we lacked environmental information like ionizing radiation and benzene, so that gene–environment interaction cannot be evaluated. Further studies with larger sample size and more environmental information were needed.

In summary, our study found that seven loci identified in population of European descent in ALL were also associated with AML in Chinese population. Further studies are warranted to clarify the biological mechanisms of these loci with AML risk and determine the causal variants in AML carcinogenesis.

Conflict of interest The authors declare that they have no conflict of interest.

References

Avgeris M, Koutalellis G, Fragoulis EG, Scorilas A (2008) Expression analysis and clinical utility of L-Dopa decarboxylase (DDC) in prostate cancer. Clin Biochem 41:1140–1149

Bănescu C, Tilinca M, Benedek EL, Demian S, Macarie I, Duicu C, Dobreanu M (2013) XRCC3 Thr241Met polymorphism and risk of acute myeloid leukemia in a Romanian population. Gene 526:478–483

Belson M, Kingsley B, Holmes A (2007) Risk factors for acute leukemia in children: a review. Environ Health Perspect 115:138–145

Bourquin JP, Subramanian A, Langebrake C, Reinhardt D, Bernard O, Ballerini P, Baruchel A, Cavé H, Dastugue N, Hasle H, Kaspers GL, Lessard M, Michaux L, Vyas P, van Wering E, Zwaan CM, Golub TR, Orkin SH (2006) Identification of distinct molecular phenotypes in acute megakaryoblastic leukemia by gene expression profiling. Proc Natl Acad Sci USA 103:3339–3344

Chang LW, Payton JE, Yuan W, Ley TJ, Nagarajan R, Stormo GD (2008) Computational identification of the normal and perturbed genetic networks involved in myeloid differentiation and acute promyelocytic leukemia. Genome Biol 9:R38

Chokkalingam AP, Hsu LI, Metayer C, Hansen HM, Month SR, Barcellos LF, Wiemels JL, Buffler PA (2013) Genetic variants in ARID5B and CEBPE are childhood ALL susceptibility loci in Hispanics. Cancer Causes Control 24:1789–1795

Deschler B, Lübbert M (2006) Acute myeloid leukemia: epidemiology and etiology. Cancer 107:2099–2107

Eden T (2010) Aetiology of childhood leukaemia. Cancer Treat Rev 36:286–297

Ellinghaus E, Stanulla M, Richter G, Ellinghaus D, te Kronnie G, Cario G, Cazzaniga G, Horstmann M, Panzer Grümayer R, Cavé H, Trka J, Cinek O, Teigler-Schlegel A, ElSharawy A, Häsler R, Nebel A, Meissner B, Bartram T, Lescai F, Franceschi C, Giordan M, Nürnberg P, Heinzow B, Zimmermann M, Schreiber S, Schrappe M, Franke A (2012) Identification of germline

susceptibility loci in ETV6-RUNX1-rearranged childhood acute lymphoblastic leukemia. Leukemia 26:902–909

Geomela PA, Kontos CK, Yiotakis I, Fragoulis EG, Scorilas A (2012) L-DOPA decarboxylase mRNA expression is associated with tumor stage and size in head and neck squamous cell carcinoma: a retrospective cohort study. BMC Cancer 12:484

Gutiérrez-Camino Á, López-López E, Martín-Guerrero I, Sánchez-Toledo J, García de Andoin N, Carboné Bañeres A, García-Miguel P, Navajas A, García-Orad Á (2013) Intron 3 of the ARID5B gene: a hot spot for acute lymphoblastic leukemia susceptibility. J Cancer Res Clin Oncol 139:1879–1886

Han S, Lee KM, Park SK, Lee JE, Ahn HS, Shin HY, Kang HJ, Koo HH, Seo JJ, Choi JE, Ahn YO, Kang D (2010) Genome-wide association study of childhood acute lymphoblastic leukemia in Korea. Leuk Res 34:1271–1274

Healy J, Richer C, Bourgey M, Kritikou EA, Sinnett D (2010) Replication analysis confirms the association of ARID5B with childhood B-cell acute lymphoblastic leukemia. Haematologica 95:1608–1611

Huang X, Ma D, Dong W, Li P, Lu T, He N, Tian T, Liu N, DU Y, Ji C (2013) Gene expression profiling of the DNMT3A R882 mutation in acute leukemia. Oncol Lett 6:268–274

Krajinovic M, Labuda D, Richer C, Karimi S, Sinnett D (1999) Susceptibility to childhood acute lymphoblastic leukemia: influence of CYP1A1, CYP2D6, GSTM1, and GSTT1 genetic polymorphisms. Blood 93:1496–1501

Krajinovic M, Sinnett H, Richer C, Labuda D, Sinnett D (2002) Role of NQO1, MPO and CYP2E1 genetic polymorphisms in the susceptibility to childhood acute lymphoblastic leukemia. Int J Cancer 97:230–236

Li N, Xu Y, Zheng J, Jiang L, You Y, Wu H, Li W, Wu D, Zhou Y (2013) NBS1 rs1805794G > C polymorphism is associated with decreased risk of acute myeloid leukemia in a Chinese population. Mol Biol Rep 40:3749–3756

Lightfoot TJ, Johnston WT, Painter D, Simpson J, Roman E, Skibola CF, Smith MT, Allan JM, Taylor GM, United Kingdom Childhood Cancer Study (2010) Genetic variation in the folate metabolic pathway and risk of childhood leukemia. Blood 115:3923–3929

Linabery AM, Blommer CN, Spector LG, Davies SM, Robison LL, Ross JA (2013) ARID5B and IKZF1 variants, selected demographic factors, and childhood acute lymphoblastic leukemia: a report from the Children's Oncology Group. Leuk Res 37:936–942

Mi S, Lu J, Sun M, Li Z, Zhang H, Neilly MB, Wang Y, Qian Z, Jin J, Zhang Y, Bohlander SK, Le Beau MM, Larson RA, Golub TR, Rowley JD, Chen J (2007) MicroRNA expression signatures accurately discriminate acute lymphoblastic leukemia from acute myeloid leukemia. Proc Natl Acad Sci USA 104:19971–19976

Migliorini G, Fiege B, Hosking FJ, Ma Y, Kumar R, Sherborne AL, da Silva Filho MI, Vijayakrishnan J, Koehler R, Thomsen H, Irving JA, Allan JM, Lightfoot T, Roman E, Kinsey SE, Sheridan E, Thompson P, Hoffmann P, Nöthen MM, Mühleisen TW, Eisele L, Zimmermann M, Bartram CR, Schrappe M, Greaves M, Stanulla M, Hemminki K, Houlston RS (2013) Variation at 10p12.2 and 10p14 influences risk of childhood B-cell acute lymphoblastic leukemia and phenotype. Blood 122:3298–3307

Perez-Andreu V, Roberts KG, Harvey RC, Yang W, Cheng C, Pei D, Xu H, Gastier-Foster J, E S, Lim JY, Chen IM, Fan Y, Devidas M, Borowitz MJ, Smith C, Neale G, Burchard EG, Torgerson DG, Klussmann FA, Villagran CR, Winick NJ, Camitta BM, Raetz E, Wood B, Yue F, Carroll WL, Larsen E, Bowman WP, Loh ML, Dean M, Bhojwani D, Pui CH, Evans WE, Relling MV, Hunger SP, Willman CL, Mullighan CG, Yang JJ (2013) Inherited GATA3 variants are associated with Ph-like childhood

acute lymphoblastic leukemia and risk of relapse. Nat Genet 45:1494–1498

Pakakasama S, Sirirat T, Kanchanachumpol S, Udomsubpayakul U, Mahasirimongkol S, Kitpoka P, Thithapandha A, Hongeng S (2007) Genetic polymorphisms and haplotypes of DNA repair genes in childhood acute lymphoblastic leukemia. Pediatr Blood Cancer 48:16–20

Papaemmanuil E, Hosking FJ, Vijayakrishnan J, Price A, Olver B, Sheridan E, Kinsey SE, Lightfoot T, Roman E, Irving JA, Allan JM, Tomlinson IP, Taylor M, Greaves M, Houlston RS (2009) Loci on 7p12.2, 10q21.2 and 14q11.2 are associated with risk of childhood acute lymphoblastic leukemia. Nat Genet 41:1006–1010

Qiu W, Zhang S, Xiao C, Xu W, Ma Y, Liu Y, Wu Q (2003) Molecular cloning and characterization of a mouse spermatogenesis-related ring finger gene znf230. Biochem Biophys Res Commun 306:347–353

Redaelli A, Laskin BL, Stephens JM, Botteman MF, Pashos CL (2005) A systematic literature review of the clinical and epidemiological burden of acute lymphoblastic leukaemia (ALL). Eur J Cancer Care (Engl) 14:53–62

Rudant J, Orsi L, Bonaventure A, Goujon-Bellec S, Corda E, Baruchel A, Bertrand Y, Nelken B, Robert A, Michel G, Sirvent N, Chastagner P, Ducassou S, Rialland X, Hémon D, Leverger G, Clavel J (2013) Are ARID5B and IKZF1 polymorphisms also associated with childhood acute myeloblastic leukemia: the ESCALE study (SFCE)? Leukemia 27:746–748

Schnatter AR, Armstrong TW, Thompson LS, Nicolich MJ, Katz AM, Huebner WW, Pearlman ED (1996) The relationship between low-level benzene exposure and leukemia in Canadian petroleum distribution workers. Environ Health Perspect 104(Suppl 6):1375–1379

Siegel R, Ma J, Zou Z, Jemal A (2014) Cancer statistics, 2014. CA Cancer J Clin 64:9–29

Song H, Su D, Lu P, Yang J, Zhang W, Yang Y, Liu Y, Zhang S (2008) Expression and localization of the spermatogenesis-related gene, Znf230, in mouse testis and spermatozoa during postnatal development. BMB Rep 41:664–669

Sorour A, Ayad MW, Kassem H (2013) The genotype distribution of the XRCC1, XRCC3, and XPD DNA repair genes and their role for the development of acute myeloblastic leukemia. Genet Test Mol Biomarkers 17:195–201

Treviño LR, Yang W, French D, Hunger SP, Carroll WL, Devidas M, Willman C, Neale G, Downing J, Raimondi SC, Pui CH, Evans WE, Relling MV (2009) Germline genomic variants associated with childhood acute lymphoblastic leukemia. Nat Genet 41:1001–1005

Wang Y, Chen J, Li J, Deng J, Rui Y, Lu Q, Wang M, Tong N, Zhang Z, Fang Y (2013) Association of three polymorphisms in ARID5B, IKZF1 and CEBPE with the risk of childhood acute lymphoblastic leukemia in a Chinese population. Gene 524:203–207

Xu W, Zhang S, Qiu W, He G, Liu Y, Sun Y, Ma Y, Dong J, Zhang W (2009) Spermatogenesis-related ring finger gene ZNF230 promoter: identification and functional analysis. Mol Biol Rep 36:1187–1193

Xu H, Yang W, Perez-Andreu V, Devidas M, Fan Y, Cheng C, Pei D, Scheet P, Burchard EG, Eng C, Huntsman S, Torgerson DG, Dean M, Winick NJ, Martin PL, Camitta BM, Bowman WP, Willman CL, Carroll WL, Mullighan CG, Bhojwani D, Hunger SP, Pui CH, Evans WE, Relling MV, Loh ML, Yang JJ (2013) Novel susceptibility variants at 10p12.31-12.2 for childhood acute lymphoblastic leukemia in ethnically diverse populations. J Natl Cancer Inst 105:733–742