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Focused Screening of a Panel of Cancer-Related Genetic Polymorphisms Reveals New Susceptibility Loci for Pediatric Acute Lymphoblastic Leukemia

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Background. A genetic predisposition to acute lymphoblastic leukemia (ALL) in childhood is well established. Currently known risk loci, however, explain only one third of the estimated total risk related to common genetic variations. ***Procedure.*** We genotyped 1,421 polymorphisms in 407 candidate genes from the SNP500Cancer database (National Cancer Institute) using the Illumina Cancer SNP Panel. We investigated 78 cases (aged 0–19 years at diagnosis, and mixed ethnic background) of childhood B-precursor ALL and compared genotype data with those of 1,417 HapMap controls. To account for the ethnic diversity of the study population, structured association by genetically matching cases and controls using identity-by-state similarity was used. Case-control association analyses were performed using Cochran–Mantel–Haenszel tests, adjusted for the population substructure. ***Results.*** Common variations rs6966 (3′ UTR of *PPP1R13L*, chr 19q13.32, $P = 4.55 \times 10^{-9}$) and rs414580 (intron 2 of *MSR1*, chr 8p22, $P = 6.09 \times 10^{-8}$) were significantly associated with ALL. These SNPs remained significant after adjustment for multiple testing. The SNP rs6966 tags a haplotype block which includes SNPs in *PPP1R13L* and *ERCC2* genes, which are related to DNA repair and cell survival. rs6966 and rs414580 conferred allelic odds ratios of 3.74 (95% confidence interval [CI] 2.31–6.04) and 3.93 (95% CI 2.31–6.69), respectively. ***Conclusions.*** These findings reveal two independent novel susceptibility loci for childhood ALL. Pediatr Blood Cancer 2014;61:1411–1415.

Key words: candidate gene association study; childhood acute lymphoblastic leukemia; ERCC2; MSR1; PPP1R13L

INTRODUCTION

Acute lymphoblastic leukemia (ALL) represents almost one third of pediatric cancer diagnoses, making it the most common malignancy in childhood [1]. ALL is most commonly of the B cell lineage and its incidence peaks between ages 2 and 4 years. B-precursor ALL (B-ALL)—despite the high rate of cure—remains one of the leading causes of cancer-related death among children [2]. Somatically acquired genetic aberrations in ALL lymphoblasts are prognostic and can guide risk-directed therapy. The extent to which germline variation contributes to ALL susceptibility, however, is less clear and is subject of current research.

Direct evidence for a genetic predisposition to ALL is provided by the high risk associated with Bloom syndrome, neurofibromatosis, ataxia teleangiectasia, and Down's syndrome. The heritable basis of susceptibility to ALL is further supported by recent candidate gene (CGAS) and genome-wide association studies (GWAS), suggesting that co-inheritance of multiple germline variants may contribute to disease risk. Five GWAS have been performed so far with populations between 50/50 and 3,275/4,817 ALL cases/healthy control individuals [3–7]. These studies identified several risk loci with allelic odds ratios (OR) of the disease-related allele between 1.34 and 9.99.

Enciso-Mora et al. [8] calculated that 25% of the total variation in B-ALL risk is accounted for by common genetic variation. On the other hand, previous GWAS-identified loci (*IKZF1*, *CDKN2A*, *ARID5B*, and *CEBPE*) explain only 8% of this total. The data provide the rationale for continued investigation of additional susceptibility loci that were likely missed by previous GWAS. Although GWAS represent a powerful approach to the identification of disease loci, the *P*-value requirement for defining a significant association, in turn, may increase the probability of missing a true association [9].

In the present study we, therefore, have chosen a CGAS approach which was based on the assumption that known risk loci for many types of cancer are *a priori* also potential risk loci for B-ALL. Single nucleotide polymorphisms (SNPs) were selected from the SNP500Cancer database, which is biased towards SNPs that lie within or are situated close to cancer "candidate" genes [10]. We genotyped 1,421 polymorphisms in 407 candidate genes using the Illumina Cancer SNP Panel BeadChip assay (Illumina, San Diego, CA). We investigated an unselected population of B-ALL patients recruited in a single center irrespective of ethnic background to identify risk loci independent of ethnicity.

METHODS

Clinical Samples

Patients diagnosed with acute lymphoblastic leukemia (ALL) who were diagnosed and treated at the Children's Hospital of

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Brecht and Zolk share senior authorship.

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Michigan, Detroit, USA between 1993 and 2007 were screened for inclusion. Genomic DNA was extracted from discarded blood samples obtained for routine clinical hematology studies. All samples were anonymized prior to testing. The research protocol was approved by the Human Investigation Committee of Wayne State University School of Medicine.

Seventy-eight children with B-precursor ALL who had finished the treatment protocols and had remission blood or bone marrow samples available were recruited. Patient characteristics are summarized in Table I. Genomic DNA was extracted from the samples using Qiagen genomic DNA extraction kits (QIAGEN, Inc., Valencia, CA). Quantity and quality of the gDNA was evaluated by using Molecular Probes PicoGreen Assay (Molecular Probes, Eugene, OR).

SNP Selection, Genotyping, and Quality Control

Genotyping was performed using the Illumina Cancer SNP Panel on the GoldenGate Assay system according to the manufacturer's instructions (Illumina). The Cancer Panel contains 1,421 SNPs in 407 hypothesized cancer-related genes from the SNP500Cancer database (Cancer Genome Anatomy Project, National Cancer Institute). SNPs were chosen from public databases and reports, and the choice of genes includeds a bias towards non-synonymous and promoter SNPs in genes that have been implicated in one or more cancers (PMID 16381944, 14681474). The Illumina Cancer SNP Panel includes genes of several cancer-related pathways, such as oncogenesis, tumor suppression, oxidative and hypoxic stress, detoxification, DNA mismatch repair, regulation of transcription and cell cycle, metabolism and immune regulation, and different carriers and transport proteins. Genes and pathways covered by the Cancer SNP Panel are shown in the Supplemental Table I. In the Cancer SNP Panel, more than three SNP assays were selected, on average, for each gene represented. It was not the primary intention of this study to replicate previous GWAS or CGAS results but to find novel candidates. In fact, there is only a small overlap between SNPs and genes covered by the Illumina Cancer SNP Panel and loci identified in previous association studies. For example, 56% of the genes and 22% of the SNPs identified in the meta-analysis of CGAS by Vijayakrishnan et al. [11] were included in the Cancer SNP Panel.

Mathematical clustering and automatic genotype calling algorithms, implemented in the GenomeStudio software (Illumina), was used to analyze the raw intensity data. To assess the genotype quality, we manually inspected the cluster plots and corrected genotype assignment where automatic genotype calling failed.

SNPs that could not be clustered or were non-polymorphic were excluded from further analyses. The average genotyping call rate for all samples was 98.8%. If the call rate for any sample was below 95%, the sample was excluded from further analysis. Other quality criteria included minor allele frequency (MAF) $\geq$0.01 and *P*-value for the Hardy–Weinberg equilibrium test $>$0.01. Forty-two SNPs were removed during quality control, leaving 1,387 SNPs for analysis.

To exclude genotyping artifacts, candidate SNPs were genotyped with an independent technology. We used the TaqMan platform and predesigned SNP Genotyping Assays Reagents (Applied Biosystems, Foster City, CA) to re-genotype rs6966 (C_2615637_10) and rs414580 (C_1865305_10) as described before [12].

We used the HapMap population (N = 1,417) as a control. Genotype data were retrieved from the publicly accessible HapMap database (1,417 samples; HapMap Genome Browser release #28, The International Hapmap Project, available at http://hapmap.ncbi.nlm.nih.gov/; genotype data were available for 1,169 SNPs included in the Illumina Cancer SNP Panel) and from Illumina (subset of 269 CEU, CHB/JPT, and YRI samples from the HapMap population, genotype data were available for all 1,421 SNPs).

Statistical Analysis

To adjust for inflation due to population stratification, structured association by genetically matching cases and controls using identity-by-state (IBS) similarity as implemented in PLINK [13] was used. Complete linkage agglomerative clustering was performed, based on pairwise IBS distance, with some modifications to the clustering process: restrictions based on a significance test for whether two individuals belong to the same population (i.e., do not merge clusters that contain significantly different individuals), a phenotype criterion (i.e., all clusters must contain at least one ALL case and one control) and cluster size restrictions (i.e., such that, with a cluster size of two, the subsequent association test would implicitly match every case with its nearest control, as long as the case and control do not show evidence of belonging to different populations). Based on the matrix of IBS pairwise distances, multi-dimensional scaling (MDS) components were obtained using the MDS-plot option in PLINK. MDS plots, generated with R, visualize substructure and provide quantitative indices of population genetic variation. Stratified case-control association analyses were performed using Cochran–Mantel–Haenszel tests, adjusted for the population substructure by inclusion of the IBS cluster information. All the statistical results are reported without correction, unless indicated otherwise. Control of the error rate under multiple testing was done using false discovery rate (FDR) adjustment as implemented in PLINK. After exclusion of

TABLE I. Patient and Biological Characteristics

	Cases (n = 78)
Sex	
Male	44 (56.4%)
Female	34 (43.6%)
Race	
African Americans	13 (16.7%)
Asian Americans & Pacific Islander Americans	4 (5.1%)
Indian Americans	3 (3.8%)
Caucasians	58 (74.4%)
Age at diagnosis	
$<$10 years	62 (79.5%)
$\geq$10 years	16 (20.5%)
Immunophenotype	
B-precursor ALL	74 (94.8%)
Mixed lineage ALL	2 (2.6%)
No information	2 (2.6%)
TEL/AML1	
Positive	16 (20.5%)
Negative or no information	62 (79.5%)
MLL/AF4	
Positive	1 (1.3%)
Negative or no information	77 (98.7%)

some SNPs after quality control and based on the LD structure of cases and controls, we calculated the effective number of independent tests in our analysis at 1,379. Power analysis was done with PS Power and Sample Size v3.0 [14].

RESULTS

Before comparing allele frequencies between cases and controls, we considered biases due to nonrandom distribution of technical artifacts or to population differences between case and control data, which would result in a non-null distribution of test statistics with excess false-positive associations. Therefore, we assessed the median distribution of test statistics with the genomic-control parameter λ_{GC} and examined the tail of the distribution of association statistics in a comparison of observed and expected *P*-values (Q-Q plot; Fig. 1). After adjustment for inflation due to population stratification, λ_{GC} was markedly reduced, falling from 5.86 to 1.29. The MDS plot shows clustering of cases within the major control populations (Fig. 2).

To exclude genotyping artifacts, candidate SNPs were genotyped with an independent technology. The concordance of genotype calls was greater than 98%, indicating that the extreme tail of low *P*-values was not substantially contaminated by genotyping artifacts.

Our analysis revealed a significant association of the (noncoding) haplotype-tagging SNPs rs6966 (NM_001142502.1: c.*486A > T, chr 19q13.3) in the protein phosphatase 1 regulatory subunit 13 like (*PPP1R13L*) gene ($P = 4.55 \times 10^{-9}$) and rs414580 (NM_002445.3: c.103 + 93A > T, chr 8p22) in the macrophage scavenger receptor 1 (*MSR1*) gene ($P = 6.09 \times 10^{-8}$) with ALL (Fig. 3). For both SNPs, the respective T alleles were associated with increased ALL risk. A third SNP, rs11762213 (NM_000245.2: c.144G > A, chr 7q31) in the MET proto-oncogene (*MET*), showed only borderline significance ($P = 2.97 \times 10^{-2}$ after correction for multiple testing). The SNPs rs6966 in *PPP1R13L*, rs414580 in *MSR1*, and rs11762213 in *MET* conferred allelic odds ratios of 3.74 (95% CI 2.31–6.04), 3.93 (95% CI 2.31–6.69), and 7.57 (95% CI 2.52–22.78), respectively. MAFs in cases/controls of the total population were 0.77/0.46 (rs414580), 0.77/0.47 (rs6966), and 0.23/0.03 (rs11762213). MAFs in cases/controls in the Caucasian subpopulations (N = 64/463) were 0.77/0.40 (rs414580), 0.85/0.35 (rs6966), and 0.23/0.04 (rs11762213).

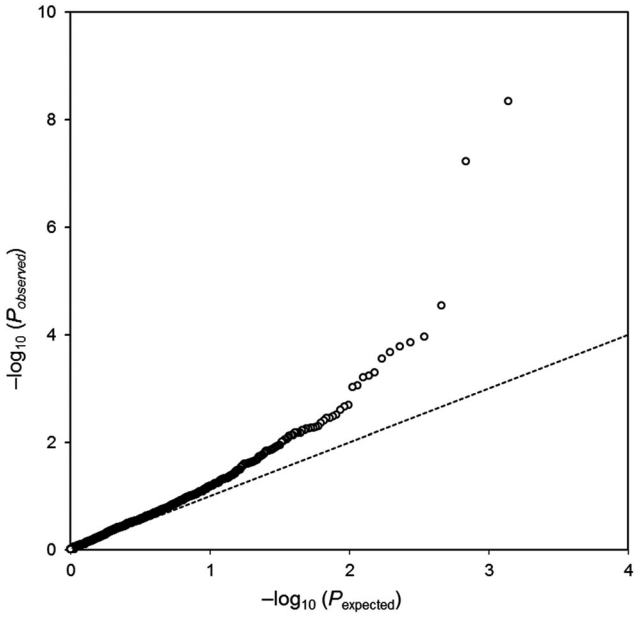

Fig. 1. Q–Q plot for the association of 1,387 tested SNPs and the ALL risk after controlling the study population (1,417 controls and 78 ALL cases) for confounding by ethnicity (identity-by-state clustering approach). The Q–Q plot allows assessment of the number and magnitude of observed associations between genotyped SNPs and ALL, compared to the association statistics expected under the null hypothesis of no association.

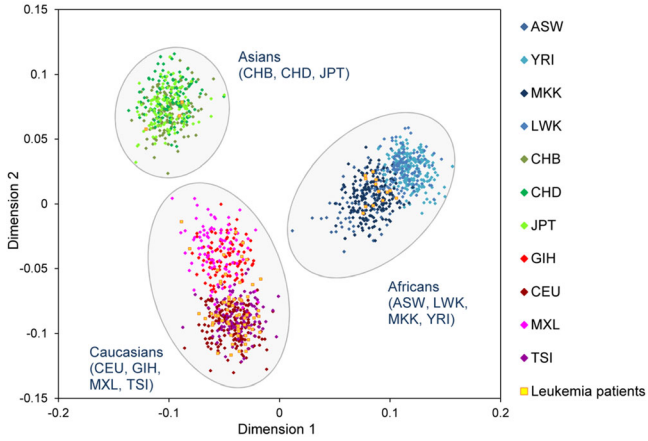

Fig. 2. Multidimensional scaling plot of the identity by state matrix.

Based on HapMap data, haplotype block organization in the rs6966 and rs414580 regions was investigated using criteria based on solid spine of linkage disequilibrium method (D′ > 0.8) with Haploview software. Figure 4 shows LD maps in the HapMap European (CEU/TSI) population (LD plots for Asian and African populations are shown in Supplemental Figs. 1 and 2). The SNP rs6966 was in LD with SNPs in *PPP1R13L* as well as excision repair cross-complementing rodent repair deficiency-complementation group 2 (*ERCC2*).

In addition to identifying new loci associated with ALL risk, we sought to replicate previous positive associations. Six SNPs previously linked in genome-wide or candidate gene association studies with ALL risk were included in the Illumina SNP Cancer Panel, namely *CDKN2A* rs3731217 ($P = 0.1022$; OR 0.54), *EPHX1* rs1051740 ($P = 0.3648$; OR 0.77), *MTHFR* rs1801133 ($P = 0.7829$; OR 0.93), *MTR* rs1805087 ($P = 0.1390$; OR 0.62), *SLC19A1* rs1051266 ($P = 0.7984$; OR 0.93), and *XRCC1* rs25487 ($P = 0.3248$; OR 1.30) [11,15–18]. The respective genotype data were thus available for analysis. None of these SNPs were significantly (after correction for multiple testing) associated with ALL in our study. It is important to note that, because our study was powered to detect an OR >2.3 (power of >80% to detect associations with OR >2.3 at a nominal significance level of 3.5×10^{-5} and a minor allele frequency of 0.3), we cannot exclude that these SNPs are significantly associated with ALL at a lower OR level.

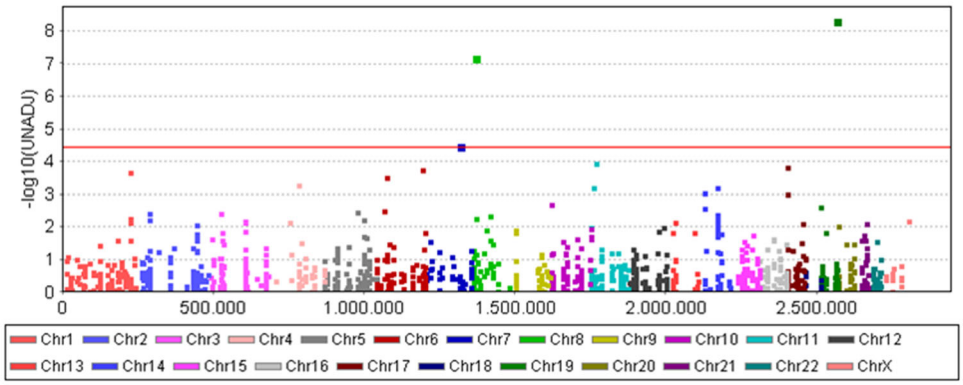

Fig. 3. Manhattan plot showing the association of SNPs with ALL. The *P*-values ($-\log_{10}P$) plotted against their respective positions on each chromosome. Each chromosome is depicted in a different color. $-\log_{10}$ (UNADJ), $-\log_{10} P$ value of Cochran–Mantel–Haenszel test unadjusted for multiple testing.

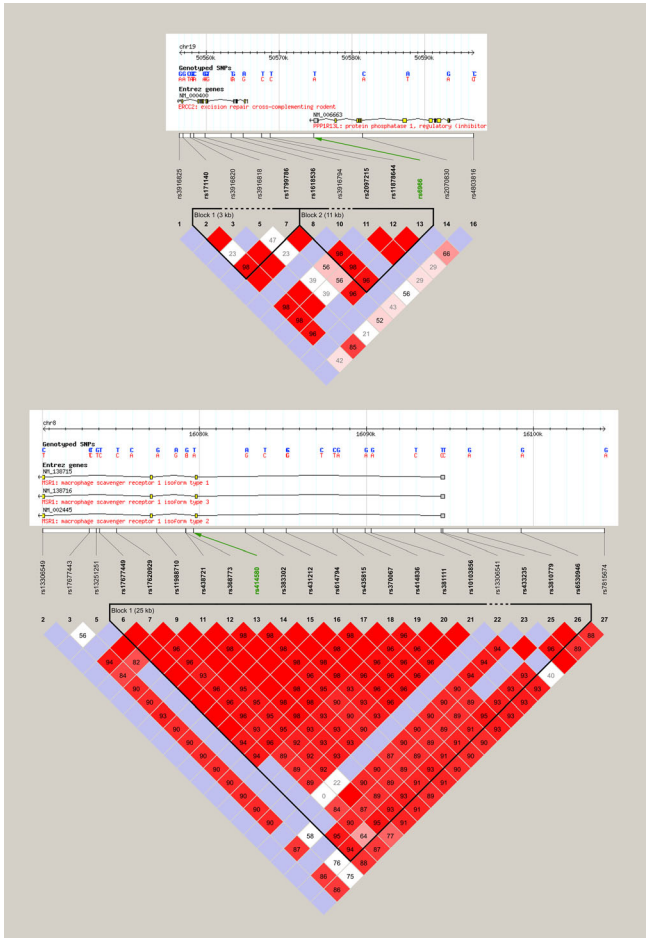

Fig. 4. LD maps of the regions adjacent to rs6966 in *PPP1R13L* and rs414580 in *MSR1* in European (CEU/TSI) populations. The SNPs rs6966 and rs414580 are highlighted in green. Shading reflects differences in pairwise LD (white $r^2 =$ low LD; red $r^2 =$ near-perfect LD). Numbers in squires are estimates of pairwise coefficients (D′), expressed in percentages. Unreported values reflect D′ of 1.0 (100%).

DISCUSSION

This is the first study evaluating an association of SNPs in "cancer genes" from the SNP500 database with childhood ALL. Similar analyses using the Illumina Cancer SNP Panel were successfully applied previously to identify risk loci for example for colorectal or prostate cancer [19,20].

The SNPs identified in our analysis, rs6966, rs414580, and rs11762213, have not been associated previously with childhood ALL in GWAS or CGAS. The tag SNP rs6966, located on chromosome 19q13.3, is in LD with polymorphisms in *ERCC2* and *PPP1R13L*, genes related to DNA repair and cell survival. *PPP1R13L* induces apoptosis by blocking NFκB or inhibits apoptosis by blocking P53 [21,22]. By either mechanism, the gene could influence the survival of precancerous lesions, and it has been speculated that *PPP1R13L* participates in the tumorigenesis process [22–24]. A first link between *PPP1R13L* and ALL was provided by the observation that *PPP1R13L* gene expression was significantly higher in cells of acute leukemia than that in cells from healthy donors or acute leukemia patients in complete remission [25].

The $5' \rightarrow 3'$ helicase protein *ERCC2* (also known as XPD) has an important role in the nucleotide excision repair (NER) pathway [26]. . The NER pathway plays a major role in cell protection against genotoxic damage by repairing DNA lesions such as those induced by UV irradiation or chemical carcinogens [27]. Inherited variations in DNA-repair efficiency have been implicated in the predisposition to *de novo* and therapy-related AML [28,29]. Moreover, Hernandez-Boluda et al. [29] identified rs13181 in *ERCC2* as an independent risk factor for leukemic transformation in primary myelofibrosis, even though their finding is not without controversy [30,31]. Several reports linked polymorphisms in the *ERCC2* gene with enhanced risk of childhood ALL [32,33], although negative results were also reported [34,35]. A meta-analysis was able to confirm an association of the *ERCC2* locus with ALL [26].

We identified rs6966 as a potential susceptibility locus, but it remains a challenge to pinpoint the causal variant, which may be located in *PPP1R13L* or *ERCC2*. Both genes have been linked with tumorigenesis or leukemic transformation and thus may play a role in the development of ALL.

The other tag SNP identified in our study, rs414580, is located in the 8p22 region in the *MSR1* gene [36]. Genetic polymorphisms in MSR1 have been shown to be related to prostate cancer risk, although the underlying mechanism is unclear [37]. In a mouse chronic myeloid leukemia (CML) model, Chen et al. [38] demonstrated that MSR1 suppresses leukemia stem cells and CML development. Interestingly, the ALL susceptibility loci MSR1 (this study) and *CEBPE* (previous studies [3,39],) both play a role in normal macrophage function [40,41].

The third significantly associated SNP in our analysis was rs11762213 in *MET*, although only at borderline significance. Germline mutations located in the *MET* proto-oncogene, which lead to a constitutive activation of the MET protein, have been linked with the development of hereditary papillary renal carcinoma [42]. Moreover, the germline genetic polymorphism rs11762213 has been associated with the risk of recurrence in patients with localized renal-cell carcinoma [43]. This SNP, however, has not been associated previously with childhood ALL.

Six SNPs previously linked with susceptibility to childhood ALL were included in our SNP panel. Previous studies showed that the effect size of these SNPs was small and associations became obvious, in some cases, only after combining results from different studies in meta-analyses (OR 1.1–1.4) [11,15–18]. Our study was powered to detect an OR >2.3, which explains the lack of association of these SNPs in our study.

Limitations of our study include the small sample size. Our study had statistical power of >80% to detect only associations with OR >2.3 at a nominal significance level of 3.5×10^{-5} (this significance threshold is required when accounting for multiple comparisons) and a minor allele frequency of 0.3. Nevertheless, this is the first study that systematically screened tagging and several coding variants in established cancer risk genes in a comprehensive manner to identify ALL susceptibility loci. The study was restricted to precursor B-ALL patients. Although the study design precludes any statements on the relevance of the identified risk loci for patients with the T-cell immunophenotype, restriction to B-ALL reduced the heterogeneity of the study population and thus improved the power. Patients were not selected according to their ethnic background, which on the one hand necessitated statistical adjustments but on the other hand enabled identification of susceptibility loci not restricted to only one major ethnic group.

In conclusion, by screening 1,421 SNPs in "cancer genes" we identified two novel loci, namely *ERCC2/PPP1R13L* and *MSR1*, which are potentially associated with susceptibility to childhood ALL. Confirmation of the association is required in an independent study population with greater statistical power. Rapid advances in the development of sequencing technologies will enable cost-effective screening of several thousand clinically relevant SNPs in childhood ALL in the near future. As a proof-of-concept, Wesolowska et al. [9] applied a novel multiplexing method with custom-designed baits to screen 25,000 SNPs in childhood ALL.

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