Chromosomal abnormalities are important for the risk stratification of acute lymphoblastic leukemia/lymphoma (ALL). However, approximately 30% of pediatric and 50% of adult patients lack abnormalities with clinical relevance by traditional cytogenetic analysis. We integrated cytogenetic, fluorescence in situ hybridization, and whole-genome single-nucleotide polymorphism array results from 60 consecutive clinical ALL cases. By cytogenetic and/or fluorescence in situ hybridization analyses, recurring abnormalities with clinical relevance were observed in 33 B-cell ALL (B-ALL), including t(9;22), hyperdiploidy, KMT2A translocation, ETV6-RUNX1, intrachromosomal amplification of chromosome 21, near haploidy or low hypodiploidy, and t(8;22). Single-nucleotide polymorphism array analysis found additional aberrations with prognostic or therapeutic implication in 21 B-ALL and two T-cell ALL, including IKZF1 deletion, intrachromosomal amplification of chromosome 21 (one case with a normal karyotype), low hypodiploidy (two cases with a normal karyotype), and one case each with fusion genes ETV6-NTRK3, CRLF2-P2RY8, NUP214-ABL1, and SET-NUP214. IKZF1 deletion was noted in nine B-ALL with t(9;22), five B-ALL with a normal karyotype, and one B-ALL with t(4;11), five B-ALL with a normal karyotype, and three B-ALL with nonrecurring karyotypic abnormalities. Combining single-nucleotide polymorphism array with chromosome and fluorescence in situ hybridization assays, the detection rate for clinically significant abnormal results increased from 56% to 75%. Whole-genome single-nucleotide polymorphism array analysis detects cytogenetically undetectable clinically significant aberrations and should be routinely applied at diagnosis of ALL. (J Mol Diagn 2016, 18: 595–603; http://dx.doi.org/10.1016/j.jmoldx.2016.03.004)
PAX5 have been frequently observed in B-ALL, and deletions of IKZF1, RB1, EBF1, and pseudoautosomal region 1 have been associated with an unfavorable prognosis. High-resolution genome-wide SNP array analysis allows determination of both copy number aberrations and copy neutral loss of heterozygosity (CN-LOH) and therefore is able to provide important insights into the often complex and unique genomic profiles for many patients. SNP array analysis requires only a small amount of DNA and can provide useful information when specimens are limited or metaphase cells are not available. In recent years, SNP arrays have been used for detecting genomic abnormalities in ALL and proved to facilitate diagnosis, risk stratification, and determination of efficient therapeutic regimens.\textsuperscript{9–14} Despite these advantages, genome-wide SNP arrays have not been routinely used for ALL by clinical laboratories. This study retrospectively reviewed results of cytogenetics, FISH, and whole-genome SNP array assays in 60 consecutive clinical ALL cases from a single institution. We found that SNP array improved the detection rate of genomic abnormalities (90% by cytogenetics and FISH versus 100% by SNP array) and provided additional prognostic and therapeutic information (56% by cytogenetics and FISH versus 75% by cytogenetics, FISH, and SNP array). These results indicate that whole-genome SNP arrays should be incorporated as standard of care for ALL patients.

Materials and Methods

Patient Samples

Beginning in March 2014, we incorporated SNP array analysis as part of our standard clinical testing for patients with newly diagnosed ALL. We retrospectively reviewed cytogenetic, FISH, and SNP array results for consecutive ALL cases from the Clinical Cytogenetics Laboratory at the University of Michigan Health System between March 2014 and June 2015. Sixty consecutive patients had SNP array results and 59 also had concurrent cytogenetic and/or FISH analyses. Cytogenetic analysis was not performed in two patients with T-ALL; FISH analysis was not performed in four patients with B-ALL and two patients with T-ALL. This study was approved by the institutional review board at the University of Michigan.

Cytogenetic and FISH Analyses

At least 20 G-banded metaphase cells were obtained from overnight and/or 24-hour cultures using standard techniques. Cases with <15 analyzable normal metaphase cells were considered inadequate. FISH analysis was performed using probe sets, including BCR-ABL1 dual fusion, KMT2A breakapart, ETV6-RUNX1 fusion, and centromere probes for chromosomes 4, 10, and 17 (Abbott Molecular, Des Plaines, IL) for pediatric patients with B-ALL and BCR-ABL1 and KMT2A probes for adults with B-ALL and most patients with T-ALL. Some of the array results were confirmed by FISH analysis using probes commonly used in the clinical cytogenetics laboratory. Karyotypic and FISH results were interpreted according to the International System for Human Cytogenetic Nomenclature. FISH images were captured using a Leica DMRA microscope with the Cytovision Imaging system (Leica Microsystems, Buffalo Grove, IL).

SNP Array Analysis

Genomic DNA was extracted from leukemic blood, bone marrow, or fluidic samples using the QIAamp DNA mini-extraction kit (Qiagen, Germantown, MD), according to the manufacturer’s instructions. Genome-wide SNP array analysis was performed using the Affymetrix CytoScan HD platform with approximately 2.7 million probes according to the manufacturer’s protocols (Affymetrix, Santa Clara, CA) as published previously.\textsuperscript{15} SNP array data were analyzed by the Affymetrix ChAS software version 2.1 (Affymetrix). Plots of two parameters, the log2 ratio and the allele peaks, providing information regarding copy number and genotype, respectively, were examined by visual inspection. All genomic positions were based on the hg19 (2009) build of the human genome sequence (http://genome.ucsc.edu/cgi-bin/hgGateway, last accessed March 17, 2016). Results were compared to databases of known common copy number variations seen in healthy controls, including the Toronto database of genomic variants (http://dgv.tcag.ca/dgv/app/home, last accessed March 17, 2016), International Standards for Cytogenomic Arrays database (http://dbsearch.clinicalgenome.org, last accessed March 17, 2016), and Children’s Hospital of Philadelphia copy number variation database (http://cnv.chop.edu, last accessed March 17, 2016); common population variants were excluded from the results. Gains or losses >35 markers within or including a known clinically significant cancer-related gene or >1 Mb outside the known clinical oncology significant regions and loss of heterozygosity >10 Mb are reported.

Results

A total of 60 consecutive ALL cases were received between March 2014 and June 2015 in the Clinical Cytogenetics Laboratory for clinical SNP array analysis. Among those, 27 (45%) were from pediatric patients (0.5 to 18 years old), 13 (21.7%) were from young adults (19 to 30 years old), and 20 (33.3%) were from adults (31 to 70 years old). Fifty-three patients (88.3%) were diagnosed as having B-ALL and seven (11.7%) as having T-ALL.

Karyotypic abnormalities were found in 47 of 58 patients (81%), and FISH abnormalities were found in 42 of 54 patients (78%) (Table 1), among whom recurring abnormalities with clinical relevance were observed in 33 patients with B-ALL. These abnormalities included t(9;22)(q34;q11.2), hyperdiploidy, KMT2A translocation, ETV6-RUNX1 fusion, intrachromosomal amplification of
SNP Array Improves ALL Prognostication

Table 1  Comparison of Cytogenetic, FISH, and SNP Array Results in 60 Consecutive Acute Lymphoblastic Leukemia/Lymphoma Cases

<table>
<thead>
<tr>
<th>Results</th>
<th>No. of samples (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Karyotype</td>
<td></td>
</tr>
<tr>
<td>Abnormal</td>
<td>47 (81)</td>
</tr>
<tr>
<td>t(9;22)</td>
<td>13</td>
</tr>
<tr>
<td>t(11q23)/KMT2A</td>
<td>4</td>
</tr>
<tr>
<td>Hyperdiploidy</td>
<td>8</td>
</tr>
<tr>
<td>Low hypodiploidy/near haploidy</td>
<td>2</td>
</tr>
<tr>
<td>t(8;22)</td>
<td>1</td>
</tr>
<tr>
<td>Normal</td>
<td>10 (17)</td>
</tr>
<tr>
<td>Inadequate</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Total samples</td>
<td>58 (100)</td>
</tr>
<tr>
<td>FISH</td>
<td></td>
</tr>
<tr>
<td>Abnormal</td>
<td>42 (78)</td>
</tr>
<tr>
<td>BCR-ABL1*</td>
<td>13</td>
</tr>
<tr>
<td>KMT2A rearrangement</td>
<td>4</td>
</tr>
<tr>
<td>iAMP21</td>
<td>2</td>
</tr>
<tr>
<td>ETV6-RUNX1</td>
<td>4</td>
</tr>
<tr>
<td>ABL1 amplification</td>
<td>1</td>
</tr>
<tr>
<td>Normal</td>
<td>12 (22)</td>
</tr>
<tr>
<td>Total samples</td>
<td>54 (100)</td>
</tr>
<tr>
<td>Abnormal karyotype and/or FISH</td>
<td>53 (90)</td>
</tr>
<tr>
<td>Recurring abnormality with prognostic implication</td>
<td>33 (56)</td>
</tr>
<tr>
<td>Abnormal array</td>
<td>60 (100)</td>
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<tr>
<td>IKZF1 deletion</td>
<td>18</td>
</tr>
<tr>
<td>Hyperdiploidy</td>
<td>8</td>
</tr>
<tr>
<td>Low hypodiploidy/near triploidy</td>
<td>4</td>
</tr>
<tr>
<td>iAMP21†</td>
<td>3</td>
</tr>
<tr>
<td>ETV6-NTRK3</td>
<td>1</td>
</tr>
<tr>
<td>CRLF2-P2RY8‡</td>
<td>1</td>
</tr>
<tr>
<td>NUP214-ABL1 amplification</td>
<td>1</td>
</tr>
<tr>
<td>SET-NUP214</td>
<td>1</td>
</tr>
<tr>
<td>Combined cytogenetics, FISH and SNP array results, recurring abnormality with clinical relevance</td>
<td>45 (75)</td>
</tr>
</tbody>
</table>

*One case with BCR-ABL1 fusion also had ETV6-RUNX1 fusion.
†Two of three cases with iAMP21 had IKZF1 deletion.
‡The case with CRLF2-P2RY8 fusion had IKZF1 deletion.
FISH, fluorescence in situ hybridization; SNP, single-nucleotide polymorphism.

chromosome 21 (iAMP21), near haploidy or low hypodiploidy, and t(8;22)(q24.1q11.2). An additional nine B-ALL and four T-ALL cases had chromosome abnormalities with unknown significance. A normal karyotype was observed in nine B-ALL and one T-ALL cases, among which six B-ALL and the T-ALL cases had normal FISH results. One B-ALL sample was inadequate for cytogenetic analysis, and ETV6-RUNX1 fusion was observed by FISH analysis. No cytogenetic results were obtained for two patients with T-ALL, and one of them was confirmed to have ABL1 amplification by FISH analysis after SNP array analysis.

Abnormal array results were observed in all 60 ALL cases. Clinically relevant aberrations with prognostic or therapeutic implication were found in 34 cases. They included submicroscopic deletions that involved the IKZF1 gene, hyperdiploidy, low hypodiploidy or duplication of low hypodiploidy, iAMP21, and the cryptic fusion genes CRLF2-P2RY8, ETV6-NTRK3, NUP214-ABL1, and SET-NUP214. Combining SNP array results with those from chromosome and FISH assays, the detection rate for clinically relevant results increased from 56% (33/59) to 75% (45/60).

Deletion of IKZF1 Gene in B-ALL

Submicroscopic deletion of the IKZF1 gene was detected in 18 B-ALL cases (30%) (Figure 1 and Supplemental Table S1). The deletion sizes varied from 0.03 to 6.2 Mb, and most had a proximal breakpoint within intron 3 (11/18, 61%). In addition, deletion of exons 1 to 8 or the entire gene was observed in three cases, and deletion of exons 2 to 6, 3 to 8, 1 to 6, 2 to 6/7, exon 1, and intron 3 was observed in one case each. Case 18 had two deletions for the IKZF1 gene: a proximal deletion of exon 1 and a distal deletion of exons 4 to 8. Case 11 had homozygous deletion of exons 2 to 6, cases 10 and 12 had deletions of different sizes on homologous chromosomes, and the remaining 15 cases had heterozygous deletions of IKZF1.

Among the cases with an IKZF1 deletion, five had a normal karyotype (cases 1 to 5), two had iAMP21 (cases 5 to 6), two had nonrecurring chromosomal abnormalities (cases 7 to 8), one had the t(4;11)(q21;q23) (KMT2A-AF4) (case 9), and nine had the t(9;22) (BCR-ABL1) (cases 10 to 18) (Supplemental Table S1). In the five cases with a normal karyotype, an IKZF1 deletion alone (case 4) or with other submicroscopic SNP array aberrations was observed in each case. Case 8 had a concomitant interstitial deletion of 316 kb at pseudoautosomal region 1, which results in juxtaposition of the gene CRLF2 to exon 1 of P2RY8, forming a fusion gene CRLF2-P2RY8. Patients with an IKZF1 deletion in the absence of BCR-ABL1 are often referred for whole exome sequencing to potentially identify targetable tyrosine kinase mutations or fusions. For example, case 7 had a novel fusion gene, JAK2-PPPI12A, which is consistent with the nonrecurring translocation t(9;12)(p24;q21) found by karyotype analysis of this patient.

Low Hypodiploidy with 31 to 39 Chromosomes or Near Triploidy

Low hypodiploidy with 31 to 39 chromosomes or near triploidy due to duplication of low hypodiploidy was detected in four B-ALL cases (6.7%) by SNP array (cases 26 to 29) (Supplemental Table S1). Cases 26 and 27 had a normal karyotype, whereas cases 28 and 29 had abnormal karyotypes. The SNP array revealed that case 26 had gain of chromosomes 1, 5, 6, 8 to 11, 14, 18 to 22, X, and Y and CN-LOH for chromosomes 3, 4, 7, 12, 13, and 15 to 17. The gains were confirmed by FISH analysis using the BCR-ABL1 and ETV6-RUNX1 probes. This genomic profile is consistent with duplication of a low-hypodiploid clone with 38
chromosomes. Case 27 had loss of chromosomes 2, 3, 7, 12 to 17, and 20, consistent with a low-hypodiploid clone with 36 chromosomes. The karyotype of case 28 was interpreted as near-haploid because of loss of the Y chromosome and gain of an additional X chromosome in a male patient. The karyotype was reinterpreted after SNP array results that the gain of the X chromosome was actually a derivative chromosome 14 that was caused by an unbalanced translocation between 3q24q29 and 14p. Therefore, case 28 was more consistent with low hypodiploidy with 34 chromosomes. Case 29 had concurrent low-hypodiploid and near-triploid clones by chromosome analysis. SNP array confirmed the relative losses and gains; however, it could not distinguish the low-hypodiploid clone from the near-triploid clone.

iAMP21

iAMP21 was detected in three B-ALL cases (5%) (cases 5, 6, and 30) (Figure 2 and Supplemental Table S1). Cases 6 and 30 had complex karyotypes, whereas case 5 had a normal karyotype. FISH analysis using the ETV6-RUNX1 probes confirmed amplification of RUNX1 in the interphase cells of all three cases; however, the iAMP21 was confirmed by metaphase FISH analysis only in the two cases with a complex karyotype. No abnormal metaphase cells were observed for case 5; however, the genomic profile of chromosome 21 has very characteristic intrachromosomal amplification involving RUNX1 and deletion of chromosome 21 terminal sequences, consistent with iAMP21, which was also confirmed by extramural expert consultation. Cases 5 and 6 also had concurrent deletion of IKZF1 gene.

Recurring Fusion Genes Detected by SNP Array Analysis

Recurring fusion genes were observed in two B-ALL (cases 8 and 24) and five T-ALL cases (cases 54 to 58) (Supplemental Table S1). Case 8 had multiple aberrations by SNP array, including the IKZF1 deletion and an interstitial deletion at pseudoautosomal region 1 which results in CRLF2-P2RY8 fusion as mentioned above. Case 24 had an additional signal for ETV6 gene on chromosome 15 by FISH analysis using the ETV6-RUNX1 probes at the time of diagnosis, and further analysis using the ETV6 break-apart probes revealed that only 3'ETV6 sequences were translocated to chromosome 15 (Figure 3A). SNP array analysis of a sample obtained at relapse revealed multiple aberrations, including a terminal gain of 12 Mb at 12p with the proximal breakpoint within intron 5 of the ETV6 gene and a terminal loss of 10 Mb on chromosome 15 with the proximal breakpoint within the NTRK3 gene. These results indicate a cryptic unbalanced translocation der(15)(12;15), which creates an ETV6-NTRK3 fusion.

Recurring fusion genes were observed in five of the seven T-ALL cases by SNP array. Case 54 had a 317-kb amplification at 9q34 with breakpoints within the NUP214 and ABL1 genes (Figure 3B). Amplification was confirmed by interphase FISH analysis using the BCR-ABL1 probes; five to nine copies of...
ABL1 per cell were observed. The amplification with these characteristic breakpoints is consistent with an NUP214-ABL1 fusion due to circularization and episomal amplification. Case 55 had a deletion of the long arm of chromosome 7 by chromosome analysis; the SNP array detected multiple losses, including the 7q deletion and also an interstitial deletion of 2.57 Mb at 9q34. The deletion of 9q34 juxtaposes 50 SET to 30 NUP214 and forms a fusion gene, SET-NUP214. Case 56 had a complex karyotype with a t(10;11)(p12;q14), consistent with an MLLT10-PICALM fusion, and a subclone with duplication of the t(10;11). The SNP array identified many aberrations, including a gain of 10p12.31q26.3 with a breakpoint within MLLT10 and a gain of 11q14.2q25 with a breakpoint slightly distal to the PICALM gene, suggesting that only the der(10)t(10;11) was duplicated in the subclone. Case 57 had a deletion of 6q as a sole cytogenetic abnormality, and case 58 had a normal karyotype; SNP array detected an interstitial deletion of 63 kb at 1p33 in both cases. The deletion resulted in a loss of exons 7 to 17 of the gene STIL and sequences between STIL and TAL1, placing TAL1 next to 50 sequences of STIL and forming a STIL-TAL1 fusion. These two cases also shared in common CN-LOH of 9p, homozygous loss of CDKN2A, and CN-LOH of 10q by SNP array.

Hyperdiploidy with >50 Chromosomes

Eight pediatric patients (13%) had hyperdiploidy with favorable gains by chromosome and FISH analyses (cases 32 to 39) (Supplemental Table S1). The SNP array results revealed gains consistent with the karyotype in case 38 and
additional abnormalities in the remaining seven cases. These additional abnormalities include deletion of 9p involving CDKN2A (cases 32 and 37), deletion of 12p with partial deletion of ETV6 (case 36), multiple losses in case 39, and CN-LOH of chromosomes 16 (case 33), 19 and 20 (case 34), 5 and 18 (case 35), 2, 13, 16, 20, and 22 (case 37).

Chromosome or FISH Abnormalities Not Detected by SNP Array Analysis

Fifteen cases had apparently balanced translocations by karyotype and/or FISH that were present in >20% of the metaphase or interphase cells. These translocations included KMT2A translocations (N = 4), t(9;22) (N = 8), and one case each for t(2;21)(p21;q22) [together with the t(9;22)], t(8;22), t(9;12), and t(14;15)(q11.2;q15). Submicroscopic deletions at the translocation breakpoints were only detected in the cases with t(8;22) and t(14;15), whereas the remaining 13 cases had no aberrations found at the translocation breakpoints. Four B-ALL with t(9;22) also had an additional Philadelphia chromosome in 15% to 95% of the metaphase cells by karyotype; however, the additional Philadelphia chromosome was only confirmed by BCR-ABL1 FISH analysis and SNP array in two cases. Interestingly, these two

Figure 3  Single-nucleotide polymorphism (SNP) array and fluorescence in situ hybridization (FISH) confirmation in acute lymphoblastic leukemia/lymphoma with fusion genes NTRK3-ETV6 (case 24) and ABL1-NUP214 (case 54). A: Patient with B-cell ALL with NTRK3-ETV6 (case 24). SNP array reveals a terminal gain at 12p with a breakpoint within intron 5 of ETV6 and a terminal loss of 15q with a breakpoint within NTRK3. Metaphase FISH using ETV6 (green)–RUNX1 (red) probes with reverse DAPI banding reveals additional ETV6 signal on chromosome 15 (blue arrow). ETV6 break-apart probes (5' green, 3' red) with DAPI banding reveals that 3'ETV6 was translocated to chromosome 15 (white arrow). B: Patient with T-cell ALL with ABL1-NUP214 amplification (case 54). SNP array detects an interstitial amplification at 9q34 with proximal breakpoint within ABL1 and distal breakpoint within NUP214. Interphase FISH analysis using the BCR (green)–ABL1 (red) probes confirmed five to nine copies of ABL1 in each cell. Original magnification, ×1000 (A and B).
cases (cases 12 and 16) had dual fusion signals in all the abnormal interphase cells, consistent with a balanced t(9;22) and no extra Philadelphia chromosome and no copy number change at 9q34 or 22q11.2 by SNP array analysis. These results suggested that the additional small chromosomes were most likely other abnormalities that appeared to look like a Philadelphia chromosome.

Discussion

Although many studies have been published using SNP arrays in ALL risk classification, this is the first study, to our knowledge, that integrates cytogenetic, FISH, and SNP array results in the clinical management of patients with B-ALL and T-ALL. According to literature review, approximately 30% of pediatric and 50% of adult patients lack abnormalities with clinical relevance for prognosis by traditional cytogenetic analysis. In this study, we found 56% of patients with ALL with clinically relevant abnormalities by chromosome and/or FISH analyses. By incorporating whole-genome SNP array analysis, the detection rate for clinically relevant abnormalities increased to 75%. This result agrees with the rate published in a previous review in which approximately 75% of childhood ALL cases harbor a recurring chromosomal alteration detectable by karyotyping, FISH, or molecular techniques.

The IKZF1 gene on chromosome 7p12.2 encodes the zinc finger protein IKAROS that promotes differentiation, inhibits proliferation, and controls migration-related properties of hematopoietic cells. IKZF1 deletions are most common in BCR-ABL1—positive cases and have been seen in >60% of them; these have also been found in B-ALL with other primary cytogenetic abnormalities. In our study, 9 of 13 BCR-ABL1-positive cases (69.2%) had an IKZF1 deletion. In addition, IKZF1 deletion was identified in the BCR-ABL1 negative cases with iAMP21, KMT2A translocation, or a normal karyotype. In contrast, none of the cases with ETV6-RUNX1 or hyperdiploidy, which are associated with a favorable prognosis, had an IKZF1 deletion.

Deletion of IKZF1 is associated with poor response to induction therapy and poor overall prognosis in B-ALL. IKZF1 has heterogeneity in the size of deletion with loss of exons 4 to 7 as the most common focal mutation. Recent studies also found that rare deletions have similarly poor or worse effect on clinical outcome as the deletion of exons 4 to 7 or the entire gene. In this study, deletions of exons 4 to 6 or 7 were detected by SNP array in 17 of 18 cases; deletions of entire gene, exons 2 to 6, 3 to 8, 1 to 6, 2 to 6/7, exon 1, and intron 3 were also observed. Patients with IKZF1 deletion often have concurrent mutations in the RAS and JAK/STAT5 pathways. Mutations in ABL1, EPO, JAK2, PDGFRB, EBF1, FLT2, IL7R, and SH2B3 have been reported. Fusion genes with kinase activity have also been seen in these patients, such as CSF2RA-CRLF2, OFD1-JAK2, and ETV6-NTRK3.

Fusions are identified, these patients are potential candidates for targeted therapies, which may significantly improve outcomes for such higher-risk patients.

It is not uncommon to have inadequate or normal cytogenetic results in ALL, which limits the value of karyotypic analysis in prognostication of ALL. In this study, SNP arrays identified chromosome aberrations in 10 cases with a normal karyotype and two cases with no karyotypic results. They included the cytogenetic entities low hypodiploidy and iAMP21. Low hypodiploidy has a nonrandom pattern of lost and retained chromosomes, with chromosomes 3 and 7 most commonly lost and chromosome 21 most often retained. Low hypodiploidy or near triploidy is often associated with T(5)31 mutation and very poor survival. For iAMP21, the standard method of detection is FISH by using probes directed to RUNXI to determine the copy number of the most highly amplified region in metaphase cells. Three or more extra copies of RUNXI on a single abnormal chromosome 21 (a total of five or more RUNXI signals per interphase cell) define iAMP21. SNP array reveals a unique pattern of amplification and deletion within chromosome 21. Patients with iAMP21 have a poor outcome and high relapse rate when treated with standard therapy; however, if treated in the intensive treatment arm, there is no significant difference in the outcome between these with or without iAMP21. Therefore, accurate identification of iAMP21 is critical for the proper risk stratification and treatment. In the absence of cytogenetics and/or metaphase FISH results with a probe for RUNXI, array analysis should be considered.

CN-LOH and submicroscopic copy number changes were found to be common in the hyperdiploid cases by SNP array in this study. Approximately 15% to 20% of children with hyperdiploid ALL relapse; however, the molecular mechanisms that contribute to relapse are largely unknown. Gene mutations within the RAS pathway and epigenetic regulators were prominent in samples obtained from patients with recurring disease. Because CN-LOH is often associated with homozygous mutations of oncogenes or tumor suppressor genes, useful correlations might be found between particular chromosomes with CN-LOH and recurrent disease. Long-term follow-up and additional studies could help elucidate the relevance of these additional abnormalities to the patients’ clinical outcomes.

In this study, the array results reveal the presence of fusion genes not routinely tested in ALL but with clinical implication for prognosis or therapy, such as NUP214-ABL1, ETV6-NTRK3, SET-NUP214, and CRLF2-P2RY8. The presence of these recurring fusion genes with tyrosine kinase activity can guide therapy of ALL. For example, NUP214-ABL1 and ETV6-NTRK3 fusion genes are sensitive to tyrosine kinase inhibitor therapy. Similarly, the presence of SET-NUP214 fusion is associated with resistance to corticosteroid/chemotherapy in T-ALL, and these patients often have a poor prognosis.

Current National Comprehensive Cancer Network guidelines (2015) emphasize the importance of clinical testing for
IKZF1 deletion in patients with ALL for prognostication and treatment. Although multiplex ligation-dependent probe amplification is used in European laboratories for specific detection of IKZF1 deletion, the test is gene specific and will not detect submicroscopic abnormalities of other genomic regions. High-resolution SNP array can detect IKZF1 deletions and other cryptic copy number aberrations as well as CN-LOH that are not detectable by chromosome analysis. Therefore, the SNP array is optimal as a complementary assay to the existing chromosome and FISH assays. In summary, our study reveals that SNP array significantly augments risk stratification and guides treatment for patients with ALL by detecting additional abnormalities of clinical relevance. We recommend that SNP array be routinely applied at diagnosis of ALL.

Supplemental Data

Supplemental material for this article can be found at http://dx.doi.org/10.1016/j.jmoldx.2016.03.004.

References


