Novel gene targets detected by genomic profiling in a consecutive series of 126 adults with acute lymphoblastic leukemia

Setareh Safavi,[1] Markus Hansson,[2] Karin Karlsson,[2] Andrea Biloglav,[1] Bertil Johansson,[1,3] and Kajsa Paulsson[1]

[1]Division of Clinical Genetics, Department of Laboratory Medicine, Lund University; [2]Division of Hematology, Skåne University Hospital, Lund University; and [3]Department of Clinical Genetics, University and Regional Laboratories, Region Skåne, Lund, Sweden

ABSTRACT

In contrast to acute lymphoblastic leukemia in children, adult cases of this disease are associated with a very poor prognosis. In order to ascertain whether the frequencies and patterns of submicroscopic changes, identifiable with single nucleotide polymorphism array analysis, differ between childhood and adult acute lymphoblastic leukemia, we performed single nucleotide polymorphism array analyses of 126 adult cases, the largest series to date, including 18 paired diagnostic and relapse samples. Apart from identifying characteristic microdeletions of the *CDKN2A*, *EBF1*, *ETV6*, *IKZF1*, *PAX5* and *RB1* genes, the present study uncovered novel, focal deletions of the *BCAT1*, *BTLA*, *NR3C1*, *PIK3AP1* and *SERP2* genes in 2-6% of the adult cases. *IKZF1* deletions were associated with B-cell precursor acute lymphoblastic leukemia (P=0.036), *BCR-ABL1*-positive acute lymphoblastic leukemia (P<0.001), and higher white blood cell counts (P=0.005). In addition, recurrent deletions of *RASSF3* and *TOX* were seen in relapse samples. Comparing paired diagnostic/relapse samples revealed identical changes at diagnosis and relapse in 27%, clonal evolution in 22%, and relapses evolving from ancestral clones in 50%, akin to what has previously been reported in pediatric acute lymphoblastic leukemia and indicating that the mechanisms of relapse may be similar in adult and childhood cases. These findings provide novel insights into the leukemogenesis of adult acute lymphoblastic leukemia, showing similarities to childhood disease in the pattern of deletions and the clonal relationship between diagnostic and relapse samples, but with the adult cases harboring additional aberrations that have not been described in pediatric acute lymphoblastic leukemia.

Introduction

In the last decades, the cure rates for childhood acute lymphoblastic leukemia (ALL) have increased dramatically and are now approaching 90%.[1] Adults with ALL, on the other hand, still have a very poor prognosis; the long-term survival rate for adult cases is a mere 30-40% and decreases with age.[2,3] Studies have shown that younger adults treated on pediatric protocols have an increased overall survival compared with those on adult protocols.[4,5] However, it should be emphasized that adult ALL differs significantly from pediatric ALL as regards complete remission rates, minimal residual disease response level and risk group assignments, even when treated on pediatric protocols.[4,6] The reasons for this are manifold, and include a larger proportion of T-cell ALL in adults and age-related genetic differences in B-cell precursor (BCP) ALL. For example, high hyperdiploidy (51-67 chromosomes) and t(12;21)(p13;q22)/*ETV6-RUNX1*, both of which are associated with a favorable outcome, are much more common in pediatric ALL, whereas t(4;11)(q21;q23)/*MLL-AFF1*, t(9;22)(q34;q11)/*BCR-ABL1* and low hypodiploidy (30-39 chromosomes), conferring a negative prognosis, are more frequently seen in adult ALL.[4,7,8] Whether the pattern of microdeletions, as ascertained by single nucleotide polymorphism (SNP) array analysis, also differs between childhood and adult BCP ALL is less well clarified because most analyses of ALL have been performed on pediatric cases.[9,10] In fact, SNP array findings in adult ALL have so far been reported in only three larger series,[11-13] one of which focused solely on *IKZF1* deletions.[13] The two other studies[11,12] identified similar gene deletions to those found in pediatric cases, namely losses of *CDKN2A*, *PAX5*, *IKZF1*, *ETV6*, *RB1*, *EBF1* and *LEF1*. However, these results were based on quite small cohorts of patients, comprising 45 and 75 adult ALL patients, respectively. In the present study, we performed SNP array analysis on a consecutive series of 126 adults with ALL at diagnosis, the largest series to date, and identified several novel gene targets that may be explored as therapeutic targets.

Methods

Patients

The study comprised a consecutive series of 205 cases of adult ALL (≥18 years) that were cytogenetically analyzed between 1985 and 2012 at the Department of Clinical Genetics, University and Regional Laboratories, Region Skåne, Lund, Sweden, as part of clinical routine. SNP array analysis results from these cases have not been previously published. The basic clinical, immunophenotypic and genetic features are given in *Online Supplementary Table S1*. The median age was 48 years (range, 18-85 years) and the male/female ratio was 1.12. The immunophenotypic features could be ascertained in 153 (75%) cases,

 doi:10.3324/haematol.2014.112912
Manuscript received on July 1, 2014. Manuscript accepted September 24, 2014.
The online version of this article has a Supplementary Appendix.
Correspondence: setareh.safavi@med.lu.se or kajsa.paulsson@med.lu.se

of which 125 (82%) had BCP ALL and 28 (18%) had T-ALL. Genetically, 51/205 cases (25%) were positive for t(9;22)(q34;q11)/*BCR-ABL*, 19 (9%) for 11q23/*MLL* rearrangements and four (2%) for t(1;19)(q23;p13)/*TCF3-PBX1*. In addition, high hyperdiploidy was present in 13 cases (6.3%) and low hypodiploidy in two cases (1.0%) based on G-banding. The investigation was approved by the Research Ethics Committee of Lund University, and informed consent was provided according to the Declaration of Helsinki.

Single nucleotide polymorphism array analysis

Samples from the time of diagnosis were available from 156 cases (76%) (*Online Supplementary Table S1*). In addition, relapse samples could be investigated in 25 patients, of whom seven did not have a corresponding diagnostic sample. Remission samples were available as comparison for 47 cases. DNA was extracted using standard methods from bone marrow or peripheral blood cells that had been stored at -80°C or in fixative at -20°C. SNP array analysis was performed using the Illumina HumanOmniExpress BeadChip platform, containing >715,000 markers, the Illumina HumanOmni1-Quad BeadChip platform, containing ~1.1 million markers, or the Illumina HumanOmni5-Quad BeadChip platform, containing ~5 million markers (Illumina, San Diego, CA, USA) (*Online Supplementary Table S1*). The analyses were done according to the manufacturer's instructions and the data were analyzed using Genome studio v2011.1 software, extracting probe positions from the GRCh37 genome build. Aberrations were identified by visual inspection of $\log_2$ ratios and B allele frequencies. Copy number changes had to involve at least seven informative markers, giving an approximate resolution of >20 kb for the HumanOmniExpress BeadChip platform, >10 kb for the HumanOmni1-Quad BeadChip platform and >5 kb for the HumanOmni5-Quad BeadChip platform depending on the marker density in the region. Uniparental isodisomies (UPID) were included if they comprised at least 4 Mb. To exclude constitutional copy number variants, remission samples were investigated in the 47 cases in which such material was available. For the remaining cases, all copy number changes <1 Mb were compared with copy number polymorphisms listed in the Database of Genomic Variants (*http://projects.tcag.ca/variation/*) and excluded from further analysis if there was substantial overlap. In addition, deletions most likely corresponding to somatic rearrangements of the T-cell receptor and immunoglobulin loci were excluded from the results.

Statistical analyses

The PASW Statistics 22 software for Windows (SPSS Inc., Chicago, IL, USA) was used for all analyses. The significance limit for two-sided *P* values was set at <0.05. The immunophenotypic features, sex, age and white blood cell (WBC) counts were compared between cases with and without deletions of *CDKN2A*, *PAX5*, *IKZF1*, *ETV6*, *RB1*, *EBF1*, *BCAT1*, *SERP2*, *NR3C1*, *PIK3AP1* and *BTLA* at the time of diagnosis using the Wilcoxon signed-rank and two-tailed Fisher exact probability tests. Whether *IKZF1* deletions were more common in *BCR/ABL1*-positive cases was investigated using a two-tailed Fisher exact probability test.

Results

Large copy number changes and uniparental isodisomies

The SNP array analysis was successful in 126 diagnostic cases (64%); the remaining cases could not be investigated because of failed SNP arrays (12%) or lack of material (24%).

A total of 238 regions of gains were identified; all of which were larger than 5 Mb. Whole chromosome gains were detected in 37 cases with chromosomes X/Y (57%), 21 (27%), 6 (24%), and 4 (19%) being the most commonly gained chromosomes (Figure 1). The SNP array analysis detected three additional high hyperdiploid cases, making a total of nine (7.1%) high hyperdiploid cases that did not have concurrent *BCR/ABL1* fusion or *MLL* rearrangement among the 126 cases that were investigated with SNP array analysis (*Online Supplementary Table S1*). In those, +X, +4, +10, +17, +18 and +21 were seen in at least 50% of cases. Furthermore, the SNP array analysis identified 1q gains in eight cases (6.3%), 17q gains in four cases (3.2%), 6q deletions in two cases (1.6%) and isochromosome 7q in two cases (1.6%). The SNP array analysis detected five additional low hypodiploid cases, making a total of six cases (4.8%) among the 126 cases (*Online Supplementary Table S1*). Among those, chromosomes X, 1, 6, 10, 19 and 21 were always retained in a heterodisomic state and chromosomes 3, 4, 7, 9, 13, 17 and 20 were lost in all cases. Excluding the chromosomal loss seen in low hypodiploid cases, whole chromosomal loss was detected in eight cases (6.3%) involving chromosomes 3, 4, 7, 9, 16 and X/Y. In addition, 381 hemizygous deletions and 73 homozygous microdeletions were identified (Figure 1). UPID were detected in 39 regions; the acquired UPID comprised whole chromosome UPID (13%) and partial UPID (87%) (Figure 1). UPID9p was always associated with deletion of *CDKN2A* (Figure 2). One case harbored a region with uniparental trisomy, involving chromosome 9 (133,702,121 Mb-qter). Subclonal genetic changes were identified in 63 regions, with extra copies of chromosomes 8, 9, 10 and 12 being most frequent (Figure 1).

Deletions of characteristic genes

Several recurrent deletions of known leukemia-associated genes were identified by the SNP array analysis. *CDKN2A* was deleted in 39 cases (31%), with 26 cases (67%) harboring homozygous deletions, five cases (13%) harboring focal hemizygous deletions and eight cases (20%) harboring larger hemizygous deletions on 9p including *CDKN2A*. The cases with homozygous *CDKN2A* deletions were either flanked by larger hemizygously deleted regions (77%) or were in regions of UPID (23%). Other well-known genes targeted by recurrent focal or non-focal hemizygous and homozygous deletions included *IKZF1* in 32 cases (25%), *PAX5* in 18 cases (14%), *ETV6* in 12 cases (10%), *BTG1* in 11 cases (9%), *RB1* in nine cases (7%), *EBF1* in seven cases (6%), *LEF1* in three cases (2%) and *NF1* in three cases (2%) (*Online Supplementary Table S2*).

Recurrent novel gene targets in adult acute lymphoblastic leukemia detected by single nucleotide polymorphism array analysis

A total of five deleted regions that have not been reported to be recurrently targeted in adult ALL before were detected, as identified by focal deletion in at least one case. These comprised *BCAT1* in seven cases (6%), *SERP2* in six cases (5%), *BTLA/CD200* in four cases (3%), *NR3C1* in four cases (3%) and *PIK3AP1* in two cases (2%). All deletions encompassing these genes are shown in *Online*

Figure 1. Overview of all genetic aberrations found with SNP array analysis of 126 cases of adult ALL (excluding whole chromosome changes in low hypodiploid cases, n=8). Minimally involved regions are shown to the right of each chromosome. For each type of aberration, each line represents a different case. (A) Green lines represent cases with hemizygous deletions and red lines represent cases with homozygous deletions. (B) Orange lines represent cases with gains. (C) Uniparental isodisomies are shown by purple lines, with one case (blue) displaying a region with uniparental trisomy. (D) Blue lines represent cases with subclonal gains and dark blue represents cases with subclonal loss. This figure was made using the GREVE, Genome-Wide Viewer software,[39] freely available at *http://www.well.ox.ac.uk/~jcazier/GWA_View.html*.

Supplementary Table S3. In cases in which only the relapse sample was available for analysis, two additional genes were found recurrently deleted in two cases each; *TOX* and *RASSF3* (*Online Supplementary Tables S2* and *S3*).

Patterns of genetic evolution in paired diagnostic/relapse samples

A total of 18 paired diagnostic and relapse samples could successfully be compared (Table 1). These displayed iden-

Table 1. Genomic aberrations that differed between the 18 paired diagnostic and relapse samples.

Case N.	Genomic imbalances/gene targets seen only at diagnosis or relapse Position (bp)	Genetic relationship
7D	+X	
7R	dup(chr1:36,637,708-226,363,155)[subclonal only], del(chr1:227,356,925-qter), dup(chr 2:59,991,047-60,597,565) [subclonal only], dup(chr 8:pter - 22,604,740), dup(chrX:pter-cen)	Ancestral clone
10D	+1, +2, +10, +11,+12, +18, +21	
10R	UPID2, UPID10, dup(chr11:cen-qter), del(chr12:76,900,956-91,479,154)[subclonal only], UPID18, del(chr22:33,176,834-qter), dup(chrX:5,172,908-26,061,628)	Ancestral clone
11D	UPID(chr1:cen-qter)	
11R	dup(chr1:cen-qter)	Ancestral clone
17D	None	
17R	None	Identical clones
25D	None	
25R	del(chr5:150,080,623-157,655,044)	Clonal evolution
27D	None	
27R	del(chr2:238,964,462-qter), del(chr3:41,591,887-54,701,001), del(chr6:16,448,637-16,661,599)	Clonal evolution
34D	+21	
34R	del(chr6:69,741,916-73,536,171), del(chr9:pter-10,367,523), del(chr9:15,007,699-19,511,096), del(chr9:20,754,419-24,619,194), del(chr9:30,130,213-30,647,534), del(chr9:35,968,663-39,158,211), del(chr12:18,507,318-20,274,936), del(chr12:25,205,241-28,763,628), del(chr12:29,404,236-30,377,630), del(chr12:42,189,272-43,014,321), del(chr12:44,032,653-48,755,642), del(chr12: 67,845,462-70,216,959), del(chr12: 74,854,750-75,377,172), del(chr12:79,311,449-84,322,342), +14	Ancestral clone
35D	None	
35R	None	Identical clones
37D	None	
37R	None	Identical clones
41D	None	
41R	None	Identical clones
42D	None	
42R	None	Identical clones
53D	del(chr7:pter-qter), del(chr11:111,221,554-117,762,288), del(chr20:41,989,275-55,920,141), dup(chr21:38,674,544-41,020,324)	
53R	dup(chr7:72,861,849-98,902,213), del(chr7:98,902,213-qter), +8	Ancestral clone
58D	pUPID(chr9:pter-36,805,874), del(chr9:21,093,083-23,518,799),+12	
58R	dup(chr9:pter-21,067,592), dup(chr9:23,488,018-cen)	Ancestral clone
70D	+6	
70R	dup(chr6:75,383,825-qter), dup(chr13: 63,095,674-qter), del(chr17:28,058,946-35,605,294)	Ancestral clone
78D	None	
78R	del(chr2:21,449,098-23,988,899)[subclonal only], del(chr2:73,547,613-75,808,132) [subclonal only], del(chr2:127,560,722-132,061,877)[subclonal only],+9,del(chr15:75,251,302-qter)[subclonal only]	Clonal evolution
85D	del(chr2:112,927,348-113,228,788), del(chr2:232,461,078-237,751,372), del(chr2:238,510,514-242,999,159), del(chr6:40,609,391-41,321,232),+9, del(chr12:5,293,941-24,932,017), del(chr12:102,267,479-106,156,001), del(chr13:49,858,213-52,382,868), del(chr19:3,174,338-3,582,479)	
85R	dup(chr5: pter-98,936,840-98) [subclonal only], del(chr8:pter-cen), dup(chr8:cen-qter)	Ancestral clone
88D	dup(chr5:pter-cen)[subclonal only], del(chr5:52,348,256-58,560,717) [subclonal only], del(chr5: 66,447,913-qter)[subclonal only], del(chr9:94,631,730-128,625,923)[subclonal only], +21 [subclonal only]	
88R	+X [subclonal only]	Ancestral clone
101D	None	
101R	pUPID(chr3:pter-61,712,041), del(chr10:62,960,805-64,745,589), del(chr18:62,339,224-62,871,749)	Clonal evolution

bp: base pairs; cen: centromere; chr, chromosome; D: diagnostic sample; del: deletion; dup: duplication; pter: p-terminal; qter: q-terminal; R: relapse sample; UPID: uniparental isodisomy.

tical genetic changes at diagnosis and relapse in five cases (27%), clonal evolution with additional imbalances seen at relapse in four cases (22%), or lastly, evidence of evolution from ancestral clones in nine cases (50%), with some aberrations present at diagnosis lacking at relapse; the relapse clones sometimes also harbored other abnormalities.

Clinical correlations

There were no statistically significant differences in immunophenotypic features, gender, age or WBC count between cases in which SNP array analysis could be performed and cases in which samples were missing or the SNP array analysis failed (*data not shown*). Deletions of *RB1* were significantly associated with women (15% of women *versus* 0% of men; P=0.001). *IKZF1* deletions were significantly correlated with BCP ALL (32% of BCP ALL *versus* 6% of T-ALL; P=0.036) and with higher WBC counts (median 65x10^9/L; range, 4.1-729x10^9/L *versus* median 9.8x10^9/L; range, 0.7-904x10^9/L; P=0.005). There were no statistically significant immunophenotypic-, gender-, age-, or WBC count-related differences for the remaining genes. *IKZF1* deletions were significantly more common in *BCR/ABL1*-positive cases (51% *versus* 15%; P<0.001).

Discussion

We present here the largest SNP array analysis to date on adult ALL, comprising a consecutive series of 126 cases. The immunophenotypic features, median age and WBC counts agree well with those in previous studies of adult ALL.[8,14] Thus, we believe that the present cohort of patients is representative of adult ALL in general. The SNP array analysis revealed more deletions than gains, agreeing well with previous reports that losses are more common than gains in both childhood and adult ALL.[9,12,13,15]

The SNP array analysis identified three additional high hyperdiploid and five additional low hypodiploid cases, showing that this method is frequently more sensitive for detection of aneuploidy than conventional cytogenetic analysis. In line with high hyperdiploid childhood ALL and a recent cytogenetic study on high hyperdiploid adult cases,[16,17] the cases in this study showed frequent gains of chromosomes X, 4, 10, 17, 18 and 21, although the pattern of chromosomal gains was less specific than in pediatric ALL. All low hypodiploid cases had retained heterodisomy for chromosomes X and 21 and lost chromosomes 7 and 17, in line with previous reports.[18-20] Furthermore, the study included one 41-year old patient (#114) with Down syndrome, being the second oldest such individual with ALL published to date.[21] The only acquired aberration detected in this case was a trisomy X, a common finding in Down syndrome-associated ALL.[22]

The most common aberration detected by the SNP array analysis was deletion of *CDKN2A* in 30% of patients, in line with ALL in general.[9,12,13,15] Characteristic gene deletions in pediatric ALL, including *IKZF1* (25%), *PAX5* (14%), *ETV6* (10%), *BTG1* (9%), *RB1* (7%), *EBF1* (6%), *LEF1* (2%) and *NF1* (2%), were also found in our adult cases, confirming the results from previous studies of adult cases.[12,13,23] *IKZF1* deletions were more common in BCP ALL (P=0.036) and in *BCR/ABL1*-positive cases (P<0.001), as has been previously reported in both childhood and adult ALL.[11,13,24] In pediatric ALL and *BCR/ABL1*-positive adult *ALL*, *IKZF1* deletions have been shown to be associated with a poor prognosis.[10,25-27] The heterogeneous treatment regimes used in our cohort prevented survival analyses, but patients with *IKZF1* deletions had higher WBC counts, indirectly suggesting a more aggressive disease. We also detected a higher incidence of *RB1* deletions in women (P=0.001); in fact, all cases with such deletions were women. This is in contrast to the findings of previous studies of adult and childhood ALL,[11,13,24] in which no gender-related differences in the frequency of *RB1* deletions were detected.

The SNP array analysis also identified gene deletions that have previously been reported in childhood ALL but not in adult ALL, namely deletions involving *SERP2*, *BTLA/CD200*, *NR3C1*, and *TOX* (*Online Supplementary Table S3*). *SERP2* (13q14.11) and *BTLA/CD200* (3q13.2), deleted in 5% and 3%, respectively, of our cases, have recently been reported to be deleted in pediatric ALL cases with Down syndrome;[22] in addition, *BTLA/CD200* has also been found deleted in *ETV6/RUNX1*-positive ALL.[28] Whereas virtually nothing is known about the function of *SERP2*, *BTLA* encodes a glycoprotein and functions as an inhibitory receptor expressed by T cells[29] and *CD200* encodes a membrane protein that regulates myeloid cell activity.[30] Deletions of *NR3C1* (5q31.3), coding for a glucocorticoid receptor, have previously been associated with relapsing childhood ALL.[10,31] NR3C1 plays an important role in glucocorticoid-induced response and *NR3C1* deletions in pediatric relapsing ALL may influence treatment response.[10] Notably, we also found a single case harboring deletion of the homologous *NR3C2* gene in 4q31.1, coding

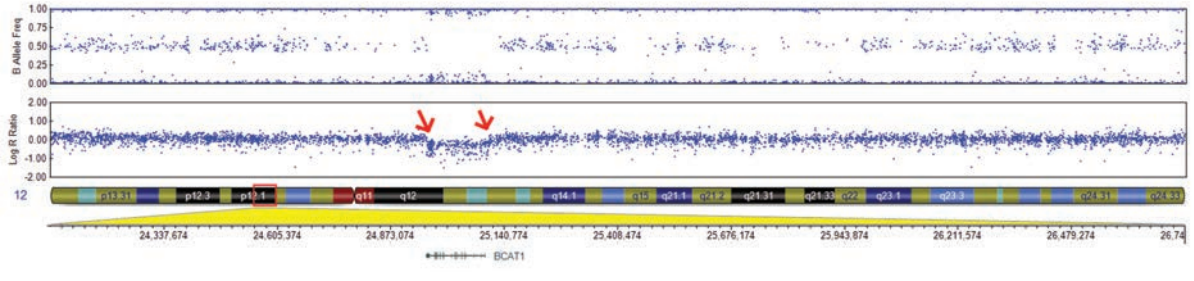

Figure 2. SNP array analysis results showing a hemizygous *BCAT1* deletion (red arrows). The top panel shows B allele frequencies (BAF), which are calculated as (signal intensity for allele B)/(signal intensities for allele A + allele B). The lower panel shows $\log_2$ ratios along the chromosomes; each dot represents the $\log_2$ ratio of one marker. The deletion is visible as a complete loss of heterozygosity in the BAF and a negative log ratio.

for a mineralocorticoid receptor. Finally, *TOX* was recurrently deleted in the relapse samples included in our study. Previous pediatric ALL studies also identified copy number alterations of *TOX* (8q12.1) at relapse, suggesting that it may be associated with relapsing ALL.[31] *TOX* codes for a protein containing a HMG box DNA-binding domain, and is involved in T-cell maturation.[32]

The SNP array analyses revealed two new recurrent gene targets that have not been previously implicated in childhood or adult ALL in the diagnostic samples, namely *BCAT1* and *PIK3AP1* (*Online Supplementary Table S3*). *BCAT1* on 12p12.1 was deleted in 6% of cases. This gene codes for a protein that is involved in the catabolism of branched-chain amino acids.[33] Aberrations in this gene have not been previously reported in ALL, but up-regulation of *BCAT1* has been implicated in gliomas and nasopharyngeal carcinoma.[33,34] However, the deletions seen in our study would rather be expected to result in underexpression of *BCAT1*. *PIK3AP1* (10q24.1), found deleted in 2% of our cases, has previously been reported to be deleted in a single case of adult ALL.[12] This gene codes for an adaptor protein functioning in the activation of phosphoinositide 3-kinase (PI3K).[35] In addition, *RASSF3* (12q14.2) was recurrently deleted in the relapse samples (*Online Supplementary Table S3*). This gene belongs to the Ras-association domain family, and has been suggested to function as a tumor suppressor in non-small cell lung cancer.[36,37]

Different evolutionary genetic patterns could be ascertained from the analyses of paired diagnostic and relapse samples, showing identical genetic changes in 27%, clonal evolution in 22%, and ancestral clones in 50%. This is the first investigation of the clonal relationship between diagnostic and relapse cases that has been reported in adult ALL using SNP array analysis. Our findings agree well with most, albeit not all, studies of childhood ALL and indicate that the mechanisms of relapse may be similar in adult and pediatric ALL.[31,38]

In conclusion, adult ALL shares common genetic imbalances with pediatric ALL; nevertheless, as only <40% of adult cases survive, cryptic genetic aberrations that differ between adult and pediatric ALL may be the key force promoting leukemogenesis. By using high-resolution SNP array analysis, we have uncovered several recurrent gene targets not previously reported in this disease, providing novel insights into the intricate puzzle of adult ALL.

Acknowledgments

This study was supported by grants from the Swedish Cancer Foundation and the Swedish Research Council.

Authorship and Disclosures

Information on authorship, contributions, and financial & other disclosures was provided by the authors and is available with the online version of this article at www.haematologica.org.

References

1. Pui CH, Relling MV, Downing JR. Acute lymphoblastic leukemia. N Engl J Med. 2004;350(15):1535-48.
2. Chessells JM, Hall E, Prentice HG, Durrant J, Bailey CC, Richards SM. The impact of age on outcome in lymphoblastic leukaemia; MRC UKALL X and XA compared: a report from the MRC Paediatric and Adult Working Parties. Leukemia. 1998;12(4):463-73.
3. Rowe JM. Prognostic factors in adult acute lymphoblastic leukaemia. Br J Haematol. 2010;150(4):389-405.
4. Toft N, Birgens H, Abrahamsson J, Bernell P, Griskevicius L, Hallbook H, et al. Risk group assignment differs for children and adults 1-45 yr with acute lymphoblastic leukemia treated by the NOPHO ALL-2008 protocol. Eur J Haematol. 2013;90(5):404-12.
5. Boissel N, Auclerc MF, Lheritier V, Perel Y, Thomas X, Leblanc T et al. Should adolescents with acute lymphoblastic leukemia be treated as old children or adolescents? Comparison of the French FRALLE-93 and LALA-94 trials. J Clin Oncol. 2003;(21):774-80.
6. Ramanujachar R, Richards S, Hann I, Webb D. Adolescents with acute lymphoblastic leukaemia: emerging from the shadow of paediatric and adult treatment protocols. Pediatr Blood Cancer. 2006;47(6):748-56.
7. Secker-Walker LM, Prentice HG, Durrant J, Richards S, Hall E, Harrison G. Cytogenetics adds independent prognostic information in adults with acute lymphoblastic leukaemia on MRC trial UKALL XA. MRC Adult Leukaemia Working Party. Br J Haematol. 1997;96(3):601-10.
8. Moorman AV, Chilton L, Wilkinson J, Ensor HM, Bown N, Proctor SJ. A population-based cytogenetic study of adults with acute lymphoblastic leukemia. Blood. 2010; 115(2):206-14.
9. Mullighan CG, Goorha S, Radtke I, Miller CB, Coustan-Smith E, Dalton JD, et al. Genome-wide analysis of genetic alterations in acute lymphoblastic leukaemia. Nature. 2007;446(7137):758-64.
10. Olsson L, Castor A, Behrendtz M, Biloglav A, Forestier E, Paulsson K, et al. Deletions of IKZF1 and SPRED1 are associated with poor prognosis in a population-based series of pediatric B-cell precursor acute lymphoblastic leukemia diagnosed between 1992 and 2011. Leukemia. 2014;28(2):302-10.
11. Paulsson K, Cazier JB, Macdougall F, Stevens J, Stasevich I, Vrcelj N, et al. Microdeletions are a general feature of adult and adolescent acute lymphoblastic leukemia: unexpected similarities with pediatric disease. Proc Natl Acad Sci USA. 2008;105(18):6708-13.
12. Okamoto R, Ogawa S, Nowak D, Kawamata N, Akagi T, Kato M, et al. Genomic profiling of adult acute lymphoblastic leukemia by single nucleotide polymorphism oligonucleotide microarray and comparison to pediatric acute lymphoblastic leukemia. Haematologica. 2010; 95(9):1481-8.
13. Iacobucci I, Iraci N, Messina M, Lonetti A, Chiaretti S, Valli E, et al. IKAROS deletions dictate a unique gene expression signature in patients with adult B-cell acute lymphoblastic leukemia. Plos One. 2012; 7(7):e40934.
14. Annino L, Vegna ML, Camera A, Specchia G, Visani G, Fioritoni G, et al. Treatment of adult acute lymphoblastic leukemia (ALL): long-term follow-up of the GIMEMA ALL 0288 randomized study. Blood. 2002;99(3):863-71.
15. Kuiper RP, Schoenmakers EFPM, van Reijmersdal SV, Hehir-Kwa JY, van Kessel AG, van Leeuwen FN, et al. High-resolution genomic profiling of childhood ALL reveals novel recurrent genetic lesions affecting pathways involved in lymphocyte differentiation and cell cycle progression. Leukemia. 2007; 21(6):1258-66.
16. Paulsson K, Johansson B. High hyperdiploid childhood acute lymphoblastic leukemia. Genes Chromosomes Cancer. 2009;48(8):637-60.
17. Chilton L, Buck G, Harrison CJ, Ketterling RP, Rowe JM, Tallman MS, et al. High hyperdiploidy among adolescents and adults with acute lymphoblastic leukaemia (ALL): cytogenetic features, clinical characteristics and outcome. Leukemia. 2014;28(7):1511-8.
18. Safavi S, Forestier E, Golovleva I, Barbany G, Nord KH, Moorman AV, et al. Loss of chromosomes is the primary event in near-haploid and low-hypodiploid acute lymphoblastic leukemia. Leukemia. 2013;27(1):248-50.
19. Harrison CJ, Moorman AV, Broadfield ZJ, Cheung KL, Harris RL, Reza Jalali G, et al. Three distinct subgroups of hypodiploidy in acute lymphoblastic leukaemia. Br J Haematol. 2004;125(5):552-9.
20. Charrin C, Thomas X, Ffrench M, Le QH, Andrieux J, Mozziconacci MJ et al. A report from the LALA-94 and LALA-SA groups on hypodiploidy with 30 to 39 chromosomes and near-triploidy: 2 possible expressions of a sole entity conferring poor prognosis in adult acute lymphoblastic leukemia (ALL). Blood. 2004; 104(8):2444-51.
21. Chapiro E, Radford-Weiss I; Cung HA, Dastuge N, Nadal N, Taviaux S et al. Chromosomal translocations involving the IGH@ locus in B-cell precursor acute lymphoblastic leukemia: 29 new cases and a review of the literature. Cancer Genetics. 2013;206(5):162-73.

22. Lundin C, Hjorth L, Behrendtz M, Nordgren A, Palmqvist L, Andersen MK, et al. High frequency of BTG1 deletions in acute lymphoblastic leukemia in children with Down syndrome. Genes Chromosomes Cancer. 2012;51(2):196-206.
23. Moorman AV, Schwab C, Ensor HM, Russell LJ, Morrison H, Jones L, et al. IGH@ translocations, CRLF2 deregulation, and microdeletions in adolescents and adults with acute lymphoblastic leukemia. J Clin Oncol. 2012; 30(25):3100-8.
24. Mullighan CG, Miller CB, Radtke I, Phillips LA, Dalton J, Ma J, et al. BCR-ABL1 lymphoblastic leukaemia is characterized by the deletion of Ikaros. Nature. 2008;453(7191): 110-4.
25. Martinelli G, Iacobucci I, Storlazzi CT, Vignetti M, Paoloni F, Cilloni D, et al. IKZF1 (Ikaros) deletions in BCR-ABL1-positive acute lymphoblastic leukemia are associated with short disease-free survival and high rate of cumulative incidence of relapse: a GIMEMA AL WP report. J Clin Oncol. 2009; 27(31):5202-7.
26. van der Veer A, Waanders E, Pieters R, Willemse ME, Van Reijmersdal SV, Russell LJ, et al. Independent prognostic value of BCR-ABL1-like signature and IKZF1 deletion, but not high CRLF2 expression, in children with B-cell precursor ALL. Blood. 2013; 122(15):2622-9.
27. Mullighan CG, Su X, Zhang J, Radtke I, Phillips LA, Miller CB, et al: Deletion of IKZF1 and prognosis in acute lymphoblastic leukemia. N Engl J Med. 2009;360(5):470-80.
28. Kuster L, Grausenburger R, Fuka G, Kaindl U, Krapf G, Inthal A, et al. ETV6/RUNX1-positive relapses evolve from an ancestral clone and frequently acquire deletions of genes implicated in glucocorticoid signaling. Blood. 2011;117(9):2658-67.
29. Watanabe N, Gavrieli M, Sedy JR, Yang JF, Fallarino F, Loftin SK, et al. BTLA is a lymphocyte inhibitory receptor with similarities to CTLA-4 and PD-1. Nat Immunol. 2003; 4(7):670-9.
30. Hatherley D, Lea SM, Johnson S, Barclay AN. Structures of CD200/CD200 receptor family and implications for topology, regulation and evolution. Structure. 2013;21(5): 820-32.
31. Mullighan CG, Phillips LA, Su X, Ma J, Miller CB, Shurtleff SA, et al. Genomic analysis of the clonal origins of relapsed acute lymphoblastic leukemia. Science. 2008;322(5906):1377-80.
32. Wilkinson B, Chen JY, Han P, Rufner KM, Goularte OD, Kaye J. TOX: an HMG box protein implicated in the regulation of thymocyte selection. Nat Immunol. 2002; 3(3):272-80.
33. Tonjes M, Barbus S, Park YJ, Wang W, Schlotter M, Lindroth AM, et al. BCAT1 promotes cell proliferation through amino acid catabolism in gliomas carrying wild-type IDH1. Nat Med. 2013;19(7):901-8.
34. Zhou W, Feng X, Ren C, Jiang X, Liu W, Huang W, et al. Over-expression of BCAT1, a c-Myc target gene, induces cell proliferation, migration and invasion in nasopharyngeal carcinoma. Mol Cancer. 2013;12:53.
35. Okada T, Maeda A, Iwamatsu A, Gotoh K, Kurosaki T. BCAP: The tyrosine kinase substrate that connects B cell receptor to phosphoinositide 3-kinase activation. Immunity. 2000;13(6):817-27.
36. Richter AM, Pfeifer GP, Dammann RH. The RASSF proteins in cancer; from epigenetic silencing to functional characterization. Biochim Biophys Acta. 2009;1796(2): 114-28.
37. Fukatsu A, Ishiguro F, Tanaka I, Kudo T, Nakagawa K, Shinjo K, et al. RASSF3 downregulation increases malignant phenotypes of non-small cell lung cancer. Lung Cancer. 2014;83(1):23-9.
38. Davidsson J, Paulsson K, Lindgren D, Lilljebjörn H, Chaplin T, Forestier E, et al. Relapsed childhood high hyperdiploid acute lymphoblastic leukemia: presence of preleukemic ancestral clones and the secondary nature of microdeletions and RTK-RAS mutations. Leukemia. 2010;24(5):924-31.
39. Cazier JB, Holmes CC, Broxholme J: GREVE. Genomic Recurrent Event ViEwer to assist the identification of patterns across individual cancer samples. Bioinformatics. 2012;28(22):2981-2.