B-precursor acute lymphoblastic leukemia (B-ALL) is the most common childhood tumor and the leading cause of cancer-related death in children and young adults. The majority of B-ALL cases are aneuploid or harbor recurring structural chromosomal rearrangements that are important initiating events in leukemogenesis but are insufficient to explain the biology and heterogeneity of disease. Recent studies have used microarrays and sequencing to comprehensively identify all somatic genetic alterations in acute lymphoblastic leukemia (ALL). These studies have identified cryptic or submicroscopic genetic alterations that define new ALL subtypes, cooperate with known chromosomal rearrangements, and influence prognosis. This article reviews these advances, discusses results from ongoing second-generation sequencing studies of ALL, and highlights challenges and opportunities for future genetic profiling approaches.

**ETV6-RUNX1 (TEL-AML1) B-ALL**

The most common rearrangement in B-ALL is the t(12;21) (p13;q22) rearrangement that encodes ETV6-RUNX1 (5). This rearrangement is usually cryptic on cytogenetic analysis but is readily detected by fluorescent in situ hybridization and molecular techniques. ETV6 is a member of the ETS family of transcription factors that are frequently targeted by rearrangements and mutations in leukemia and other malignancies (6). With CBFB, RUNX1 forms the core binding factor translocation complex and is commonly rearranged in acute myeloid leukemia (7), and harbors sequence mutations in myeloid and lymphoid disorders (8–10). Both ETV6 and RUNX1 are required for normal definitive hematopoiesis (7, 11), and the ETV6-RUNX1 protein may perturb expression of RUNX1-regulated genes, converting RUNX1 to a transcriptional repressor (12). ETV6-RUNX1 also causes overexpression of the erythropoietin receptor (EPOR) and activation of downstream JAK-STAT signaling (13). Expression of ETV6-RUNX1 promotes self-renewal in B cell progenitors but alone does not induce leukemia (14, 15). Furthermore, ETV6-RUNX1 is commonly detectable at birth (16), years prior to the onset of leukemia, suggesting that secondary genetic events are required to induce leukemia. This model is supported by genome-wide profiling studies of genetic alterations in ALL that have identified additional recurring submicroscopic genetic alterations in ETV6-RUNX1 ALL, including deletions of the B cell transcription factors PAX5 and EBF1 and deletion of the second copy of ETV6 (17–19). Moreover, monozygotic twins concordant for ETV6-RUNX1 ALL exhibit distinct submicroscopic DNA copy number alterations (CNAs), indicating that acquisition of the ETV6-RUNX1 is an early event in leukemogenesis (20). Submicroscopic genetic alterations are more common in ETV6-RUNX1 ALL than in many other ALL subtypes and include deletions targeting putative lymphoid signaling molecules (BTLA, TOX), transcriptional coactivators (TBLIX1), the glucocorticoid receptor gene NR3C1, and the putative apoptosis regulatory gene BTG1. Although these alterations may directly contribute to leukemogenesis, the genomic breakpoints of many of these deletions bear the hallmark of aberrant activity of the recombinate activation genes. Thus, further work directly examining these alterations in leukemogenesis is required.
The t(1;19)(q23;p13) translocation is a rare rearrangement with extremely poor outcome (29, 39). Tyrosine kinase inhibitors are potentially amenable to tyrosine kinase inhibitor therapy, but historically, BCR-ABL1 ALL (37).

### TCF3-PBX1 (E2A-PBX1) and TCF3-RLF2 (E2A-HLF) B-ALL

The t(1;19)(q23;p13) translocation is present in up to 6% of childhood B-ALL cases (21). The rearrangement is commonly unbalanced, with duplication of 1q distal to PBX1.

This translocation fuses the transactivation domains of TCF3 with the C-terminal region of the homeobox gene PBX1. TCF3 encodes the basic helix-loop-helix (bHLH) transcription factors E12 and E47 that are required for early lymphoid development, and loss of E12/E47 promotes the development of T cell lymphoma (22, 23). PBX1, which encodes a member of the three-amino acid loop extension family of homeodomain proteins, is required for the development of lymphoid precursors (24). TCF3-PBX1 binds HOX proteins and likely interferes with hematopoietic differentiation by disrupting HOX-regulated gene expression (25).

The t(17;19)(q22;p13) translocation is a rare rearrangement that fuses the aminoterminal transactivation domains of TCF3 to the C-terminal DNA-binding and dimerization domains of HLF, a member of the PAR family of basic leucine zipper transcription factors (26). TCF3-HLF aberrantly regulates genes that control cell death in lymphoid progenitors, including LMO2 and BCL2 (27). TCF3-HLF-positive leukemia is associated with older age and very poor outcome (28).

### BCR-ABL1 ALL

Breakpoint cluster region–ABL1 (BCR-ABL1) is generated by the der(22) of the t(9;22)(q34;q11) translocation, or Philadelphia (Ph) chromosome, which is present in over 95% of chronic myelogenous leukemia (CML) cases, 25% of adult ALL cases, and 3% to 5% of pediatric ALL cases (29). The t(9;22) fuses 5' sequences of breakpoint cluster region (BCR) to 3' sequences from ABL1, which encodes a tyrosine kinase. The breakpoints on chromosome 9 are scattered over a nearly 200-kb region within the first intron of ABL, whereas the BCR breakpoints on chromosome 22 are clustered in two areas: a 5.8-kb major BCR (M-bcr) in CML and a minor BCR (m-bcr) in most cases of childhood Ph-positive ALL (30). Fusion genes created by breaks in M-bcr (CML-type break) encode a 210-kDa fusion protein (p210), whereas fusions that occur in m-bcr (ALL-type break) encode p190.

Both forms of BCR-ABL1 can transform hematopoietic cells in vitro and induce a syndrome similar to CML in mice (31). BCR-ABL1 activates multiple signaling pathways, increases cell proliferation, and deregulates differentiation and adhesion. Treatment of BCR-ABL1-positive leukemic cells with tyrosine kinase inhibitors results in the activation of the transcription factor BCL6, which may directly influence responsiveness to treatment with these agents (32).

Additional genetic alterations are critical determinants of the lineage and progression of BCR-ABL1 leukemia. Deletion of the early lymphoid transcription factor gene IKZF1 (IKAROS) is common in BCR-ABL1 lymphoid leukemia (CML at progression to lymphoid blast crisis) but is rarely present in CML at chronic phase (33, 34). IKAROS is a zinc finger transcription factor required for the development of all lymphoid lineages (35, 36). The IKZF1 deletions result either in haploinsufficiency or expression of dominant-negative isoforms. These alterations cooperate with BCR-ABL1 in the induction of lymphoblastic leukemia and promote resistance to therapy in recent experimental models of BCR-ABL1 ALL (37).

In childhood ALL, the presence of BCR-ABL1 is associated with older age, higher leukocyte count, and more frequent CNS leukemia at diagnosis (38). Historically, BCR-ABL1 ALL has been associated with extremely poor outcome (29, 39). Tyrosine kinase inhibitors...
such as imatinib mesylate (Gleevec) have transformed the treatment and outcome of patients with BCR-ABL1–positive leukemia (40, 41). The addition of imatinib to intensive chemotherapy in childhood BCR-ABL1–positive ALL results in a 4-year event-free survival rate of 84%, more than double that of historical controls (42). A proportion of patients become resistant to these agents, typically through acquired mutations in the ABL1 kinase domain (43).

**MLL–rearranged B-ALL**

Mixed-lineage leukemia–rearranged (MLL-rearranged) leukemia is a unique entity notable for initiation in utero, for myeloid and lymphoid features, and for poor responsiveness to therapy (44, 45). Rearrangement of the MLL gene at 11q23 occurs in at least two-thirds of infants with ALL, 5% of AML, and 85% of secondary leukemias that occur in patients treated with topoisomerase II inhibitors (46, 47) but is less frequent in older individuals (48, 49). Over 80 partners of MLL rearrangement have been identified (50).

The most common MLL rearrangements are t(4;11)(q21;q23)/MLL-AFF1(AF4), found in approximately 50% of cases, followed by t(9;11)(p22;q23)/MLL-MLLT3(AF9), MLL-ENL, and t(10;11)(p13.15,q14.21)/MLL-MLLT10(AF10) (51, 52). The translocation breakpoints are located in an 8.5-kb cluster between exons 5 and 11 and juxtapose the A-T hook and methyltransferase domains to partner proteins. MLL regulates hematopoiesis through maintenance of normal homeotic gene expression (53), in part through transcriptional activation of HOX genes, mediated though the histone H3 lysine 4 (H3K4) methyltransferase activity of the SET domain (54). In contrast to other subtypes of B-ALL, additional genetic alterations are uncommon in MLL-rearranged leukemia (17, 55, 56).

MLL-rearranged ALL exhibits a distinct gene expression profile characterized by the upregulation of class I HOX genes (HOXA5, -A7, and -A9) and the HOX cofactor gene MEIS1 (57). Co-expression of HOXA genes and MEIS1 cooperates with MLL fusions in induction of leukemia and maintenance of a “stem cell-like” state of maturation (58). fms-related tyrosine kinase 3 (FLT3) is overexpressed in MLL-rearranged ALL and harbors point mutations in 10%–20% of cases (59). In animal models, FLT3 kinase inhibitors have shown potential as therapeutic agents for MLL-rearranged leukemias, and FLT3 inhibitors are currently being tested in clinical trials (59, 60). MLL-rearranged leukemias also exhibit a distinct epigenetic profile, with signatures of cytosine (61), microRNA (62) and H3K79 methylation (63) that differ from non-MLL leukemias.

Many of the MLL fusion proteins are located in protein complexes that regulate transcriptional elongation, which may be in part responsible for transcriptional dysregulation and leukemogenesis. These include polymerase-associated factor complex, which associates with the N terminus of MLL and regulates RNA polymerase II (Pol II), the pTEFb (CDK9/cyclin T) complex, which associates with the fusion partners MLLT1 (ENL), ELL, and AFF1 (AF4) to release stalled Pol II and stimulate transcriptional elongation, and the H3K79 histone methyltransferase DOT1L, which binds MLL fusion partners including AFF1, AP9, AF10, and ENL (64). H3K79 methylation is a mark of actively transcribed genes, and suppression or inactivation of DOT1L in human or murine leukemia cells leads to suppression of the MLL fusion protein–induced gene expression program (63), differentiation and/or apoptosis of leukemic cell lines, and suppression of leukemogenesis (65). DOT1L inhibition is thus being pursued as a therapeutic approach in MLL-rearranged ALL (66).

These findings highlight the potential importance of epigenetic dysregulation in other subtypes of ALL. Several studies profiling cytosine methylation have shown that different ALL subgroups exhibit distinct methylation profiles and that promoter methylation is associated with gene expression and outcome (67, 68). Additional studies are needed to comprehensively determine the relative importance of genetic and epigenetic alteration in the pathogenesis of ALL as well as the potential therapeutic role of epigenetic modifying drugs.

**Rearrangement of CRLF2 and other immunoglobulin heavy locus rearrangements in B-ALL**

Rearrangements of the immunoglobulin heavy locus (IGH@) at 14q32.33, resulting in juxtaposition of IGH@ enhancer elements with transcription factor and cytokine receptor genes, are observed in both B-ALL and T-lineage ALL (69). B-lineage leukemia/lymphoma with rearrangement of MYC is reviewed elsewhere (70).

Cytokine receptor-like factor 2 (CRLF2; also known as thymic stromal-derived lymphopoietin [TSLP] receptor) is located at the pseudoautosomal region (PAR1) at Xp22.3/Yp11.3 and is rearranged or mutated in up to 7% of B-ALL cases (71, 72). With the IL-7Rα chain, CRLF2 forms a heterodimeric receptor for TSLP. The rearrangements are either rearrangement into IGH@-CRLF2 or focal deletion immediately upstream of CRLF2, resulting in a chimeric fusion of the purinergic receptor gene P2RY8 to the entire coding region of CRLF2. Both rearrangements result in overexpression of CRLF2 on the cell surface (71). Less commonly,
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In the presence of activating mutations in the Janus kinase genes JAK1 and JAK2 (71–73, 75), which are otherwise uncommon in B-ALL. The JAK mutations in B-ALL most commonly disrupt p.Arg683 in the pseudokinase domain of JAK2, in contrast to the JAK2 p.Val617Phe mutations that are a hallmark of myeloproliferative diseases. Like the JAK2 p.Val617Phe mutation, the JAK1/2 mutant alleles observed in ALL confer cytokine-independent proliferation in cultured cells, particularly in the presence of a cytokine receptor such as the EPOR or CRLF2, suggesting that a receptor scaffold is required for mutant JAK alleles to drive proliferation and lymphoid transformation (76, 77). In non-DS ALL, CRLF2 rearrangements are associated with IKZF1 alteration, JAK mutation, and poor outcome (74, 78). Recently, activating mutations in IL-7R have been identified in both B-ALL and T-lineage ALL, including cases of CRLF2 rearrangement (10, 79, 80). Thus, the use of JAK inhibitors is actively being pursued to target leukemic cells harboring CRLF2/JAK alterations and leukemic cells with IL-7R mutations that also activate JAK/STAT signaling. Several other IGH@ translocation partners have been identified in B-ALL, including EPOR, the CEBP transcription factor gene family, the inhibitor of DNA binding 4 (ID4) gene, the LIM domain–containing protein LHX4, and rarely, IL-3 (69).

**BCR-ABL1–like ALL**

Up to 15% of childhood B-ALL cases exhibit a gene expression profile similar to that of BCR-ABL1–positive ALL, often have deletion/mutation of IZKF1, and have a very poor outcome (81–83). CRLF2 is rearranged in up to 50% of BCR-ABL1–like ALL cases, but until recently the lesions responsible for kinase activation in the remaining cases were unknown. Second-generation mRNA sequencing and whole genome sequencing of 15 BCR-ABL1–like ALL cases identified rearrangements, sequence mutations, and DNA CNAs activating kinase signaling in all cases (84), including rearrangements of PDGFRB, BCR, JAK2, and EPOR as well as deletion/mutation of SH2B3 and IL7R. Several of these alterations have been shown to result in activation of downstream (e.g., JAK/STAT) signaling pathways, and cellular transformation was attenuated with JAK or ABL1/PDGFRB inhibitors. Thus, defining kinase-activating alterations in this subtype of ALL is critical to identifying and treating patients with this subtype of leukemia.

**Hypodiploid ALL**

Hypodiploidy, with fewer than 44 chromosomes, is present in up to 3% of childhood ALL cases and is associated with a high risk of treatment failure (89). Hypodiploid ALL may be subclassified by severity of aneuploidy into near-haploid (NH; 24–31 chromosomes) and low-hypodiploid (LH; 32–44 chromosomes) cases, but until recently the concomitant submicroscopic genetic alterations were poorly characterized. NH ALL has a very high frequency of deletions and sequence mutations that activate RAS signaling, and NH and LH ALL have a high frequency of inactivating alterations of IKAROS genes IKZF2 (HELIOS) and IKZF3 (AIOLOS) that are otherwise rare in ALL (90). Moreover, LH cases have a very high frequency of loss-of-function mutations in TP53 (encoding p53) and RBI, which are otherwise uncommon at diagnosis in B-ALL.

**Submicroscopic genetic alterations in B-ALL**

The observation that up to 25% of children with ALL lack a recurring chromosomal alteration (2) and the identification of translocation-encoded fusions at birth or in years prior to the onset of leukemia (16) indicates that additional genetic alterations cooperate in leukemogenesis. The advent of array-comparative genomic hybridization and SNP microarrays has enabled interrogation of structural genetic alterations at very high resolution (91). These approaches, coupled with candidate gene sequencing and integrated gene expression profiling (92), have identified a number of critical new targets of mutation in B-ALL that often involve genes that regulate lymphoid development, cell cycle, tumor suppression, and a variety of other key cellular pathways (Table 2). The mean number of DNA CNAs is lower than in many solid tumors (an average of 6–8 lesions per case) (17, 19, 33), but over 50 recurring CNAs have been identified. The nature and frequency of these CNAs are significantly associated with ALL subtype, with few lesions in MLL-rearranged ALL (17, 55) but 6–8 lesions per case in BCR-ABL1 and ETV6-RUNX1 ALL (33, 34).

Most notably, genes encoding transcriptional regulators of B-lineage commitment and differentiation are mutated in over two-thirds of B-ALL. These include PAX5 (encoding paired box 5, mutated in over 30% of cases), EBF1 (early B cell factor 1), IKZF1–3, and lymphoid enhancer factor 1. PAX5 harbors broad deletions predicted to result in haploinsufficiency, focal intrachromosomal deletions that result in the expression of truncated PAX5 transcripts, sequence mutations that disrupt DNA binding or truncate the transactivating domain (17, 93), and translocations that create chimeric fusion proteins (17, 93, 94). These lesions usually only involve a single copy of PAX5, and expression of key PAX5 targets, such as CD19, in ALL cells is frequently normal, suggesting that PAX5 haploinsufficiency contributes to leukemogenesis. Despite their high frequency of occurrence, PAX5 alterations are not associated with outcome in ALL (81, 95). In contrast, IKZF1 alterations are less frequent (15% of B-ALLs) but are associated with adverse outcome in both BCR-ABL1–positive and negative ALL cases. IKZF1 alterations are present in up to one-third of high-risk B-ALL cases and triple the risk of treatment failure (81, 96). IKZF1, which is required for lymphoid development, binds DNA and forms homodimers or heterodimers with other IKAROS family members. IKZF1 has multiple functions including transcriptional activation, repression, and chromatin remodeling, in part mediated via the nucleosome remodeling and deacetylase complex that also contains IKZF3. The alterations observed in ALL include broad and focal deletions of IKZF1, which result in loss of func-

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### Table 2

Key novel genetic alterations in B-ALL

<table>
<thead>
<tr>
<th>Gene</th>
<th>Alteration</th>
<th>Frequency</th>
<th>Consequences of alteration</th>
<th>Clinical relevance</th>
<th>References</th>
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</thead>
<tbody>
<tr>
<td><strong>PAX5</strong></td>
<td>Focal deletions, translocations, sequence mutations</td>
<td>31.7% of B-ALL cases</td>
<td>Transcription factor required for B-lymphoid development; mutations impair DNA binding and transcriptional activation</td>
<td></td>
<td>17, 19, 33</td>
</tr>
<tr>
<td><strong>IKZF1</strong></td>
<td>Focal deletions or sequence mutations</td>
<td>15% of pediatric B-ALL cases</td>
<td>Transcription factor required for development of HSCs to lymphoid precursors; deletions and mutations result in loss of function or dominant-negative isoforms</td>
<td></td>
<td>17</td>
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<tr>
<td></td>
<td>Over 80% of BCR-ABL1 ALL cases and 66% of CML cases in lymphoid blast crisis</td>
<td></td>
<td>Associated with poor outcome</td>
<td></td>
<td>33, 34, 125</td>
</tr>
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<td></td>
<td>Approximately 30% of high-risk BCR-ABL1–negative ALL cases</td>
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<td></td>
<td><strong>Inherited variants</strong></td>
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<td><strong>JAK1/2</strong></td>
<td>Pseudokinase and kinase domain mutations</td>
<td>18%–35% of DS-ALL</td>
<td>Constitutive JAK/STAT activation; transforms hematopoietic cell lines to be growth factor independent</td>
<td></td>
<td>76, 77</td>
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<tr>
<td></td>
<td>10.7% of high-risk BCR-ABL1 ALL cases</td>
<td></td>
<td></td>
<td></td>
<td>77</td>
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<tr>
<td><strong>CRLF2</strong></td>
<td><strong>IGH@-CRLF2 or P2RY8-CRLF2</strong>, resulting in CRLF2 overexpression</td>
<td>5%–16% of pediatric and adult B-ALL cases; &gt;50% of DS ALL</td>
<td>Associated with mutant JAK in up to 50% of cases; CRLF2 mutations and JAK mutations co-transform in Ba/F3 cells and result in constitutive JAK/STAT activation</td>
<td></td>
<td>71–73, 75</td>
</tr>
<tr>
<td></td>
<td>14% of pediatric high-risk ALL cases</td>
<td></td>
<td>Associated with IKZF1 alteration and JAK mutations</td>
<td></td>
<td>74, 78</td>
</tr>
<tr>
<td><strong>CREBBP</strong></td>
<td>Focal deletion and sequence mutations</td>
<td>19% of relapsed ALL cases, especially ALL with high hyperdiploidy; also mutated in non-Hodgkin lymphoma</td>
<td>Mutations result in impaired histone acetylation and transcriptional regulation</td>
<td></td>
<td>112, 114, 115</td>
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Figure 2
Patterns of genomic evolution from diagnosis to relapse in ALL. Leukemic clones at relapse are frequently related to leukemic clones present at diagnosis. In more than half of cases, the relapse clone arises from a clone present prior to diagnosis, retaining some but not all of the lesions found at diagnosis and containing some additional mutations. The relapse clone is often present as a rare subclone within the diagnostic sample. Alternatively, cases of relapse can stem from the diagnosis clone, acquiring additional mutations. Less commonly, the relapse clone may be identical to the diagnosis clone or appear to be an unrelated second leukemia.

Genetics of relapse in ALL
ALL genomes are not static, frequently acquiring secondary karyotypic and genetic alterations during disease progression (101–103). Genome-wide profiling has enabled key questions in the genetic basis of treatment failure to be investigated, including the nature of genetic alterations that are acquired with disease progression, the genetic relationship between the diagnosis and relapsed leukemic clones, and the degree of clonal heterogeneity present at the time of diagnosis.

Microarray profiling has shown that relapse samples exhibit striking differences in the patterns of genomic alterations from the matched diagnosis samples (104–108), with the majority of relapse samples exhibiting the loss of CNAs present at diagnosis and the acquisition of new genetic alterations. Importantly, most paired diagnosis-relapse samples share a common clonal origin. Moreover, lesions detected at relapse are often detectable in diagnostic samples, indicating that the predominant relapse clone(s) are present at low levels at diagnosis. Genetically unrelated second leukemias (at least at the level of DNA CNA analysis by SNP array) are infrequent but may be more common in late relapse (109). Approximately one-third of cases show a pattern of linear clonal evolution (with the acquisition of new genetic changes by the relapse clone in addition to those seen at relapse), and over 50% show a complex picture with both loss of diagnosis CNAs and the acquisition of new lesions, as well as evidence of low levels of relapse clones at diagnosis (Figure 2).

Together, these data suggest that a pre-diagnosis “ancestral” clone harboring one or more genetic alterations (such as a founding translocation) undergoes divergent evolution into multiple clones that acquire different genetic alterations and emerge as the predominant clones at diagnosis and relapse. This is supported by studies of monozygotic twins concordant for ALL, showing different secondary CNAs in each twin (20), and recent xenotransplantation studies that have modeled clonal evolution and heterogeneity by engrafting ETv6-RUNX1 and BCR-ABL1 samples into immunocompromised mice. These studies have confirmed clonal heterogeneity in the majority of cases at the time of diagnosis and have shown that specific genetic alterations (e.g., deletion of CDKN2A/CDKN2B) influence the efficiency and tempo of engraftment (110, 111).

Genome-wide sequencing is required to comprehensively identify all sequence and structural variants contributing to the pathogenesis of ALL, and a number of sequencing efforts are ongoing. However, a recent study performed Sanger sequencing of 300 genes in 23 matched diagnosis-relapse samples, with recurrence testing of over 300 paired and unpaired ALL samples (112). This study identified a number of uncharacterized mutations in ALL, most notably deleterious mutations in CREBBP (encoding CREBBP), in over 20% of relapse ALL samples (112). The mutations were present at relapse and were detected in either the predominant clone or a subclone at diagnosis. CREBBP is a transcriptional coactivator, histone and non-histone acetylase, and ubiquitin ligase (113). Mutations were common in the histone acetyltransferase (HAT) domain and resulted in impaired acetylation of histone targets (112). CREBBP mutations are highly enriched
in hyperdiploid ALL (114) and are common at diagnosis in B cell lymphoma samples (115). Importantly, the HAT mutations impair the normal CREBBP-mediated transcriptional response to glucocorticoids, which are widely used in ALL therapy. Thus, CREBBP mutations may impair the response of leukemic cells to glucocorticoids and influence treatment responsiveness, and therapeutic approaches modifying acetylation may reverse glucocorticoid resistance. Mutations in TP53, which are otherwise infrequent in ALL, are also enriched in relapsed ALL (116).

**Inherited genetic variation and risk of ALL**

Several candidate gene studies have implicated inherited genetic variation, for example in the folate metabolic pathway, in the risk of developing leukemia (117). Multiple genome-wide association studies have reproducibly identified variations at several genomic loci that are associated with ALL risk, including IKZF1, ARID5B (encoding the AT-rich interactive domain 5B transcription factor), and CEBPE (encoding the transcription factor CCAAT/enhancer-binding protein, epsilon) (118, 119). All three genes encode proteins considered important for normal lymphoid development and/or lymphoid leukemogenesis. CEBPE is a target of translocations in ALL, and Arid5B knockout mice exhibit defects in the B lymphoid compartment (120). Although the functional effects of these inherited variants are poorly understood, the IKZF1 variants may influence level of IKZF1 gene expression (119), suggesting a direct role for these variants in disease susceptibility.

**Conclusions**

The use of contemporary technologies to identify genetic alterations in B-ALL has been tremendously informative, but clearly much work remains to be done. Microarray and candidate gene sequencing approaches are incapable of identifying mutations at nucleotide-level resolution, and initial second-generation sequencing of ALL genomes has identified multiple new genes targeted in ALL. An additional high-priority area of investigation is ALL in older children, adolescents, and adults, who typically have a substantially inferior prognosis. Profiling of ALL in these age groups, as well as in additional uncommon but high-risk ALL subtypes, is ongoing and likely to yield additional insights and therapeutic approaches.

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