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Advances in B-cell Precursor Acute Lymphoblastic Leukemia Genomics

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Abstract

In childhood B-cell precursor acute lymphoblastic leukemia (BCP-ALL), cytogenetic abnormalities remain important diagnostic and prognostic tools. A number of well-established abnormalities are routinely used in risk stratification for treatment. These include high hyperdiploidy and *ETV6-RUNX1* fusion, classified as good risk, while Philadelphia chromosome (Ph) positive ALL and rearrangements of the *KMT2A* (*MLL*) gene define poor risk. A poor risk subgroup of intrachromosomal amplification of chromosome 21 (iAMP21-ALL) has been described, in which intensification of therapy has greatly improved outcome.

Until recently, no consistent molecular features were defined in around 30% of BCP-ALL (known as B-other-ALL). Recent studies are classifying them into distinct subgroups, some with clear potential for novel therapeutic approaches. For example, in 1 poor risk subtype, known as Ph-like/BCR-ABL1-like ALL, approximately 10% have rearrangements of ABL-class tyrosine kinases: including *ABL1*, *ABL2*, *PDGFRB*, *PDGFRA*, and *CSF1R*. Notably, they show a poor response to standard chemotherapy, while they respond to treatment with tyrosine kinase inhibitors, such as imatinib. In other Ph-like-ALL patients, deregulation of the cytokine receptor, CRLF2, and *JAK2* rearrangements lead to activation of the JAK-STAT signaling pathway, implicating a specific role for JAK inhibitors in their treatment. Other novel subgroups within B-other-ALL are defined by the *IGH-DUX4* translocation, related to deletions of the *ERG* gene and a good outcome, while fusions involving *ZNF384*, *MEF2D*, and intragenic *PAX5* amplification ($PAX5^{AMP}$) are linked to a poor outcome. Continued genetic screening will eventually lead to complete genomic classification of BCP-ALL and define more molecular targets for less toxic therapies.

Introduction

Acute lymphoblastic leukemia (ALL) is the most common cancer of childhood, with an annual incidence of 35 per million children aged 0 to 14 years.[1] There is a peak incidence between the ages of 2 to 5 years, with more than 75% of cases occurring in this age group.[2] More than 80% are B-cell precursor ALL (BCP-ALL), while the remainder comprise T-lineage ALL. BCP-ALL is generally associated with a good outcome in children, with cure rates approaching 90% for patients treated on modern risk-adjusted protocols.[3] Despite these improvements in treatment response, ALL remains one of the leading causes of cancer-related mortality in children, with patients succumbing to relapse or treatment-related death.[2] Survivors of ALL also endure long-term effects of toxic chemotherapy.[4] It is, therefore, important to continue to identify those patients who require less intensive therapy to achieve cure and to identify new targets for the development of novel, less toxic therapeutic agents.

The important risk factors used in stratification for treatment include age, white blood cell count, indicators of the National Cancer Institute risk status, treatment response, measured by the level of minimal residual disease (MRD), and cytogenetics. Over the past 4 decades, cytogenetics has proved to be a powerful tool in understanding the genetic basis of ALL, while providing essential diagnostic and prognostic information. A number of the well-established chromosomal abnormalities are routinely incorporated into clinical trials and used in risk stratification for treatment, which has significantly contributed to the improved outcomes seen in childhood ALL today. Recent innovative approaches have led to the identification of many novel genetic changes shown to impact on outcome. In this article, historical and new genetic subtypes will be reviewed in relation to their biological and clinical significance, within the context of modern therapeutic approaches.

Cytogenetics of BCP-ALL: A historical perspective

Established chromosomal abnormalities of prognostic relevance

Results from cytogenetic studies over the past 45 years have classified the majority of BCP-ALL according to their primary cytogenetic abnormalities (Fig. 1).[5] Trial-based studies showed

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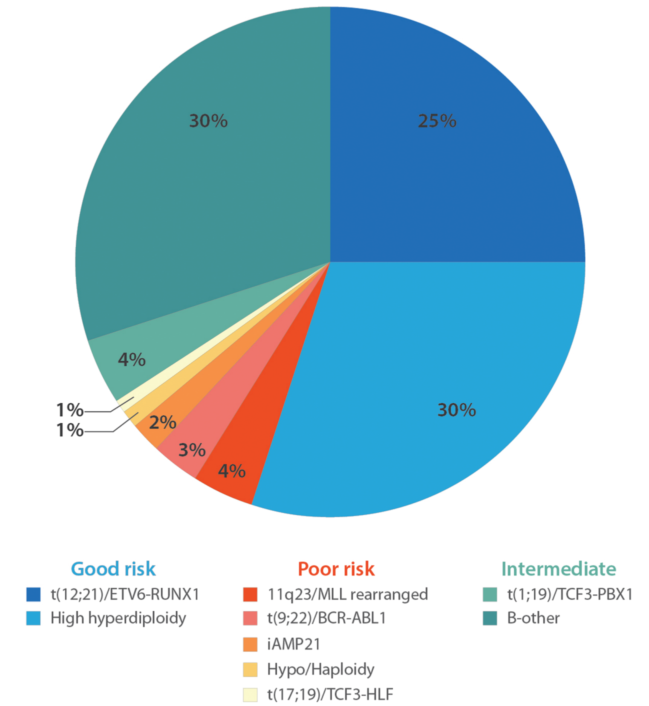

Figure 1. Pie chart showing the frequency of the major cytogenetic subgroups in BCP-ALL: good risk cytogenetic groups are shown in blue and the poor risk groups in orange. Green indicates intermediate risk. BCP-ALL = B-cell precursor acute lymphoblastic leukemia.

that these cytogenetic subgroups correlated with age and were strongly linked to outcome.[6] For example, the translocation, t(12;21)(p13;q22)/*ETV6-RUNX1* fusion, and high hyperdiploidy (51–65 chromosomes) occur predominantly in children, together they account for more than 50% of childhood BCP-ALL, and are associated with a good prognosis. On the contrary, translocations involving *KMT2A* (formerly *MLL*) at 11q23 are associated with a poor prognosis. They occur in approximately 2% of childhood and adult BCP-ALL, with an elevated incidence of 85% in infants with ALL. A number of rearrangements involving the *NUTM1* gene are also prevalent in infants, in particular among those who lack *KMT2A* rearrangements.[7,8]

The translocation, t(9;22)(q34;q11)/*BCR-ABL1* fusion, is also a marker of poor outcome, with incidence increasing with age from about 2% in children to around 25% in younger adults. Near-haploidy (<30 chromosomes) and low hypodiploidy (30–39 chromosomes) remain linked to poor survival across the range of modern contemporary treatment protocols. The translocation, t(1;19)(q23;p13)/*TCF3-PBX1* fusion, accounts for approximately 4% of BCP-ALL. Originally classified as poor risk, outcome for these patients has improved significantly on modern therapeutic regimens. However, prognosis of the rare variant translocation, also involving *TCF3*, t(17;19)(q22;p13)/*TCF3-HLF* fusion, remains dismal on all treatment protocols. For many years, these abnormalities have provided the basic gold standard genetic classification of BCP-ALL worldwide. Classical techniques of cytogenetics, fluorescence in situ hybridization (FISH), and reverse transcription polymerase chain reaction (RT-PCR) have facilitated robust and accurate detection for streamlined and universally applied risk stratification.

ALL with intrachromosomal amplification of chromosome 21

More recently, intrachromosomal amplification of chromosome 21-ALL (iAMP21-ALL) has been included in the risk stratification algorithm as a distinct entity of BCP-ALL recognized by World Health Organization (WHO).[9] These patients account for approximately 2% of BCP-ALL, they present at an older age (median 9 years) and usually with a low white cell count.[10] The iAMP21 chromosome is a grossly abnormal copy of chromosome 21, comprising multiple regions of gain, amplification, inversion, and deletion. It was first identified from routine FISH screening for the presence of the *ETV6-RUNX1* fusion. In a subset of patients without the *ETV6-RUNX1* fusion, multiple copies of the *RUNX1* gene, clustered on a single abnormal chromosome, were observed.[11] Although the chromosome morphology and patterns of loss and gain varied markedly between patients (Fig. 2A), genomic profiling identified a common region of amplification.[12] The majority of patients also have deletions of the telomeric end of chromosome 21. Whole genome sequencing demonstrated that the iAMP21 chromosome is generated over several cell divisions, involving multiple mutational processes including: breakage-fusion-bridge cycles following telomere attrition, chromothripsis, and large-scale chromosomal duplications.[13]

The amplified region usually includes the *RUNX1* gene, so FISH using probes to target *RUNX1* remains a reliable detection method for iAMP21-ALL. Currently, the internationally accepted definition of iAMP21-ALL is 3 or more extra copies of *RUNX1* on a single abnormal chromosome 21 (a total of 5 or more *RUNX1* signals per cell) (Fig. 2B).[14] For laboratories unable to perform FISH, determination of copy number, using copy number arrays (Fig. 2C) or Multiplex Ligation-dependent Probe Amplification, with specifically designed kits containing probes targeting chromosome 21, provide alternative methods to identify iAMP21-ALL.[15]

Accurate diagnosis of iAMP21-ALL is important in the clinical setting, as patients have a high relapse rate when treated on standard therapy.[16] Data from the UK ALL97 trial showed that patients with iAMP21-ALL had a 10-year event-free survival (EFS) of only 15%. However, the overall survival (OS) was significantly higher at 71%, indicating that these patients responded well to more intensive postrelapse therapy.[6,17] Based on these observations, children with iAMP21-ALL treated on the subsequent trial, UKALL2003, were treated with intensive chemotherapy from the time of diagnosis. This stratification resulted in significant improvements in 5-year EFS (from 29% to 78%), relapse risk (reduced from 70% to 16%), and OS (from 67% to 89%).[18] These findings were validated within the Children's Oncology Group (COG), which showed similar results in treatment trials in the United States.[19]

Genomic and copy number profiling have shown that patients with iAMP21-ALL also harbor secondary genetic abnormalities, which may be amenable to therapy with targeted agents. Targeted sequencing showed that approximately 60% of iAMP21-ALL patients had mutations in genes within the RAS signaling pathway. iAMP21-ALL cells in vitro showed reduced viability in response to treatment with the RAS pathway inhibitor, selumetinib.[20] In addition, approximately 20% of iAMP21-ALL patients harbor the *P2RY8-CRLF2* fusion. This fusion leads to deregulated expression of the cytokine receptor, *CRLF2*,[21] and activation of the JAK-STAT signaling pathway,[22] suggesting that aberrant JAK-STAT signaling is important in iAMP21-ALL leukemogenesis. The report of a subset of

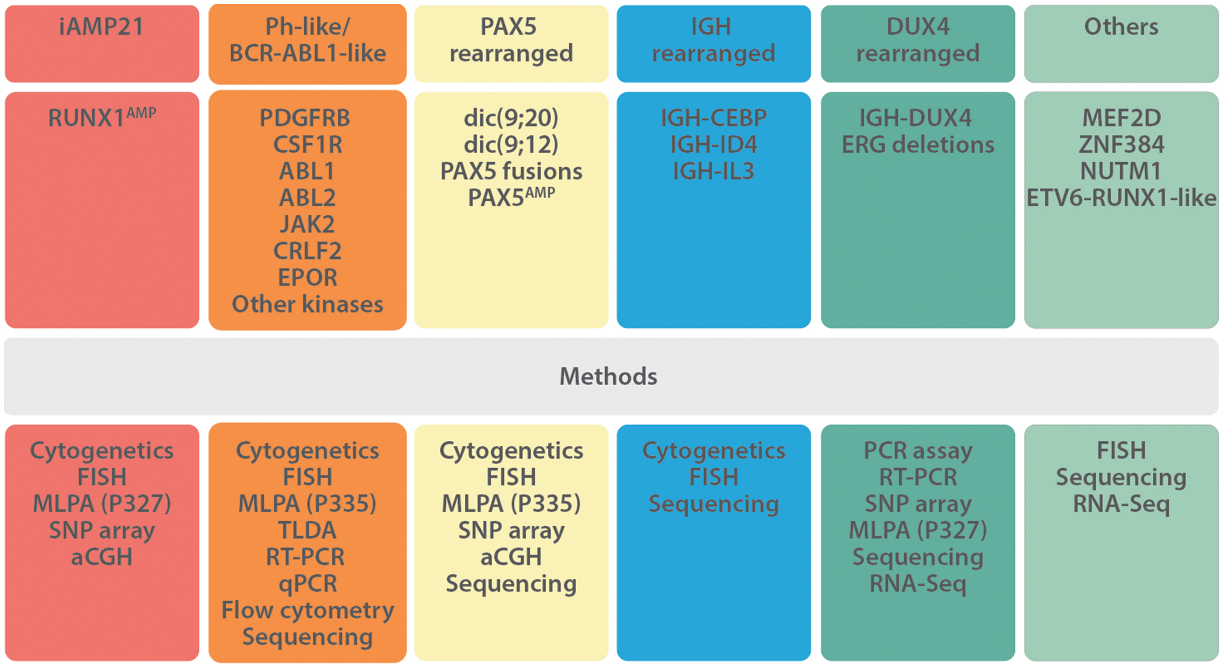

Figure 2. iAMP21-ALL. (A) The chromosome morphology of each iAMP21 chromosome, as seen by standard cytogenetics, is different, as illustrated in the 4 pairs of chromosomes 21 from 4 different iAMP21-ALL patients showing the variable morphology of the abnormal chromosome 21 on the right of each pair. (B) Diagrammatic representation of the expected normal FISH signal pattern using a probe for *ETV6* (green) and *RUNX1* (red), (i) on metaphase chromosomes 12 and 21, respectively, and (ii) in interphase. The expected abnormal signal pattern of iAMP21-ALL is shown in (iii) by multiple copies of *RUNX1* (red) on the iAMP21 chromosome, and in (iv) as clustered red signals in interphase. (C) An example of a characteristic copy number profile of chromosome 21 in iAMP21-ALL, generated from telomeric loss, breakage fusion bridge cycles and chromothripsis, indicated in this profile, by (i) irregular copy number changes, (ii) a common region of amplification that includes *RUNX1*, and (iii) telomeric loss. FISH = fluorescence in situ hybridization, iAMP21-ALL = intrachromosomal amplification of chromosome 21 acute lymphoblastic leukemia.

iAMP21-ALL patients with deletions of *SH2B3*,[23] an abnormality which also leads to activation of the JAK-STAT pathway in BCP-ALL,[24,25] has further highlighted the involvement of this pathway and the potential role of JAK inhibitors in treatment of patients with iAMP21-ALL. Ongoing studies to decipher the genomic complexity of the iAMP21 chromosome will identify genes on chromosome 21 as potential targets for novel therapies, to reduce the toxicities of their current high-risk treatment.

Novel genetic abnormalities in B-other-ALL

B-other-ALL

Until recently, approximately 30% of BCP-ALL patients remained unclassified at the genetic level, having none of the established cytogenetic changes mentioned above. These patients were grouped together and classified as intermediate risk, within a so-called B-other-ALL subgroup (Fig. 1). In recent years, a number of distinct, recurrent abnormalities have emerged from within this highly genetically heterogeneous subgroup. Thus as B-other-ALL diminishes in size, these novel abnormalities have defined important new subgroups of variable outcome, as shown in Figures 3 and 4,[6,26–36] replacing the default assignment of intermediate risk to these patients with increasingly more accurate prognostic information for improved treatments. These novel subgroups are described in more detail below.

Ph-like/*BCR-ABL1*-like ALL

Two independent studies identified a subgroup of B-other patients from gene expression profiling with similar expression signatures to *BCR-ABL1* positive patients, but lacking the *BCR-ABL1* fusion.[26,27,37,38] This group, named Ph-like/*BCR-ABL1*-like ALL, accounts for up to 15% of the original B-other-ALL subgroup and shows the same poor outcome as *BCR-ABL1*-positive ALL. The 2 studies used different methods and different cohorts to identify these patients, but, while the incidence of specific genetic abnormalities differed between the 2 cohorts, the association with poor risk was consistent.[39] The Ph-like group, as defined by the COG, is characterized by a high incidence of *IKZF1* deletions in approximately 70% of cases and over-expression of *CRLF2* in about 50%. By contrast, in the *BCR-ABL1*-like group reported by Den Boer et al, the frequency of *IKZF1* loss and *CRLF2* over-expression was lower at 40% and 16%, respectively.[40] Further investigations in Italian and Japanese cohorts have also identified patients with a similar gene expression profile to *BCR-ABL1* positive patients, but again the spectra of genetic abnormalities in these cohorts were distinct.[41,42] As a consensus gene expression profile to define this patient subgroup has failed to emerge, individual international study groups have chosen a range of different approaches to identify these cases. For example, COG has developed a TaqMan-based reverse transcriptase PCR low-density array based on the expression of 8 or 15 genes to identify Ph-like-ALL.[31,43] Nevertheless, in both of the original studies, a similar proportion of patients harbored novel fusions involving kinase genes, in about 17% of cases.[31,43–45] Thus, alternative screening approaches, for example, using FISH and RT-PCR, for the detection of the genetic abnormalities underlying these signatures, is proving to be clinically useful.[46]

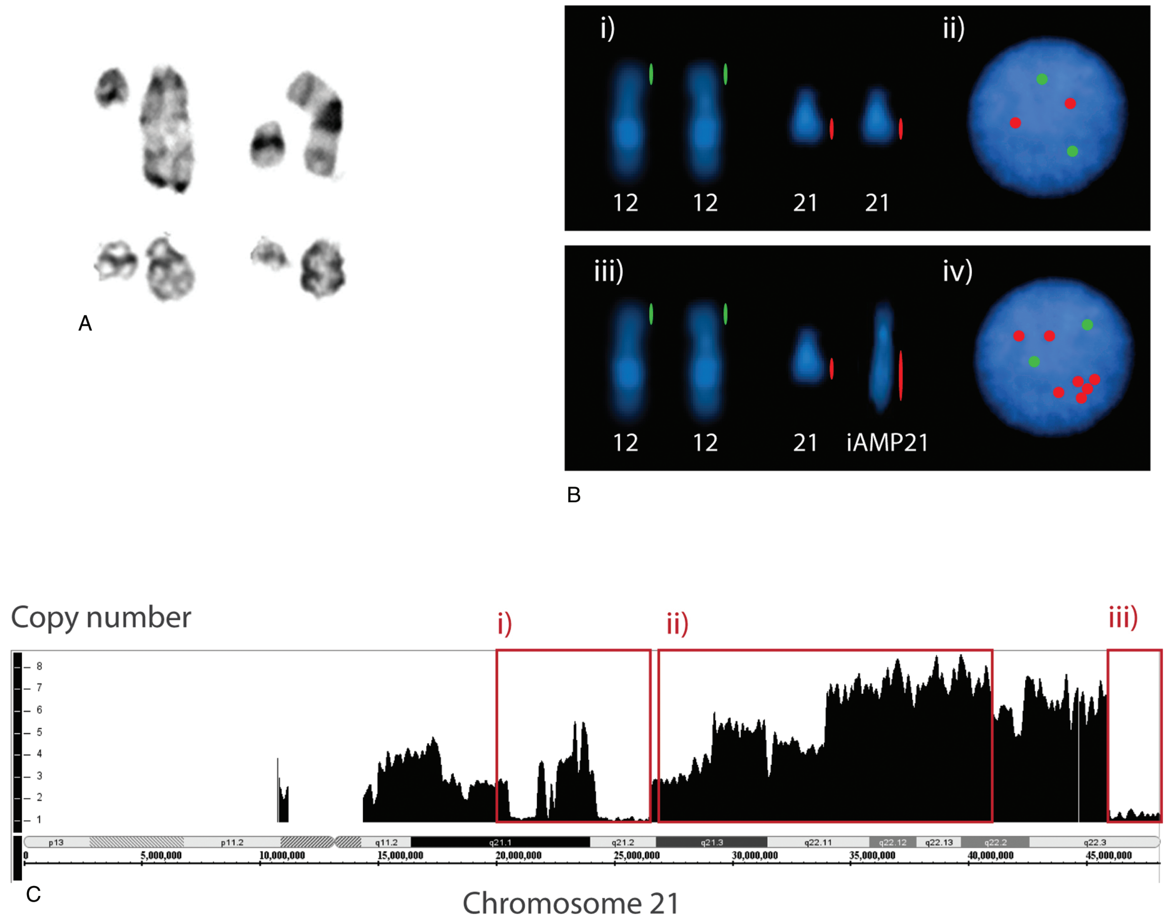

Figure 3. The range of genetic abnormalities comprising B-other ALL. The relative distribution of abnormalities is approximated from reports in the literature. Largely the color scheme indicates the associated prognosis, with orange (denoting Ph-like/*BCR-ABL1*-like) indicating a poor outcome, green indicating a good prognosis, while the remainder are classified as intermediate risk at this time. The proportion of cases currently undefined at the genomic level are indicated in purple. ALL = acute lymphoblastic leukemia.

ABL-class fusions

Approximately 10% of patients in the Ph-like subgroup have fusions involving the tyrosine kinase genes: *ABL1*, *ABL2*, *PDGFRB*, *PDGFRA*, and *CSF1R*.[31,43–45] Multiple and overlapping partner genes have been described for each kinase gene (Fig. 5).[31,43–48] Many of these fusions have been reported in only single cases; however, a number has been shown to be recurrent. The most frequently identified fusion is *EBF1-PDGFRB*, which occurs in approximately 3% of the original B-other-ALL cohort.[46] *NUP214-ABL1* fusion, a common finding in T-ALL, has now also been identified among this subgroup.[27,31,49] The *MEF2D-CSF1R* and *ATF7IP-PDGFRB* fusions, as a result of t(1;5)(q21;q33) and t(5;12)(p13;q33) translocations, respectively, have also been reported in a number of patients.[50,51]

As with the *BCR-ABL1* fusion, the 5′ sequences of the partner gene are fused to the 3′ sequences of the kinase gene, resulting in constitutive kinase activity. Treatment with tyrosine kinase inhibitors (TKI), in addition to chemotherapy, has led to improvements in outcome for *BCR-ABL1* positive ALL patients.[52] Similarly, it has been shown that patients with ABL-class fusions respond well to treatment with TKI. For instance, case reports have described patients with *EBF1-PDGFRB*, who were refractory to conventional induction chemotherapy, showing complete response to imatinib.[31,46,53,54] Experimental studies in vitro and in vivo have shown that cells from patients with other ABL-class fusions may also be responsive to TKI.[27,31,50,51] As these patients are often refractory to induction therapies or have high levels of MRD,[46] TKI treatment has become an important consideration when designing screening algorithms for childhood ALL.[55]

Rare fusions involving other kinase genes, including *NTRK3*, *FGFR1*, *TYK2*, and *BLNK*, have been reported in Ph-like ALL, for which specific inhibitors may be available for modified treatment in the future.[31,43,45]

Aberrations in the JAK-STAT signaling pathway

Deregulation of the cytokine receptor gene, *CRLF2*, occurs in 5% of childhood BCP-ALL overall.[56] There are 3 genetic mechanisms by which *CRLF2*-deregulation (CRLF2-d) can occur: (1) a cryptic translocation involving chromosome 14, (2) an interstitial deletion in the pseudo-autosomal region (PAR1) of the sex chromosomes at Xp22 and Yp11, and (3) rarely activating mutations, such as CRLF2-F232C. The former 2 mechanisms result in over-expression of *CRLF2* as a result of the gene being placed under the transcriptional control of either the *IGH* enhancer at 14q32 (*IGH-CRLF2*) or the *P2RY8* promoter in the PAR1 region (*P2RY8-CRLF2*).[21] *CRLF2* rearrangements, particularly as a result of *P2RY8-CRLF2*, have been shown to occur

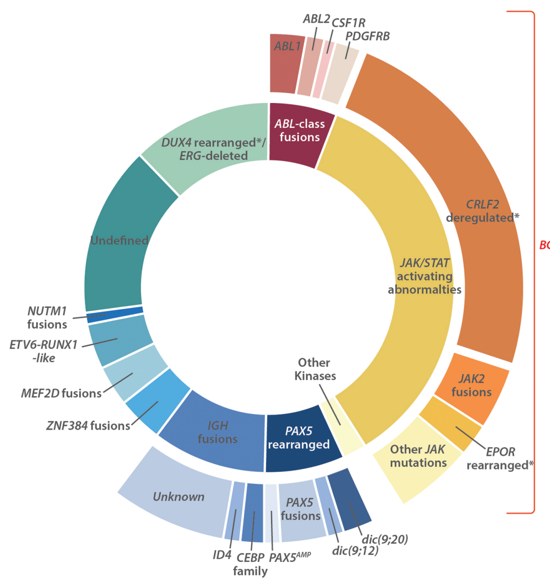

Figure 4. Summary of iAMP21-ALL along with the novel genetic subtypes reported in B-other ALL and the methods used to identify them. †P327-iAMP21-ERG kit includes 46 different probes detecting specific sequences on chromosome 21, including 13 probes for the *ERG* gene, and 6 probes for *RUNX1*. ‡P335-IKZF1-MLPA kit includes probes to detect deletion within the PAR1 region which results in *P2RY8-CRLF2* and 6 probes for *PAX5* to detect *PAX5*^{AMP}*qPCR and flow cytometry are used to detect over-expression of CRLF2. iAMP21-ALL = intrachromosomal amplification of chromosome 21 acute lymphoblastic leukemia.

within all BCP-ALL cytogenetic subgroups; however, it is more prevalent in some groups than others. For example, it is present in approximately 50% of the B-other-ALL subgroup, Ph-like ALL[31,57] and 20% of iAMP21-ALL.[10] Notably, *CRLF2*-d occurs in around 60% of patients with Down syndrome ALL.[58] The prognostic relevance of *CRLF2*-d is unclear. While some studies have reported poor EFS for *CRLF2* rearranged patients, in other cohorts the outcome has been reported as intermediate.[56,59,60] For example, *CRLF2*-d patients treated on the UK treatment trial, ALL97, had a similar outcome to those in the intermediate

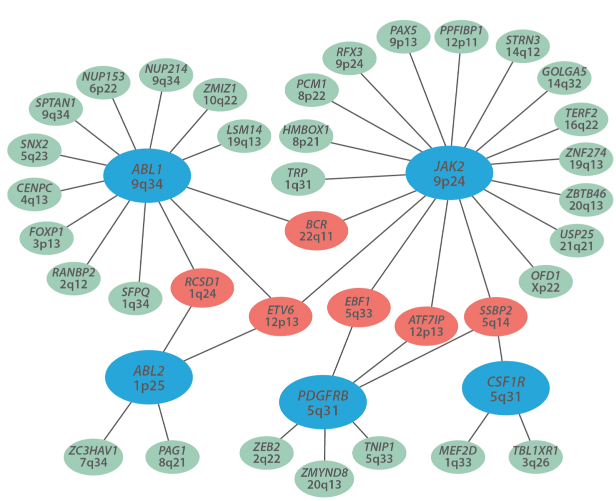

Figure 5. Network of gene fusions reported in Ph-like/*BCR-ABL1*-like ALL. Kinase genes are shown in blue. Gene partners of multiple kinases are shown in red and those so far identified as partner of single kinases are shown in green. ALL = acute lymphoblastic leukemia.

cytogenetic risk group (OS at 5 years 81% vs 85%). In around 40% of patients, the *CRLF2* rearrangement is accompanied by activating mutations of *JAK1* or *JAK2*, resulting in constitutive JAK-STAT signaling.[60] It has been shown that *CRLF2* rearranged cells are sensitive to JAK inhibitors, which raise the potential for targeted treatment of these patients.[61,62] In fact a Phase 2 study of the JAK inhibitor, Ruxolitinib, with chemotherapy in childhood ALL is currently in progress (ClinicalTrials.gov Identifier: NCT02723994).

Rearrangements of *JAK2* other than mutations, have been reported at a low incidence, in individual cases of ALL.[30,63] However, approximately 7% of patients within the Ph-like subgroup harbor fusion genes that preserve the kinase domain of *JAK2*.[31,64] A range of fusion partners has been reported (Fig. 5) of which the most common is *PAX5*. It fuses to *JAK2* as the result of a cryptic inversion involving the short arm of chromosome 9. The *SSBP2-JAK2* fusion arises from the translocation, t(5;9)(q14;p23). Primary patient cells harboring *JAK2* fusions have shown sensitivity to Ruxolitinib in experimental studies,[27,31,65] showing promise for targeted therapies in cases with *JAK2* rearrangements, as well as mutations.

The *EPOR* gene at 19p13, which encodes the erythropoietin receptor, is also a recurrent molecular target in Ph-like ALL.[27,31,66] The *IGH-EPOR* rearrangement has been identified from the reciprocal translocation, t(14;19)(q32;p13), readily visible by cytogenetics and FISH.[67] However, a subsequent study revealed a number of cytogenetically cryptic rearrangements involving *EPOR*, including insertions of *EPOR* into the *IGH* or *IGK* loci, as well as intrachromosomal inversions that place *EPOR* upstream of the *LAIR1* gene at 19q13.[66] Unlike t(14;19)(q32;p13), these abnormalities cannot be detected by FISH and their identification relies on Next-Generation Sequencing technologies. However, the common consequence of all *EPOR* rearrangements is over-expression of a truncated EPOR protein, which is hypersensitive to erythropoietin and results in activated JAK-STAT signaling. As for other JAK-STAT-related abnormalities, *EPOR*-rearranged patient cells show sensitivity to JAK inhibitors.[66]

DUX4-rearranged ALL

Several groups have recently described a distinct subgroup of B-other-ALL with rearrangements of the *DUX4* gene.[28,34,68] The existence of this group had long been recognized from gene expression studies, which noted a cluster of cytogenetically unclassified patients with a distinct gene expression profile.[69] Genomic studies showed that more than 50% of patients within this cluster harbored intragenic deletions of *ERG*.[38,70] *ERG* deletions occurred exclusively within this subgroup, although they were not considered to be primary genetic abnormalities, as they were often subclonal and inconsistent between diagnosis and relapse.[29,71,72] Subsequent transcriptome studies revealed that all patients with this gene expression profile showed over-expression of DUX4, driven by insertion into the *IGH* locus in the majority of cases.[28,34,68] Despite an incidence of 5% in childhood BCP-ALL, this abnormality remained elusive until recently, likely due to the small size of the rearrangement, the repetitive nature of the gene, up to 100 copies of *DUX4* can be present within a normal genome, and its location within the subtelomeric regions of both chromosomes 4 and 10. These features also mean that *DUX4* rearrangements are difficult to identify by FISH or standard techniques of PCR. Although attempts are being made to develop a simple diagnostic test to identify these patients, transcriptome sequencing remains the most reliable detection method for expression of DUX4 as well as the *DUX4* rearrangement itself. Due to the specific association between *ERG* deletions and *DUX4* rearrangements, an alternative diagnostic strategy would be to use *ERG* deletions as a surrogate marker for the identification of *DUX4* rearranged patients. Several studies have shown that deletions of *ERG* are associated with a good outcome when treated on standard therapies, which is not attenuated by the presence of poor risk features, such as loss of *IKZF1* and intermediate MRD levels.[29,72]

ZNF384 fusions

The *ZNF384* gene at 12p13 is the target of multiple recurrent translocations. Sporadic cases of *ZNF384* fusions were first described in the early 2000s from investigations into rare but recurrent translocations identified by cytogenetics, including t(12;17)(p13;q11), t(12;22)(p13;q12), and t(12;19)(p13;p13).[73–76] More recently genome and transcriptome sequencing has shown that up to 6% of children and 15% of adults with BCP-ALL harbor *ZNF384* rearrangements.[36,68,77–79] Their mutual exclusivity from other established chromosomal abnormalities has indicated that these rearrangements define a new subgroup, which has emerged from B-other-ALL. The fusion genes include almost all of the coding sequence of the *ZNF384* gene translocated to a range of 5′ partner genes, including *EP300* (22q13), *CREBBP* (16p13), *TAF15* (17q12), *SYNRG* (17q12), *EWSR1* (22q21), *TCF3* (19p13), *BMP2K* (4q21), *SMARCA2* (9q24), and *ARID1B* (6q25). Patients with *ZNF384* fusions show similar gene expression profiles, distinct from other subtypes of BCP-ALL, and share a characteristic immunophenotype with low CD10 and aberrant expression of the myeloid markers CD13 and/or CD33.[36] Further studies are required to determine the true prognostic significance of *ZNF384* rearrangements, as currently there is debate over whether the partner gene has an effect on outcome. However, overall results from small cohorts indicate that they have an intermediate prognosis.[36,78]

MEF2D fusions

Rearrangements involving the *MEF2D* gene, located to chromosome 1q22, have been reported in approximately 5% of B-other-ALL patients.[35,80] The first report of a *MEF2D* fusion in ALL was *MEF2D-DAZAP1*, occurring as a result of the translocation, t(1;19)(q22;p13).[73,81,82] More recently, novel fusion partner genes have been identified, of which *BCL9* (1q21) is the most common. The close proximity of *ZNF384* and *BCL9* on chromosome 1 has made detection of this particular fusion difficult by cytogenetics or FISH. However, as *MEF2D* fusions are frequently associated with copy number abnormalities at both the *MEF2D* and partner gene loci, copy number arrays may provide clues to the presence of these fusions, in particular *MEF2D-BCL9*.[35] Other fusion partners include *CSF1R* (5q33), *SS18* (18q11), *FOXJ2* (12p13), and *HNRNPUL1* (19q13). The *MEF2D-CSF1R* fusion, mentioned above, is associated with a Ph-like gene expression signature and cells expressing this fusion have been shown to be sensitive to TKI treatment.[35,51] The remaining *MEF2D* fusions share a distinct gene expression profile, resulting from deregulation of MEF2D targets. *MEF2D* rearrangements occur in older children and adolescents and have been associated with an inferior outcome.[35,80] Leukemic cells expressing *MEF2D* fusion have been shown to be sensitive to treatment with histone deacetylation inhibitors, highlighting the potential for targeted therapies in these patients.[35,80]

Abnormalities of *PAX5*

Cytogenetically visible abnormalities of the short arm of chromosome 9 are frequent in B-other-ALL. The majority are visible deletions of *PAX5*, which have also been observed across all BCP-ALL subtypes and are often associated with deletions of *CDKN2A/B*.[26,33,83] A number of recurrent chromosomal abnormalities, including translocations and dicentric chromosomes,[84] have been reported, particularly in B-other-ALL, in which *PAX5* is targeted.[30,83] The consequence of many of these aberrations is whole or partial deletion of the *PAX5* gene; however, a subset of them result in the expression of in-frame fusion genes encoding chimeric proteins.[85] The *PAX5* gene encodes a transcription factor, which plays a key role in B-cell commitment and maintenance.[86]

The most frequently reported abnormality is dic(9;20)(p13;q11), found in 1% to 2% of BCP-ALL overall, although it is usually restricted to the B-other-ALL subgroup, being mutually exclusive of the major cytogenetic abnormalities.[87–89] Although rearrangements may appear to be identical by cytogenetics, the breakpoints within *PAX5* and 20q11 are heterogeneous at the molecular level, suggesting that loss of genetic material rather than expression of a fusion protein is the functional consequence of this aberration.[90,91] The dicentric chromosome, dic(9;12)(p11~12;p11~13), occurs at a lower frequency than dic(9;20). It is often found within *ETV6-RUNX1* positive ALL, where it is associated with loss of the nontranslocated copy of *ETV6* and the entire *PAX5* gene.[6,92] By contrast, when it occurs in B-other-ALL, it is present as a *PAX5-ETV6* fusion.[92,93] Expression of this *PAX5-ETV6* fusion in B-cell precursor cells has been shown to alter gene expression, with an opposite dominant effect over wild-type PAX5, which is thought to be the driver of leukemogenesis in these patients.[94] *PAX5* has been described as a promiscuous gene, as many other fusion gene partners have been identified, although often only reported in few or single cases.[30,83] Therefore, elucidation of the functional consequences and prognostic significance of *PAX5* fusions remains unclear.

Intragenic amplification of *PAX5* exons 2 to 5 ($PAX5^{AMP}$) has been described in a small but distinctive subgroup of around 3% of B-other-ALL. The majority of patients with $PAX5^{AMP}$ lack the recurrent cytogenetic alterations used in risk stratification for treatment, suggesting that it defines a novel subgroup of BCP-ALL, which is relapse prone (occurring in approximately 40% of cases) and associated with a poor outcome (5-year EFS and OS rates of 49% and 67%, respectively).[95]

ETV6-RUNX1-like-ALL

Recently, a subgroup of patients with ALL have been identified, who share the same gene expression profile and/or methylation signature as *ETV6-RUNX1* positive patients, but lack the *ETV6-RUNX1* fusion.[8,34] Within this group, novel gene fusions and deletions of the *ETV6*, *RUNX1*, and *IKZF1* genes have been described. It is tempting to speculate that *ETV6-RUNX1*-like patients may also share the same good prognosis as *ETV6-RUNX1*-positive patients and indeed few relapses have been reported among them. However, the number of patients identified to date is small, highlighting the need for further trial-based studies.[34,96]

IGH rearrangements

Rearrangements involving the *IGH* locus are seen in approximately 5% of ALL overall, occurring in both the T- and B-lineage,[32] although individually they are rare. They essentially form part of the B-other-ALL group, as translocations have been noted with a range of partner genes (Fig. 3), including *CRLF2*, *EPOR*, and *DUX4*, as discussed above. Other partners have been reported, which include *IL3* at 5q31, a rare translocation with a strong association with hypereosinophilia as reported by WHO,[9] *ID4* at 6p14[97] and 5 members of the *CEBP* gene family: *CEBPA* (19q13), *CEBPB* (20q13), *CEBPD* (8q11), *CEBPE* (14q11), and *CEBPG* (19q13).[98] Whether *IGH* can define these abnormalities as belonging to an independent group is somewhat unlikely, regarding the range of functional roles of the partner genes. The important molecular consequence of all *IGH* translocations is high levels of over-expression of the partner gene as a result of its juxtaposition to the potent *IGH* enhancer. *IGH* rearrangements are present in all age groups, with the peak incidence in adolescents and young adults. Collectively, they have been associated with an adverse outcome in adults, although they did not represent an independent prognostic factor in children and adolescents.[32]

Conclusions and future perspectives

Chromosomal abnormalities have provided a reliable basis on which risk stratification of ALL has been built over the last 4 decades. As a result of continuous advances in new state-of-the-art technologies of Next-Generation Sequencing of genomes and transcriptomes, as well as improved resolution for detection of copy number changes, the identification of novel genetic abnormalities in ALL over recent years has significantly refined risk stratification algorithms. As a result, the proportion of B-other-ALL cases in which a genetic abnormality has not been identified has diminished significantly (Fig. 3). With further technological advances, it is likely that every case of ALL will become assigned to a genetic subtype of known clinical relevance. The wide choice of targeted molecular methodologies now available for the detection of the full range of genetic abnormalities means that individual laboratories can select the screening approaches most suited to their expertise and traditions, in order to achieve the same results. Targeted approaches are highly adaptable, allowing the integration of novel targets for each new abnormality as it is discovered. As many of the recently described abnormalities are rare, continued investigations at the biological and clinical levels are essential to determine their true prognostic relevance.

The explosion of technologies has not only accurately defined the genetic subtype of the majority of ALL patients, but has been instrumental in highlighting novel molecular targets for therapy. Following the paradigm changing discovery of the sensitivity of *BCR-ABL1*- positive leukemias to treatment with TKI, a range of specific genetic subtypes has been identified, which not only show response to TKI treatments experimentally, but also in patients with otherwise refractory disease, as exemplified by carriers of the ABL-class fusions, notably *EBF1-PDGFRB*. This specific modification of treatment for patients responsive to TKI has been a major breakthrough, which hopefully will be mirrored by targeted treatment of a wider range of abnormalities in the near future, to assist in reduction of toxicity associated with current conventional therapies.

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