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Genomic Characterization of Paediatric Acute Lymphoblastic Leukaemia: an Opportunity for Precision Medicine Therapeutics

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Abstract

Major advances in genetic and epigenetic profiling of acute lymphoblastic leukaemia (ALL) have enhanced the understanding of key biological subsets of *de novo* and relapsed ALL, which has led to improved risk stratification of patients. These achievements have further defined critical leukaemia-associated pathways and somatic alterations that may be preferentially sensitive to treatment with kinase inhibitors, epigenetic therapy or other novel agents. Therapeutic success in childhood ALL currently relies upon refined risk stratification of patients based on (1) underlying biological and clinical characteristics and (2) depth of initial treatment response with appropriate modulation of chemotherapy intensity. This review describes the current mutational landscape of childhood ALL and discusses opportunities for substantial improvements in survival with implementation of molecularly targeted therapies.

Keywords

acute lymphoblastic leukaemia; genomics; paediatrics; precision medicine; therapy

INTRODUCTION

Remarkable advances have been made during the past 60 years in the treatment of patients with acute lymphoblastic leukaemia (ALL), the most common childhood cancer. In the 1960s, fewer than 10% of children with ALL were long-term survivors. With contemporary therapy, 5-year event-free survival (EFS) and overall survival (OS) rates now approach or exceed 85% and 90%, respectively (Hunger, *et al* 2012) (Figure 1). Key factors contributing

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FINANCIAL DISCLOSURES AND CONFLICTS OF INTEREST

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to this dramatic improvement in outcomes include integration of central nervous system (CNS)-directed treatment and development of risk-adapted multi-agent chemotherapy regimens. Enhanced supportive care has also decreased morbidity and mortality and contributed to improved survival (Pui, *et al* 2015a).

Serial improvements in both EFS and OS first occurred with identification of superior therapeutic strategies via phase 3 clinical trials conducted by paediatric oncology consortia in Europe and in North America (Hunger, *et al* 2012, Pui, *et al* 2015a). These cooperative group trials have demonstrated that age and initial white blood cell (WBC) count are consistent predictors of outcome. Older children and/or those with higher WBC counts fare less well than younger children and/or those with lower WBC counts, probably partly due to inherent biological differences of these leukaemias (Hunger, *et al* 2012, Pui, *et al* 2015a). These key diagnostic factors were used to delineate standard risk and high risk subtypes of ALL by the National Cancer Institute (NCI)-Rome criteria (Smith, *et al* 1996). NCI-Rome risk classification is used by many paediatric oncology consortia for stratification of children with B-lymphoblastic leukaemia (B-ALL), but is not prognostic in T-lymphoblastic leukaemia (T-ALL) (Pui, *et al* 2015a).

Risk stratification of children with ALL has been further refined by development and clinical implementation of sensitive, highly reproducible minimal residual disease (MRD) response monitoring techniques. Children with MRD positivity above specific pre-defined thresholds (typically 0.01%) at the end of induction therapy have a significantly higher risk of treatment failure and/or relapse regardless of underlying leukaemia-associated alterations (Borowitz, *et al* 2015, Pui, *et al* 2015b). Recent studies have further demonstrated particularly dismal outcomes for children with B-ALL and T-ALL who remain MRD positive approximately 3 months after starting therapy (Borowitz, *et al* 2015, Schrappe, *et al* 2011).

Numerous germline genetic variants and somatic alterations have been identified in *de novo* and relapsed childhood ALL (Pui, *et al* 2015a), which may also have prognostic implications. Efforts are now ongoing to characterize the epigenetic, biochemical, and other functional sequelae of these mutations that may provide therapeutic vulnerabilities. Ultimately, tailored therapeutic strategies to target ALL-associated driver lesions and pathways may increase anti-leukaemia efficacy and decrease relapse, as well as reduce undesirable off-target toxicities.

B-CELL ACUTE LYMPHOBLASTIC LEUKAEMIA

Approximately 80-85% of paediatric ALL is of B cell origin, resulting from arrest at an immature B-precursor cell stage. Most B-ALL cases appear to arise spontaneously and are classified by the presence of recurrent somatic cytogenetic or molecular alterations (Hunger and Mullighan 2015). The underlying aetiologies of most cases of childhood ALL remain largely unknown, although various environmental, ethnic, immunological, infectious, socioeconomic and other epidemiological factors have been rigorously evaluated as potential contributors to leukaemogenesis (Wiemels 2012). Childhood ALL is also associated with uncommon constitutional leukaemia predisposition syndromes, such as trisomy 21 and *TP53*

mutations (Li-Fraumeni syndrome) (Stieglitz and Loh 2013). Rare germline *ETV6* and *PAX5* mutations and *ARID5B*, *CEBPE*, *GATA3*, and *IKZF1* polymorphisms have also been linked to increased ALL occurrence (Perez-Andreu, *et al* 2015, Shah, *et al* 2013, Zhang, *et al* 2015).

Somatic Chromosomal Gains and Losses

Hyperdiploidy—Cytogenetic and/or fluorescence *in situ* hybridization (FISH) assays are routinely used to identify structural chromosomal gains or losses within leukaemia cells (Table I). High hyperdiploidy (51-67 chromosomes per leukaemia cell, most often with +4, +6, +10, +14, +17, +18, +21 and +X) occurs in approximately 25% of childhood ALL and is more common in younger children (Paulsson, *et al* 2015). Children with high-hyperdiploid B-ALL have excellent outcomes and may be candidates for reduced-intensity chemotherapy, which has been demonstrated to minimize treatment toxicities without compromising survival (Vora, *et al* 2013). The inferior clinical outcomes previously associated with low-hyperdiploidy (47-50 chromosomes) appear to be ameliorated with contemporary therapy regimens (Hunger and Mullighan 2015, Pui, *et al* 2015a).

Hypodiploidy—Conversely, hypodiploid B-ALL (<44 chromosomes) comprises 1-2% of childhood ALL and is associated with inferior survival, particularly in those with end-of-induction MRD positivity. While many patients with hypodiploid ALL empirically undergo haematopoietic stem cell transplantation (HSCT) in first complete remission given their unfavourable prognoses, it is not clear that HSCT is necessary or will improve outcomes for all patients (Mehta, *et al* 2015, Mullighan, *et al* 2015). *TP53* mutations occur commonly in children with low-hypodiploid (30-39 chromosomes) ALL, many of whom have germline *TP53* mutations consistent with Li-Fraumeni syndrome (Holmfeldt, *et al* 2013, Safavi, *et al* 2015). Preclinical studies suggest potential therapeutic activity of phosphatidylinositol-3-kinase (PI3K) or mitogen/extracellular signal-regulated kinase (MEK) inhibitors in hypodiploid ALL (Holmfeldt, *et al* 2013, Safavi, *et al* 2015).

Recurrent Chromosomal Translocations

Sentinel chromosomal translocations occur in nearly all of childhood B-ALL, many of which have prognostic significance. Most recurrent ALL-associated translocations appear to be very early or initiating events that drive leukaemogenesis. Some rearrangements are not readily detectable by routine cytogenetic analyses of metaphase chromosomes, but can be identified via reverse-transcription polymerase chain reaction (RT-PCR) amplification of fusion genes created by these translocations or via FISH assays.

ETV6-RUNX1 Rearrangement—Approximately 25% of standard risk childhood B-ALL cases have a cryptic t(12;21)(p13;q22), which results in *ETV6-RUNX1* (*TEL-AML1*) fusion. While detection of *ETV6-RUNX1* fusions in preserved blood spots from children who subsequently develop ALL implicates potential prenatal origin of leukaemogenesis, these fusions are also detectable in children who do not develop ALL. These latter data suggest that *ETV6-RUNX1* translocations cooperate with additional necessary mutations to contribute to ALL pathogenesis (Greaves 2009). In general, children with standard risk B-ALL with *ETV6-RUNX1* fusion have extremely favourable outcomes with standard

therapy (Hunger and Mullighan 2015). As in high hyperdiploid ALL, successful treatment with lower-intensity regimens may also be feasible for some patients with *ETV6-RUNX1* ALL (Vora, *et al* 2013).

Very recently, a small number of “*ETV6-RUNX1*-like” B-ALL cases have been reported, which lack classic *ETV6-RUNX1* rearrangement, but are associated with other *ETV6* fusions and with *IKZF1* deletions. The clinical outcomes of such rare patients remain incompletely elucidated, although relapse does not appear to be common (Lilljebjorn, *et al* 2016).

TCF3 Rearrangement—Other recurrent chromosomal translocations in B-ALL include t(1;19)(q23;p13.3) resulting in *TCF3-PBX1* (*E2A-PBX1*) fusion. While previously associated with inferior prognosis, *TCF3-PBX1* rearrangement is no longer considered a poor risk factor with contemporary treatment (Felice, *et al* 2011). Although rare (<0.5% of children with B-ALL), the *TCF3-HLF* fusion resulting from t(17;19)(q22;p13.3) is associated with extremely poor outcomes (Mullighan 2012). Some preclinical studies have demonstrated activity of the tyrosine kinase inhibitor (TKI) dasatinib in *TCF3*-rearranged ALL (Lenz, *et al* 2014).

KMT2A (MLL) Rearrangement—Somatic translocations of *KMT2A* (*lysine methyltransferase 2A*; formerly *MLL*, *mixed lineage leukaemia*) occur in approximately 75% of infants with B-ALL, particularly in those <6 months of age. Interestingly, infant *KMT2A*-rearranged (*KMT2A-R*) ALL has a remarkable paucity of other genetic alterations (Andersson, *et al* 2015, Bernt and Armstrong 2011). *KMT2A* translocations also occur in about 2% of older children, adolescents and adults with ALL, with >100 fusion partners identified to date (Bernt and Armstrong 2011). Clinical prognoses vary somewhat based upon the specific *KMT2A* translocation, although outcomes of infants and children with *KMT2A-R* ALL are generally inferior to those of patients with non-*KMT2A-R* ALL. Outcomes are particularly dismal for infants diagnosed at <90 days of age, raising the question of HSCT in first complete remission for this highest-risk population, although data suggest that other infants with ALL do not benefit from HSCT (Mann, *et al* 2010).

Research to characterize dysregulated signalling and transcriptional pathways in *KMT2A-R* ALL is ongoing with a goal of identifying potential new therapeutic targets (Andersson, *et al* 2015). *FLT3* (*fms-related tyrosine kinase 3 receptor*) overexpression is common in *KMT2A-R* infant ALL (Brown, *et al* 2005). Unfortunately, addition of the FLT3 inhibitor (FLT3i) lestaurtinib to chemotherapy in infants with *KMT2A-R* ALL did not improve EFS versus chemotherapy alone (Brown, *et al* 2016). Similarly, no appreciable clinical responses were observed in infants with relapsed *KMT2A-R* ALL treated on a phase 1 trial with the selective FLT3i quizartinib and chemotherapy (Cooper, *et al* 2016). Additional investigation is thus needed to determine potential efficacy of FLT3-targeted therapies (perhaps with more potent or selective FLT3 inhibitors) in *KMT2A-R* ALL.

Another potential therapeutic approach for infant ALL relies upon the discovery of frequent epigenetic dysregulation in *KMT2A-R* leukaemias (Bernt and Armstrong 2011). Drugs targeting histone deacetylases (*e.g.*, vorinostat, panobinostat, bromodomain inhibitors) or

methyltransferases (*e.g.*, decitabine, 5-azacytidine, disruptor of telomeric silencing 1-like histone H3K79 methyltransferase [DOT1L] inhibitors) are under early-phase clinical evaluation in adults and children with *KMT2A-R* leukaemias (NCT02141828, NCT01483690, NCT01321346, NCT02828358).

BCR-ABL1 Rearrangement—*BCR-ABL1* fusion resulting from t(9;22)(q34;q11.2) (the Philadelphia chromosome, Ph⁺) occurs in nearly all patients with chronic myeloid leukaemia (CML) and a subset of patients with ALL, including 3-5% of childhood B-ALL. *BCR-ABL1* fusion results in constitutive activation of ABL1 kinase and associated downstream signalling. Most Ph⁺ ALL cases also have deletions in transcription factors that regulate B-cell development, including *IKZF1* (*Ikaros*) and *PAX5* (*paired box 5*) (Mullighan, *et al* 2009a), which has been associated with poor outcomes in both Ph⁺ and Ph⁻ ALL.

Prior to the 21st century, children and adults with Ph⁺ ALL had dismal clinical outcomes despite maximal intensity of conventional chemotherapy and frequent utilization of HSCT (Arico, *et al* 2010). Pivotal studies conducted in the early 2000s demonstrated remarkable clinical efficacy of the ABL TKI, imatinib, in adults with CML, resulting in major cytogenetic and molecular remissions. Childhood leukaemia cooperative group trials subsequently demonstrated safety of combining imatinib with intensive chemotherapy in children with Ph⁺ ALL, as well as dramatic improvements in survival (Biondi, *et al* 2012, Schultz, *et al* 2009). Mature clinical trial data now show that most children with Ph⁺ ALL can be successfully treated with imatinib and chemotherapy without the need for HSCT, and the 10-year OS for this population now approaches 80% (Schultz, *et al* 2014). These remarkable clinical responses further establish *BCR-ABL1* as a driver oncogene in Ph⁺ ALL and provides a precedent for successful precision medicine therapies in childhood ALL.

Selective pressure of imatinib therapy over time can lead to development of ABL tyrosine kinase domain (TKD) point mutations that confer reduced TKI sensitivity or overt therapeutic resistance. Limited available data suggest that *BCR-ABL1* TKD mutations occur in very small number of children with Ph⁺ ALL who relapse after imatinib and chemotherapy, presumably because combination therapy significantly overcomes selective pressure of TKI monotherapy (Cazzaniga, *et al* 2015, Chang, *et al* 2012).

Second- and third-generation ABL TKIs (*e.g.*, dasatinib, nilotinib, bosutinib, ponatinib, bafetinib) have been developed to overcome therapeutic resistance (Leoni and Biondi 2015). Many of these drugs also inhibit SRC kinases and have improved CNS penetration. While superiority of one TKI has not been definitively proven in Ph⁺ leukaemias (Leoni and Biondi 2015), comparably excellent remission rates and outcomes with dasatinib and imatinib have been demonstrated in adults with Ph⁺ ALL (Foa, *et al* 2011). In paediatric trials, treatment with combined dasatinib and intensive multi-agent chemotherapy also resulted in outstanding 3-year EFS and OS, which were analogous to outcomes of children with Ph⁺ ALL treated with continuous imatinib and chemotherapy (Schultz, *et al* 2014, Slayton, *et al* 2015). Additional trials of ABL1-targeting TKIs in children with Ph⁺ ALL are ongoing or in development.

BCR-ABL1-Like or Philadelphia Chromosome-Like ALL—Philadelphia

chromosome-like (Ph-like) or *BCR-ABL1*-like ALL is a recently-described subset of B-ALL defined by an activated kinase gene expression profile similar to that of Ph⁺ ALL and associated with a diverse range of genetic alterations that activate cytokine receptor signalling pathways (Den Boer, *et al* 2009, Mullighan, *et al* 2009a, Roberts, *et al* 2014). In paediatrics, the Ph-like subtype comprises approximately 10% of NCI standard risk and 13% of NCI high risk ALL cases. The incidence of Ph-like ALL further increases with age, accounting for 21% and 27% of B-ALL cases in adolescents and younger adults (<40 years), respectively (Roberts, *et al* 2014).

As in Ph⁺ ALL, deletions and inactivating mutations of *IKZF1* and other lymphoid-associated transcription factors genes are common in Ph-like ALL (Den Boer, *et al* 2009, Mullighan, *et al* 2009a). In North America, *CRLF2* (*cytokine receptor-like factor 2*) rearrangement with resulting gene overexpression occur in 50% of Ph-like ALL cases, including *P2RY8* (*purinergic receptor P2Y, G-protein coupled, 8*)-*CRLF2* fusions and *IGH* (*immunoglobulin heavy locus*)-*CRLF2* translocations (Mullighan, *et al* 2009b, Russell, *et al* 2009). *CRLF2* rearrangements occur more commonly in older adolescents and young adults (AYAs) and in patients of Native American and Hispanic/Latino genetic ancestry, which may contribute to differences in Ph-like ALL incidence reported in European and North American studies (Attarbaschi, *et al* 2012). Concomitant *JAK2* or *JAK1* point mutations occur in about half of *CRLF2*-rearranged ALL cases (Mullighan, *et al* 2009b, Russell, *et al* 2009).

An additional 15-20% of Ph-like ALL cases (without *CRLF2* rearrangement) activate kinase signalling via cryptic translocations involving “ABL class” genes *ABL1* (*Abelson kinase 1*), *ABL2* (*Abelson kinase 2*), *CSF1R* (*colony stimulating factor 1 receptor*) or *PDGFRB* (*platelet-derived growth factor receptor beta*) (Roberts, *et al* 2014). These rearrangements involve a diverse variety of translocation partners and encode fusion proteins that activate receptor tyrosine kinase (RTK) and non-RTK intracellular signalling. Another 10-15% of Ph-like ALL harbour *JAK2* fusions or truncating rearrangements of *EPOR*, resulting in activated JAK/STAT signalling (Iacobucci, *et al* 2016, Roberts, *et al* 2014). Other rare fusions potentially sensitive to kinase inhibitors have also been identified in Ph-like ALL (Roberts, *et al* 2014).

Importantly, children and adolescents with Ph-like ALL have high rates of treatment failure, relapse and death when treated with conventional cytotoxic chemotherapy (Den Boer, *et al* 2009, Mullighan, *et al* 2009a). Given these poor clinical outcomes and robust preclinical data demonstrating constitutive activation of kinase signalling in Ph-like ALL (Roberts, *et al* 2014), development of new therapeutic approaches is imperative. Various preclinical studies have reported *in vitro* and/or *in vivo* sensitivity of models of Ph-like ALL with ABL class fusions to imatinib and dasatinib and of *CRLF2*-, *JAK2*-, and *EPOR*-rearranged ALL models to the JAK inhibitor ruxolitinib (Iacobucci, *et al* 2016, Maude, *et al* 2012, Roberts, *et al* 2014).

Anecdotal reports of remarkable responses of children with *PDGFRB*-rearranged ALL with poor early responses to chemotherapy when imatinib or dasatinib was added to

chemotherapy have now been published (Roberts, *et al* 2014). It is now clear that *PDGFRB* rearrangements occur frequently in patients with induction failure (defined as $\geq 25\%$ residual leukaemia after induction therapy) (Schwab, *et al* 2016). Clinical testing for *PDGFRB* alterations is thus recommended for such patients.

Taken together, these data strongly suggest potential clinical efficacy of kinase inhibitors in specific subsets of patients with Ph-like ALL and raise the possibility of combinatorial therapy, either via addition of a kinase inhibitor to a chemotherapy backbone or via dual inhibitor therapy targeting discrete signalling pathways. Clinical trials are now underway (NCT01406756, NCT02723994) or under active development by paediatric oncology cooperative groups to test the efficacy of addition of dasatinib or ruxolitinib to chemotherapy for patients with Ph-like ALL harbouring ABL-class fusions or JAK pathway alterations, respectively. Such efforts have required extensive multi-disciplinary collaboration to develop testing algorithms capable of identifying the diverse milieu of Ph-like ALL genomic alterations in relative real time. Ideally, rapid identification of children and AYA with Ph-like ALL via comprehensive genomic testing will occur during induction therapy. Patients can then be allocated to clinical trials testing the efficacy of combined kinase inhibition and chemotherapy, as has been the therapeutic paradigm for Ph⁺ ALL.

Trisomy 21-Associated ALL

Children with trisomy 21 (Down Syndrome) have a 10-fold increased risk of developing B-ALL (DS-ALL), although the contribution of germline trisomy 21 to leukaemogenesis remains incompletely understood. Interestingly, DS-associated ALL is almost always B-lineage and has a lower incidence of hyperdiploidy and fewer recurrent cytogenetic translocations than in non-DS-ALL. Children with DS-ALL also have increased risk of chemotherapy-related toxicity and inferior survival (Buitenkamp, *et al* 2014).

CRLF2 rearrangements are prevalent in children with DS-ALL, occurring in 50-60% of patients. The *P2RY8-CRLF2* fusion, resulting from interstitial deletion of the pseudoautosomal region of the sex chromosomes, is most common (Russell, *et al* 2009). Concomitant JAK mutations occur in approximately 50% of *CRLF2*-rearranged DS-ALL cases, most frequently a *JAK2* R683G point mutation (Bercovich, *et al* 2008). To date, JAK inhibitors have not been formally evaluated in children with DS-ALL.

Intrachromosomal Amplification of Chromosome 21

Intrachromosomal amplification of chromosome 21 (iAMP21) was initially discovered via detection of multiple *RUNX1* copies on *ETV6-RUNX1* FISH testing. iAMP21 ALL occurs in 2% of childhood B-ALL and is more prevalent in older children and was previously associated with poor outcomes. Appropriate high-risk therapy intensification has improved survival substantially in this group of patients without the need for HSCT (Harrison, *et al* 2014). The very rare constitutional Robertsonian translocation rob(15;21)(q10;q10)c is associated with a dramatically increased risk of developing iAMP21 ALL (Li, *et al* 2014).

DUX4 Rearrangement and ERG Dysregulation

Recurrent *IGH-DUX4* (*double homeobox 4*) fusions, resulting in *DUX4* overexpression and a unique gene expression signature, were very recently reported in up to 7% of childhood B-ALL cases. *DUX4* rearrangement results in loss of function of *ERG* (*ETS-related gene*) via intragenic deletion or via induction of a dominant-negative isoform that inhibits wild-type *ERG* (Zhang, et al 2016). *ERG-DUX4* fusions have also been reported (Lilljebjorn, et al 2016). Despite frequent concomitant *IKZF1* deletions, patients with *DUX4* rearrangements appear to have excellent clinical prognoses with standard chemotherapy treatment (Clappier, et al 2014, Lilljebjorn, et al 2016, Yasuda, et al 2016, Zhang, et al 2016).

MEF2D and ZNF384 Rearrangements

Rearrangements involving *MEF2D* (*myocyte enhancer factor 2D*) or *ZNF384* (*zinc finger protein 384*) were recently described in subsets of childhood B-ALL and are associated with distinct gene expression signatures (Liu, et al 2016). *MEF2D*-rearranged ALL occurs in 3-6% of childhood B-ALL, more commonly in older children and adolescents, and may be associated with poor outcomes. Preclinical data suggest a possible role for histone deacetylase inhibitors in *MEF2D*-rearranged ALL. Rearrangements involving *ZNF384* were also recently described in approximately 3% of childhood B-ALL and appear associated with an intermediate prognosis. Preclinical data demonstrate upregulation of JAK/STAT signalling in *ZNF384*-rearranged ALL, also suggesting therapeutic potential with JAK inhibitors (Liu, et al 2016).

RAS pathway-mutant ALL

Activating mutations in various Ras pathway-associated genes, including the GTPases *KRAS*, *NRAS*, *HRAS* and *PTPN11* (*protein tyrosine phosphatase, non-receptor type 11*), *CBL* (*Casitas B-lineage lymphoma*) and *FLT3*, have been reported in various subtypes of childhood ALL, including high hyperdiploid ALL, hypodiploid ALL, infant ALL, and a subset of Ph-like ALL (Holmfeldt, et al 2013, Paulsson, et al 2015). In some studies, RAS mutations are associated with early risk of relapse and poor clinical outcomes (Irving, et al 2014), while other groups have not identified inferior clinical outcomes. Additional studies are required to clarify the driver versus passenger nature of these mutations in ALL.

Targeting of mutant *RAS* remains of great theoretical interest in human cancer, but has proven quite challenging to accomplish. Recent efforts have instead focused upon targeting aberrant MAPK or PI3K signalling networks. Preclinical studies have demonstrated enhanced sensitivity of RAS-mutant ALL cells to MEK inhibitors or PI3K/mTOR inhibitors (Dail, et al 2010, Irving, et al 2014). Clinical trials of MEK inhibitors in children with relapsed/refractory RAS-mutant leukaemias are now in development.

T-CELL ACUTE LYMPHOBLASTIC LEUKAEMIA (T-ALL)

T-ALL comprises 10-15% of childhood ALL and is more common in males, older children and adolescents, and patients of African-American ethnicity (Hunger and Mullighan 2015). While the prognosis for children with T-ALL was historically inferior to that of B-ALL, children treated with contemporary intensive therapies now achieve >85% 5-year EFS

(Hunger and Mullighan 2015, Wood, *et al* 2014). Nonetheless, T-cell immunophenotype remains an adverse risk factor in multivariate analyses of data from several childhood leukaemia clinical trials (Hunger, *et al* 2012, Vora, *et al* 2013). Unlike in B-ALL, age at diagnosis and presenting WBC count have very little prognostic impact in T-ALL and are not used for risk stratification of patients (Pui, *et al* 2015a). Genomic alterations in T-ALL are frequently cytogenetically cryptic, and the prognostic significance of recurrent T-ALL-associated mutations remains incompletely understood (Figure 2, Table I). Risk stratification of patients with T-ALL instead is largely determined by CNS status and early response to therapy, as measured by MRD testing (Schrappe, *et al* 2011, Wood, *et al* 2014).

While exciting advances have occurred in genomic characterization of T-ALL, development of precision medicine treatment approaches for T-ALL has proven more challenging. The nucleoside analogue nelarabine demonstrated impressive early activity in patients with relapsed/refractory T-ALL, but was associated with neurotoxicity that precluded further clinical testing for some time. Subsequently, the safety of adding nelarabine to multi-agent chemotherapy for children and AYAs with newly diagnosed T-ALL was demonstrated. Ongoing analyses of the recently completed Children's Oncology Group (COG) AALL0434 clinical trial will determine whether addition of nelarabine to combination therapy improves outcome (Winter, *et al* 2015). A current COG phase 3 trial is studying the potential for enhanced activity of chemotherapy combined with the proteasome inhibitor bortezomib in children and adolescents with *de novo* T-ALL (NCT02112916).

Recurrent Chromosomal Translocations

T Cell Receptor Gene Rearrangement—Approximately 50% of childhood T-ALL cases have chromosomal translocations involving fusion of T-cell receptor genes to oncogenes or interstitial deletions resulting in juxtaposition of two genes. Comprehensive expression profiling studies have also more fully characterized the genomic and epigenomic landscape of these leukaemias. These data have facilitated “binning” of T-ALL into four major subtypes: (1) *TLX1* (previously termed *HOX11*), (2) *LYL1*, (3) *TAL1/LMO2*, and (4) *TLX3* (previously termed *HOX11L2*) (Van Vlierberghe and Ferrando 2012). While the prognostic and therapeutic significance of these T-ALL subsets has not been well-elucidated, patients with *TLX1* alterations appear to have more favourable responses to standard therapy. Other rare alterations in T-ALL include t(8;14)(q24;q11) resulting in *TRA-MYC* or *TRD-MYC* fusion (Van Vlierberghe and Ferrando 2012).

KMT2A Rearrangement—As in B-ALL, 11q23 translocations resulting in *KMT2A* rearrangement have been reported in 10-15% of T-ALL. It is not known whether *KMT2A-R* T-ALL cases overexpress wild-type FLT3, as in infant B-ALL, or if FLT3 inhibitors could improve outcomes for such patients.

PICALM-MLLT10 Rearrangement—Occurring also in acute myeloid leukaemias (Savage, *et al* 2010), the t(10;11)(p13;q21) translocation resulting in PICALM (phosphatidylinositol binding clathrin assembly protein)-MLLT10 (mixed-lineage leukaemia; translocated to 10) (previously termed *CALM-AF10*) fusion has been associated

with particularly poor survival in children with T-ALL. More recent data demonstrate intermediate outcomes with intensive therapy (Lo Nigro, *et al* 2013).

ABL1 Rearrangement—*NUP214-ABL1* fusion resulting from t(5;14) occurs in 5-10% of T-ALL. Preclinical studies demonstrate activated ABL1 kinase signalling in *NUP214-ABL1* T-ALL analogous to that of Ph⁺ and subsets of Ph-like B-ALL, as well as *in vitro* inhibition of the ABL1 target phosphoproteins CrkL and STAT5 and increased cell death with dasatinib or nilotinib treatment (De Keersmaecker, *et al* 2014, Quintas-Cardama, *et al* 2008). As predicted, anecdotal clinical efficacy of imatinib or dasatinib treatment of patients with refractory *NUP214-ABL1* ALL has also been reported (Deenik, *et al* 2009), but no well-controlled clinical trials have yet been performed.

JAK inhibition (*e.g.*, momelotinib, ruxolitinib, tofacitinib) may also have therapeutic relevance in *ABL1*-rearranged and other subsets of T-ALL. Point mutations and indels in *IL7R* (*interleukin-7 receptor*), *JAK1*, *JAK3*, and *SH2B3* (*SH2B adaptor protein 3*) genes are common in T-ALL, particularly in the early thymic precursor (ETP) subtype discussed below (Vicente, *et al* 2015). Preclinical activity of JAK inhibition was recently reported in models of childhood T-ALL (Maude, *et al* 2015a).

Alterations in X Chromosome Genes

Inactivating mutations and deletions in *PHF6* (*plant homeodomain finger 6*) occur frequently in the *TLX1*, *TAL1/LMO2*, and *TLX3* subsets. *PHF6* is involved in nucleosome remodelling and deacetylation and may function as a tumour suppressor (Van Vlierberghe, *et al* 2010). The location of *PHF6* on the X chromosome may partly explain the greater observed occurrence of T-ALL in males (Van Vlierberghe, *et al* 2010). Similarly, somatic loss-of-function mutations in the X-linked histone H3K27me3 demethylase ubiquitously transcribed X chromosome also occur frequently in T-ALL, are enriched in males, and appear sensitive *in vitro* to inhibitors of the histone methyltransferase EZH2 (Van der Meulen, *et al* 2015).

NOTCH1 Mutations

Somatic mutations in *NOTCH1*, which encodes a transmembrane receptor responsible for T-cell lineage commitment and survival, occur in >50% of T-ALL cases. Constitutive activation of PI3K/mTOR signalling has been reported in T-ALL, particularly in leukaemias with *NOTCH1* mutations or deletions of *PTEN* (*phosphatase and tensin homolog*), a negative regulator of PI3K signalling. Common cooperating deletions of tumour suppressor *CDKN2A* or mutations in ubiquitin protein ligase *FBXW7* may further enhance aberrant PI3K signalling via attenuation of NOTCH1 protein degradation (Weng, *et al* 2004).

In general, patients with *NOTCH1*-mutant T-ALL have favourable outcomes with standard chemotherapy treatment. Nonetheless, the high frequency of *NOTCH1* mutations in T-ALL has inspired significant efforts to develop new treatment approaches that may further improve outcomes. In addition to potential therapeutic relevance of PI3K inhibition, anti-NOTCH1 antibody immunotherapies and gamma secretase inhibitors (GSIs) that block NOTCH1 degradation have been investigated. While preclinical studies of GSIs demonstrated remarkable leukaemia cytotoxicity (Real, *et al* 2009), the significant on

target/off tumour gastrointestinal toxicity of first-generation GSIs has limited their clinical efficacy to date. Clinical testing of newer GSIs with more favourable toxicity profiles is currently in progress in adults with relapsed T-ALL (Papayannidis, *et al* 2015).

Early Thymic Precursor ALL

The early thymic precursor or early T-cell precursor (ETP) subtype comprises 10-15% of childhood T-ALL and is diagnosed by its characteristic immature flow cytometric immunophenotype (CD1a⁻, CD8⁻, CD5⁻ or CD5^{dim} with co-expression of myeloid or stem cell markers) (Coustan-Smith, *et al* 2009). Association of ETP-ALL with high rates of chemoresistance and relapse and dismal clinical outcomes was initially reported (Coustan-Smith, *et al* 2009). Data from more recent clinical trials showed that children and AYAs with ETP-ALL responded more slowly to induction chemotherapy and had frequent end-induction MRD positivity when compared to those with non-ETP-ALL. However, most patients with ETP-ALL achieved molecular remission after three months of chemotherapy, and recent cooperative group data demonstrate comparable outcomes of children with ETP-ALL and non-ETP ALL when stratified by MRD responses with an overall 80-85% 5-year EFS (Patrick, *et al* 2014, Wood, *et al* 2014).

As in other ALL subtypes, frequent activating mutations in RAS pathway and cytokine receptor signalling genes, IL7R pathway genes and haematopoietic development and histone modification genes have been reported in ETP-ALL (Zenatti, *et al* 2011, Zhang, *et al* 2012). The mutational landscape of ETP-ALL has striking similarity to that of myeloid leukaemias, suggesting that ETP-ALL may be part of a spectrum of leukaemias arising from very early haematopoietic progenitor cells and/or stem cells. Preclinical studies in childhood T-ALL (including ETP) models demonstrate potential therapeutic efficacy of targeting activated cytokine receptor signalling networks with FLT3, JAK, or PI3K/mTOR inhibitors (Maude, *et al* 2015a, Neumann, *et al* 2013).

RELAPSED ALL

Modern risk stratification and appropriate therapeutic intensification have resulted in markedly improved outcomes for children with ALL. While relapse risk is now known to be greatest in genomically-defined high-risk subsets of childhood ALL, leukaemia recurrence occurs across the genetic spectrum. Relapsed ALL is frequently associated with treatment resistance, possibly arising from enrichment of pre-existing resistant subclone(s) and/or from mutation acquisition during chemotherapy exposure (Hunger and Mullighan 2015). The roles of leukaemia oligoclonality in initial chemotherapy responses and at time of leukaemia recurrence remain incompletely understood, but are probably critical determinants of relapse risk and of durable remission (Gaynon and Sun 2016).

Detailed genomic profiling of matched diagnosis, remission and relapsed ALL specimens has furthered our understanding of clonal evolution, chemoresistance mechanisms, and evolution of new genetic mutations (Irving, *et al* 2016, Ma, *et al* 2015, Mullighan, *et al* 2008). Most relapsed ALL specimens preserve key genetic features present at initial diagnosis, particularly sentinel chromosome translocations that are probably very early (possibly initiating) events in leukaemogenesis. However, new genetic alterations are

detectable in nearly 100% of relapsed ALL cases, which imply further dynamic evolution of leukaemogenesis at recurrence (Ma, *et al* 2015). These studies further demonstrate the eradication of initial diagnostic bulk leukaemia clone and persistence of rare, pre-existing mutation-prone subclones. Genome-wide association studies have also identified enrichment of several germline single nucleotide polymorphisms in children with relapsed ALL (Yang, *et al* 2009).

Approximately 20% of relapsed ALL specimens harbour mutations in *CREBBP* (*CREB-binding protein*) (Malinowska-Ozdowy, *et al* 2015, Mullighan, *et al* 2011). The *CREBBP* (also known as CBP) protein functions in glucocorticoid-mediated transcription and histone deacetylation, and preclinical activity of histone deacetylase inhibitors in chemoresistant ALL has been reported (Gang, *et al* 2014, Mullighan, *et al* 2011). Co-occurrence of *CREBBP* and *KRAS* mutations has also been observed frequently in relapsed ALL, which suggests potential therapeutic efficacy of MEK or PI3K/mTOR pathway inhibition (Malinowska-Ozdowy, *et al* 2015). To date, clinical investigation of kinase inhibitors in children with relapsed/refractory ALL has largely focused upon mTOR inhibition in combination with chemotherapy (NCT01523977, NCT01614197, NCT01403415).

Gain-of-function somatic mutations in *NT5C2* (*5'-nucleotidase, cytosolic II*) have also been identified in nearly 20% of children with relapsed B- or T-ALL, particularly those who relapse while receiving maintenance chemotherapy (Meyer, *et al* 2013, Tzoneva, *et al* 2013). The *NT5C2* enzyme is involved in nucleoside analogue metabolism and inactivation. Similarly, relapse-specific mutations in *PRPS1* (*phosphoribosyl pyrophosphate synthetase I*) were recently reported in up to 7% of relapsed B-ALL cases, which appeared to occur independently of *NT5C2* mutations (Li, *et al* 2015). In mechanistic studies, *PRPS1*-mutant leukaemia cells were associated with impaired thiopurine metabolism and decreased conversion of 6-mercaptopurine to 6-thioguanine and its metabolites (Li, *et al* 2015). Taken together, the frequent acquisition of *NT5C2* and *PRPS1* mutations in children with relapsed ALL highlights their probable role in conferring decreased sensitivity to anti-metabolite chemotherapies and facilitating chemoresistant relapse.

Activating mutations in RAS pathway-associated genes (*e.g.*, *KRAS*, *NRAS*, *FLT3* and *PTPN11*) have also been identified in up to 50% of relapsed ALL cases, and potent anti-leukaemic activity of MEK inhibition in preclinical models of RAS-mutant childhood ALL has been reported (Irving, *et al* 2014). Deletions in the DNA mismatch repair gene *MSH6* and the glucocorticoid receptor *NR3C1* and mutations in the H3K36 trimethyltransferase *SETD2*, the lysine-specific demethylase *KDM6A*, and the epigenetic regulator *KMT2D* (previously termed *MLL2*) have also been reported, further highlighting the genomic complexity of relapsed ALL and potential for alternative therapies (Mar, *et al* 2014, Yang, *et al* 2008).

SUMMARY: GENOMICS INFORM THERAPEUTICS

The complete genomic, epigenomic and transcriptomic landscape of *de novo* childhood ALL remains incompletely defined, as highlighted by recent discovery of *IGH-DUX4* fusions in 5-10% of B-ALL (Lilljebjorn, *et al* 2016, Yasuda, *et al* 2016, Zhang, *et al* 2016). Recent

observations of frequent chemoresistance-associated mutations and leukaemia-predisposing gene polymorphisms further highlight the dynamic biological complexity of ALL. Continued elucidation of the biology of this remarkably genetically heterogeneous group of diseases and its associated biochemical, immunological and transcriptional sequelae will continue to inform risk stratification of patients.

Clinical development of “more tailored, less toxic” precision medicine therapies for children with ALL will continue to rely upon sensitive diagnostic testing to identify known (and currently unknown) prognostic leukaemia-associated alterations and to assign patients to appropriately intensive therapy. The rapidity and depth of leukaemia remission after induction chemotherapy remain critical determinants of long-term outcomes (Conter, *et al* 2014, Paganin, *et al* 2014). However, the years of multi-agent chemotherapy required to achieve cure are well-associated with deleterious short- and long-term sequelae (Robison 2011). Therapeutic reduction in carefully selected lowest-risk children (*e.g.*, rapid early responders with *ETV6-RUNX1* or hyperdiploid ALL) has been investigated or is under current evaluation by several childhood cancer cooperative groups. Several studies have demonstrated excellent feasibility of this approach without compromise in cure rates (Moricke, *et al* 2008, Vora, *et al* 2013, Zenatti, *et al* 2011).

For highest risk patients with targetable genetic or epigenetic lesions, access to biologically relevant inhibitors with established safe paediatric dosing is critical. Incorporation of TKIs into chemotherapy for children with Ph⁺ ALL has provided a great paradigm for precision medicine in paediatric oncology, and similar therapeutic strategies for children with other potentially targetable ALL-associated mutations are of great interest. However, such approaches are early in development.

A major obstacle in successful clinical realization of precision medicine approaches in childhood ALL is that new agents are usually first studied as monotherapy in patients with multiply relapsed disease. While phase 1 trials are critical to assess drug safety and to define a tolerable dose, these studies do not always include patients with defined genetic mutations who are predicted to respond to a novel agent. Furthermore, lack of therapeutic efficacy in the phase 1 setting does not necessarily predict clinical responses in children with *de novo* ALL or when the agent is administered on a chemotherapy backbone. It is becoming increasingly apparent that combination therapies are probably required to achieve long-term cure and to minimize development of resistance mutations and escape pathways. Finally, clinical trials to evaluate new drugs in increasingly smaller genetically- or epigenetically-defined “boutique” subsets of patients will surely require (a) comparison to accurate historical control data for standard chemotherapy treatment and (b) development of robust biomarkers to most accurately define biological activity and to prioritize further drug development. Innovative trial designs and international collaboration among childhood cancer consortia are probably necessary to maximize efficient patient accrual and study completion.

While significant advances in the genomic characterization of childhood ALL have identified new potential therapeutic vulnerabilities, additional studies are necessary to decipher more fully the molecular dependencies of childhood ALL and to bring targeted

therapies to fullest fruition. Ultimately, it is expected that the paradigm of imatinib for Ph⁺ ALL will continue to inspire successful precision medicine treatment approaches for other genomically-defined subsets of childhood ALL that will improve outcomes and perhaps also minimize toxicities. In addition, tremendous efficacy of new CD19- and CD22-targeted antibody- and T cell-based immunotherapies has been recently reported with high rates of remission achieved in patients with multiply relapsed or refractory B-ALL (Gore, *et al* 2014, Kantarjian, *et al* 2016, Lee, *et al* 2015, Maude, *et al* 2014). These exciting new treatment modalities have potential to define new therapeutic paradigms for childhood ALL and are discussed in detail elsewhere (Jabbour, *et al* 2015, Maude, *et al* 2015b). In 2016 and beyond, the major current challenges in childhood ALL are to improve cure rates through more precise risk stratification and increased use of molecularly-targeted therapies, as well as to minimize late effects by identifying the least toxic regimens that can cure low-risk patients.

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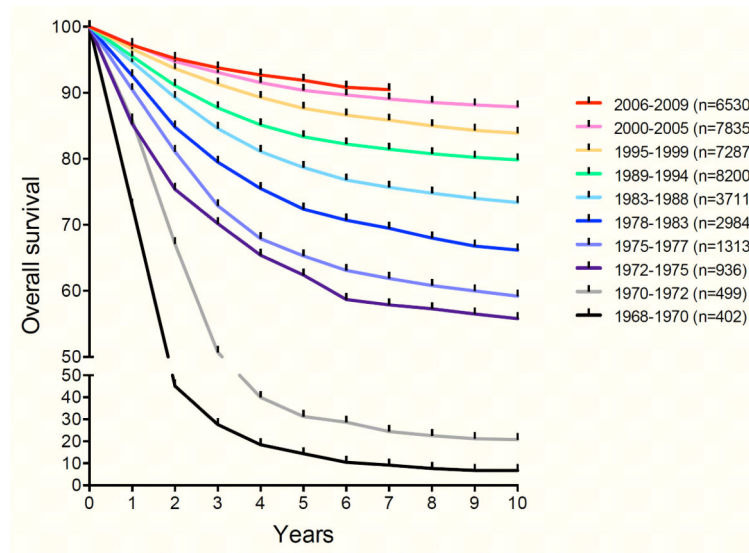


Figure 1. Improved overall survival of children with ALL treated on cooperative group trials in North America

Parentetical numbers indicate number of subjects analysed for each treatment era. Longer-term follow-up is available for some populations (not shown). Data provided by the Children's Oncology Group.

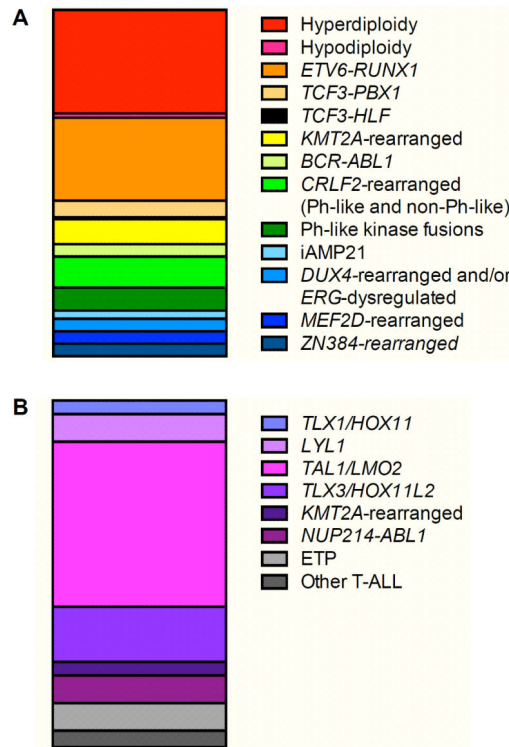


Figure 2. Recurrent genomic alterations in childhood ALL

Relative incidence of major translocations and other alterations are delineated for (A) B cell acute lymphoblastic leukaemia (B-ALL) and (B) T cell acute lymphoblastic leukaemia (T-ALL).

Table 1

Common genetic alterations in childhood ALL

Note that percentages may total more than 100% due to co-occurrence of genetic lesions. Data are summarized from those delineated in the main text and updated from Tasian *et al* (2015)

Genetic subtype	Common alterations	Frequency in ALL	Prognosis	Comment
B-ALL				
<i>Abnormalities in Chromosome Number</i>				
High hyperdiploidy (51-67 chromosomes)		25%	Favourable	
Low hyperdiploidy (47-50 chromosomes)		14%	Previously unfavourable, now intermediate	
Hypodiploidy (<44 chromosomes)	Near-haploidy (24-31 chromosomes), low-hypodiploidy (32-39 chromosomes)	1-2%	Unfavourable	Association with <i>TP53</i> mutations, <i>IKZF2</i> and <i>IKZF3</i> deletions, and RAS and PI3K pathway mutations
<i>Recurrent Chromosomal Translocations</i>				
t(12;21)(p13;q22)	<i>ETV6-RUNX1 (TEL-AML1)</i>	20%	Favourable	
t(1;19)(q23;p13.1)	<i>TCF3-PBX1 (E2A-PBX1)</i>	4%	Intermediate	
t(17;19)(q22;p13)	<i>TCF3-HLF</i>	<0.5%	Unfavourable	
<i>KMT2A (MLL) rearrangements</i>				
t(1;11)(q21;q23)	<i>KMT2A-MLLT11</i>	5-6%	Less unfavourable	Rare
t(4;11)(q21;q23)	<i>KMT2A-AFF1 (AF4)</i>		Particularly unfavourable	Comprises 50% of infant <i>KMT2A</i> -rearranged ALL
t(9;11)(p22;q23)	<i>KMT2A-MLLT3 (AF9)</i>			Comprises 15% of infant <i>KMT2A</i> -rearranged ALL
t(10;11)(p12;q23)	<i>KMT2A-MLLT10 (AF10)</i>			Comprises 5% of infant <i>KMT2A</i> -rearranged ALL
t(11;19)(q23;p13.3)	<i>KMT2A-MLLT1 (ENL)</i>			Comprises 20-25% of infant <i>KMT2A</i> -rearranged ALL
Other fusion partners				
t(9;22)(q34;q11.2)	<i>BCR-ABL1</i>	3-5%	Unfavourable prior to TKI therapy, intermediate with	Associated with <i>IKZF1</i> deletions

Genetic subtype	Common alterations	Frequency in ALL	Prognosis	Comment
<i>Other</i>			TKI therapy?	
Ph-like	<i>IGH-CRLF2, P2RY8-CRLF2</i> <i>ABL1, ABL2, CSF1R, PDGFRB</i> rearrangements <i>EPOR, JAK2</i> rearrangements <i>P2RY8-CRLF2, JAK2</i> mutations	7-8% 5-6% 2% 50-60% of DS-ALL	Unfavourable Unfavourable Unfavourable Intermediate	50% of Ph-like; associated with <i>JAK1</i> and <i>JAK2</i> mutations, <i>CDKN2A/B</i> deletions, <i>IKZF1</i> deletions; increasing incidence with older age; possibly targetable with TKIs 10-20% of Ph-like; potentially targetable with TKIs 10% of Ph-like; potentially targetable with TKIs
Trisomy 21-associated ALL				
iAMP21	Multiple copies of <i>RUNX1</i>	2%	Unfavourable	Rare rob(15;21)(q10;q10)c associated with greatly increased risk of iAMP21 ALL
<i>DUX4</i> rearrangements	<i>IGH-DUX4, ERG-DUX4</i>	3-7%	Favourable	Associated with <i>IKZF1</i> deletions, <i>ERG</i> dysregulation, aberrant CD2 expression
<i>MEF2D</i> rearrangements	<i>MEF2D-BCL9, MEF2D-HNRNPUL1</i>	3-6%	Unfavourable	Multiple fusion partners, possible role for epigenetic therapies
<i>ZNF384</i> rearrangements	<i>EP300-ZNF384</i>	4%	Intermediate	Multiple fusion partners, possible role for JAK inhibitors
T-ALL				
<i>Recurrent Chromosomal Translocations</i>				
t(10;14)(q24;q11)	<i>TLX1 (HOX11)</i> fusions	5-10% of T-ALL	Favourable	Associated with <i>PHF6</i> mutations
t(7;19)(q34;p13)	<i>LXL1</i> fusions	10% of T-ALL	Unfavourable	
t(1;14)(p32;q11), t(1;7)(p32;q34), t(11;14)(p15;q11), t(11;14)(p13;q11)	<i>TAL1, LMO1, LMO2</i> fusions	50-60% of T-ALL	Unfavourable	Associated with <i>PHF6</i> mutations
t(11;14)(p15;q11), t(5;14)(q35;q32)	<i>TLX3 (HOX11L2)</i> fusions	20-25% of T-ALL	Unfavourable (some studies), intermediate (some studies), favourable (some studies)	
t(8;14)(q24;q11)	<i>TRA-MYC, TRC-MYC</i>	1% of T-ALL	Probably unfavourable	Associated with MYC activation and aggressive phenotype
7p15 translocations	<i>HOXA10, HOXA9</i> overexpression	3% of T-ALL	Unfavourable	

Genetic subtype	Common alterations	Frequency in ALL	Prognosis	Comment
<i>KMT2A</i> (11q23) rearrangements	<i>KMT2A-AFF1</i> , <i>KMT2A-MLL1</i>	5% of T-ALL	Possibly favourable	
t(10;11)(p13;q21)	<i>PICALM-MLL10 (CALM-AFI0)</i>	5-10% of T-ALL	Unfavourable (some studies), intermediate (other studies)	Associated with <i>EZH2</i> alterations
t(9;14)(q34;q32)	<i>NUP214-ABL1</i>	5-15% of T-ALL	Unfavourable (some studies), intermediate (other studies)	Associated with <i>TLX1</i> and <i>TLX3 (HOX11L2)</i> overexpression
<i>Other</i>				
<i>NOTCH1</i> mutations		50-60% of T-ALL	Favourable	Associated with <i>CDKN2A</i> and <i>FBXW7</i> deletions
ETP		10-15% of T-ALL	Unfavourable (some studies), intermediate (other studies)	Associated with Ras pathway mutations; characteristic immunophenotype (CD1a-, CD8-, CD5- or CD5-dim with co-expression of myeloid or stem cell markers)
<i>FBXW7</i> mutation		15% of T-ALL		Associated with <i>NOTCH1</i> activation via impairment of proteasomal degradation of <i>NOTCH1</i>
Other T-ALL		6% of T-ALL		
Relapsed ALL				
	<i>CREBBP</i> mutation	20% of relapsed ALL		Associated with chemotherapy resistance
	<i>NT5C2</i> mutation	20% of relapsed ALL		Probably confers resistance to glucocorticoids
	<i>PRPS1</i> mutation	7% of relapsed ALL		Probably confers resistance to nucleoside analogues
	<i>MSH6</i> deletion			Probably confers resistance to nucleoside analogues
	<i>NR3C1</i> deletion			Probably confers resistance to nucleoside analogues
	<i>SETD2</i> mutation	12% of relapsed ALL		Suggests possible role for epigenetic therapies
	<i>KDM6A</i> mutation			
	<i>KMT2D (MLL2)</i> mutation			

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Genetic subtype	Common alterations	Frequency in ALL	Prognosis	Comment
	RAS pathway mutations	30-50% of relapsed ALL		

ALL = acute lymphoblastic leukaemia; B-ALL = B cell acute lymphoblastic leukaemia; DS-ALL = Down syndrome-associated ALL; iAMP21 = intrachromosomal amplification of chromosome 21; T-ALL = T cell acute lymphoblastic leukaemia; TKI = tyrosine kinase inhibitor.