# Genetic and Epigenetic of Pediatric Acute Lymphoblastic Leukemia

Subjects: Allergy

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Acute lymphoblastic leukemia is the most common malignancy in children and is characterized by numerous genetic and epigenetic abnormalities. Epigenetic mechanisms, including DNA methylations and histone modifications, result in the heritable silencing of genes without a change in their coding sequence.

Keywords: pediatric acute lymphoblastic leukemia ; genomics ; epigenetics

## 1. Introduction

Leukemia is the most common malignancy in children and adolescents, and is responsible for a third of childhood cancer deaths. Most childhood leukemias are acute lymphocytic leukemia (ALL), followed by acute myeloid leukemia (AML), and chronic leukemias are rare in children. ALL results from the clonal proliferation of lymphoid stem or progenitor cells, with more than 80% being originated from B-cell progenitors (B-ALL) [1]. Both B-ALL and T-ALL immunophenotype groups comprise multiple subtypes defined by chromosome alterations that are believed to be leukemia-initiating lesions.

## 2. Genetic and Epigenetic Characteristics of Pediatric ALL

### 2.1. B-Cell Acute Lymphoblastic Leukemia (B-ALL)

B-cell acute lymphoblastic leukemia is the most common form of ALL, and accounts for approximately 80–85% of pediatric ALL, resulting from arrest at an immature B-precursor cell stage. Although various environmental, ethnic, socioeconomic, infectious, immunological factors have been evaluated as potential contributors to leukemogenesis, the underlying etiologies of most cases of pediatric ALL remain unknown [2]. Most cases of B-ALL appear to arise spontaneously and are classified by the presence of recurrent somatic cytogenetic or molecular alteration [3]. The three major types of genetic alteration are chromosomal aneuploidy, rearrangements and point mutations (**Table 1**). Accumulating evidence suggests that the pathogenesis and phenotypic characteristics of leukemia are the results of the combination of specific targeted and genome-wide alterations of DNA methylation [4]. In addition, aberrant promoter methylation is associated with cytogenetic alterations [5], cytogenetic subtypes [6], prognosis [7], and relapse [8].

**Table 1.** Genetic alterations and potential targeted therapy in pediatric B- and T-acute lymphoblastic leukemia.

| Classification | Frequency | Prognosis | Potential Therapeutic Implications |
|---|---|---|---|
| **B-cell acute lymphoblastic leukemia** | | | |
| **High hyperdiploidy (HeH)** | **~25% of pediatric ALL** | **Excellent prognosis** | **Reduction of intensity** |
| **Hypodiploidy** | **~1–2% of ALL** | **Inferior survival** | **BCL2 inhibitors** |
| **t(12;21)(p13;q22) encoding *ETV6-RUNX1*** | **~25% of standard risk pediatric B-ALL** | **Excellent prognosis** | **Reduction of intensity** |
| ***ETV6-RUNX1*-like** | | **Favorable prognosis** | **Reduction of intensity** |
| ***KMT2A* (*MLL*) rearranged** | **~75% of infants with B-ALL** | **Dismal survival** | **DOT1L inhibitors, menin inhibitors, proteasome inhibitors, HDAC inhibitors, BCL2 inhibitors** |

| Classification | Frequency | Prognosis | Potential Therapeutic Implications |
|---|---|---|---|
| t(9;22)(q34;q11.2) encoding *BCR-ABL1* | 3–5% of pediatric B-ALL | Historically poor prognosis, improved with tyrosine kinase inhibitors | ABL1 inhibitors, FAK inhibitors, rexinoids, BCL2 inhibitors |
| t(1;19)(q23;p13.3) encoding *TCF3-PBX1* | 4% of ALL | Favorable prognosis | |
| iAMP21 | ~2% of pediatric B-ALL, older children | High-risk therapy for good outcomes | Intensification of therapy |
| Ph-like | 12–15% of pediatric B-ALL | Poor survival | ABL1 inhibitors, JAK inhibitors, PI3K inhibitors, BCL2 inhibitors |
| *DUX4* rearranged | 7% of childhood B-ALL | Favorable prognosis | Reduction of intensity |
| *MEF2D* rearranged | 3–6% of childhood B-ALL | Poor survival | HDAC inhibitors |
| *ZN384* rearranged | 3% of childhood B-ALL | Intermediate prognosis | FLT3 inhibitors |
| *NUTM1* rearranged | 1–2% of pediatric B-ALL | Excellent prognosis | HDAC inhibitors, bromodomain inhibitors |
| T-cell acute lymphoblastic leukemia | | | |
| *NOTCH1* mutation | >50% of childhood T-ALL | Favorable outcomes | Standard chemotherapy |
| *TAL1* deregulation | 30% of childhood T-ALL | Enrichment of mutations in PI3K signaling pathway | PI3K inhibitors, nelarabine, BCL2 inhibitors |
| *TLX3* deregulation | 19% of childhood T-ALL | Poor prognosis | Nelarabine, BCL2 inhibitors |
| *HOXA* deregulation | 5% of childhood T-ALL | Frequent mutations in JAK-STAT pathway, *KMT2A* rearrangements | JAK inhibitors, nelarabine, BCL2 inhibitors |
| *TLX1* deregulation | 8% of T-ALL | Favorable prognosis | Nelarabine, BCL2 inhibitors |
| *LMO2/LYL1* deregulation | 13% of childhood T-ALL | Poor prognosis | JAK inhibitors, nelarabine, BCL2 inhibitors |
| *NUP214-ABL1* with 9q34 amplification | ~5–10% of childhood T-ALL | Neutral prognosis | ABL1 inhibitors, nelarabine, BCL2 inhibitors |
| *NKX2-1* deregulation | 8% of T-ALL | Frequent co-operating mutation in ribosomal genes | Nelarabine, BCL2 inhibitors |
| Early T-cell precursor ALL | 10–15% of T-ALL | Poor prognosis | JAK inhibitors, BCL2 inhibitors |

#### 2.1.1. High Hyperdiploidy (HeH)

High hyperdiploidy (51–67 chromosomes per leukemia cell) is a common subtype of pediatric ALL, and occurs in approximately 25% of childhood ALL [9]. HeH is characterized by the nonrandom gain of chromosomes 4, 6, 10, 14, 17, 18, 21, and X [10], and the most prominent epigenetic feature of HeH is a strong hypomethylation signature compared to the other ALL subtypes [11]. Paulsson et al. suggested that chromosomal gains were early driving events in HeH pathogenesis through whole-genome sequencing, and they found that HeH is associated with mutations in the Ras pathway, chromatin modifiers such as *CREBBP* [9]. The patients with high-hyperdiploid B-ALL have excellent outcomes, and the inferior clinical outcomes previously associated with low-hyperdiploidy (47–50 chromosomes) appear to be improved with contemporary therapy [12].

#### 2.1.2. Hypodiploidy

Hypodiploid B-ALL (less than 44 chromosomes) accounts for 1–2% of pediatric ALL and is associated with inferior survival, especially in those with end-of-induction minimal residual disease (MRD) positivity [13]. *TP53* mutations commonly occur in children with low-hypodiploid (30–39 chromosomes) ALL [14]. Low hypodiploidy (31–39 chromosomes) occurs in 1% of children with ALL but in more than 10% of adults. Holmfeldt et al. found that low hypodiploidy is characterized by the deletion of *IKZF2* and by near- universal *TP53* mutations and can be inherited in approximately half

the patients [14]. Another chromosomal aneuploidy is near haploidy (24–30 chromosomes), which is present in approximately 2% of children with ALL and is associated with Ras mutations and deletions of *IKZF3*. The latter two chromosomal alterations are both associated with unfavorable outcomes [15].

#### 2.1.3. ETV6-RUNX1 Rearrangement

The *ETV6-RUNX1* fusion gene occurs in approximately 25% of standard-risk childhood B-ALL cases who have a t(12;21)(p13;q22), and is a favorable prognostic marker [13]. Greaves et al. suggested that *ETV6-RUNX1* translocations cooperated with additional necessary mutations to contribute to ALL pathogenesis [16]. *ETV6-RUNX1*-like ALL is characterized by a gene expression profile and immunophenotype ($CD27^+$, $CD44^{low/negative}$) similar to that of ALL with *ETV6-RUNX1* rearrangement [17][18]; this subtype occurs almost exclusively in children (approximately 3% of pediatric ALL) and is associated with relative favorable outcomes [19].

#### 2.1.4. KMT2A Rearrangement

Lysine-specific methyltransferase 2A (*KMT2A*) is a promiscuous gene with more than 80 different gene-fusion partners, which is also known as *MLL* (mixed-lineage leukemia) [20]. In addition, the somatic translocation of *KMT2A* occurs in approximately 75% of infants with B-ALL, especially in those <6 months of age [13], which comprise a distinct disease entity with an aggressive disease with poor prognosis [21]. Approximately 2% of older children, adolescents, and adults with ALL also have *KMT2A* translocation, and more than 100 fusion partners have been identified to date [22]. Infants with *KMT2A* rearrangement ALL have a remarkable paucity of other genetic abnormalities, but display typical DNA methylation profiles [23]. In addition, the DNA methylation pattern might underlie functionally relevant changes depending on the translocation partner of *KMT2A*. Pediatric ALL with *KMT2A* rearrangement are generally inferior to those of patients with non-*KMT2A* rearrangement ALL, and infants diagnosed at <90 days of age have a particularly dismal outcome [13].

#### 2.1.5. BCR-ABL1 Rearrangement

Philadelphia chromosome (Ph+) or t(9;22)(q34;q11.2) occurs in 3–5% of childhood B-ALL and nearly all patients with chronic myeloid leukemia (CML), which results in *BCR-ABL1* fusion gene [13]. *BCR-ABL1* fusion is a prognostic indicator of an advanced disease and a biomarker for targeted therapy with imatinib or dasatinib [24]. A multi-center randomized clinical study that we did in collaboration with St Jude Children's Research Hospital showed that pediatric patients who received chemotherapy with dasatinib had better EFS, overall survival (OS), and CNS disease control when compared to patients who received imatinib [25]. *BCR-ABL1* fusion is the most difficult subtype of ALL to distinguish based on DNA methylation [26], thus the DNA methylation signatures need to be further clarified.

#### 2.1.6. TCF3 Rearrangement

*TCF3-PBX1* fusion gene results from the translocation t(1;19)(q23;p13.3) and occurs in approximately 4% of ALL cases, which is associated with an intermedia risk and more frequent CNS relapse [13]. Another rare fusion gene *TCF3-HLF* occurs in <0.5% of children with B-ALL, resulting from t(17;19)(q22;p13.3). In addition, *TCF3-HLF* fusion is associated with extremely poor outcomes [27].

#### 2.1.7. dic(9;20)

The chromosomal aberration dic(9;20)(p13.2;q11.2) occurs in up to 5% of B-ALL cases [28]. The translocation results in the loss of chromosome arms 9p and 20q and produces a fusion gene involving *PAX5* in some cases [29]. It is not yet known whether the oncogenic mechanism underlying the dic(9;20) subtypes is a gene fusion, loss of DNA from 9p and 20q, or a combination of both.

#### 2.1.8. iAMP21

Intra chromosome amplification of chromosome 21 (iAMP21) occurs in approximately 2% of childhood B-ALL and is more prevalent in older children, which was previously associated with a high risk of relapse and poor outcomes [30]. In addition, the prognosis of ALL with iAMP21 has improved with intensified treatment protocols [24]. The unifying feature of all iAMP21 cases is the amplification of the *RUNX1* locus on chromosome 21, and there is an overlapping signature between the iAMP21 and HeH cases [13].

#### 2.1.9. Philadelphia Chromosome-like ALL

*BCR-ABL1*-like or Philadelphia chromosome-like ALL is 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 signaling pathways [31]. Ph-like subtype of pediatric ALL occurs in 10% of NCI standard risk and 13% of NCI high risk ALL cases [30].

Deletions and inactivating mutations of *IKZF1* and other lymphoid-associated transcription factors genes are common in Ph-like ALL [32]. In addition, children with Ph-like ALL have high incidences of treatment failure, relapse, and death when treated with conventional cytotoxic chemotherapy [33].

#### 2.1.10. Trisomy 21-Associated ALL

Children with trisomy 21 (Down Syndrome) have a 20-fold increased risk of developing ALL (also known as DS-ALL) [34]. In addition, DS-ALL is almost always B-lineage and has a lower incidence of hyperdiploidy and fewer recurrent cytogenetic translocations than in non-DS-ALL. Buitenkamp et al. reported that children with DS-ALL have an increased risk of chemotherapy-related toxicity and inferior survival [35]. The Philadelphia chromosome-like subtype of ALL is the most common form in DS-ALL. Kubota et al. reported that hypermethylation of *RUNX1* on chromosome 21 was found in DS-ALL, and they suggested that the hypermethylation of the *RUNX1* promoter in B-cell precursors might be associated with increased incidence of B-ALL in DS patients [36].

#### 2.1.11. DUX4 Rearrangement

*DUX4* (double homeobox 4) rearrangement was reported in up to 7% of childhood B-ALL cases and results in loss of function of *ERG* (*EST-related gene*) [13]. *DUX4* rearranged B-ALL has a distinct gene expression profile and immunophenotype ($CD2^+$, $CD371^+$) [37]. *ERG-DUX4* fusion has frequent concomitant *IKZF1* deletions (approximately 40% of cases), but also has excellent clinical outcomes with standard chemotherapy [38].

#### 2.1.12. MEF2D and ZN384 Rearrangements

ALL with *MEF2D* (myocyte enhancer factor 2D) rearrangement occurs in 3–6% of childhood B-ALL, more commonly in older children and adolescents, which may be associated with poor outcomes [13]. *MEF2D*-rearranged ALL has a distinct immunophenotype ($CD10^-$, $CD38^+$), and this rearrangement results in increased HDAC9 expression and sensitivity to histone deacetylase inhibitors [39][40][41]. *ZN384* (zinc finger protein 384) rearrangements have been described in approximately 3% of childhood B-ALL, and were associated with an intermediate prognosis [1].

#### 2.1.13. NUTM1 Rearrangements

*NUTM1* (nuclear protein in testis carcinoma family 1) rearrangements occur in 1–2% of pediatric B-ALL and is associated with excellent outcome, which could be fused to genes encoding various transcription factors and epigenetic regulators, such as *ACIN1*, *BRD9*, *IKZF1*, and *ZNF618*. *NUTM1* is supposed to result in global changes in chromatin acetylation and increased sensitivity to histone deacetylase inhibitors or bromodomain inhibitors [42].

### 2.2. T-Cell Acute Lymphoblastic Leukemia (T-ALL)

T-cell acute lymphoblastic leukemia (T-ALL) are immature lymphoid tumors localizing in the bone marrow, mediastinum, central nervous system, and lymphoid organs. They account for 10–15% of pediatric and about 25% of adult ALL cases. T-ALL arises in the thymus from an immature thymocyte as a result of a stepwise accumulation of genetic and epigenetic abnormalities (**Table 1**) [43]. Epigenetically, T-ALL is characterized by the gene expression changes caused by hypermethylation of tumor suppressor genes, histone modifications, and miRNA and lncRNA alterations [43]. Compared to B-ALL, T-ALL has a worse outcome, and the prognostic significance of recurrent T-ALL-associated mutations remains incompletely understood. Despite a growing understanding of genetic abnormalities in ALL, there are currently no other known reliable molecular genetic markers than the MRD for identifying patients with a higher risk of relapse specifically in T-ALL [43]. Risk stratification of patients with T-ALL is largely determined by CNS status and early response to therapy, which are measured by MRD testing [44].

#### 2.2.1. Number and Types of Chromosomal Abnormalities

Approximately 50% of cytogenetically abnormal pediatric T-ALL cases have only one chromosomal aberration [43]. Structural chromosome changes are much more common than numerical changes, and 90% of T-ALL with single chromosomal changes are structural and 10% numerical. Therefore, T-ALL is typically karyotypically characterized by the presence of only one or a few structural chromosomal aberrations [43].

#### 2.2.2. Recurrent Chromosome Translocations

The chromosomal translocations involving the fusion of T-cell receptor genes to oncogenes or interstitial deletions leading to the juxtaposition of two genes account for about 50% of pediatric T-ALL cases [13]. These chromosomal translocations result in altered expression of the transcription factors, subsequently leading to abnormal expression of genes involved in regulation of T cell development [45]. The genomic and epigenomic profiles studies have divided T-ALL into four major

subtypes: (i) *TLX1* (T cell leukemia homeobox protein 1, previously termed *HOX11*), (ii) *LYL1*, (iii) *TAL1/LMO2*, and (iv) *TLX3* (previously termed *HOX11L2*), although the prognostic and therapeutic significance of the subtypes has not been well-elucidated [45]. Subsequently, a comprehensive genomic analysis of more than 260 pediatric and young adult T-ALL patients classified these patients into eight major groups based on the translocated gene and its dysregulated expression, including *TLX1*, *TLX3*, *TAL1*, *TAL2*, *LMO1/2*, *NKX2-1*, *HOXA*, and *LMO2-LYL1* [46].

More than 75 fusion genes have so far been reported in T-ALL, which are generated mainly through translocations, deletions, insertions [43]. Approximately 5–10% of pediatric T-ALL cases have *NUP214-ABL1* fusion resulting from t(5;14), and *KMT2A* rearrangement has been reported in 10–15% of T-ALL resulting from 11q23 [13]. *PICALM* (phosphatidylinositol binding clathrin assembly protein)-*MLLT10* (mixed-lineage leukemia; translocated to 10) fusion resulting from t(10;11)(p13;q21) has been reported to be associated with particularly poor survival in pediatric T-ALL cases [46].

#### 2.2.3. NOTCH1 Mutations

*NOTCH1* is a transmembrane heterodimeric receptor composed of two subunits, which is crucial for T-cell fate and differentiation. Insertion and deletion mutations are observed in more than 60% of T-ALL cases, causing constitutive activation of *NOTCH1* signaling [47]. Activated *NOTCH1* signaling leads to a massive expansion of immature T cells, consequently increasing the risk of additional leukemia lesion acquisition [48]. Moreover, constitutive activation of *NOTCH1* signaling might affect other signaling pathways including cell cycle and *NF-κB* signaling [49]. In addition, the inactivating mutations in the gene that encodes the tumor-suppressor *FBXW7* are also commonly observed in T-ALL patients, which regulates the proteasome-mediated deregulation of *NOTCH1*, resulting in the loss of *NOTCH1* protein deregulation and subsequent activation of *NOTCH1* signaling [50]. Although patients with *NOTCH1*-mutant T-ALL have favorable outcomes with standard chemotherapy, the high frequency of *NOTCH1* mutations in T-ALL has inspired significant efforts to develop new treatment protocols to improve outcomes.

#### 2.2.4. Early Thymic Precursor ALL

The early thymic precursor or early T-cell precursor (ETP) ALL occurs in 10–15% of pediatric T-ALL [51]. Recently, genetics studies have shed new light on the biology of ETP-ALLs, which are characterized by a distinct immunophenotype and a gene expression signature indicative of a very early arrest in T-cell development. Coustan-Smith et al. recognized the immunophenotypes of ETP-ALL, which is characterized by the absence of CD1a and CD8 expression, weak CD5, and expression of at least one or more of the following myeloid or stem-cell markers: CD117, CD34, human leucocyte antigen (HLA)-DR, CD13, CD33, CD11b, or CD65 [51]. This immunophenotype signature distinguishes ETP-ALL from all other T-ALL subtypes, including early T-ALL, late cortical T-ALL, and mature T-ALL (none-ETP-ALL). Coustan-Smith et al. reported that ETP-ALL is associated with high rates of chemoresistance, relapse, and dismal clinical outcomes [51]. However, Patrick et al. demonstrated that the rates of 5-year EFS and OS do not differ significantly between ETP-ALL and non-ETP-ALL in a study using a risk-adapted approach with intensified initial treatment [52]. ETP-ALL has been reported to have frequent activating mutations in RAS pathway, cytokine receptor signaling genes, IL7R pathway genes, and histone modification genes [53]. The *LMO/LYL1* and *TLX3*-mutated subgroups have a higher prevalence of ETP-ALL cases [54], and ETP-ALL patients show a similar mutational profile to that of AML patients, with hematopoietic stem-cell like gene expression profiles [55][56]. This evidence suggests that ETP-ALL might arise in very early progenitor cells with multi-lineage potential.

#### 2.2.5. Epigenetic Abnormalities in T-ALL

Mutations in epigenetic modifiers can change the accessibility of certain parts of chroma tin to transcription factors. If this mutation occurs at the wrong stage of T cell maturation, abnormal gene expression will occur, which leads to the pathogenesis of T-ALL. The epigenetic regulators most frequently reported to be involved in T-ALL, are *PHF6*, *KDM6A*, and the member of *PRC2*, such as *EED*, *EZH2*, and *SUZ12* [57].

The recurrent mutated genes encoding chromatin modifiers and epigenetic regulators have a higher incidence among *TLX3*-positive and *TLX1*-positive cases, and particularly inactivating mutations of the gene encoding the plant homeodomain-like finger family member *PHF6* were reported to occur in approximately 16% of pediatric and 33% of adult T-ALL cases [58]. *PHF6* inactivation is often associated with genetic abnormalities of the *JAK/STAT* pathway members, such as *IL7R*, *JAK1*, *JAK3*, and *STAT5B* [59].

*KDM6A* (also termed *UTX*) is an H3K27me3 histone demethylase that functions as a tumor suppressor gene. In addition, the loss-of-function mutations of *KDM6A* occur in approximately 5–15% of T-ALLs [60][61]. The core components of the

*PRC2* complex, including *EZH2*, *EED*, and *SUZ12*, are epigenetic modulators that mediates the methylation of H3K27. The reduction or abolishment of PRC2 activity results in the decreased level of H3K27 methylation.

# 3. Genetics and Epigenetics in Relapsed ALL

## 3.1. Genetics of Relapse

Some gene mutations have been reported to be enriched at relapse of B-ALL, such as the histone acetyltransferase gene *CREBBP*, the histone methyltransferase gene *SETD2*, and the steroid receptor gene *NR3C1* and *NR3C2* [62]. These mutations confer chemotherapy resistance and might have implications for therapeutic decisions and disease monitoring. Monitoring for the emergence of relapse-associated mutations or monitoring the dynamics of mutations clearance during induction therapy will help us to identify those patients who might benefit from early modification of therapy. Further studies will identify more relapse-associated mutations to guide therapeutic decisions [15].

## 3.2. DNA Methylation as a Biomarker to Predict Relapse of ALL

Several studies have attempted to use DNA methylation signatures to predict relapse of ALL at diagnosis. The DNA methylation patterns underlying MLL-rearranged ALL in infants have been explored, and distinct promoter CpG island methylation patterns separated different genetic subtypes. The researchers found that MLL translocations t(4;11) and t(11;19) were characterized by extensive methylation, whereas infant ALL with t(9;11) and wild-type MLL epigenetically resembled normal bone marrow. Additionally, the degree of promoter hypermethylation among infant ALL patients carrying t(4;11) or t(11;19) appeared to affect relapse-free survival and predicted a high risk of relapse [63]. More importantly, CIMP classification appears to predict relapse independently of MRD, though the pattern was observed in relatively small T-ALL sample sets [64]. One common finding in most of these studies is that the children with lower methylation levels at diagnosis were more likely to relapse compared to the patients that escaped relapse [11].

## 3.3. Histone Modifications in Relapsed ALL

Combined with posttranslational modifications of histone proteins and DNA constitute the chromatin of each cell and play a pivotal role in temporal and cell-specific regulations of gene expression. Meanwhile, dynamic modification of chromatin, which results from the interaction of histone marks and DNA methylation, may contribute to the malignant transformation of normal hematopoietic precursor cells into ALL cells. However, chemical modifications of histone proteins as epigenetic marks have been less studied than DNA methylation, especially in ALL. In addition, these important and extensively described histone protein modifications include histone lysine acetylation, histone lysine methylation, and histone phosphorylation.

Histone acetylation regulated by histone lysine acetyltransferases (KATs) and histone deacetylases (HDACs) is involved in gene transcription, chromatin structure, and DNA repair, which are basic cellular phenomena in physiology and in cancers [65][66]. CREBBP is a histone acetyltransferase that can acetylate various residues in several histones, particularly in histone H3 lysine 18 (H3K18) [67]. *CREBBP* mutations and deletions were shown to be very common in relapsed cases of B-ALL (18.3% of patients). Mar et al. subsequently reported a similar frequency of *CREBBP* gene mutations in pediatric relapsed ALL cases [68].

Methylation of various lysine residues of histone proteins is regulated by histone lysine methylases and demethylases. Several histone methyltransferases were reported to play an important role in the pathogenesis of B-ALL, especially KMT2A. KMT2A is a histone H3 lysine 4 (H3K4) methyltransferase and the methylation of H3K4 is typically associated with transcriptional activation and euchromatin [67]. *KMT2A* rearrangements are a prototypical example of leukemia driven by deregulation of the epigenetic process, which disrupt the normal function of *KMT2A* by a fusion protein partner [11]. In addition, the *KMT2A* fusion protein is regarded as a powerful cancer driven gene [23], the most common *KMT2A* rearrangement is the *KMT2A-AF4* fusion gene resulting from the translocation t(4;11)(q21;q23) in infant-ALL.

Histone phosphorylation plays an important role in transcription, chromatin condensation, mitosis, apoptosis, and DNA replication [67]. Aberrant phosphorylation of several histone proteins and mutations in genes involved in histone phosphorylation are reported in multiple cancers, but there is a lack of such reports in ALL. Janus kinase (JAK) is a site of recurrent rearrangements in ALL, and JAK2 was recently reported to be able to phosphorylate histone H3 at tyrosine 41 (H3Y41), which results in dissociation of some effector proteins from chromatin [69]. Other than that, there are no studies reporting on mutations or rearrangements involved in histone phosphorylation, further studies are needed to prove the associations of histone phosphorylation markers and ALL.

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