# Analysis and Identification of Rare and Prevalent Breakpoints in Chromosomal rearrangements in Adult and Pediatric with B-Acute Lymphoblastic Leukemia (B-ALL): A Systematic Review

Roghayeh Shahshahani MSc<sup>1</sup>, Mehri Khatami PhD<sup>\*1</sup>, Mohammad Mehdi Heidari PhD<sup>1</sup>, Parisa Naji MSc<sup>1</sup>

1. Department of Biology, Yazd University, Yazd, Iran \*Corresponding author: Mehri Khatami, Department of Biology, Yazd University, Yazd, Iran. E-mail: <a href="mailto:m.khatami@yazd.ac.ir">m.khatami@yazd.ac.ir</a>, ORCID ID: 0000-0002-5840-5399.

**Received:** 20 October 2023 **Accepted:** 30 January 2024

#### Abstract

**Background:** B-cell acute lymphoblastic leukemia (B-ALL) is a complex disorder that includes multiple genetic changes, one of the main causes of which is rare and common chromosomal translocations that lead to abnormal gene fusions. This abnormal fusion produces a new protein that causes the leukemia cells. These types of rearrangements usually occur in lymphoma and result in the movement of genetic material between different chromosomes or within chromosomes. This systematic review aims to evaluate published studies and investigate the role and importance of common and rare chromosomal translocations in the occurrence of B-ALL.

Material and Methods: This systematic review investigated and evaluated the evidence regarding the effect of chromosomal translocations in adults and pediatrics with B-ALL. This review was based on the preferred reporting items for systematic reviews and meta-analysis checklists. A literature search was conducted using international databases (such as PubMed, Web of Science, Scopus, Research Gate, Google Scholar, and Cochrane Systematic Reviews database). Only English-language articles published between January 2010 and January 2023 including MESH terms such as ALL, B-ALL, and chromosomal translocations were selected. Seventy-five related studies had the necessary criteria to be examined in the present study.

**Results:** A total of 237 articles were retrieved in the online search. The excluded articles included research on other types of leukemia in adults and children, descriptive studies, case studies, studies related to animal models of leukemogenesis, and comparisons of common treatment methods of leukemia grouping cancers. Finally, seventy-five studies were identified as eligible for inclusion in this systematic review.

**Conclusion:** This review provides a comprehensive assessment of common and rare chromosomal translocations that can lead to the development of cancer cells. Chromosomal translocations play a role as diagnostic markers and important prognostic indicators and help specialists adjust treatment approaches according to their occurrence.

Keywords: B-Cell Lymphoma, Chromosomal Translocation, Gene Fusions, Oncogene

### Introduction

B-cell acute lymphoblastic leukemia (B-ALL) is a subset of lymphoblastic leukemia characterized by the unrestricted proliferation of non-mature B cells in the bone marrow and blood, it is the most frequent pediatric tumor and also, leads to a significant level of mortality in affected adults and children (1, 2). The genetic basis of B-ALL includes a series of chromosomal translocations that lead to fusion genes of that facilitate leukemogenesis (3).

While B-ALL is more common in children, it is, however, a much more dangerous malignancy in adulthood, with a long-term survival rate of 30-40% in adults and 80-90% in children (4). B-ALL is characterized by Chromosomal changes, include hyperdiploidy which hypodiploidy with more significant than 50 chromosomes and approximately fewer than 43 chromosomes, respectively, as well as several chromosomal rearrangements.

Chromosomal translocations were observed in both pediatrics and adults. B-ALL translocations involve the fusion of genes that are normally separate on different chromosomes. The resulting fusion gene produces an abnormal protein that disrupts normal cellular processes and causes leukemogenesis (5). The most prevalent translocations in B-ALL are:

- a) t(12;21)(p13;q22), which creates the combination of *TEL* (ETV6) on 12p13 and *AML1* (*RUNX1*) on 21q22. This translocation occurs in approximately 20% of children and is associated with a favorable prognosis (6).
- t(9;22)(q34;q11),it involves exchange of genetic material between chromosome 9 and chromosome resulting in a fusion of two genes: BCR on chromosome 22 and ABL1 on chromosome 9. The BCR-ABL1 fusion gene produces an abnormal protein that has increased tyrosine kinase activity, which promotes the growth and survival of the cancer cells. c) t(1;19)(q23;p13) encoding for TCF3-PBX1 (also known as E2A-PBX1). This translocation involves the fusion of two genes: TCF3 on chromosome 19 and PBX1 chromosome 1. This on translocation is common in adolescents with an intermediate prognosis. TCF3-PBX1 fusion gene produces an affects abnormal protein that the development and function of B-cells.
- d) t(4;11)(q21;q23), the resultant *MLL-AF4* (KMT2-AF4) fusion protein is consist of *MLL* (mixed-lineage-leukemia) on chromosome 11 and *AF4* (*AFF1*) on chromosome 4. These translocations are associated with poor outcomes and are less likely to respond to treatment. These approaches have shown that chromosomal translocations play significant roles in initiating tumorigenesis, and their detection can lead to early diagnosis of B-ALL (7-9).

translocations In contrast, including t(4;14)(q35;q32), which juxtaposes IGH 14q32 DUX4 4a35. to t(5;9)(q23;q34), which sets SNX2 on 5q23 close to ABL1 on 9q34, t(5;14)(q31;q32) with create of IL3-IGH gene fusion, t(9;12)(q34;p13) that fuses JAK2 on 9p24 to *MLL* on 12p13, t(8;14)(q24;q32) with create of MYC-IGH gene fusion, and t(11;14)(q24;q32) that juxtaposes IGH on 14q32 to miR125b-1 on 11q24, are among rare translocations that found in at least few patients entirely with a poor prognosis (10-13).

Similarly, studies utilizing monozygotic twins with leukemia, retrospective analyses, and molecular screening have demonstrated these chromosomal abnormalities could result in kinase activation (ABL1, JAK2, PDGFRB), gene deletion (IKZF1, Pax5), tumor suppression gene regulation (TP53, RB1, CDKN2A/B), and overexpression in Cytokine receptorlike factor 2 (CRLF2), miR-125b-1, interleukin-3, c-MYC, and HLA-DM, etc. (3, 5).

of The identification rare **B-ALL** translocations is significant in diagnosis and treatment. Identification of fusion genes associated with rare translocation events can help in establishing an exact diagnosis, which is necessary for proper therapy (14). Many of these rare translocations are associated with a poor prognosis which highlights the importance of their identification in the clinical setting **B-ALL** translocations significant effects on the outcome and treatment of the diseases. For instance, patients with the favorable t(12;21)translocation have a better prognosis and respond well to chemotherapy, with a fiveyear survival rate of over 90%. In contrast, patients with unfavorable t(9;22) or t(4;11) translocations have a poor prognosis and are more likely to relapse after following treatment (8, 16). The purpose of this systematic review is to identify and overview the impacts of these chromosomal translocations and their role in leukemogenesis.

### **Materials and Methods**

This systematic review comprehensively searched various databases such as Google Scholar and MEDLINE /PubMed, Scopus, Research Gate, Cochrane Systematic Reviews database, and Web of Science for articles published in gene translocations in B-ALL patients from 2010 to 2023.

Based on the search strategy, this review was organized according to the PRISMA (Preferred Items for Systematic Reviews and Meta-Analyses) statement (17). To find relevant articles, patient, intervention, comparison, and outcome (PICO) research questions were asked. These questions related how to chromosomal translocations are related to the process of carcinogenesis in children and adults. The literature review excluded published before 2010 because they were The scientific journals that obsolete. contained potentially relevant studies for systematic review, including the ELSEVIER, Science Direct, HINDAWI, BLOOD, Nature, Frontiers in Oncology, MDPI, WILEY, AJSP, BMC Cancer, Cancer Research, JCI, Taylor & Francis, Research Gate, BJH were searched. No gray literature searches were conducted for this systematic review. The PubMed search was based on a mix of genetic keywords and Medical Subject Headings (MeSH) terms, which included "Acute Lymphoblastic Leukemia" OR "B-cell Acute Lymphoblastic Leukemia" OR "B-ALL" AND "Oncogene" AND "Tumor Suppressor Gene" combination with "Gene Translocation" OR "Gene Rearrangement". References were also searched for original articles and related reviews. A period of thirteen years, from January 2010 to February 2023 was selected in this research.

To avoid scattering the search, only articles written in English were selected. health clinical trial conferences, and congresses were also reviewed. Case report articles, studies that non-B-ALL included diseases, unpublished and hard-to-find theses, as well as articles published in less reputable sources, were not reviewed. Duplicate studies and reports were also removed by screening the titles. Moreover, articles related to patients with B-ALL were chosen regardless of their age and gender from different nationalities.

The selection criteria of the articles included the quality and originality of the article, the English language of the texts, access to the full texts of the articles, and complete relevance to the research topic. Another exclusion criterion was animal model studies. Regarding the quality of the searched articles, two molecular genetics expert authors independently judged the title of the articles, the journal that published the article, scientific publications, and the number of research citations to the articles. To avoid scattered work and inadvertent mistakes and to evaluate the quality of the articles more accurately, the modified Jadad guidelines (18) were used and scoring was done for each article. After evaluating the quality of the articles, the Kappa coefficient of more than 80 was considered desirable, and articles with lower values were excluded from the research list.

### **Ethical consideration**

The present study was approved by the Ethics Committee of the Shahid Sadoughi University of Medical Sciences (IR.MEDICINE.REC.1397.163).

### **Results**

### **Published articles selection**

In Figure I, the flow diagram for the article's collection was shown according to

PRISMA instructions. A total of 237 published articles were extracted through online search. After excluding duplicate articles, 190 articles remained. Also, after evaluation of the titles and abstracts, 110 articles were selected to be assessed in terms of inclusion criteria. All articles were evaluated for quality and originality. Finally, 75 studies were considered suitable enough to be included in this systematic review.

# Impact of chromosomal rearrangements in leukemia

Chromosomal rearrangement is a type of genetic mutation that changes the structure and function of chromosomes in the cells. Chromosomal rearrangement can result in the loss (deletion), gain (duplication), or exchange of genetic material (inversion or between translocation) different chromosomes, leading to abnormal gene expression and signaling pathways that depending on the type, location, and frequency the rearrangements, of promotes leukemia development progression. Chromosomal translocations are common in B-ALL that can be balanced or unbalanced, reciprocal or Robertsonian, and may cause various health problems depending on the genes involved by influencing hematopoietic cells and blocking their differentiation into mature B-cells. Consequently, it is of prime importance to consider signaling pathways, which are significant in B cell differentiation and leukemia to identify the prognosis and treatment of the diseases (19, 20). Each translocation could account different deregulations. following, most B-ALL translocations are evaluated regardless of their frequency. One of the most obvious examples is the translocation of chromosomes 9 and 22. Studies show that proto-oncogene ABL1 located on chromosome 9 can rearrange with eight different genes including BCR, ETV6, RCSD1, SFPQ, ZMIZ1, NUP214,

FOXP1, and SNX2, except for BCR, the rest of them are considered as rare rearrangements (21, 22). The incidence of the B-ALL with ABL1 fusion partners is significant, as ABL1 is a tyrosine kinase that regulates cell proliferation differentiation. Thus, leukemia may respond to tyrosine kinase inhibitors (TKIs). The most popular BCR-ABL breakpoint is t(9;22)(q34;q11), also known as the Philadelphia chromosome, and results in the fusion of two genes: BCR on chromosome 22 and ABL1 on chromosome 9. BCR-ABL fusion produces an abnormal protein that increases tyrosine kinase activity, which promotes the growth and survival of cancer cells (Table I). Thus, it is associated with poor prognosis and resistance to conventional chemotherapy. However, targeted therapy with TKI, such as imatinib has improved the outcome (23). More than two-thirds of patients have shown IKZF1 loss-of-function (a tumor suppressor gene) and RAG gain-offunction which is responsible for gene deletion (exon 3-6) and the IK6 production (24). Moreover, CDKN2A/B, a tumor suppressor gene, was deleted approximately half of patients, regardless of their age (25, 26). Similarly, the deletion in the PAX5 (paired box 5) gene been observed in 30-40% Philadelphia B-cell acute lymphoblastic leukemia cases (27). Looking at the details, one of the infrequent ABL partner genes is RCSD1, which creates an ABL1-RCSD1 fusion gene, by juxtaposing ABL1 9q34 into RCSD1 on 1q24, on t(1;9)(q24;q34), and caused 70 kb deletion at 7p12.2, which deregulates the IKZF1 gene that codes Ikaros (28). Another translocation is ETV6-ABL1 (previously known as translocation-ETS-leukemia-ABL, (TEL-ABL), which appears in approximately 25% of the B-cell precursor (BCP) ALL cases (29). Previous research has shown that hyperactive tyrosine kinase

and kinase-activating aberrations respond to specific TKIs (30). On the other hand, other translocations are extremely rare (Table II).

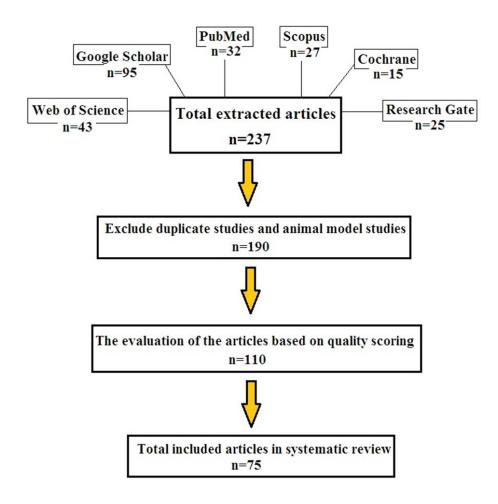


Figure 1. Flow chart of article selection steps for the systematic review

Table 1: Summarizing some of the common chromosomal translocations in adult and pediatric patients with B-ALL

Translocation	involved Genes	Clinical features	Ref.
t(9;22)(q34;q11)	BCR-ABL1	Poor prognosis; targeted by tyrosine kinase inhibitors	(31)
t(9;12)(q34;p13)	ETV6- ABL1 (TEL-ABL)	Eosinophilia appears to be a common feature of malignancies associated with the ETV6-ABL1 fusion gene.	(28)
t(12;21)(p13;q22)	ETV6-RUNX1 (TEL-AML1)	Most common in children, this rearrangement causes an increase in the expression of HLA-DR and HLA-DM molecules on the cell surface with a good prognosis.	(32)
t(1;19)(q23;p13.3)	TCF3-PBX1 (E2A-PBX1)	Common in adult and pediatric patients, it produces an abnormal protein that disrupts the unregulated B-cells and contributes to their malignant transformation, with an intermediate prognosis. This translocation affects the expression of genes that are involved in B-cell differentiation, proliferation, and survival, such as WNT16, ANKS1B, and EBF3.	(7, 33-35)
t(4;11)(q21;q23)	MLL-AF4 (KMT2A-AFF1)	A fusion protein that leads to uncontrolled cell growth and leukemia in the first year of life. Patients with this translocation show a high level of WBC with an unfavorable prognosis and relapse.	(36)
t(9;12)(p24;q11.2)	MLL- JAK2	Overexpression of JAK2 may be significant in leukemogenesis	(13)
t(11q23.3)	MLL- Various partner genes (AF9, AF10, ENL, MLLT10)	Primarily seen in infants; with poor prognosis.	(37)
t(1;9)(p13;p22)	JAK2-RNPC3	Fusion protein has an increased kinase activity, up-regulates growth and survival cells, and stimulates several signaling pathways. This fusion protein is resistant to conventional chemotherapy and has a poor prognosis.	(38)
t(5;12)(q33;p13)	PDGFRB- ATF7IP	It is classified as Ph-like ALL. Fusion protein has a receptor tyrosine kinase activity involved in various cellular processes such as growth, differentiation, migration, and angiogenesis.	(39)
t(8;14)(q24;q32)	MYC-IGH	MYC gene under the control of the IGH gene enhancer, leading to atypical expression of MYC in B-cells. This can cause abnormal B-cell survival and resistance to chemotherapy.	(40)
t(7;9)(q11;p13)	PAX5-ELN	This fusion gene produces an abnormal protein that disrupts the normal regulation of B-cells at the pre-B-cell stage and contributes to their malignant transformation. Moreover, This translocation is often associated with secondary mutations in genes that activate signaling pathways that promote cell growth, such as PTPN11, KRAS, JAK3, and PAX5 itself.	(41)

Table II: Summarizing some of the rare chromosomal translocations in adult and pediatric patients with B-ALL

Chromosomal	Gene fusion	with B-ALL Function in leukemogenesis	Ref.
translocation			
t(1;9)(p34;q34)	SFPQ-ABL1	A nuclear protein is involved in various cellular processes,	(42)
		including mRNA splicing, translation, and transcriptional	
		regulation. SFPQ-ABL1 blocks cell death and is predicted	
		to show various responses to TKI therapy.	
t(9;10)(q34;q22.3)	ZMIZ1-ABL1	It has a tyrosine kinase domain and the proline-rich	(43)
t(2,10)(q34,q22.3)	EMIEI TIBEI	•	(43)
		domains which take in protein-protein interactions and	
		promotes cellular transformation by encoding an activated	
		tyrosine kinase.	
t(3;9)(p12;q34)	FOXP1-ABL1	A transcription factor that has a significant impact on B-	(15, 44)
		cell malignancies development, treatment, and relapse.	
t(5;9)(q23;q34)	SNX2-ABL1	It belongs to the sortin nexin (SNX) family, which plays a	(11)
		role in the endocytic network (endocytosis, endosomal	
		signaling).	
t(9;9)(q34;q34)	NUP214-ABL1	This translocation is sensitive to TKI; therefore, treatment	(45)
,,,,,		with Imatinib helped the patients.	
t(1;9)(q24;q34)	RCSD1-ABL1	This translocation caused an approximately 70 kb deletion,	(21)
		which disrupted the IKZF1 gene. Deletions and mutations	
		of IKZF1 are recurring abnormalities in B-ALL and are	
		associated with a poor prognosis.	
- (4.0) ( 24.21)	GERO ARIA		(46)
t(1;9)(p34;q34)	SFPQ-ABL1	This fusion is localized to the nuclear compartment and is a	(46)
		driver for cellular proliferation, upregulation of cell cycle,	
		DNA replication, and spliceosome pathways, and	
		downregulation of signal transduction pathways, including	
		ErbB, NF-κB, VEGF, and MAPK signaling.	

t(5;14)(q31;q32)  t(8;14)(q24.1;q11.2)	IL3-IGH TRAD-MYC	This fusion is frequently found in males, and more common in older children and young adults with a poor prognosis. It leads to interleukin-3 overproduction and release of mature eosinophils in the blood.  This rare translocation leads to overexpression of MYC in B-cells, uncontrollable proliferation of cancerous cells, and CDKN2A/B gene deletion with poor prognosis.	(48)
t(8;18)(q24;q21)	MYC-BCL2	It results in BCL2 protein overexpression, and inhibition of apoptosis, because it may affect the P53 binding site, and the caspase cleavage site at D34 with a very poor overall survival.	(49)
t(4;14)(q35;q32)	IGH- DUX4	The abnormal fusion gene is characterized by the expression of DUX4, a transcription factor normally expressed only in early embryos. Moreover, DUX4 expression causes a distinctive gene expression profile and deregulation of ERG, another transcription factor that regulates B-cell development.	(12, 50)
t(6;14)(p22;q32)	IGH-ID4	This fusion disrupts the normal regulation of B cells. It is characterized by the overexpression of ID4; a gene that is associated with the helix-loop-helix transcription factors family, and can act as a tumor suppressor.	(51)
t(5;14)(q31;q32)	IGH-IL3	This translocation is associated with a unique feature of eosinophilia, a high number of eosinophil cells, a type of white blood cell that is involved in allergic reactions and parasitic infections, representing a reactive population that is stimulated by the overexpression of IL3; a gene encodes a growth factor for eosinophil cells and other blood cells.	(52, 53)

t(3;9)(p13;p13)  PAX5- FOXP1  This fusion protein may contribute to the development and progression of leukemia by acting as a dominant-negative inhibitor of PAX5 and disturbing normal differentiation programs in both adults and children. This translocation is associated with a poor prognosis and a high risk of relapse.  t(14;18)(q32;q21)  IGH-BCL2  This translocation brings the BCL2 gene under the control of the IGH gene enhancer, leading to overexpression of BCL2 in B-cells. This can cause abnormal B-cell survival
inhibitor of PAX5 and disturbing normal differentiation programs in both adults and children. This translocation is associated with a poor prognosis and a high risk of relapse.  t(14;18)(q32;q21)  IGH-BCL2  This translocation brings the BCL2 gene under the control of the IGH gene enhancer, leading to overexpression of BCL2 in B-cells. This can cause abnormal B-cell survival
programs in both adults and children. This translocation is associated with a poor prognosis and a high risk of relapse.  t(14;18)(q32;q21)  IGH-BCL2  This translocation brings the BCL2 gene under the control of the IGH gene enhancer, leading to overexpression of BCL2 in B-cells. This can cause abnormal B-cell survival
associated with a poor prognosis and a high risk of relapse.  t(14;18)(q32;q21)  IGH-BCL2  This translocation brings the BCL2 gene under the control of the IGH gene enhancer, leading to overexpression of BCL2 in B-cells. This can cause abnormal B-cell survival
t(14;18)(q32;q21)  IGH-BCL2  This translocation brings the BCL2 gene under the control (55)  of the IGH gene enhancer, leading to overexpression of  BCL2 in B-cells. This can cause abnormal B-cell survival
of the IGH gene enhancer, leading to overexpression of BCL2 in B-cells. This can cause abnormal B-cell survival
BCL2 in B-cells. This can cause abnormal B-cell survival
and resistance to chemotherapy.
t(14;17)(q32;q21) IGH-IGF2BP1 This translocation may result in the overexpression of the (56, 57)
IGF2BP1 gene, which is a proto-oncogenic RNA-binding
protein that regulates the post-transcriptional expression of
several genes involved in cell growth and survival and it is
associated with ETV6-RUNX1 translocation.
t(14;19)(q32;p13.1) IGH-EPOR This translocation causes the EPOR gene overexpression, a (58, 59)
cytokine receptor associated with kinase signaling that
stimulates the production of red blood cells. It occurs in
young patients with high levels of cellularity in their bone
marrow and blast percentages, which showed CD20
expression, and also CD13 and CD33 expression. It is
associated with a poor prognosis and a high risk of relapse
in B-ALL patients.
t(14;14)(q11;q32) IGH-CEBPE This translocation causes the CEBPE gene overexpression, (60)
which encodes a basic leucine zipper transcription factor,
which is crucial for terminal differentiation as a part of
CCAAT enhancer binding protein epsilon (C/EBP epsilon).
The CEBPE gene is mainly expressed in blood cells,
especially in granulocytes, and plays an oncogenic role,
which showed a high level of gene expression.

t(8;14)(q11.2;q32) t(X;14)(p22;q32)	IGH-CEBPD  CRLF2-IGH	This translocation causes the CEBPD gene overexpression, which encodes a basic leucine zipper transcription factor, which may affect the development and function of B cells, and it can result in TP53 locus loss, CEBPD deregulation, and high-level expression of CRLF2.  This fusion gene leads to CRLF2 overexpression, in the	(63)
t(Y;14)(p11;q32)	P2RY8-CRLF2	rare causes of B-ALL.  This fusion gene leads to CRLF2 overexpression, in the	(63)
t(8;21)(q22;q22)	RUNX1-RUNXITI	rare causes of B-ALL.  This fusion gene encodes a transcription factor that affects	(64)
		the expression of many other genes involved in blood cell development and differentiation. Hence, the fusion protein becomes an oncogene and inhibits lymphoid differentiation.	
t(11;14) (p13; q11)	TRD-LMO2	This fusion gene leads to abnormal expression of LMO2 in T-cells and B-cells, which can interfere with their normal maturation and cause them to proliferate uncontrollably.	(64)
t(11;14)(q24;q32)	IGH-miR-125b-1	It was resulting in miR-125b-1 overexpression in B-ALL patients, which is associated with anti-apoptotic effects unconnected with the p53 pathway and unrestrained proliferation and deregulates the expression of ARID3.	(10, 65)
t(8;17)(q12;p11)	NCOR1-LYN	This fusion produces an abnormal protein that causes constitutive activation of LYN kinase and downstream signaling pathways that promote cell growth and survival.	(66, 67)

t(17;19)(q22;p13)	TCF3-HLF	This translocation produces an abnormal fusion which (68)
		disrupts the normal regulation of B cells and contributes to
		their malignant transformation. It is associated with a poor
		prognosis, as patients with this translocation often have a
		high risk of relapse and death within two years of
		diagnosis.

### **Discussion**

B-ALL is the most common type of ALL, making up 80% to 85% of all cases with diverse cytogenetic features, such as aneuploidy or structural changes. The survival rate of B-ALL in children has increased significantly to approximately 90% in recent decades (69). Translocations are complex and diverse genetic alterations that affect the prognosis and treatment of the disease, as they can activate different signaling pathways that promote the growth and survival of leukemia cells (70). Thus, identifying B-cell common and rare chromosomal translocations and impact on B-ALL have revealed new information about the pathogenicity of the translocation and its correlation with leukemia. In the present review, the most and chromosomal common rare translocations that lead to B-ALL were investigated to improve our understanding of genomic and chromosomal changes in patients for more accurate diagnoses and targeted therapies in the future. Among all these chromosomal translocations, BCR-ABL1 translocation is the most common cytogenetic abnormality that affects 20 to 40% of adults and 2 to 5% of children, and its diagnosis in patients is important for choosing the type of effective treatment because the possibility of recurrence and adverse consequences of leukemia always threaten these patients (71).

According to recent studies, the ABL1 gene can rearrange with seven other genes besides BCR: ETV6, RCSD1, SFPQ, ZMIZ1, NUP214, FOXP1, and SNX2. Translocations of ABL1 with other partner genes are rarer, and there is limited information characteristics, on the morphology, response to therapy, and the future of B-ALL with these alterations. Therefore, the identification of ABL1 fusion genes in new cases is critical, as they have implications for therapeutic strategies (31, 72). Studies have shown that because the ABL1 gene produces a protein that has tyrosine kinase (TK) activity, targeted therapy with specific greatly kinase inhibitors improved patients outcomes for with ABL1 translocations (73). In addition, the IGH gene is one the infrequent genes, which affects 2-3% of B-ALL cases and there are many IGH translocations, depending on the partner gene. Generally, translocations involving the IGH locus are frequent in mature B-cell neoplasms and occur in a range of 5% and 10% in childhood and adult cases, respectively (74). Recent studies have also shown that IGH rearrangements usually involve translocations with different partner genes and can have different consequences, depending on the partner gene and the genetic background of the patient. Therefore, identifying characterizing these translocations important for better diagnosis, prognosis, and treatment of B-ALL. The main partner

genes include C-MYC, DUX4, ID4, CFRL2, IL3, IGF2BP1, and CEBPA (75). In addition, the MYC proto-oncogene regulates cell growth and division, so it could be involved in chromosomal translocations in B-ALL. Although rare, they can affect the expression of various partner genes that play an important role in normal or abnormal hematopoiesis. New findings show that TRAD-MYC translocation in B-ALL is a rare genetic abnormality that affects one in 12 patients with a highly aggressive form of B-cell progenitor acute lymphoblastic leukemia (B-ALL) that is linked to resistance to chemotherapy treatment and has a poor prognosis. The mechanism and frequency of TRAD-MYC translocation in B-ALL are not well understood, and more research is needed to identify the risk factors, markers, effective diagnostic and treatments for this subtype of leukemia (48). Moreover, double-hit lymphomas (DHL) are uncommon cancers that grow fast and are hard to treat with a low survival rate. Moreover, the diagnosis and treatment of DHL are challenging because it has a wide range of shapes and immune features. Research showed that the first of patient DHL with BCL2-MYC translocation demonstrates both DLBCL precursor B-ALL heterogeneity (immunophenotype characteristics morphology) with poor overall outcome and chemotherapy response. Finally, it is necessary to consider that these results are based on limited studies. Therefore, more research on this topic and other papers in different languages is needed.

This systematic review considers the clinical significance of translocations, which helps in a better understanding of the disease, its causes (identifying risk factors, such as genetic mutations, environmental exposures, or lifestyles that increase the risk of developing B-ALL), progression, and its treatment. Thus, the

study of B-ALL translocations in patients' profiles as new molecular biomarkers is a good diagnostic and prognostic tool for B-ALL in humans. Therefore, developing new treatments, such as targeted therapies, immunotherapies, gene therapies, and generating personalized medicine will be considered to improve outcomes and reduce side effects. Further studies on the biological processes and recognition risk factors of this topic should be addressed. There were also limitations in this systematic review. The researchers did not have access to all online articles, even after correspondence with the original authors; the full text of some articles was not available. In addition, only published English articles were considered for review and finally only databases available at Yazd University were searched.

### Acknowledgments

We sincerely thank all the authors of the articles included in this review. Also, we appreciate the officials of the central library of Yazd

### **Author Contribution**

Mehri Khatami and Mohammad Mehdi Heidari: supervising and advising the research and editing the manuscript text; Roghayeh Shahshahani: collecting data, doing experiments, and analyzing data; Parisa Naji: collecting data and analyzing data; Mehri Khatami: writing the main manuscript text.

### Conflict of interest

There are no conflicts of interest.

### **Funding**

There is no funding

## References

Iran J Ped Hematol Oncol. 2024, Vol 14, No 3, 227- 243

- Naji P, Khatami M, Heidari MM, Hashemi A, Jenabzadeh A, Chamani R, et al. Mutational Analysis of the VPREB1 Gene of Pre-BCR Complex in a Cohort of Sporadic Pediatric Patients With B-Cell Acute Lymphoblastic Leukemia. J Pediatr Hematol Oncol 2022; 44 (5): 210-219.
- 2. Naji P, Khatami M, Heidari MM, Zardini H, Chamani R. MicroRNAs as a New Molecular Biomarker for Diagnosis and Prognosis of T-cell Acute Lymphoblastic Leukemia (T-ALL): A Systematic Review. Iran J Ped Hematol Oncol 2020; 10: 184-199.
- 3. Mullighan CG. The genomic landscape of acute lymphoblastic leukemia in children and young adults. Hematol. Educ. Program Am. Soc 2014; 14 (1): 174-180.
- 4. Patel S, Mason CC, Glenn MJ, Paxton CN, South ST, Cessna MH, et al. Genomic analysis of adult B-ALL identifies potential markers of shorter survival. Leuk Res 2017; 56: 44-51.
- 5. Mullighan CG. The molecular genetic makeup of acute lymphoblastic leukemia. Hematology Am Soc Hematol Educ Program 2012; 2012: 389-396.
- 6. van der Weyden L, Giotopoulos G, Wong K, Rust AG, Robles-Espinoza CD, Osaki H, et al. Somatic drivers of B-ALL in a model of ETV6-RUNX1; Pax5(+/-) leukemia. BMC Cancer 2015; 15: 585-591.
- 7. Tirado CA, Shabsovich D, Yeh L, Pullarkat ST, Yang L, Kallen M, et al. A (1;19) translocation involving TCF3-PBX1 fusion within the context of a hyperdiploid karyotype in adult B-ALL: a case report and review of the literature. Biomark Res 2015; 3: 4-10.
- 8. Komorowski L, Fidyt K, Patkowska E, Firczuk M. Philadelphia Chromosome-Positive Leukemia in the Lymphoid Lineage-Similarities and Differences with the Myeloid Lineage and Specific Vulnerabilities. Int J Mol Sci 2020; 21 (16): 1-30.

- 9. Chou KN, Lin YC, Liu MY, Chang PY. Temozolomide-related acute lymphoblastic leukemia with translocation (4;11)(q21;q23) in a glioblastoma patient. J Clin Neurosci 2014; 21 (4): 701-704.
- 10. Chapiro E, Russell LJ, Struski S, Cave H, Radford-Weiss I, Valle VD, et al. A new recurrent translocation t(11;14)(q24;q32) involving IGH and miR-125b-1 in B-cell progenitor acute lymphoblastic leukemia. Leukemia 2010; 24 (7): 1362-1364.
- 11. Mu Q, Guo L, Hu Y, Sheng L, Zhang Y, Wu N, et al. SNX2–ABL1-positive acute lymphoblastic leukemia possibly has a poor prognosis. Leuk Lymphoma 2017; 58 (9): 2261-2263.
- 12. Schumich A, Zaliova M, Fortschegger K, Nebral K, Attarbaschi A, Fiser K, et al. CD371 cell surface expression: a unique feature of DUX4-rearranged acute lymphoblastic leukemia. Haematologica 2019; 104 (8): e352-355.
- 13. Tirado CA, Shabsovich D, DeNicola M, Rao D, Yang L, Garcia R, et al. A case of pediatric B-Lymphoblastic leukemia presenting with at (9; 12)(p24; q11. 2) involving JAK2 and concomitant MLL rearrangement with apparent insertion at 6q27. Biomark Res 2013; 1 (1): 1-6.
- 14. Khandany B, Heidari MM, Khatami M. Induced pluripotent stem cells (iPSCs) based approaches for hematopoietic cancer therapy. Iran J Ped Hematol Oncol 2019; 9 (2): 117-130.
- 15. Ernst T, Score J, Deininger M, Hidalgo-Curtis C, Lackie P, Ershler WB, et al. Identification of FOXP1 and SNX2 as novel ABL1 fusion partners in acute lymphoblastic leukaemia. Br J Haematol 2011; 153 (1): 43-46.
- 16. de Barrios O, Galaras A, Trincado JL, Azagra A, Collazo O, Meler A, et al. HDAC7 is a major contributor in the pathogenesis of infant t (4; 11) proB acute lymphoblastic leukemia. Leukemia 2021; 35 (7): 2086-2091.

- 17. Panic N, Leoncini E, de Belvis G, Ricciardi W, Boccia S. Evaluation of the endorsement of the preferred reporting items for systematic reviews and meta-analysis (PRISMA) statement on the quality of published systematic review and meta-analyses. PloS one 2013; 8 (12): e83138-83143.
- 18. Zeng X, Zhang Y, Kwong JS, Zhang C, Li S, Sun F, et al. The methodological quality assessment tools for preclinical and clinical studies, systematic review and meta-analysis, and clinical practice guideline: a systematic review. JEBM 2015; 8 (1): 2-10.
- 19. Put N, Deeren D, Michaux L, Vandenberghe P. FOXP1 and PAX5 are rare but recurrent translocations partners in acute lymphoblastic leukemia. Cancer Genet 2011; 204 (8): 462-464.
- 20. Young RM, Phelan JD, Wilson WH, Staudt LM. Pathogenic B-cell receptor signaling in lymphoid malignancies: new insights to improve treatment. Immunol Rev 2019; 291 (1): 190-213.
- 21. Kamran S, Raca G, Nazir K. RCSD1-ABL1 Translocation Associated with IKZF1 Gene Deletion in B-Cell Acute Lymphoblastic Leukemia. Case Rep Hematol 2015; 2015: 353247-353253.
- 22. Zheng J, Wu S, Hu Y, Gao L, Ling J, Lu Q, et al. Management of ETV6-ABL1-positive childhood acute lymphoblastic leukaemia: report of two cases, a literature review and a call for action. Br. J. Haematol 2021; 193 (1): 197-200.
- 23. Shimada A. Hematological malignancies and molecular targeting therapy. Eur. J. Pharmacol 2019; 862: 172641-172645.
- 24. Dong Y, Liu F, Wu C, Li S, Zhao X, Zhang P, et al. Illegitimate RAG-mediated recombination events are involved in IKZF1  $\Delta 3$ –6 deletion in BCR-

- ABL1 lymphoblastic leukaemia. Clin. Exp. Immunol 2016; 185 (3): 320-331.
- 25. Kathiravan M, Singh M, Bhatia P, Trehan A, Varma N, Sachdeva MS, et al. Deletion of CDKN2A/B is associated with inferior relapse free survival in pediatric B cell acute lymphoblastic leukemia. Leuk Lymphoma 2019; 60 (2): 433-441.
- 26. Ghasemi F, Khatami M, Heidari MM, Chamani R. In-silico study to identify the pathogenic single nucleotide polymorphisms in the coding region of CDKN2A gene. Iran J Ped Hematol Oncol 2021; 11-16.
- 27. Jia Z, Gu Z. PAX5 alterations in B-cell acute lymphoblastic leukemia. Front. Oncol 2022; 12: 1023606-1023611.
- 28. De Braekeleer E, Douet-Guilbert N, Rowe D, Bown N, Morel F, Berthou C, et al. ABL1 fusion genes in hematological malignancies: a review. Eur. J. Haematol 2011; 86 (5): 361-371.
- 29. Yao J, Xu L, Aypar U, Meyerson HJ, Londono D, Gao Q, et al. Myeloid/lymphoid neoplasms with eosinophilia/basophilia and ETV6-ABL1 fusion: cell-of-origin and response to tyrosine kinase inhibition. haematologica 2021; 106 (2): 614-619.
- 30. Buka RJ, Chandra D, Sutton DJ. Cancer is not a single disease: is it safe to extrapolate evidence from trials of direct oral anticoagulants in cancer-associated venous thromboembolism to patients with haematological malignancies? Br J Haematol 2021; 193 (1): 194-197.
- 31. Jain S, Abraham A. BCR-ABL1–like B-acute lymphoblastic leukemia/lymphoma: A comprehensive review. Arch. Pathol. Lab. Med 2020; 144 (2): 150-155.
- 32. Rodríguez-Hernández G, Casado-García A, Isidro-Hernández M, Picard D, Raboso-Gallego J, Alemán-Arteaga S, et al. The second oncogenic hit determines the cell fate of ETV6-RUNX1 positive

- leukemia. Front. Cell Dev. Biol 2021; 9: 704591-704596.
- 33. Yilmaz M, Kantarjian HM, Toruner G, Yin CC, Kanagal-Shamanna R, Cortes JE, et al. Translocation adult t(1;19)(q23;p13)acute in lymphoblastic leukemia a distinct subtype with favorable prognosis. Leuk Lymphoma 2021; 62 (1): 224-228.
- 34. Jia M, Hu B-F, Xu X-J, Zhang J-Y, Li S-S, Tang Y-M. Clinical features and prognostic impact of TCF3–PBX1 in childhood acute lymphoblastic leukemia: a single-center retrospective study of 837 patients from China. CPCCR 2021; 45 (6): 100758-100761.
- 35. Teppo S, Mehtonen J, Eldfors S, Heckman CA, Müschen M, Heinäniemi M, et al. Transcriptional Regulatory Landscape of TCF3-PBX1-Positive Leukemia and Novel Targeted Treatments. Blood 2016; 128 (22): 4077-4082.
- 36. El Chaer F, Keng M, Ballen KK. MLL-rearranged acute lymphoblastic leukemia. Curr. Hematol. Malig. Rep 2020; 15: 83-89.
- 37. Fazio G, Bardini M, De Lorenzo P, Grioni A, Quadri M, Pedace L, et al. Recurrent genetic fusions redefine MLL germ line acute lymphoblastic leukemia in infants. Blood, Am. J. Hematol 2021; 137 (14): 1980-1984.
- 38. Chen X, Wang F, Zhang Y, Ma X, Liu M, Cao P, et al. Identification of RNPC3 as a novel JAK2 fusion partner gene in B-acute lymphoblastic leukemia refractory to combination therapy including ruxolitinib. Mol. Genet. Genomic Med 2020; 8 (3): e1110-1113.
- 39. Kobayashi K, Mitsui K, Ichikawa H, Nakabayashi K, Matsuoka M, Kojima Y, et al. ATF7IP as a novel PDGFRB fusion partner in acute lymphoblastic leukaemia in children. Br J Haematol 2014; 165 (6): 836-841.
- 40. Li Y, Gupta G, Molofsky A, Xie Y, Shihabi N, McCormick J, et al. B Lymphoblastic leukemia/lymphoma with

- Burkitt-like morphology and IGH/MYC rearrangement: report of three cases in adult patients. Am. J. Surg. Pathol 2018; 42 (2): 269-275.
- 41. Jamrog L, Chemin G, Fregona V, Coster L, Pasquet M, Oudinet C, et al. PAX5-ELN oncoprotein promotes multistep B-cell acute lymphoblastic leukemia in mice. PNAS 2018; 115 (41): 10357-10362.
- 42. Brown LM, Hediyeh-Zadeh S, Sadras T, Huckstep H, Sandow JJ, Bartolo RC, et al. SFPQ-ABL1 and BCR-ABL1 use different signaling networks to drive B-cell acute lymphoblastic leukemia. Blood Adv 2022; 6 (7): 2373-2387.
- 43. Reshmi SC, Harvey RC, Roberts KG, Stonerock E, Smith A, Jenkins H, et al. Targetable kinase gene fusions in highrisk B-ALL: a study from the Children's Oncology Group. Blood, Am. J. Hematol 2017; 129 (25): 3352-3361.
- 44. Tamaddon G, Bahraini M, Fazeli A. Evaluation of FOXP1 gene expression in pediatric B-cell precursor acute lymphoblastic leukemia patients at remission induction therapy. Iran J Ped Hematol Oncol 2020; 10 (4): 257-265.
- 45. Stukaite-Ruibiene E, Norvilas R, Dirse V, Stankeviciene S, Vaitkeviciene GE. Case Report: Specific ABL-Inhibitor Imatinib Is an Effective Targeted Agent as the First Line Therapy to Treat B-Cell Acute Lymphoblastic Leukemia With a Cryptic NUP214::ABL1 Gene Fusion. Pathol Oncol Res 2022; 28: 1610570-1610576.
- 46. Brown LM, Hediyeh-Zadeh S, Sadras T, Huckstep H, Sandow JJ, Bartolo RC, et al. SFPQ-ABL1 and BCR-ABL1 use different signaling networks to drive B-cell acute lymphoblastic leukemia. Blood Adv 2022; 6 (7): 2373-2387.
- 47. WU C, CHEN Z, CAI C, ZHENG Y, LE S, LI J. IL3-IGH fusion genepositive pediatric acute lymphoblastic leukemia with hypereosinophilia as the first presentation: report of 1 case and

- review of literature. J. Leuk. Lymphoma 2022: 484-487.
- 48. Wang T, Ni J, Zhang H, Hui S, Liu T, Zhang X, et al. P377: Genetic characteristics and cd7-car-t therapy of trad:: myc translocation positive acute lymphoblastic leukemia patients. HemaSphere 2022; 6: 277-278.
- 49. Oberoi S, Dawson A, Marko D, Almiski M, Higgins R, Israels SJ. Precursor B-Cell Acute Lymphoblastic Leukemia With MYC and BCL2 Rearrangements Presenting as Extensive Extranodal Disease in an Adolescent. J. Pediatr. Hematol. Oncol 2021; 43 (4): e501-e504.
- 50. Tian L, Shao Y, Nance S, Dang J, Xu B, Ma X, et al. Long-read sequencing unveils IGH-DUX4 translocation into the silenced IGH allele in B-cell acute lymphoblastic leukemia. Nat Commun 2019; 10 (1): 2789-2795.
- 51. Tirado CA, Dobin S, Eastwood K, Guardiola MT, Hurtado R, Rao A. A B-ALL Pediatric Patient with a Cryptic IGH Rearrangement Within the Context of a Complex Karyotype. JAGT 2023; 49 (2): 88-92.
- 52. Fournier B, Balducci E, Duployez N, Clappier E, Cuccuini W, Arfeuille C, et al. B-ALL With t(5;14)(q31;q32); IGH-IL3 Rearrangement and Eosinophilia: A Comprehensive Analysis of a Peculiar IGH-Rearranged B-ALL. Front Oncol 2019; 9: 1374-1379.
- 53. Guenzel AJ, Smadbeck JB, Golden CL, Williamson CM, Demasi JCB, Vasmatzis G, et al. Clinical utility of next generation sequencing to detect IGH/IL3 rearrangements [t (5; 14)(q31. 1; q32. 1)] in B-lymphoblastic leukemia/lymphoma. Ann. Diagn. Pathol 2021; 53: 151761-151769.
- 54. Smeenk L, Werner B, Azaryan A, Busslinger M. Role of PAX5 fusion proteins in B-cell precursor acute

- lymphoblastic leukemia. Exp. Hematol 2013; 41 (8): S46-S51.
- 55. Bomken S, Enshaei A, Schwalbe EC, Mikulasova A, Dai Y, Zaka M, et al. Molecular characterization and clinical outcome of B-cell precursor acute lymphoblastic leukemia with IG-MYC rearrangement. Haematologica 2023; 108 (3): 717-721.
- 56. Li Z, Chang T-C, Junco JJ, Devidas M, Li Y, Yang W, et al. Genomic landscape of Down syndrome—associated acute lymphoblastic leukemia. Blood, T Am. J. Hematol 2023; 142 (2): 172-184.
- 57. Gu G, Sederberg MC, Drachenberg MR, South ST. IGF2BP1: a novel IGH translocation partner in B acute lymphoblastic leukemia. Cancer Genet 2014; 207 (7-8): 332-334.
- 58. Jaso JM, Yin CC, Lu VW, Zhao M, Abruzzo LV, You MJ, et al. B acute lymphoblastic leukemia with t(14;19)(q32;p13.1) involving IGH/EPOR: a clinically aggressive subset of disease. Mod Pathol 2014; 27 (3): 382-389.
- 59. Niswander LM, Loftus JP, Lainey É, Caye-Eude A, Pondrom M, Hottman DA, et al. Therapeutic potential of ruxolitinib and ponatinib in patients with EPOR-rearranged Philadelphia chromosome-like acute lymphoblastic leukemia. haematologica 2021; 106 (10): 2763-2769.
- 60. Zerrouki R, Benhassine T, Bensaada M, Lauzon P, Trabzi A. The complex translocation (9;14;14) involving IGH and CEBPE genes suggests a new subgroup in B-lineage acute lymphoblastic leukemia. Genet Mol Biol 2016; 39 (1): 7-13.
- 61. Messinger YH, Higgins RR, Devidas M, Hunger SP, Carroll AJ, Heerema NA. Pediatric acute lymphoblastic leukemia with a t(8;14)(q11.2;q32): B-cell disease with a high proportion of Down syndrome: a

- Children's Oncology Group study. Cancer Genet 2012; 205 (9): 453-458.
- 62. Thompson MA, Seegmiller A, Zarnegar-Lumley Smith C. S. Montgomery KW, Wheeler FC, et al. 50. Loss of TP53 in a pediatric patient with B-lymphoblastic Down syndrome, leukemia, and the t(8;14)(q11.2q32) CEBPD/IGH translocation. Cancer Genet 2019; 233-234.
- 63. Wang Y, Li J, Xue TL, Tian S, Yue ZX, Liu SG, et al. Clinical, biological, and outcome features of P2RY8-CRLF2 and CRLF2 over-expression in pediatric B-cell precursor acute lymphoblastic leukemia according to the CCLG-ALL 2008 and 2018 protocol. Eur. J. Haematol 2023; 110 (6): 669-679.
- 64. Yamamoto K, Kitao A, Watanabe M, Kanehira H, Joyce M, Hirakawa Y, et al. RUNX1 rearrangement in mature B-cell acute lymphoblastic leukemia with non-L3 morphology. JCEH 2023; 63 (4): 240-245. 65. Puissegur MP, Eichner R, Quelen C, Coyaud E, Mari B, Lebrigand K, et al. B-cell regulator of immunoglobulin heavy-chain transcription (Bright)/ARID3a is a direct target of the oncomir microRNA-
- 2012; 26 (10): 2224-2232.
  66. Dai HP, Yin J, Li Z, Yang CX, Cao T, Chen P, et al. Rapid Molecular Response to Dasatinib in a Pediatric Relapsed Acute Lymphoblastic Leukemia With NCOR1-LYN Fusion. Front Oncol

2020; 10: 359-364.

125b in progenitor B-cells. Leukemia

- 67. Tomii T, Imamura T, Tanaka K, Kato I, Mayumi A, Soma E, et al. Leukemic cells expressing NCOR1-LYN are sensitive to dasatinib in vivo in a patient-derived xenograft mouse model. Leukemia 2021; 35 (7): 2092-2096.
- 68. Li M-J, Yu C-H, Chou S-W, Su Y-H, Liao K-W, Chang H-H, et al. TCF3-HLF-Positive Acute Lymphoblastic Leukemia Resembling Burkitt Leukemia: Cell Morphologic and Immunophenotypic Findings. JCO Precis. Oncol 2022; 6-11.

- 69. Ravich JW, Huang S, Zhou Y, Brown P, Pui C-H, Inaba H, et al. Impact of high disease burden on survival in pediatric patients with B-ALL treated with tisagenlecleucel. Transplant Cell Therap 2022; 28 (2): 73. e71-73.
- 70. Iacobucci I, Roberts KG. Genetic alterations and therapeutic targeting of Philadelphia-like acute lymphoblastic leukemia. Genes 2021; 12 (5): 687-692.
- 71. Jasinski S, De Los Reyes FA, Yametti GC, Pierro J, Raetz E, Carroll WL. Immunotherapy in pediatric B-cell acute lymphoblastic leukemia: advances and ongoing challenges. Paediatr. Drugs 2020; 22: 485-499.
- 72. Cario G, Leoni V, Conter V, Baruchel A, Schrappe M, Biondi A. BCR-ABL1-like acute lymphoblastic leukemia in childhood and targeted therapy. Haematologica 2020; 105 (9): 2200-2207.
- 73. Płotka A, Lewandowski K. BCR/ABL1-like acute lymphoblastic leukemia: from diagnostic approaches to molecularly targeted therapy. Acta Haematol 2022; 145 (2): 122-131.
- 74. Fournier B, Balducci E, Duployez N, Clappier E, Cuccuini W, Arfeuille C, et al. B-ALL With t (5; 14)(q31; q32); IGH-IL3 rearrangement and eosinophilia: a comprehensive analysis of a peculiar IGH-rearranged B-ALL. Front. Oncol 2019; 9: 1374-1378.
- 75. Gu G, Sederberg MC, Drachenberg MR, South ST. IGF2BP1: a novel IGH translocation partner in B acute lymphoblastic leukemia. Cancer Genet 2014; 207 (7-8): 332-334.