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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

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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 the fusion of genes 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, which include hyperdiploidy and hypodiploidy with more significant than 50 chromosomes and approximately fewer than 43 chromosomes, respectively, as well as several chromosomal rearrangements.

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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).

b) t(9;22)(q34;q11), it involves the exchange of genetic material between chromosome 9 and chromosome 22, 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* on chromosome 1. This translocation is common in adolescents with an intermediate prognosis. The *TCF3-PBX1* fusion gene produces an abnormal protein that affects 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).

In contrast, translocations including t(4;14)(q35;q32), which juxtaposes *IGH* on 14q32 to *DUX4* on 4q35, 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 receptor-like factor 2 (*CRLF2*), miR-125b-1, interleukin-3, *c-MYC*, and *HLA-DM*, etc. (3, 5).

The identification of 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 (15). B-ALL translocations have 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 five-year 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

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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 were related to how chromosomal translocations are related to the process of carcinogenesis in children and adults. The literature review excluded articles published before 2010 because they were obsolete. The scientific journals that contained potentially relevant studies for the systematic review, including 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. Global health clinical trial sites, conferences, and congresses were also reviewed. Case report articles, studies that included non-B-ALL 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

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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 translocation) between different chromosomes, leading to abnormal gene expression and signaling pathways that depending on the type, location, and frequency of the rearrangements, it promotes leukemia development and 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 for different deregulations. In the 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 and 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-of-function which is responsible for gene deletion (exon 3-6) and the IK6 production (24). Moreover, *CDKN2A/B*, a tumor suppressor gene, was deleted in approximately half of patients, regardless of their age (25, 26). Similarly, the deletion in the *PAX5* (paired box 5) gene has been observed in 30-40% of 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* on 9q34 into *RCSD1* on 1q24, 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

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

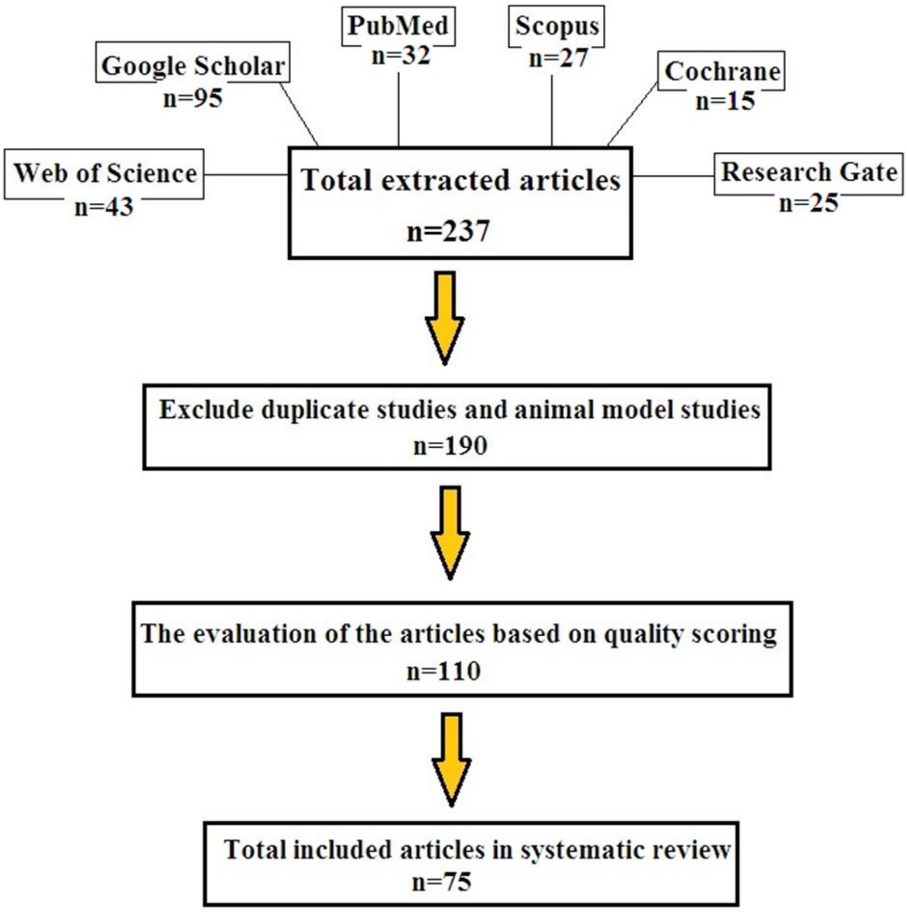

Figure 1. Flow chart of article selection steps for the systematic review

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Table I: 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)

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

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

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t(5;14)(q31;q32)	*IL3-IGH*	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.	(47)
t(8;14)(q24.1;q11.2)	*TRAD-MYC*	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)

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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.	(19, 54)
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 and resistance to chemotherapy.	(55)
t(14;17)(q32;q21)	*IGH-IGF2BP1*	This translocation may result in the overexpression of the 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.	(56, 57)
t(14;19)(q32;p13.1)	*IGH-EPOR*	This translocation causes the EPOR gene overexpression, a 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.	(58, 59)
t(14;14)(q11;q32)	*IGH-CEBPE*	This translocation causes the CEBPE gene overexpression, 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.	(60)

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t(8;14)(q11.2;q32)	*IGH-CEBPD*	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.	(61, 62)
t(X;14)(p22;q32)	*CRLF2-IGH*	This fusion gene leads to CRLF2 overexpression, in the rare causes of B-ALL.	(63)
t(Y;14)(p11;q32)	*P2RY8-CRLF2*	This fusion gene leads to CRLF2 overexpression, in the rare causes of B-ALL.	(63)
t(8;21)(q22;q22)	*RUNX1-RUNX1T1*	This fusion gene encodes a transcription factor that affects the expression of many other genes involved in blood cell development and differentiation. Hence, the fusion protein becomes an oncogene and inhibits lymphoid differentiation.	(64)
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)

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t(17;19)(q22;p13)	*TCF3-HLF*	This translocation produces an abnormal fusion which 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.	(68)

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 their 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 common and rare chromosomal 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 on the characteristics, 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 kinase inhibitors greatly improved outcomes for patients 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 clinical consequences, depending on the partner gene and the genetic background of the patient. Therefore, identifying and characterizing these translocations is important for better diagnosis, prognosis, and treatment of B-ALL. The main partner

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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, diagnostic markers, and effective 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 patient of DHL with *BCL2-MYC* translocation demonstrates both DLBCL and precursor B-ALL heterogeneity characteristics (immunophenotype and 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.

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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

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