Gene Mutation of Childhood B-acute Lymphoblastic Leukemia: A Systematic Review

Abstract

Introduction: Research on the importance of cancer mainly been performed in acute lymphoblastic leukemia (ALL) B-cell populations. All B-cell is the most common leukemia occurs in 2–5-years old of children. Chromosome translocations, chromosome numerical alterations, and specific gene mutations are the genetic abnormalities which have found in 75% of B-ALL cases. Somatic mutations in 45 genes with different frequency and different cellular pathways were the subject of this investigation. Materials and Methods: An electronic search of peer-reviewed articles was systematically performed to obtain the relevant literature with the Cumulative Index to Nursing and Allied Health Literature, PsycINFO, and PubMed databases. In this systematic review, 48 articles from 1998 to 2020 were collected. The keywords included B-cell ALL, genes, mutations, pediatric, and systematic review. The inclusion criteria for the reviews were that the documents were original qualitative research and published in English. Articles that were not directly relevant to the present objective were excluded. Results: The results are limited to these specific them as B-cell, ALL, pediatric, genes, mutations, and systematic review. This article focused on the pediatric B-cell ALL, support of cancer patients from diverse and heterogeneous groups globally. By collecting the articles and reviewing them, alterations in different genes with different molecular pathways which had the effects on B-ALL pathogenicity were found and alteration list discussed. Conclusion: The present outcome of these review resources suggest that it may be helpful for clinicians to address genetics, epigenetic regulators, particularly with regard to prevention, healing, and survival of pediatric cancer patients. This article indicates that it may be useful for clinical oncologists to be informed of the prevalence of the use of mutated genes in medicine in their specialized field. In addition, patients should routinely be asked about the use of prevention medicine as the part of every cancer patient’s evaluation.

Keywords: Acute lymphoblastic leukemia, B-cell, genes, mutations, pediatric, systematic review

Introduction

The clonal proliferation and a malignant transformation of lymphoid progenitor in the blood, bone marrow, and extramedullary sites cause acute lymphoblastic leukemia (ALL). It is the single-most common malignancy accounting for 75% of all newly diagnosed leukemias and one-fourths of all pediatric cancer in younger than 15 years of age. Two-to-five years of age is the universal peak onset emerge for pediatric acute lymphoblastic. The main cause of children and young adults’ disease death is ALL, so it is better to understand the role of genetic abnormalities and biological subtypes. In general, the type, distribution, and prognosis of cancer in children are significantly different from adult. About 80%–85% of all the ALL cases are B-ALL; however, the rest are T-ALL. A small percentage of ALL cases associate with Down syndrome and with inherited syndromes, such as Li-Fraumeni syndrome, mismatch repair deficiency, Nijmegen breakage syndrome, Fanconi anemia, neurofibromatosis, Shwachman syndrome, Bloom syndrome, and ataxia-telangiectasia. Approximately 100% of molecular aberrations are identified in pediatric ALL by using conventional test such as polymerase chain reaction and high-resolution karyotype, in association with advanced methodology as well as genome-wide association (GWA), single-nucleotide polymorphism arrays, gene expression profile, and next-generation sequencing (NGS). Genetic alterations, chromosomal translocations, and epigenetic are the

three mechanisms participating in leukemia. Along with genetic alterations, histone modifications such as HES5 histone de-acetylation and DNA abnormal methylation such as NOTCH3, HES4, and HES5 promoter methylation in B-ALL cases are the important mechanisms in tumor-suppressor silencing which contribute to leukemogenesis. Gene inactivation or activation mechanisms cause tumor formation. Genes inactivation plays a key role in leukemia prognosis and pathogenesis.[1] In this article of systematic review, we summarize the genes and their alternations which cause pediatric B-ALL.

**Pediatric B-acute lymphoblastic leukemia genetic alterations**

Chromosome translocations, chromosome number alterations, and specific gene mutations such as the deletion are the numbers of genetic abnormalities which have found in almost 75% of infant precursor B-cell ALL/lymphoma cases.[3] Notably, t (12; 21) (p13; q22), t (9; 22) (q34; q11), t (4; 11) (q21; q23), t (9; 11) (p22; q23), t (11; 19) (q23; p13), t (1; 19) (q23; p13), t (2; 14) (p12; q32), t (15; 21) (q10; q10), t (5; 14) (q31; q32), t (1; 1) (q21; q22), and t (1; 19) (q22; p13.2) are the chromosome translocations, which lead to various protein fusions.[1‑8] Down syndrome in about 2%–3% of B-ALL, high hyperdiploidy in 20%–25% of pediatric B-ALL cases, near haploid, low hypodiploid, near triploidy, and near tetraploidy are chromosome number alterations.[2]

B-ALL genomic lesions include IKZF1 deletions (B-lymphoid transcription factor genes), JAKSTAT somatic mutations, FLT3, NTRK3, BLNK, TYK2, PTK2B alterations, NRAS, KRA5, PTPN11, and NF1 somatic mutations (RAS signaling). Somatic mutations in 45 genes with different frequency and different cellular pathways had found in pediatric B-ALL pathogenesis. Furthermore, several inherited genetic variants in ARID5B, CEBPE, PIP4K2A, GATA3, LHPP, and ELK3 genes have identified in the association with adolescent and childhood B-ALL risk by using GWAS.[2]

Figure 1 shows the summary of key genes alterations in the different signaling pathways involved in B- and T-cell ALL in adults and children.

The existence of amplifications in B-ALL is a rare event, and its pathological effect is still elusive.[1] In addition to the alterations mentioned above, intragenic amplifications of PAX5 in exon 2, 5, and 2–5 have been reported.[2] Approximately 2% of B-ALL cases had intrachromosomal RUNXI amplifications. There were five RUNXI copies in cases with amplification.[1]

Hof et al. had reported RUNXI and ABL1 gene amplifications and ETV6/RUNX1 fusion gene copy number increase in five B-ALL cases which were identified by fluorescence in situ hybridization method.[2]

Intrachromosomal amplification of chromosome 21 (iAMP21) is a recognized chromosomal abnormality in
B-ALL and defines an individual cytogenetic subgroup of this hematological malignancies. Deletion, amplification, multiple regions of gain, and inversion are the iAMP21 variability and complexity reasons in B-cell precursor-ALL cases. 5.1 Mb of chromosome 21 (32.8–37.9 Mb) is the common region of highest-level amplification within which RUNX1 is sited.[3]

Table 1 summarizes B-ALL genes mutations such as substitutions, deletions, insertions, and frameshift mutation.

The somatic mutations of KRAS, NRAS, PTPN11, and FLT3 showing a significant role of these genes in p. B-ALL.[20] Paulsson et al. discovered 26 mutations of KRAS, NRAS, PTPN11, and FLT3 in 78 high hyperdiploid p. B-ALL cases. They found 1 codon 12 and 4 codon 13 in KRAS gene, 3 codons 12, 4 codons 13, and 1 codon 61 of NRAS mutation, 6 exons 3 and 1 exon 13 PTPN11 mutation, and 6 Asp835/Ile836 mutations and 1 ITD of FLT3 gene. All of these mutations were commonly exclusive, a fact highlights the importance of RAS/RAF/mitogen-activated protein kinase/extracellular signal-regulated kinase pathway activation in leukemogenesis.[27,28]

Mono-allelic deletions, frameshift, and internal deletions[6-8] also sequence mutations (V26G, P34Q, and P80R), and translocations have been identified as PAX5 aberration.[20] PAX5 p. P80R (c.239C > G) alteration is usually associated with CDKN2A bi allelic deletion, alterations of the RAS pathway, and inactivation of the second PAX5 allele sequences.[20] Recent genetic alterations of PAX5 cases affected B-cell development (IKZF1, VPREB1, and BTLA deletions), cell cycle regulation (CDKN2A, RB1, and BTG1 deletions), epigenetic modification (e.g., KMT2A, ATRX, and KDM6A), and transcriptional regulation (e.g., ZFp36 L2, ETV6, and LEF1).[20]

Twelve percent of B-ALL cases had SETD2 mutations which harbored RAS pathway mutations cited in the literature. Mar et al. had identified 7 loss of function, nonsense, and frameshift mutations which had no noticeable hotspot mutations. Thirteen percent ETV6-RUNX1 and

<table>
<thead>
<tr>
<th>Gene symbol</th>
<th>Type of mutations</th>
<th>Missense alterations (aminoacid change)</th>
<th>References</th>
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</thead>
<tbody>
<tr>
<td>CRLF2</td>
<td>Rearrangements and translocations</td>
<td>-</td>
<td>[1,5,6]</td>
</tr>
<tr>
<td>JAK1/2</td>
<td>Missense and splice site</td>
<td>T514T and R683G</td>
<td>[3-6]</td>
</tr>
<tr>
<td>IKZF1</td>
<td>Deletions and mutations</td>
<td>-</td>
<td>[3,7,8]</td>
</tr>
<tr>
<td>NRAS</td>
<td>Missense</td>
<td>G12S, G12D, G13D, G13C, and Q61H</td>
<td>[9,10]</td>
</tr>
<tr>
<td>KRAS</td>
<td>Missense</td>
<td>Gly13Asp, Gly12Asp</td>
<td>[9,10]</td>
</tr>
<tr>
<td>FLT3</td>
<td>Missense, frameshift, and deletions</td>
<td>D835Y, D835H, D835V, and p.1836del</td>
<td>[9,11,12]</td>
</tr>
<tr>
<td>ETV6</td>
<td>Missense, frameshift, and insertions</td>
<td>P214L, L349P, R359X, R369Q, N385fs, and R399C</td>
<td>[9,13,14]</td>
</tr>
<tr>
<td>MUC4</td>
<td>Alterations</td>
<td>-</td>
<td>[9]</td>
</tr>
<tr>
<td>CDKN2A/B</td>
<td>Missense, deletions, and insertions</td>
<td>A97T</td>
<td>[9,15-17]</td>
</tr>
<tr>
<td>ADARB2</td>
<td>Alterations</td>
<td>-</td>
<td>[9]</td>
</tr>
<tr>
<td>ASMTL</td>
<td>Alterations</td>
<td>-</td>
<td>[9]</td>
</tr>
<tr>
<td>TBL1XR1</td>
<td>Deletions</td>
<td>-</td>
<td>[9]</td>
</tr>
<tr>
<td>IRF8</td>
<td>Alterations</td>
<td>-</td>
<td>[9]</td>
</tr>
<tr>
<td>VPREB1</td>
<td>Missense and deletions</td>
<td>Unpublished</td>
<td>Unpublished</td>
</tr>
<tr>
<td>IGLL1</td>
<td>Missense</td>
<td>-</td>
<td>[18]</td>
</tr>
<tr>
<td>ERG</td>
<td>Deletions</td>
<td>-</td>
<td>[19,20]</td>
</tr>
<tr>
<td>BRAF</td>
<td>Alterations</td>
<td>-</td>
<td>[21]</td>
</tr>
<tr>
<td>BCL2</td>
<td>Alterations</td>
<td>-</td>
<td>[21]</td>
</tr>
<tr>
<td>IL7R</td>
<td>Missense, insertions, and deletions</td>
<td>S185C</td>
<td>[6]</td>
</tr>
</tbody>
</table>
22% of MLL rearranged B-ALL subtypes had different types of SETD2 mutations. L1609P, I1615fs, T1663M, and K2546X alterations occurred in SET domain and POLR2A interaction, respectively.\[25\]

**Pediatric B-acute lymphoblastic leukemia noncoding region alterations**

Beside coding regions mutations, alterations in noncoding regions such as splice site and intronic had occurred in the diagnostic pattern.\[4\] Mar et al. identified 24 mutations in different regions of SETD2 gene.\[25\] In hematopoietic malignancies, 4 splice site mutations in SETD2 gene had recognized by Inthal et al.\[26\] The reduced levels of exon inclusion in actively transcribed genes and a total change of splice sites are the result of shRNA-mediated loss of SETD2 [Figure 2].\[24\]

Splice site and intronic alterations in various genes of p. B-ALL cases are described in Table 2.

**Materials and Methods**

Electronic searches in the area of ALL till 2020 had done to report the purposes of this systematic review.

**Search strategy for studies identification**

OXFORD, PLOS ONE, HINDAWI, NIH public PMC, Bio Med Central, Dove Press, Karger, Science Direct, ELSEVIER, MDPI, Research Gate, Cell Press, and Nature are different Databanks which used for 217 acceptable articles in this systematic review. No gray literature searches were made for this article.

Medical subject headings terms and genetic keywords in PubMed are used for the articles from 1998 to 2020: “Acute Lymphoblastic Leukemia” OR “B-Cell Acute Lymphoblastic Leukemia” OR “Pediatric B Cell Acute Lymphoblastic Leukemia” OR “children B Cell Acute Lymphoblastic Leukemia” OR “B-ALL” OR “B-ALL,” AND “Mutations” OR “Alterations” AND different gene symbol.

**Standards of chosen articles**

Criteria of rejection and annexation were identified before the search strategy begin. These criteria related to the types of participants (B-cell ALL children), the article publication year (1998–2020), and the types of studies (research, review, and systematic review) were the target of this investigation.

**Types of participants**

Our priority was patients whose affected with B-ALL, but we have reported ALL in general in some cases. In B-ALL, age and sex were excluded from this study.

The individual patient selected for this article were from different countries, notably Spain, Iran, China, the United States of America, the United Kingdom, etc.

**Results**

**Articles collection**

Figure 3 shows the flow chart details for the article’s chosen procedure according to PRISMA instructions. The search pattern for current investigation revealed 233 peer review paper, and we excluded synchronized studies for genuine results. Twenty-nine articles were reviewed for eligibility after omitting the articles in the area of other types of leukemia such as T-cell ALL and adult ALL. Furthermore, the results are limited to these specific them as B-cell, ALL, pediatric, genes, mutations, and systematic review. This article focused on the pediatric B-cell ALL, support of cancer patients from diverse, and heterogeneous groups globally. By collecting the articles and reviewing

### Table 2: Splice site and intronic alterations in the various genes of pediatric B-acute lymphoblastic leukemia

<table>
<thead>
<tr>
<th>Gene symbol</th>
<th>Noncoding region</th>
<th>Alterations</th>
<th>rs ID</th>
<th>Researcher</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>TP53</td>
<td>Splice site (Exon 8)</td>
<td>g. 13762 G&gt;A</td>
<td>-</td>
<td>Hof et al.</td>
<td>[2]</td>
</tr>
<tr>
<td>PA5</td>
<td>Intronic</td>
<td>NG_033894.1:g. 18643C&gt;T</td>
<td>rs377355229</td>
<td>Erbilgin et al.</td>
<td>[4]</td>
</tr>
<tr>
<td>JAK2</td>
<td>Splice site</td>
<td>NG_009904.1:g. 89709G&gt;A</td>
<td>rs565502628</td>
<td>Erbilgin et al.</td>
<td>[4]</td>
</tr>
<tr>
<td>JAK2</td>
<td>Intronic</td>
<td>NG_009904.1:g. 89837 T&gt;C</td>
<td>Novel</td>
<td>Erbilgin et al.</td>
<td>[4]</td>
</tr>
<tr>
<td>CREBBP</td>
<td>Splice site (Exon 21)</td>
<td>c. 3836+1G&gt;A</td>
<td>-</td>
<td>Inthal et al.</td>
<td>[26]</td>
</tr>
<tr>
<td>IL7R</td>
<td>Intronic</td>
<td>NG_009567.1:g. 22664 T&gt;C</td>
<td>rs202114203</td>
<td>Erbilgin et al.</td>
<td>[4]</td>
</tr>
<tr>
<td>CRLF2</td>
<td>Intronic</td>
<td>NG_034237.1:g. 20998 G&gt;A</td>
<td>Novel</td>
<td>Erbilgin et al.</td>
<td>[4]</td>
</tr>
<tr>
<td>ARID5B</td>
<td>Intronic</td>
<td>NG_030027.1:g. 43883A&gt;C</td>
<td>rs7073837</td>
<td>Orsi et al.</td>
<td>[27]</td>
</tr>
<tr>
<td>ARID5B</td>
<td>Intronic</td>
<td>NG_030027.1:g. 54092A&gt;G</td>
<td>rs10994982</td>
<td>Tao et al.</td>
<td>[28]</td>
</tr>
<tr>
<td>ARID5B</td>
<td>Intronic</td>
<td>NG_030027.1:g. 62467C&gt;A</td>
<td>rs10740055</td>
<td>Orsi et al.</td>
<td>[27]</td>
</tr>
<tr>
<td>ARID5B</td>
<td>Intronic</td>
<td>NG_030027.1:g. 96147T&gt;G</td>
<td>rs7089424</td>
<td>Orsi et al.</td>
<td>[27]</td>
</tr>
<tr>
<td>ANKR44</td>
<td>Intronic</td>
<td>NC_000002.12:g. 197083099A&gt;C</td>
<td>rs930372</td>
<td>Orsi et al.</td>
<td>[27]</td>
</tr>
</tbody>
</table>
them, alterations in different genes with different molecular pathways which had affects on B-ALL pathogenicity were found and alteration listed in the figures and tables.

Conclusion

B-cell ALL is the most common malignancy in the pediatric age group (birth age to 21).\cite{29,30} It is characterized by genetic alterations which block lymphoid precursor cells proliferation and differentiation.\cite{4} Although several great genomic studies of B-ALL have been published in the recent years, the exact role of molecular mutations is still unclear.\cite{15} The desire to recognize the genetic basis of differences in children with B-ALL has been catalyzed by using high-throughput NGS technology.\cite{29} Here, we introduces almost all different gene mutations in different molecular pathways such as transcriptional regulation and lymphoid differentiation and development, RAS-signaling pathway, JAK/STAT-signaling pathway, TP53 and cell cycle signaling pathway, chromatin structure modifiers, and epigenetic regulators.\cite{1} There are more than 80 genetic alterations in various genes which had collected in this article. However, because of the complexity of the B-ALL pathogenesis mechanism, widespread studies are needed in various fields at the gene, expression, and protein levels.

Pediatric B-acute lymphoblastic leukemia and treatment

Relapse and drug-resistance of B-ALL have been generally described with different genetics lesions.\cite{20} CDKN2A/B, ETV6, and IKZF1 mutations are connected to high-treatment failure risk.\cite{30} NGS of 300 genes of 264 samples revealed mutations in 32 genes, such as CREBBP, NCOA1, ERG, SPI1, TCF4, and TCF7 L2 in the relapse samples. A study of p. B-ALL relapsed cases by Alsagaby et al. had reported an important association between deleted genes such as BTG1, NR3C1, and TBL1XR1 (glucocorticoid signaling) with in the therapy failure.\cite{29,31}

Table 3 summarized some genes and proteins, which play the roles in B-ALL relapse and drug-resistance. Gene symbols are in italic.

Acknowledgments

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Nil.

Conflicts of interest

There are no conflicts of interest.

References


8. Lopes BA, Barbosa TC, Souza BK, Poubel CP, Pombo-de-Oliveira MS, Emerenciano M, et al. IKZF1

| Table 3: Genes or proteins associated with relapse and drug resistance\cite{29} |
| Relapse | Drug resistance |
| APC, PTPRO, CDKN2A, SETD2, KDM6A, MLL2, CREBBP, NCOA1, ERG, SPI1, TCF4, TCF7L2, KRAS, BTG1, NR3C1, TBL1XR1, EBF1, IKZF1, PYGL, and PDE4B | HRK and MCL-1 |
| Elosin, Ezrin, actin-regulatory protein CAP-G, heat-shock cognate 71 kDa Protein A, T-complex protein 1 subunits beta, epsilon, nonmetastatic cells 2, collin 1, voltage-dependent anion-selective channel protein 1, ER-60 protease, galactin, and high-mobility group protein B2 |


