Review Article

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 quantitative 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*

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Introduction

The clonal proliferation and a malignant transformation of lymphoid progenitor in the blood, bone marrow, and extramedullary sites cause acute lymphoblastic leukemia (ALL).[1] 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 old of age.[1] Two-to-five years of age is the universal peak onset emerge for pediatric acute lymphoblastic.[2,3] 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.[1] In general, the type, distribution, and prognosis of cancer in children are significantly different from adult.[1] About 80%–85% of all the ALL cases are B-ALL; however, the rest are T-ALL.[3] 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.[1-3] 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).[1]

Genetic alterations, chromosomal translocations, and epigenetic are the

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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*, *KRAS*, *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 *RUNX1* amplifications. There were five *RUNX1* copies in cases with amplification.[1]

Hof *et al*. had reported *RUNX1* 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]

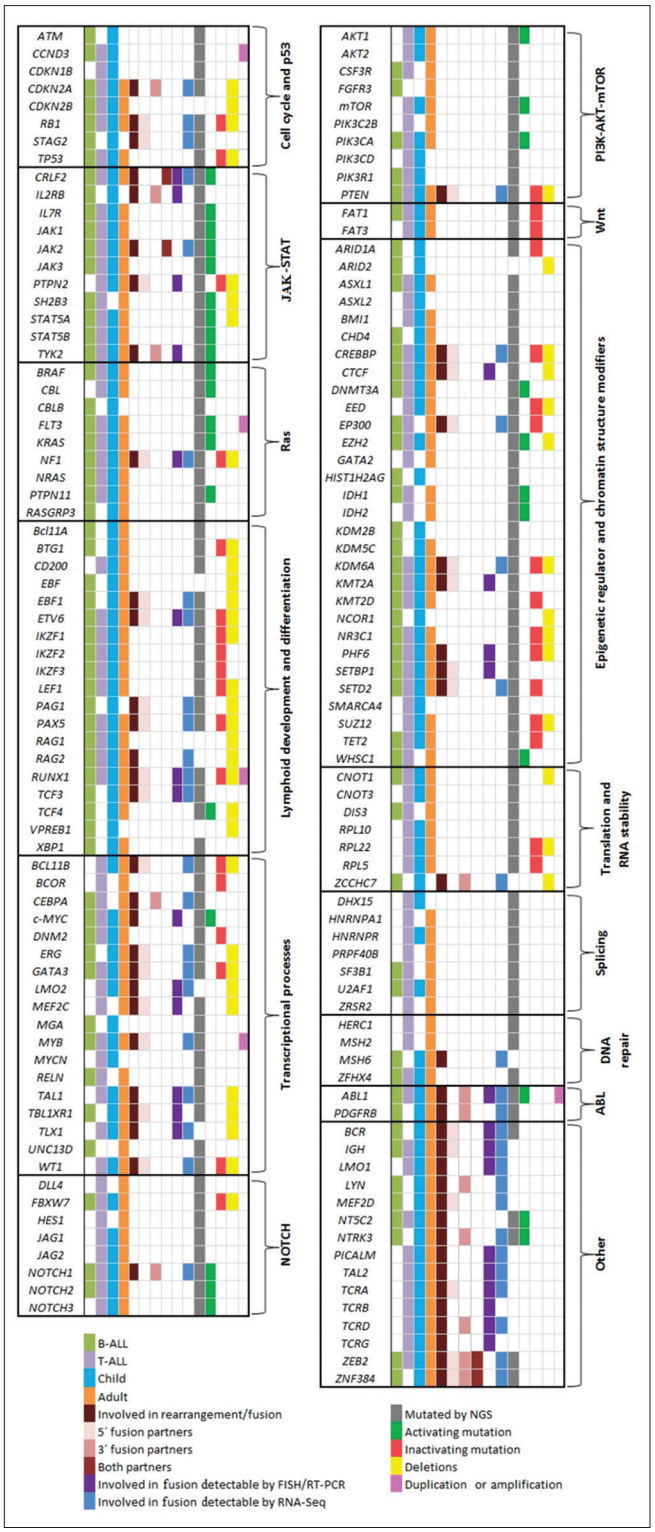

Figure 1: Acute lymphoblastic leukemia somatic mutations, deletions, duplications, rearrangement/fusion, and other genetic alterations[1]

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*, *FLT3*, *PTPN11, PAX5,* and *SETD2* genes identified by NGS methods reveal the greater frequencies in B-ALL.[1]

Ninety-eight percent of mutations occurred in *KRAS, NRAS*, *PTPN11,* and *FLT3* showing a significant role of these genes in p. B-ALL.[26] 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.[26] *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.[26] Recurrent 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*).[26]

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 1: Summary of gene alterations of pediatric B-acute lymphoblastic leukemia

Gene symbol	Type of mutations	Missense alterations (aminoacid change)	References
TP53	Missense, deletions, insertions, splice site, frameshift, in-frame, nonsense	S127F, G245R, M246V, R248W, R248Q, R273C, D281A, D281E, R282W, R282G, R282P, R290L and E298K	[2]
PAX5	Deletions, frameshift, and translocations	L23R, L33F, G24W, V26G, P34Q, P80R, and N106S	[3,4]
CRLF2	Rearrangements and translocations	-	[1,5,6]
JAK1/2	Missense and splice site	T514T and R683G	[3-6]
IKZF1	Deletions and mutations	-	[3,7,8]
CREBBP	Nonsynonymous, frameshift, splice site, and deletions	G1411E, G1411R, C1421Y, Q1491K, I1483T, D1435G, S56C, and R1446H	[3]
NRAS	Missense	G12S, G12D, G13D, G13C, and Q61H	[9,10]
KRAS	Missense	Gly13Asp, Gly12Asp	[9,10]
FLT3	Missense, frameshift, and deletions	D835Y, D835H, D835V, and p.I836del	[9,11,12]
PTPN11	Missense	D61V, D61Y, E69K, A72V, T73I, and S502L	[9]
ETV6	Missense, frameshift, and insertions	P214L, L349P, R359X, R369Q, N385fs, and R399C	[9,13,14]
MUC4	Alterations	-	[9]
CDKN2A/B	Missense, deletions, and insertions	A97T	[9,15-17]
ADARB2	Alterations	-	[9]
ASMTL	Alterations	-	[9]
TBL1XR1	Deletions	-	[9]
IRF8	Alterations	-	[9]
VPREB1	Missense and deletions	Unpublished	Unpublished
IGLL1	Missense	-	[18]
ERG	Deletions	-	[19,20]
BRAF	Alterations	-	[21]
BCL2	Alterations	-	[21]
NT5C2	Missense and inframe indel	R238W, p.D396-A400del, p.K404delinsKD, p.S408-D415del, S445F p.S445-R446delinsFQ and p.Q523*	[22,23]
IL7R	Missense, insertions, and deletions	S185C	[6]
SETD2	Missense, frameshift, deletions, nonsense, and splice site	K2R, E19G, V261I, S470P, T499A, K519fs, Y794X, S1076P, S1093G, F1117fs, T1171A, D1351G, G1365E, E1416X, D1453N, L1609P, I1615fs, T1663M, T1753fs, L1821P, V1915A, E1920V, P2361S, and K2546X	[24,25]

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.

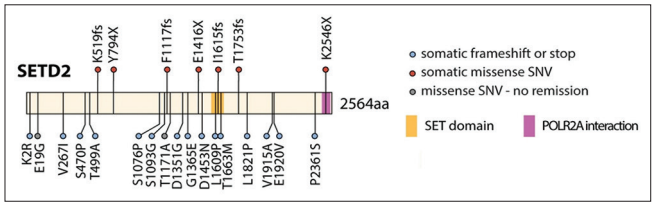

Figure 2: Graphic of p. B-acute lymphoblastic leukemia *SETD2* gene somatic mutations[25]

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

Criterions 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

Gene symbol	Noncoding region	Alterations	rs ID	Researcher	References
TP53	Splice site (Exon 8)	g. 13762 G>A	-	Hof *et al*.	[2]
PAX5	Intronic	NG_033894.1:g. 18643C>T	rs377355229	Erbilgin *et al*.	[4]
JAK2	Splice site	NG_009904.1:g. 89709G>A	rs565502628	Erbilgin *et al*.	[4]
JAK2	Intronic	NG_009904.1:g. 89837 T>C	Novel	Erbilgin *et al*.	[4]
CREBBP	Splice site (Exon 21)	c. 3836+1G>A	-	Inthal *et al*.	[26]
IL7R	Intronic	NG_009567.1:g. 22664 T>C	rs202114203	Erbilgin *et al*.	[4]
CRLF2	Intronic	NG_034237.1:g. 20998 G>A	Novel	Erbilgin *et al*.	[4]
ARID5B	Intronic	NG_030027.1:g. 43883A>C	rs7073837	Orsi *et al*.	[27]
ARID5B	Intronic	NG_030027.1:g. 54092A>G	rs10994982	Tao *et al*.	[28]
ARID5B	Intronic	NG_030027.1:g. 62467C>A	rs10740055	Orsi *et al*.	[27]
ARID5B	Intronic	NG_030027.1:g. 96147T>G	rs7089424	Orsi *et al*.	[27]
ANKRD44	Intronic	NC_000002.12:g. 197083099A>C	rs930372	Orsi *et al*.	[27]

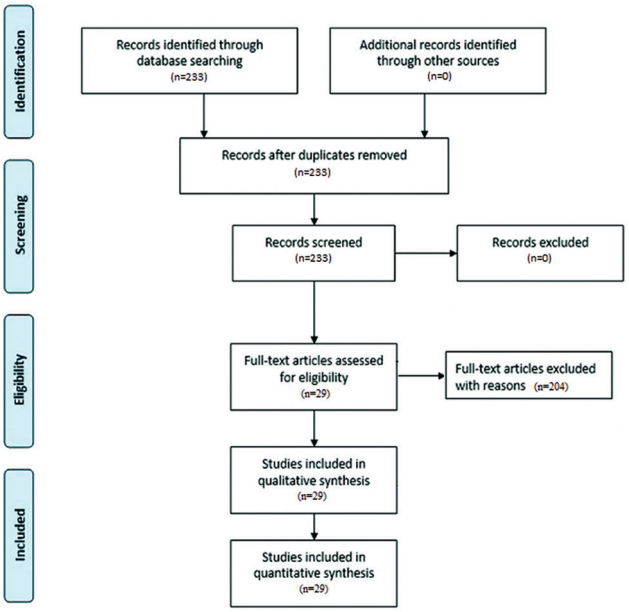

Figure 3: PRISMA instructions flow diagram of the systematic review

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).[29,30] It is characterized by genetic alterations which block lymphoid precursor cells proliferation and differentiation.[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.[15] The desire to recognize the genetic basis of differences in children with B-ALL has been catalyzed by using high-throughput NGS technology.[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.[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.[20] *CDKN2A/B*, *ETV6,* and *IKZF1* mutations are connected to high-treatment failure risk.[30] NGS of 300 genes of 264 samples revealed mutations in 32 genes, such as *CREBBP*, *NCOR1*, *ERG*, *SPI1*, *TCF4,* and *TCF7 L2* in the relapse samples. A study of p. B-ALL relapsed cases by Alsagaby *et al*. had reported

Table 3: Genes or proteins associated with relapse and drug resistance[29]

Relapse	Drug resistance
APC, PTPRO, CDKN2A, SETD2, KDM6A, MLL2, CREBBP, NCOR1, ERG, SPI1, TCF4, TCF7L2, KRAS, BTG1, NR3C1, TBL1XR1, EBF1, IKZF1, PYGL, and *PDE4B*	*HRK* and *MCL-1* Elsolin, Ezrin, actin-regulatory protein CAP-G, heat-shock cognate 71 kDa Protein A, T-complex protein 1 subunits beta, epsilon, nonmetastatic cells 2, cofilin 1, voltage-dependent anion-selective channel protein 1, ER-60 protease, galactin, and high-mobility group protein B2

an important association between deleted genes such as *BTG1*, *NR3C1,* and *TBL1XR1* (glucocorticoid signaling) with in the therapy failure.[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*.

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Nil.

Conflicts of interest

There are no conflicts of interest.

References

1. Montaño A, Forero-Castro M, Marchena-Mendoza D, Benito R, Hernández-Rivas JM. New challenges in targeting signaling pathways in acute lymphoblastic leukemia by NGS approaches: An update. Cancers (Basel) 2018;10:110.
2. Hof J, Krentz S, van Schewick C, Körner G, Shalapour S, Rhein P, *et al*. Mutations and deletions of the TP53 gene predict nonresponse to treatment and poor outcome in first relapse of childhood acute lymphoblastic leukemia. J Clin Oncol 2011;29:3185-93.
3. Loh ML, Mullighan CG. Advances in the genetics of high-risk childhood B-progenitor acute lymphoblastic leukemia and juvenile myelomonocytic leukemia: Implications for therapy. Clin Cancer Res 2012;18:2754-67.
4. Erbilgin Y, Firtina S, Mercan S, Ng OF, Karaman S, Tasar O, *et al*. Prognostic gene alterations and clonal changes in childhood B-ALL. Leuk Res 2019;83:106159.
5. Hu Y. Acute lymphoblastic leukemia: Genetic events and molecular signatures. Am J Biomed Sci 2014;6:238-53.
6. Tasian SK, Loh ML. Understanding the biology of CRLF2-overexpressing acute lymphoblastic leukemia. Crit Rev Oncog 2011;16:13-24.
7. Churchman ML, Qian M, Te Kronnie G, Zhang R, Yang W, Zhang H, *et al*. Germline genetic IKZF1 variation and predisposition to childhood acute lymphoblastic leukemia. Cancer Cell 2018;33:937-48. e8.
8. Lopes BA, Barbosa TC, Souza BK, Poubel CP, Pombo-de-Oliveira MS, Emerenciano M, *et al*. IKZF1

gene in childhood B-cell precursor acute lymphoblastic leukemia: Interplay between genetic susceptibility and somatic abnormalities. Cancer Prev Res (Phila) 2017;10:738-44.
9. Zhang J, Mullighan CG, Harvey RC, Wu G, Chen X, Edmonson M, *et al*. Key pathways are frequently mutated in high-risk childhood acute lymphoblastic leukemia: A report from the Children's Oncology Group. Blood J Am Soc Hematol 2011;118:3080-7.
10. Perentesis JP, Bhatia S, Boyle E, Shao Y, Shu XO, Steinbuch M, *et al*. RAS oncogene mutations and outcome of therapy for childhood acute lymphoblastic leukemia. Leukemia 2004;18:685-92.
11. Zhang HH, Wang HS, Qian XW, Fan CQ, Li J, Miao H, *et al*. Genetic variants and clinical significance of pediatric acute lymphoblastic leukemia. Ann Transl Med 2019;7:296.
12. Braoudaki M, Karpusas M, Katsibardi K, Papathanassiou CH, Karamolegou K, Tzortzatou-Stathopoulou F. Frequency of FLT3 mutations in childhood acute lymphoblastic leukemia. Med Oncol 2009;26:460-2.
13. Topka S, Vijai J, Walsh MF, Jacobs L, Maria A, Villano D, *et al*. Germline ETV6 mutations confer susceptibility to acute lymphoblastic leukemia and thrombocytopenia. PLoS Genet 2015;11:e1005262.
14. Hock H, Shimamura A. ETV6 in hematopoiesis and leukemia predisposition. Semin Hematol 2017;54:98-104.
15. Zaliova M, Stuchly J, Winkowska L, Musilova A, Fiser K, Slamova M, *et al*. Genomic landscape of pediatric B-other acute lymphoblastic leukemia in a consecutive European cohort. Haematologica 2019;104:1396-406.
16. Xu H, Zhang H, Yang W, Yadav R, Morrison AC, Qian M, *et al*. Inherited coding variants at the CDKN2A locus influence susceptibility to acute lymphoblastic leukaemia in children. Nat Commun 2015;6:7553.
17. Gutierrez-Camino A, Martin-Guerrero I, de Andoin NG, Sastre A, Bañeres AC, Astigarraga I, *et al*. Confirmation of involvement of new variants at CDKN2A/B in pediatric acute lymphoblastic leukemia susceptibility in the Spanish population. PLoS One 2017;12:e0177421.
18. Minegishi Y, Coustan-Smith E, Wang YH, Cooper MD, Campana D, Conley ME. Mutations in the human λ5/14.1 gene result in B cell deficiency and agammaglobulinemia. J Exp Med 1998;187:71-7.
19. Zhang X, Rastogi P, Shah B, Zhang L. B lymphoblastic leukemia/lymphoma: New insights into genetics, molecular aberrations, subclassification and targeted therapy. Oncotarget 2017;8:66728-41.
20. Qian M, Xu H, Perez-Andreu V, Roberts KG, Zhang H, Yang W, *et al*. Novel susceptibility variants at the ERG locus for childhood acute lymphoblastic leukemia in Hispanics. Blood 2019;133:724-9.
21. Al-Anazi W, Dridi W, Al-Anazi K. Cytogenetics, molecular genetics and epigenetics and their impact on the management of acute lymphoblastic leukemia. J Mol Genet Med 2017;11:1747-0862.1000308.
22. Dieck CL, Tzoneva G, Forouhar F, Carpenter Z, Ambesi-Impiombato A, Sánchez-Martín M, *et al*. Structure and mechanisms of NT5C2 mutations driving thiopurine resistance in relapsed lymphoblastic leukemia. Cancer Cell 2018;34:136-47. e6.
23. Meyer JA, Wang J, Hogan LE, Yang JJ, Dandekar S, Patel JP, *et al*. Relapse-specific mutations in NT5C2 in childhood acute lymphoblastic leukemia. Nat Genet 2013;45:290-4.
24. Skucha A, Ebner J, Grebien F. Roles of SETD2 in leukemia-transcription, DNA-damage, and beyond. Int J Mol Sci 2019;20:1029.
25. Mar BG, Bullinger LB, McLean KM, Grauman PV, Harris MH, Stevenson K, *et al*. Mutations in epigenetic regulators including SETD2 are gained during relapse in paediatric acute lymphoblastic leukaemia. Nat Commun 2014;5:3469.
26. Inthal A, Zeitlhofer P, Zeginigg M, Morak M, Grausenburger R, Fronkova E, *et al*. CREBBP HAT domain mutations prevail in relapse cases of high hyperdiploid childhood acute lymphoblastic leukemia. Leukemia 2012;26:1797-803.
27. Paulsson K, Horvat A, Strömbeck B, Nilsson F, Heldrup J, Behrendtz M, *et al*. Mutations of FLT3, NRAS, KRAS, and PTPN11 are frequent and possibly mutually exclusive in high hyperdiploid childhood acute lymphoblastic leukemia. Genes, Chromosomes and Cancer 2008;47:26-33.
28. Tao R, Liu YJ, Liu LF, Li W, Zhao Y, Li HM, *et al*. Genetic polymorphisms of ARID5B rs7089424 and rs10994982 are associated with B-lineage all susceptibility in Chinese pediatric population. J Chin Med Assoc 2019;82:562-7.
29. Alsagaby SA. Omics-based insights into therapy failure of pediatric B-lineage acute lymphoblastic leukemia. Oncol Rev 2019;13:435.
30. Movafagh A, Mirfakhraei R, Mousavi-Jarrahi A. Frequent incidence of double minute chromosomes in cancers, with special up-to-date reference to leukemia. Asian Pac J Cancer Prev 2011;12:3453-6.
31. Movafagh A, Maleki F, Fadaie S, Gashb EA. Persistent unstable chromosomal aberrations in lymphocytes of radiotherapy workers after 1st mitotic division in Tehran, Iran. Pak J Med Sc 2007;23:254-8.