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*Short communication*

# Genetic markers in pediatric B-cell acute lymphoblastic leukemia: implications for risk stratification

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## Introduction

B-cell precursor acute lymphoblastic leukemia (B-ALL) is a heterogeneous hematologic malignancy characterized by the clonal proliferation of abnormal B-cell precursors (lymphoblasts) in the bone marrow, peripheral blood, and other organs. Risk stratification in pediatric B-ALL has traditionally relied on clinical factors such as age and white blood cell count, however, the disease is now recognized as a molecularly heterogeneous malignancy composed of multiple genetic subtypes with distinct prognostic and therapeutic implications. Generally, pediatric B-ALL treatment protocols incorporate clinical factors, minimal residual disease (MRD) assessment, and evaluation of recurrent genetic abnormalities such as ETV6::RUNX1, BCR::ABL1, TCF3::PBX1, TCF3::HLF, and MLL::AFF1 for risk stratification and treatment planning (SIOPE, 2022). Many current protocols also consider other abnormalities which have become increasingly important for risk stratification. The aim of this review is to summarize and evaluate the current evidence for the prognostic impact of these markers in B-ALL and their association with defining new molecular subtypes.

## Genetic markers as a potential tool for prognosis

*Favorable prognostic markers*

The genetic markers predictive of favorable outcome remain quite limited. Despite the well-recognized ETV6::RUNX1 subtype, high hyperdiploidy (HeH), defined by the presence of 51–67 chromosomes in leukemic cells is generally associated with a favorable prognosis in B-ALL, with certain chromosomal gains contributing differently to clinical outcomes. Among these, trisomy 18 is most consistently linked to a favorable outcome, whereas, gain of additional copies of chromosome 5 and 20 are associated with poorer prognosis. DUX4-rearranged ALL is another recently discovered subtype associated with excellent survival (Zhang et al., 2022).

*Unfavorable prognostic markers*

One of the subtypes with poorest event-free survival (EFS) is hypodiploidy (≤ 44 chromosomes). Its occurrence is observed in 1% of pediatric patients with B-ALL and the EFS is from 35 to 50% **(**Lejman et al., 2022**).** Intrachromosomal amplification of chromosome 21 (iAMP21) defines a genetic subtype of pediatric B-ALL, characterized by complex chromosomal rearrangements and focal amplification of chromosome 21. The frequency of iAMP21 in B-

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ALL is 2% and the 5 year EFS is 29% (Hidalgo et al.,) The marker IKZF1 encodes Ikaros, a transcription factor essential for the development of all lymphoid lineages and its deletions are associated with inferior outcomes. Furthermore, deletions affecting CDKN2A and CDKN2B genes, as critical tumor suppressor genes located on 9p21, play an important role for risk stratification. Alterations in PAX5 are observed in approximately 26.6% to 33% of B-ALL cases, making it one of the most frequently affected genes in this disease. Garcia-Solorio J et al. (2024) reported deletions account for 75% of alterations, sequence mutations for 7-10%, while the remaining are focal intragenic amplifications and translocations. Generally, if PAX5 deletions are co-occurring with IKZF1 deletions, they form a key component of the so-called "IKZF1$^{plus}$" profile, which is defined by an IKZF1 deletion together with additional deletions in PAX5, CDKN2A/2B (homozygous only), or the PAR1 region, in the absence of an ERG deletion, and is associated with a 3.7-fold increased risk of death. Another potentially adverse genetic abnormality is intragenic amplification (PAX5igAMP), a rare alteration which according to a cohort study done in 2024 by Garcia-Solorio J et al. is occurring in approximately 1% of B-ALL cases with a male predominance. ERG (ETS-related gene) deletions are clinically significant because they mitigate the adverse prognostic impact of IKZF1 deletions, leading to improved survival rates compared to IKZF1 deletion alone. However, prognostic effects can vary depending on subtype context. Finally, the importance of chromosome X can be seen in its numerical gains and additional alterations in the pseudoautosomal region 1 (PAR1). Genes located within or close to this region include CRLF2, CSF2RA and IL3RA. CRLF2 rearrangements are present in approximately 5% of B-ALL cases and typically occur as the P2RY8::CRLF2 fusion, IGH::CRLF2 translocation, or as activating somatic point mutations such as F232C. According to Zhang L et al. (2022), 50% of the cases with Ph-like ALL (BCR::ABL1–like profile), exhibit deregulated CRLF2 expression. Also, both CSF2RA and IL3RA could have focal alterations that contribute in determining the IKZF1$^{plus}$ profile. Research indicates that patients with CRLF2 rearrangements have a 4-year relapse-free survival (RFS) of approximately 35% compared to the 71% without these alterations (Lejman et al., 2022). Finally, MEF2D-rearranged B-ALL is associated with an adverse prognosis, largely due to higher minimal residual disease (MRD) levels and suboptimal early treatment response (Lejman et al., 2022).

*Intermediate prognostic markers*

Mutations such as PAX5 P80R and other PAX5 alterations, as well as ZNF384-rearranged and TCF3::PBX1 B-ALL are generally associated with intermediate-risk outcomes (Lejman et al., 2022). These, along with a subset of cytogenetically undefined ('B-other') cases are strongly influenced by the MRD response.

## Conclusion

This review presents evidence for genetic markers which hold significant promise for evaluation of the prognosis, enabling more personalized treatment strategies and improving the clinical outcomes. Further validation through large-scale clinical studies as well as molecular profiling is needed to facilitate the translation of these biomarkers into routine pediatric leukemia management.

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