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Genomic Profiling and Mutation Signatures in Pediatric Blood Cancers: Toward Precision Diagnosis and Risk Stratification

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Abstract

Pediatric blood cancers, including leukemias and lymphomas, represent a diverse group of hematological malignancies with complex molecular underpinnings. Despite significant advancements in treatment, these cancers remain a leading cause of cancer-related mortality in children worldwide. Recent developments in next-generation sequencing (NGS) and bioinformatics have enabled comprehensive genomic profiling, unveiling specific mutation signatures and pathways associated with disease onset, progression, and relapse. This article explores the emerging role of genomic profiling in pediatric blood cancers, emphasizing how specific mutation signatures can refine diagnosis, enable personalized therapy, and support accurate risk stratification. We also discuss the challenges and prospects of integrating genomic data into clinical workflows to improve outcomes for young patients.

Keywords: Childhood hematologic malignancies; Somatic mutations in childhood cancers; Precision medicine for pediatric leukemia; Pediatric cancer biomarkers; Germline variants in leukemia; Multi-omics pediatric oncology; Genetic risk factors in childhood cancers; Targeted therapy in pediatric hematology

Introduction

Pediatric blood cancers account for approximately 30–40% of all childhood malignancies, with acute lymphoblastic leukemia (ALL), acute myeloid leukemia (AML), and various lymphomas being the most prevalent [1]. Despite high overall survival rates due to chemotherapy and supportive care advancements, a significant subset of patients relapses or suffer long-term side effects, highlighting the limitations of traditional, one-size-fits-all treatment approaches [2]. In recent years, the application of genomic profiling technologies especially next-generation sequencing (NGS), whole-exome sequencing (WES), and transcriptomic analyses has revealed a more detailed molecular landscape of pediatric blood cancers. These technologies have uncovered novel gene fusions, point mutations, chromosomal abnormalities, and mutational signatures that provide a clearer understanding of tumor biology and disease heterogeneity [3]. The identification of these molecular markers allows clinicians to predict disease aggressiveness, tailor treatment intensity, and introduce targeted therapies based on individual genetic profiles. Importantly, pediatric blood cancers differ genomically from their adult counterparts, necessitating disease-specific and age-specific approaches [4]. Pediatric malignancies often harbor fewer mutations overall but tend to include unique gene rearrangements or developmental pathway disruptions. This underscores the need for pediatric-focused genomic investigations and databases [5]. As precision medicine becomes a clinical reality, integrating genomic data into pediatric hematology-oncology practice represents a transformative opportunity to reduce toxicity, avoid overtreatment, and improve survival outcomes across all risk groups [6].

Historically, diagnosis and risk stratification in pediatric hematologic malignancies have relied on clinical factors such as age, white blood cell count, cytogenetics, and response to therapy. However, these indicators often lack the resolution needed for accurate prognostication [7]. The advent of high-throughput genomic technologies, especially whole-genome sequencing (WGS), whole-exome sequencing (WES), and targeted gene panels, has transformed our understanding of the genetic landscape of pediatric blood cancers [8].

This review delves into how genomic profiling and mutation signatures are shaping the future of pediatric hematology-oncology, particularly with regard to early diagnosis, therapeutic decision-making, and risk stratification.

Lymphomas

Pediatric lymphomas, including Hodgkin and non-Hodgkin subtypes, show age-specific mutational patterns. In anaplastic large cell lymphoma (ALCL), ALK gene rearrangements (e.g., NPM1-ALK) are a common feature and serve as a potential therapeutic target. Similarly, mutations in MYC, BCL2, and TP53 are often seen in Burkitt lymphoma and diffuse large B-cell lymphoma (DLBCL), affecting prognosis and treatment planning. Mutation signatures refer to patterns of somatic mutations resulting from specific endogenous or exogenous processes, such as DNA repair defects, replication stress, or environmental exposures.

Some notable signatures in pediatric hematologic malignancies include:

Hypermutation in mismatch repair deficiency (MMR-D), seen in some leukemias associated with inherited syndromes (e.g., Lynch syndrome). Common in relapsed ALL, indicating therapy-induced mutagenesis.

Rare but noted in lymphomas of immunocompromised children. Understanding these mutation signatures provides insight into tumor

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biology, origin, and therapy resistance mechanisms. For instance, APOBEC-induced hypermutation may render certain leukemias resistant to standard chemotherapy but vulnerable to novel agents targeting DNA damage response pathways. Classify leukemias into molecular subtypes with distinct prognoses. Detect minimal residual disease (MRD) using personalized genomic markers. Identify germline mutations that predispose to leukemia (e.g., TP53, PAX5) Uncover cryptic fusions undetectable by traditional cytogenetics. In ALL, the IKZF1plus profile (deletion of IKZF1 with other gene deletions) is a high-risk marker. In AML, combinations of FLT3-ITD with NPM1 mutations significantly alter risk categorization. Such stratification enables personalized therapy intensifying treatment in high-risk patients and reducing toxicity in low-risk groups, thereby improving survival while minimizing long-term sequelae. Genomic profiling not only informs diagnosis and risk but also guides therapy.

- Tyrosine Kinase Inhibitors (TKIs) for Ph-positive and Ph-like ALL
- FLT3 inhibitors (e.g., gilteritinib) for FLT3-mutant AML
- BCL-2 inhibitors for leukemias with high BCL-2 expression
- Immune checkpoint inhibitors in hypermutated or mismatch repair-deficient cases

Ongoing clinical trials are exploring personalized regimens combining standard chemotherapy with targeted agents based on genomic profiles. These efforts aim to increase remission rates and reduce treatment-related complications.

Conclusion

Genomic profiling is revolutionizing the landscape of pediatric blood cancer diagnosis and management. By identifying mutation signatures and molecular subtypes, clinicians can more accurately stratify patients based on risk and personalize treatment strategies. This precision-medicine approach holds the potential to improve cure rates, reduce treatment toxicity, and uncover novel therapeutic targets.

As genomic technologies become more integrated into clinical practice, collaborative efforts across research, clinical, and bioinformatics disciplines will be vital. Ensuring equitable access to genomic diagnostics, especially in low- and middle-income countries, will also be essential in making precision oncology a reality for all children battling hematologic malignancies.

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