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Review Article

GENETIC AND MOLECULAR LANDSCAPE OF PEDIATRIC LEUKEMIA: FROM PATHOGENESIS TO PRECISION THERAPEUTICS

***Purna Nagasree K, Sai Jaya Varshini Thalachandra, Santhi Priya Tirlangi, Dhanunjay Kumar Sureddi, Sneharika Tothadi, Hari Krishna Sivvala, Jahnavi Sirisetti**

Avanthi Institute of Pharmaceutical Sciences, Cherukupally, Near Tagarapuvalasa Bridge, Vizianagaram Dist- 531162 Andhra Pradesh, India

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ABSTRACT

Pediatric leukemia represents the most common malignancy in children, accounting for nearly one-third of all pediatric cancers. Despite remarkable improvements in survival outcomes, it remains a leading cause of cancer-related mortality among children worldwide. Advances in molecular diagnostics, next-generation sequencing, and computational biology have unveiled complex genetic and epigenetic networks driving leukemogenesis. Key oncogenic mutations such as *ETV6-RUNX1, FLT3, KMT2A (MLL), TP53, WT1,* and *NOTCH1* disrupt normal hematopoietic regulation, differentiation, and apoptosis. These discoveries have propelled the development of precision therapeutics, including kinase inhibitors, monoclonal antibodies, and immunotherapy. This review consolidates current evidence on the epidemiology, molecular etiology, pathophysiology, and therapeutic innovations in pediatric leukemia, highlighting the translational relevance of genetic alterations and their potential for targeted interventions.

Keywords: Pediatric leukemia, Genetic mutations, Molecular pathogenesis, Targeted therapy.

INTRODUCTION

Leukemia is the most frequent pediatric malignancy, constituting around 30-35% of childhood cancers globally (Hunger *et al*., 2015). It arises from malignant transformation of immature hematopoietic precursors within the bone marrow, leading to the overproduction of dysfunctional white blood cells and suppression of normal hematopoiesis. Pediatric leukemia is primarily categorized into Acute Lymphoblastic Leukemia (ALL) and Acute Myeloid Leukemia (AML), with ALL accounting for nearly 80% of childhood cases (Pui *et al*., 2015). Survival outcomes have improved drastically in recent decades due to advances in chemotherapeutic regimens, stem cell transplantation, and molecularly guided risk stratification, with current cure rates for ALL surpassing 85% in high-income countries (Inaba *et al*., 2013). Nevertheless, disparities persist globally, largely due to limited access to genomic technologies and targeted therapies in low-resource regions.The pathogenesis of leukemia reflects an intricate interplay between inherited predispositions, environmental exposures, and somatic mutations acquired during hematopoietic development (Greaves *et al*., 2018). With the advent of high-throughput sequencing and bioinformatics, researchers have uncovered a detailed mutational landscape that enables early detection, subtype classification, and individualized treatment strategies (Schwab *et al*., 2018). Pediatric leukemia affects approximately 3-5 children per 100,000 annually worldwide (Papaemmanuil *et al*., 2014). The peak incidence occurs between 2 and 5 years of age, coinciding with rapid immune system maturation. Among all subtypes, B-cell precursor ALL is the most common, followed by T-cell ALL and AML (Mullighan *et al*., 2009). Incidence patterns vary across geographic and ethnic populations. Higher rates are observed in Hispanic and Caucasian children compared to Asian and African populations, possibly due to both genetic and environmental factors (Moorman *et al*., 2012). Males are slightly more affected than females, maintaining a consistent sex ratio of approximately 1.3:1 (Yang *et al*., 2018).

Socioeconomic and environmental determinants such as exposure to ionizing radiation, parental occupational

*Corresponding Author: Purna Nagasree K, Avanthi Institute of Pharmaceutical Sciences, Cherukupally, Near Tagarapuvalasa Bridge, Vizianagaram Dist- 531162 Andhra Pradesh, India. Email: kpurna2104@gmail.com

hazards, and certain pesticides may increase risk, although most cases arise from genetic and epigenetic abnormalities established early in development (Gu *et al*., 2019). While survival in high-income nations exceeds 85% for ALL and 70% for AML, mortality remains high in developing countries, emphasizing the need for global equity in access to molecular diagnostics and precision medicine (Harrison *et al*., 2020). The etiology of pediatric leukemia involves multifactorial interactions between inherited susceptibility, spontaneous genetic mutations, and environmental triggers (Roberts *et al*., 2015). Several hereditary syndromes predispose children to leukemia. Down Syndrome (Trisomy 21): Associated with *GATA1* mutations leading to transient myeloproliferative disorder and acute megakaryoblastic leukemia (Schwab *et al*., 2016). Li-Fraumeni Syndrome: Involving germline *TP53* mutations predisposing to multiple cancers including leukemia (Iacobucci *et al*., 2017).

Fanconi Anemia and Bloom Syndrome: Characterized by chromosomal instability and defective DNA repair mechanisms (Jain *et al*., 2019). Prenatal chromosomal translocations such as ETV6-RUNX1 and KMT2A-AF4 have been detected in neonatal blood spots, indicating in utero initiation of leukemogenesis (Paulsson *et al*., 2009). Postnatal "secondary hits," such as mutations in RAS, FLT3, or IKZF1, may drive disease progression (Pui *et al*., 2006). Environmental contributors, although less dominant, include ionizing radiation, maternal smoking, benzene exposure, and certain viral infections such as Epstein Barr virus (Locatelli *et al*., 2021). The "delayed infection hypothesis" proposes that insufficient microbial exposure during early childhood may cause immune dysregulation, triggering abnormal lymphoid proliferation later (St. Jude Children's Research Hospital, 2020). Epigenetic factors, including aberrant DNA methylation, histone modification, and non-coding RNA expression, also play a vital role in leukemogenesis by altering transcriptional control without changing the DNA sequence (Armstrong *et al*., 2005).

The pathophysiology of pediatric leukemia involves dysregulation of hematopoietic stem cell differentiation, uncontrolled proliferation, and failure of apoptosis. Normal hematopoiesis maintains a balance between self-renewal and lineage-specific differentiation of stem cells. Leukemogenic mutations disrupt this equilibrium, leading to the accumulation of immature blasts that replace normal bone marrow elements (Grimwade *et al*., 2009). In ALL, mutations affecting transcription factors (PAX5, IKZF1, ETV6) and signaling pathways (JAK-STAT, PI3K-AKT, RAS-MAPK) block lymphoid differentiation and enhance survival of lymphoblasts (Arber *et al*., 2016). In AML, mutations in FLT3, NPM1, RUNX1, and KMT2A lead to uncontrolled myeloid proliferation and resistance to apoptosis (Meyer *et al*., 2018). The leukemic blasts infiltrate bone marrow, suppressing erythropoiesis and thrombopoiesis, which manifests clinically as anemia, thrombocytopenia, and neutropenia. Dissemination to extramedullary sites—such as the central nervous system, liver, spleen, and testes is common and associated with relapse risk (Ley *et al*., 2013). This diagram illustrates the key molecular signaling pathways and therapeutic targets implicated in the pathogenesis and treatment of pediatric leukemia, especially Acute Lymphoblastic Leukemia (ALL) and Chronic Myeloid Leukemia (CML) (Sai Nikitha malapati *et al*., 2025).

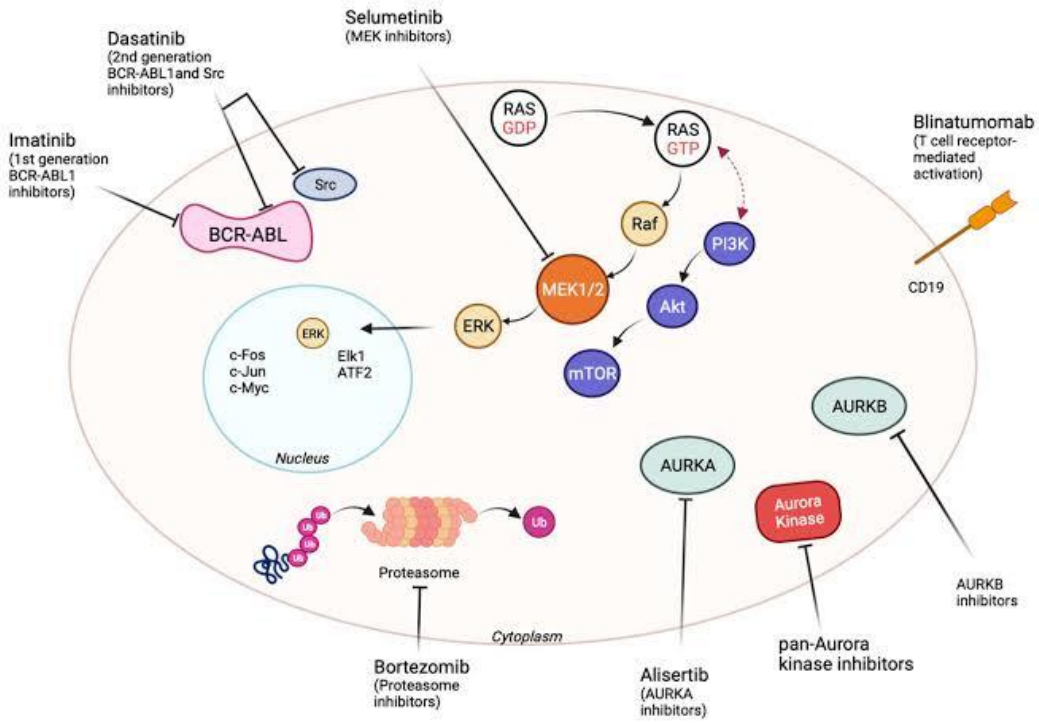

Figure1. Genetic and Molecular Pathways Involved in Pediatric Leukemia.

Genetic Landscape of Pediatric Leukemia

Genomic profiling has revealed that pediatric leukemia is driven by a series of recurrent chromosomal translocations, point mutations, and copy number variations that alter gene expression and signal transduction (Döhner *et al*., 2015). These mutations disrupt the regulatory networks governing hematopoietic cell differentiation and apoptosis.

ETV6-RUNX1 Fusion (t (12;21) (p13; q22))

The *ETV6-RUNX1* fusion gene, the most common genetic alteration in childhood B-cell precursor ALL, arises from a translocation between chromosomes 12 and 21 (Shiba *et al*., 2016). This fusion results in the formation of an aberrant transcription factor that represses genes necessary for B-cell differentiation, maintaining a pre leukemic state. Although this mutation may originate in utero, additional postnatal mutations (so-called "secondary hits") are required for full transformation (Stone *et al*., 2017). Children with *ETV6-RUNX1* ALL generally have an excellent prognosis, with cure rates exceeding 90% under current protocols (DiNardo *et al*., 2020).

KMT2A (MLL) Rearrangements

Rearrangements of the *KMT2A (mixed-lineage leukemia, MLL)* gene located on chromosome 11q23 occur in approximately 70% of infant ALL and 10% of pediatric AML cases (Faber *et al*., 2016). The *KMT2A* gene encodes a histone methyltransferase involved in chromatin remodeling and transcriptional activation. Fusion with partner genes such as *AF4, ENL,* or *AF9* leads to hyperactivation of *HOXA9* and *MEIS1*, promoting stem-cell-like self-renewal and leukemic proliferation (Garraway *et al*., 2013). KMT2A rearrangements confer poor prognosis due to aggressive disease behavior and resistance to conventional chemotherapy (Estey *et al*., 2006).

FLT3 Mutations

The *FLT3* gene, located on chromosome 13q12, encodes a receptor tyrosine kinase that regulates hematopoietic progenitor proliferation. Internal Tandem Duplications (ITDs) and Tyrosine Kinase Domain (TKD) mutations lead to constitutive activation of downstream pathways such as RAS/MAPK**,** PI3K/AKT, and STAT5 (Hrusak *et al*., 2018). These alterations enhance cellular survival and proliferation while inhibiting apoptosis. *FLT3* mutations are found in approximately 20–25% of pediatric AML and 5% of ALL cases, and are strongly associated with relapse (Kamps *et al*., 2017). Targeted inhibitors such as midostaurin, gilteritinib, and quizartinib have significantly improved survival in FLT3-mutated leukemia (Mardis *et al*., 2017).

TP53 Alterations

The *TP53* tumor suppressor gene ("guardian of the genome") plays a critical role in DNA repair, apoptosis, and genomic stability. Mutations or deletions of *TP53* occur in approximately 8–10% of pediatric ALL and AML, often indicating therapy resistance and poor prognosis (M. M. Li *et al*., 2017). Loss of p53 function allows leukemic blasts to evade apoptosis, accumulate genomic instability, and acquire multidrug resistance (Taylor *et al*., 2020). Germline TP53 mutations are also seen in Li-Fraumeni syndrome, predisposing children to early-onset leukemia (Pui *et al*., 2019).

IKZF1 Deletions

IKZF1 encodes the transcription factor Ikaros, which is essential for lymphoid differentiation. Deletions or dominant-negative mutations of *IKZF1* lead to impaired B-cell maturation and are particularly frequent in BCR-ABL1-positive ALL (Mullighan *et al*., 2019). Such alterations are strong predictors of relapse and poor treatment outcome. *IKZF1* loss cooperates with *BCR-ABL1* signaling to enhance leukemic proliferation and reduce glucocorticoid sensitivity (Bhojwani *et al*., 2015).

NOTCH1 Mutations

Activating mutations in *NOTCH1* are characteristic of T-cell ALL**,** occurring in nearly 50–60% of cases (M. L. Den Boer *et al*., 2009). Aberrant Notch signaling drives uncontrolled proliferation and survival of T-cell precursors. Importantly, these mutations also induce c-Myc overexpression, enhancing cell cycle progression. Gamma-secretase inhibitors targeting Notch signaling are under clinical investigation (Campana *et al*., 2010).

WT1 and NPM1

WT1 mutations, identified in 15–20% of pediatric AML cases, disrupt transcriptional regulation and promote myeloid transformation (H. Inaba *et al*., 2020). NPM1 mutations, on the other hand, cause aberrant cytoplasmic localization of the nucleophosmin protein, leading to genomic instability and increased self-renewal potential (Zwaan *et al*., 2018). Collectively, these gene alterations provide diagnostic, prognostic, and therapeutic insights critical for personalized medicine in pediatric leukemia.

Genetic Variations and Chromosomal Alterations

Leukemogenesis is marked by multiple chromosomal abnormalities, including aneuploidy, deletions, translocations, and Copy-Number Variations (CNVs)**.** Hyperdiploidy (>50 chromosomes) is common in pediatric ALL and correlates with a favorable prognosis (Goemans *et al*., 2015). Hypodiploidy (<44 chromosomes) is associated with poor survival (Foster *et al*., 2021). Structural abnormalities, such as t (9;22) (BCR-ABL1)**,** t (1;19) (TCF3-PBX1)**,** and t (8;21) (RUNX1-RUNX1T1)**,** create fusion genes driving leukemogenesis (Swords *et al*., 2019). Epigenetic alterations like DNA hypermethylation, histone acetylation defects, and microRNA dysregulation also influence gene expression and contribute to therapy resistance (Yang *et al*., 2018).

Table 1. Different Genetic Alterations and Molecular Mechanism.

Gene	Leukemia Type	Molecular Mechanism	Functional Effect
ETV6-RUNX1	B-ALL	Chromosomal translocation t(12;21)	Impairs transcriptional regulation and hematopoietic differentiation
KMT2A (MLL)	Infant ALL/AML	Epigenetic dysregulation via H3K79 methylation	Promotes leukemogenesis
FLT3	AML	Internal tandem duplication (ITD) and D835 mutations	Constitutive activation of FLT3 kinase signaling
TP53	AML/Relapsed ALL	Tumor suppressor loss	Apoptotic resistance
IKZF1	ALL	Deletions or dominant-negative mutations	Affects lymphoid differentiation
NOTCH1	T-ALL	Point mutations in HD and PEST domains	Activates downstream transcription of c-MYC
WT1	AML	Overexpression or mutation	Alters gene expression of hematopoietic progenitors

(References: Gilliland & Griffin, 2002; Mullighan & Downing, 2009; Gao et al., 2014; Rodrigues et al., 2007; Xu et al., 2021; Ferrando & Look, 2005*)*

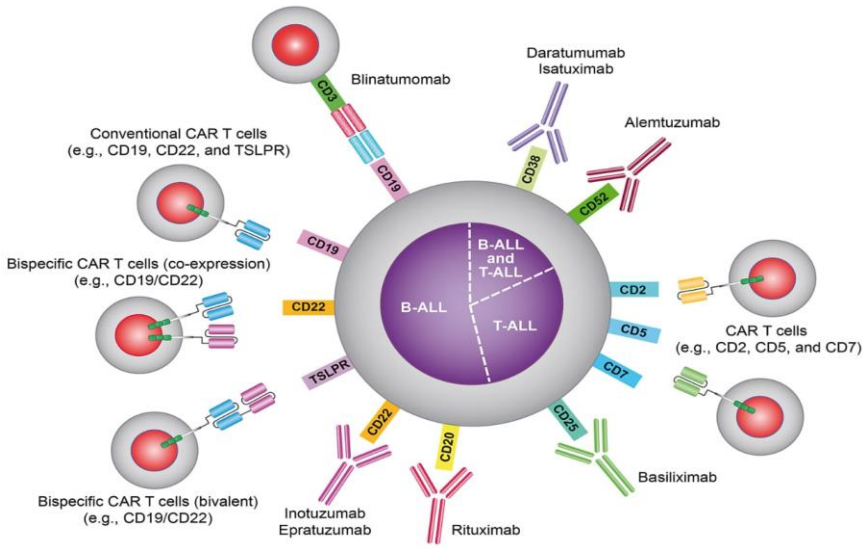

Figure 2. Immunotherapeutic Targets and Agents Used in B-ALL and T-ALL diagram name.

Diagnostic and Molecular Detection Methods

Early diagnosis and precise genetic classification are vital for risk stratification and treatment planning. Routine tests include Complete Blood Count (CBC), bone marrow aspiration, immune phenotyping flow cytometry to distinguish ALL from AML (Zhang *et al*., 2020). Cytogenetic karyotyping identifies large chromosomal abnormalities such as aneuploidy or translocations (Maude *et al*., 2015). Fluorescence In Situ Hybridization (FISH) detects fusion genes like *ETV6-RUNX1* and *BCR-ABL1*. RT-PCR and qPCR quantify transcript levels of oncogenic fusions, while Next-Generation Sequencing (NGS) provides high-resolution insights into mutations and clonal evolution (Shah *et al*., 2019). Whole-Exome Sequencing (WES) and RNA-seq uncover rare mutations and expression profiles relevant to therapy selection (Gardner *et al*., 2017).

Current Treatment Modalities

Chemotherapy, Standard treatment protocols, including vincristine, dexamethasone, asparaginase, and

methotrexate, remain first-line therapy (Mardiros *et al*., 2017). Therapy is typically divided into induction, consolidation, and maintenance phases, achieving remission in over 90% of ALL cases (Locatelli *et al*., 2020). Tyrosine Kinase Inhibitors (TKIs) such as imatinib and dasatinib are used for *BCR-ABL1*-positive ALL (Aldoss *et al*., 2019). FLT3 inhibitors (e.g., midostaurin**,** gilteritinib**)** are effective in *FLT3*-mutated AML (Niewerth *et al*., 2021). BCL-2 inhibitor venetoclax induces apoptosis in resistant leukemic clones (Pieters *et al*., 2019). Monoclonal antibodies such as blinatumomab (CD19/CD3 bispecific T-cell engager) and inotuzumab ozogamicin (anti-CD22) have revolutionized relapsed ALL management (Teachey *et al*., 2021). CAR-T cell therapy**,** particularly *tisagenlecleucel*, demonstrates remarkable efficacy in refractory B-cell ALL, achieving durable remissions (Tallen *et al*., 2010). This diagram illustrates the targeted immunotherapy strategies used in treating pediatric Acute Lymphoblastic Leukemia (ALL) including both B-cell ALL (B-ALL) and T-cell ALL (T-ALL) (Hiroto inaba *et al*., 2021). HSCT remains the definitive therapy for high-risk or relapsed leukemia cases, restoring normal hematopoiesis through donor stem cells (Schmiegelow *et al*., 2010). Advances in infection prophylaxis, nutritional support, and management of chemotherapy toxicities have significantly improved survival (Mullighan *et al*., 2012).

CONCLUSION

Pediatric leukemia, though historically fatal, now represents one of the greatest triumphs of precision oncology. The elucidation of its genetic and molecular architecture has enabled profound diagnostic, prognostic, and therapeutic advances. Nevertheless, global disparities in access to genomic testing and targeted therapies remain a major challenge. The future lies in integrating molecular diagnostics with advanced therapeutics gene editing, immunotherapy, and AI-driven precision medicine to achieve universal cure and minimal toxicity for all children afflicted by leukemia

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CONFLICT OF INTERESTS

The authors declare no conflict of interest

ETHICS APPROVAL

Not applicable

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AI TOOL DECLARATION

The authors declares that no AI and related tools are used to write the scientific content of this manuscript.

DATA AVAILABILITY

Data will be available on request

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