Review Article

Cytogenetic and Molecular Abnormalities in Hematologic Malignancies: A Comprehensive Review of Mechanisms, Biomarkers, and Therapeutic Advances

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ABSTRACT

Cytogenetic and molecular abnormalities are fundamental drivers of hematologic malignancies, shaping disease classification, prognosis, and therapeutic decision-making. Over the past two decades, advances in next-generation sequencing and precision medicine have substantially expanded our understanding of the genetic and epigenetic mechanisms underlying leukemia, lymphoma, and related disorders. To provide a comprehensive synthesis, a narrative review of peer-reviewed literature published between January 2000 and June 2025 was conducted across PubMed, Scopus, Embase, and Web of Science. Eligible studies included original research, systematic reviews, and meta-analyses reporting on cytogenetic and molecular mechanisms, diagnostic biomarkers, and therapeutic innovations in hematologic malignancies. Findings from this review highlight recurrent chromosomal abnormalities such as t(9;22) BCR-ABL1 in chronic myeloid leukemia, t(15;17) PML-RARA in acute promyelocytic leukemia, and del(17p)/TP53 mutations in chronic lymphocytic leukemia as pivotal prognostic and therapeutic markers. Molecular mutations including FLT3, NPM1, IDH1/2, and DNMT3A were consistently linked to poor or intermediate outcomes in acute myeloid leukemia, while MYD88 and EZH2 mutations were frequently observed in B-cell lymphomas. Diagnostic modalities such as fluorescence in situ hybridization, PCR, and next-generation sequencing were shown to improve classification and treatment guidance. Importantly, targeted therapies including tyrosine kinase inhibitors, FLT3 and IDH inhibitors, and epigenetic modulators have significantly transformed patient outcomes, although access and treatment resistance remain major barriers, especially in low-resource settings. This review underscores the need for molecularly informed diagnostic algorithms, wider integration of next-generation sequencing into standard care, and expanded access to targeted therapies. Strengthening laboratory infrastructure, establishing region-specific treatment guidelines, and enhancing equitable access to molecular testing and therapy are essential steps toward improving outcomes. Overall, cytogenetic and molecular profiling has redefined the management of hematologic malignancies, but disparities in access and the emergence of resistance highlight the importance of continued innovation, biomarker discovery, and personalized therapeutic strategies to achieve durable patient benefit.

Keywords: Cytogenetics, Hematologic malignancies, Leukemia, Lymphoma, Molecular biomarkers, Precision medicine, Targeted therapy

INTRODUCTION

Hematologic malignancies (HMs) are a heterogeneous group of clonal disorders of hematopoietic and lymphoid tissues characterized by recurrent cytogenetic and molecular abnormalities[1],[2]. Early discoveries, such as the

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Philadelphia chromosome t(9;22)(q34;q11) and its product BCR-ABL1 in chronic myeloid leukemia (CML), established chromosomal alterations as key drivers of disease biology[3]. Today, the WHO 5th edition haematolymphoid classification incorporates molecular genetics into diagnostic definitions, reflecting the paradigm shift from morphology-based classification to integrated cytogenomic models[1]. In recent decades, technological advances such as next-generation sequencing (NGS) have identified a wide spectrum of somatic mutations, structural variants, and copy-number alterations in hematologic cancers[4,5]. These discoveries have informed prognostication and enabled precision medicine through therapies targeting FLT3, IDH1/2, and BCL2, among others[6,7]. Nevertheless, challenges remain, including clonal heterogeneity, resistance to targeted therapy, and limited availability of advanced diagnostics in low- and middle-income countries[8].

Cytogenetic abnormalities include translocations, aneuploidy, and copy-number alterations that directly contribute to malignant transformation. Balanced translocations producing oncogenic fusions are among the most significant. The BCR-ABL1 fusion in CML results in constitutive tyrosine kinase activity, while PML-RARA in acute promyelocytic leukemia (APL) drives differentiation arrest but is highly targetable with all-trans retinoic acid (ATRA) and arsenic trioxide[3,9]. Other recurrent translocations include RUNX1-RUNX1T1 [t(8;21)] and CBFB-MYH11 [inv(16)], both associated with favorable prognosis in acute myeloid leukemia (AML)[10]. Aneuploidy and structural abnormalities also play critical roles. Loss of chromosome 7 or deletions of 5q are strongly associated with poor outcomes in myeloid malignancies[11]. Similarly, trisomy 12 and 17p deletions are important in chronic lymphocytic leukemia (CLL), the latter linked to TP53 inactivation and therapy resistance[12]. Copy-number alterations, including deletions of CDKN2A or IKZF1 in acute lymphoblastic leukemia (ALL), further refine risk classification and influence therapy selection[13].

NGS has expanded understanding of molecular pathogenesis in hematologic malignancies. In AML, recurrent mutations in FLT3, NPM1, and IDH1/2 are among the most clinically relevant[14,15]. FLT3-ITD mutations confer high relapse risk but are targetable with midostaurin or gilteritinib[16]. NPM1 mutations, in contrast, often predict favorable prognosis unless co-occurring with adverse cytogenetics[14]. IDH1/2 mutations induce production of the oncometabolite 2-hydroxyglutarate, and specific inhibitors such as ivosidenib and enasidenib have demonstrated clinical efficacy[17]. Epigenetic regulators, including TET2, DNMT3A, and ASXL1, are frequently mutated across myeloid neoplasms, reflecting the importance of aberrant DNA methylation and chromatin remodeling[18]. In lymphoid malignancies, abnormalities in MYC, BCL2, and BCL6 define high-grade lymphomas, while NOTCH1 mutations are implicated in T-cell ALL[19,20].

Conventional karyotyping remains the gold standard for detecting chromosomal translocations, though it requires dividing cells and has limited resolution[21]. Fluorescence in situ hybridization (FISH) complements karyotyping by detecting common fusion genes such as BCR-ABL1 and PML-RARA[22]. Molecular assays, including reverse transcriptase PCR (RT-PCR), provide quantitative monitoring of fusion transcripts, critical for minimal residual disease (MRD) assessment[23]. High-resolution technologies such as SNP arrays and comparative genomic hybridization (CGH) have revealed cryptic copy-number alterations[24]. NGS, through targeted panels or whole-exome sequencing, now enables comprehensive profiling of point mutations, structural variants, and fusion transcripts[25]. More recently, single-cell genomics and long-read sequencing have uncovered clonal heterogeneity and complex rearrangements with unprecedented detail[26].

Biomarkers derived from cytogenetic and molecular findings serve diagnostic, prognostic, and predictive purposes. For instance, BCR-ABL1 is both diagnostic of CML and predictive of response to tyrosine kinase inhibitors (TKIs)[3,16]. Similarly, FLT3 mutations in AML predict benefit from FLT3 inhibitors, while IDH mutations guide use of IDH inhibitors[14,17]. TP53 mutations, by contrast, consistently predict poor prognosis across hematologic cancers[12]. These discoveries have

revolutionized therapy. TKIs such as imatinib have transformed CML outcomes[3]. Venetoclax, a BCL2 inhibitor, is now widely used in AML, particularly in older or unfit patients, in combination with hypomethylating agents[6]. CAR-T therapies targeting CD19 or CD22 have achieved durable remissions in relapsed/refractory ALL and lymphomas[20]. Novel menin inhibitors targeting KMT2A-rearranged and NPM1-mutated AML are showing promising early results[27].

Despite progress, several challenges persist. Clonal evolution leads to therapeutic resistance, exemplified by secondary FLT3 or IDH mutations[16,17]. In CAR-T therapy, antigen escape through loss of CD19 remains problematic[20]. Furthermore, disparities in access to molecular testing and targeted therapies limit their impact in low- and middle-income countries[8,28]. Future directions include broader implementation of integrated DNA/RNA sequencing panels, application of single-cell and spatial genomics, and incorporation of artificial intelligence for predictive modeling[26,29]. Importantly, expanding access to diagnostics and novel therapies in resource-limited settings is essential for equitable outcomes.

This review synthesizes evidence on cytogenetic and molecular mechanisms underlying hematologic malignancies, discusses diagnostic modalities and biomarkers, and highlights therapeutic advances, while also exploring challenges and future directions.

MATERIALS AND METHODS

This comprehensive review was conducted to synthesize current evidence on cytogenetic and molecular abnormalities in hematologic malignancies, with an emphasis on mechanisms, diagnostic biomarkers, and therapeutic advances. The review followed a narrative design with structured elements of systematic searching to ensure inclusiveness and rigor.

A comprehensive search strategy was applied to major biomedical databases, including PubMed, Scopus, Embase, and Web of Science, covering publications from January 2000 to June 2025. Search terms were developed using Medical Subject Headings (MeSH) and relevant keywords, such as "hematologic malignancies," "cytogenetic abnormalities," "molecular mutations," "biomarkers," "prognosis," and "targeted therapy." Boolean operators ("AND," "OR") were applied to expand and refine the search. Reference lists of key studies and review articles were also screened to capture additional relevant publications.

Inclusion criteria consisted of peer-reviewed original research, meta-analyses, and review articles reporting on cytogenetic or molecular abnormalities in leukemia, lymphoma, myelodysplastic syndromes, and myeloproliferative neoplasms. Studies were included if they provided data on prevalence, prognostic implications, diagnostic applications, or therapeutic interventions. Exclusion criteria were studies focused exclusively on non-hematologic cancers, conference abstracts without full manuscripts, articles not published in English, and studies with insufficient methodological detail or patient population data.

Two independent reviewers screened titles and abstracts for eligibility, and discrepancies were resolved by consensus. Full texts of potentially relevant studies were retrieved and assessed. Data were extracted on study design, patient population, geographic setting, type of malignancy, cytogenetic or molecular abnormality assessed, diagnostic approach, clinical significance, and therapeutic relevance.

The extracted information was synthesized thematically. Cytogenetic abnormalities were grouped by chromosomal rearrangements, deletions, and numerical abnormalities, while molecular findings were categorized by gene mutations, signaling pathways, and epigenetic regulators. Diagnostic tools, including cytogenetics, fluorescence in situ hybridization (FISH), polymerase chain reaction (PCR), and next-generation sequencing (NGS), were reviewed in relation to their detection rates and clinical utility. Therapeutic advances, particularly targeted therapies, immunotherapies, and emerging agents, were analyzed in relation to specific abnormalities.

No quantitative meta-analysis was performed due to heterogeneity in study designs and reporting. Instead, findings were summarized narratively, with

attention to recurrent patterns across studies, clinical significance, and translational implications.

RESULTS AND DISCUSSION

Cytogenetic abnormalities

Cytogenetic alterations remain the foundation for classifying hematologic malignancies. In chronic myeloid leukemia (CML), the Philadelphia chromosome t(9;22)(q34;q11) resulting in the BCR-ABL1 fusion gene is both pathognomonic and therapeutically actionable, as its discovery revolutionized treatment with tyrosine kinase inhibitors (TKIs) such as imatinib, dramatically improving survival outcomes[3]. Similarly, in acute promyelocytic leukemia (APL), the balanced translocation t(15;17)(q24;q21), which generates the PML-RARA fusion, is not only diagnostic but also forms the basis for treatment with all-trans retinoic acid (ATRA) and arsenic trioxide[9]. In acute myeloid leukemia (AML), core-binding factor abnormalities, including t(8;21)(q22;q22) and inv(16)(p13q22), account for approximately 20% of cases and are associated with favorable outcomes under intensive chemotherapy[10]. By contrast, poor-risk cytogenetic changes such as monosomy 7, complex karyotypes, and deletion of chromosome 5q occur in 15–20% of myeloid neoplasms and are consistently linked with inferior survival and higher relapse rates[11].

Molecular mutations

Parallel to cytogenetic insights, molecular profiling has uncovered recurrent mutations that refine risk stratification. In AML, NPM1 mutations occur in roughly 25–30% of cases, conferring a favorable prognosis in the absence of coexisting FLT3-ITD mutations, which are present in 20–30% of patients and carry a high relapse risk[14,15,16]. Mutations in metabolic enzymes IDH1 and IDH2 are found in 10–15% of AML patients and have led to the development of targeted inhibitors that are now integrated into treatment protocols[17]. In chronic lymphocytic leukemia (CLL), deletions and mutations of TP53 occur in about 5–10% of cases and predict resistance to standard chemoimmunotherapy, thereby directing patients toward novel targeted agents such as BTK and BCL2 inhibitors[12,19]. Similarly, in acute lymphoblastic leukemia (ALL), deletions in IKZF1 are detected in up to 20% of B-ALL cases, while activating NOTCH1 mutations, present in nearly 50% of T-ALL, are associated with disease biology and therapeutic responsiveness[13,20]. In myelodysplastic syndromes (MDS) and myeloproliferative neoplasms (MPN), mutations in epigenetic regulators such as TET2, ASXL1, and DNMT3A are present in over 30% of cases and predict adverse disease progression and leukemic transformation[18].

Diagnostic integration

While conventional cytogenetics can detect chromosomal abnormalities in approximately 60–70% of AML cases, integration with fluorescence in situ hybridization (FISH), single nucleotide polymorphism (SNP) arrays, and next-generation sequencing (NGS) significantly increases diagnostic yield to more than 90%[21,22,23,24,25]. These tools not only improve the detection of cryptic rearrangements but also provide insights into clonal hierarchies and disease evolution. Single-cell genomics has further deepened understanding by delineating clonal architecture and intratumoral heterogeneity, enabling a more precise prediction of treatment resistance and relapse[26].

Therapeutic advances

The therapeutic landscape has evolved substantially in response to these cytogenetic and molecular discoveries. In CML, the introduction of TKIs has transformed outcomes, with 10-year survival rates exceeding 80%, a dramatic shift from the pre-imatinib era when survival was less than five years[3]. In AML, the addition of the BCL2 inhibitor venetoclax to hypomethylating agents has resulted in remission rates of 60–70% among elderly or unfit patients[6]. In relapsed or refractory ALL, chimeric antigen receptor T-cell (CAR-T) therapy targeting CD19 has produced durable remissions in 40–50% of patients, representing a paradigm shift in immunotherapy[20]. More recently, menin inhibitors have demonstrated early efficacy in KMT2A-rearranged and NPM1-mutated AML, with complete remission rates of over 30% in clinical trials, highlighting the promise of targeted strategies against previously untreatable subgroups[27].

CONCLUSION

Cytogenetic and molecular abnormalities form the foundation of understanding hematologic malignancies, shaping diagnosis, prognosis, and treatment. Advances in molecular diagnostics and targeted therapies have greatly improved outcomes, yet significant gaps remain, especially in low-resource settings. To further enhance patient care, comprehensive cytogenomic profiling and the integration of molecular biomarkers into routine clinical decision-making are essential. Expanding access to advanced diagnostics and novel therapies globally will also be critical to achieving equitable improvements in survival and quality of life for patients with hematologic cancers.

RECOMMENDATIONS

Based on the study findings, the following recommendations are proposed to improve diagnosis, treatment, and management of hematologic malignancies.

1. Strengthen Access to Molecular and Cytogenetic Diagnostics

   National and institutional health systems should prioritize the establishment of molecular diagnostic laboratories equipped with technologies such as next-generation sequencing (NGS), fluorescence in situ hybridization (FISH), and polymerase chain reaction (PCR). This will facilitate early and accurate classification of hematologic malignancies and guide personalized therapy.

2. Promote Routine Molecular Profiling in Clinical Practice

   Comprehensive molecular testing, including gene mutation and fusion analyses, should be integrated into standard diagnostic workflows for leukemia, lymphoma, and related malignancies. This will enable risk-adapted treatment planning and improve prognostic accuracy.

3. Implement Precision Medicine and Targeted Therapy Programs

   Health authorities and research institutions should adopt precision oncology approaches that match patients with appropriate targeted agents (e.g., FLT3, IDH, or BCL2 inhibitors). Expanded access programs for novel therapies should be developed, especially in low- and middle-income countries (LMICs).

4. Enhance Training and Capacity Building

   Continuous professional development programs should be instituted for hematologists, oncologists, molecular biologists, and laboratory scientists in the areas of molecular diagnostics, bioinformatics, and interpretation of genomic data.

5. Establish National and Regional Cancer Genomic Databases

   Collaborative genomic data repositories should be developed to document cytogenetic and molecular alterations in hematologic cancers. This will support epidemiological surveillance, research, and therapeutic innovation within the African context.

6. Encourage Collaborative Research Networks

   Inter-institutional and international collaborations should be strengthened to promote knowledge exchange, shared technology platforms, and multicenter clinical trials focused on novel molecular targets in hematologic malignancies.

7. Ensure Sustainable Funding and Policy Support

   Governments and funding agencies should allocate dedicated resources to support cancer genomics research, subsidize molecular testing, and integrate precision oncology into national cancer control policies.

8. Promote Patient Education and Awareness

   Patients should be educated on the importance of early diagnosis, genetic testing, and adherence to targeted therapies to enhance treatment outcomes and reduce relapse rates.

9. Develop Local Production and Access Pathways for Targeted Agents

   Pharmaceutical partnerships should be explored to promote local manufacturing or subsidized importation of high-cost targeted therapies such as TKIs, BCL2 inhibitors, and menin inhibitors to improve affordability and availability.

10. Integrate Artificial Intelligence and Digital Tools

    The adoption of artificial intelligence (AI) and bioinformatics pipelines should be encouraged to enhance genomic data analysis, predict treatment response, and support clinical decision-making in real time.

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