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MARROW-MECH: AI-Assisted Identification of Mechanistic Biomarkers Distinguishing Adaptive Somatic Rescue from Malignant Clonal Evolution in GATA2 Deficiency and SAMD9/SAMD9L Syndromes

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Abstract

Background

Inherited bone marrow failure syndromes (IBMFS), including GATA2 deficiency and SAMD9/SAMD9L syndromes, confer a markedly increased lifetime risk of myelodysplastic syndrome (MDS) and acute myeloid leukemia (AML). However, disease evolution remains highly heterogeneous. Similar acquired somatic alterations including chromosome 7 abnormalities, copy-neutral loss of heterozygosity, and secondary mutations may either restore hematopoiesis through adaptive somatic rescue or represent the earliest stages of

malignant clonal evolution. Current molecular biomarkers inadequately distinguish these biologically distinct trajectories, limiting risk stratification, therapeutic development, and clinical trial design.

Methods

We developed MARROW-MECH, an artificial intelligence-assisted extension of the Monarch Initiative's Disease Mechanism (DisMech) framework. Using publicly available biomedical literature and curated knowledge resources, including PubMed, PubMed Central, ClinVar, ClinGen, Mondo, Human Phenotype Ontology, and DisMech, the framework extracts and normalizes germline variants, secondary somatic

alterations, cytogenetic abnormalities, phenotypes, signaling pathways, and clinical outcomes. Foundation-model reasoning is then used to integrate evidence across studies while preserving temporal sequence, biological context, and evidence provenance. Mechanistic evidence is synthesized to classify clonal events into adaptive somatic rescue, maladaptive rescue, malignant clonal evolution, or indeterminate biological states. Performance will be evaluated through blinded expert adjudication and comparison with existing literature retrieval and knowledge graph approaches.

Results

We anticipate generating the first state-aware mechanistic atlas of clonal evolution in GATA2 deficiency and SAMD9/SAMD9L syndromes, identifying candidate biomarkers associated with adaptive rescue and leukemic progression. The resulting framework is expected to improve

biological interpretation of clonal evolution, prioritize biomarker hypotheses for future validation, and establish a reproducible benchmark for mechanism-focused AI research in inherited bone marrow failure syndromes.

Conclusion

Distinguishing adaptive somatic rescue from malignant progression remains one of the central unanswered questions in inherited bone marrow failure syndromes. MARROW-MECH introduces a transparent, evidence-grounded computational framework for mechanistic biomarker discovery that may facilitate future translational studies, biomarker validation, and precision therapeutic development. By extending an existing community knowledge resource rather than creating a standalone platform, this work aims to provide an open and reproducible foundation for future investigations into leukemogenesis and rare hematologic malignancies.

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