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Targeting Genetic Mutations in Chronic Myeloid Leukemia: Insights into MUC3A Mutation and Regulatory Alterations in MIR5195 for Personalized Therapeutic Approaches

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INTRODUCTION & AIM

Chronic Myeloid Leukemia (CML) is a myeloproliferative disorder driven by the BCR-ABL fusion gene and characterized by a gradual transition from the chronic phase (CP) to more aggressive stages, the accelerated phase (AP) and blast crisis (BC). Although tyrosine kinase inhibitors (TKIs) have improved outcomes, disease progression and treatment resistance remain major clinical challenges. Emerging evidence suggests that secondary genetic mutations and alterations in non-coding regions contribute to this progression by reshaping transcriptional and signaling networks.

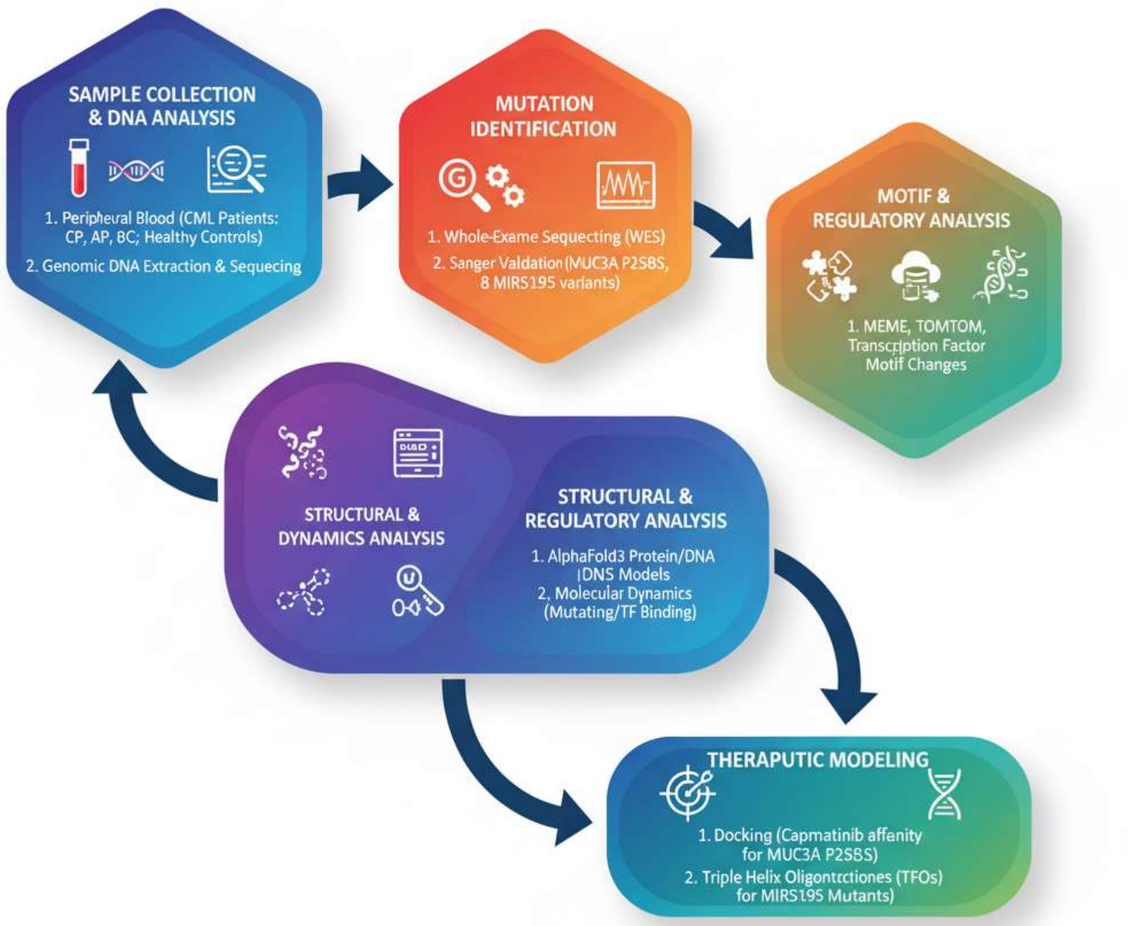
In this study, we investigated two potential molecular contributors to CML progression. A novel missense mutation (P258S) in the *MUC3A* gene, which may influence protein stability and drug interactions. Downstream mutations in the MIR5195 regulatory region, which could alter transcription factor binding and disrupt gene expression control.

OBJECTIVES

1. Identify MUC3A and MIR5195 mutations linked to CML CML progression.
2. Evaluate their structural, regulatory, regulatory, and therapeutic impact to assess potential ass biomararkers and treatment targets.

POTENTIAL FOR PERSONANIZED CML THERAPY

METHOD



RESULTS & DISCUSSION

MUC3A

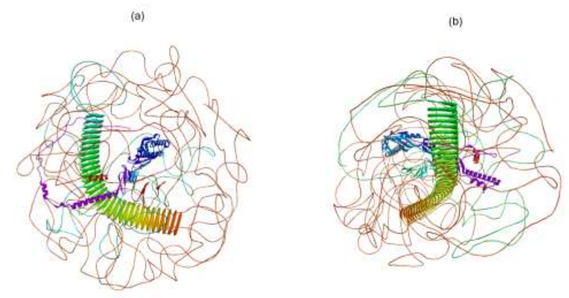


Figure 1 tertiary structure of MuC3A (a) wild type (b) mutant

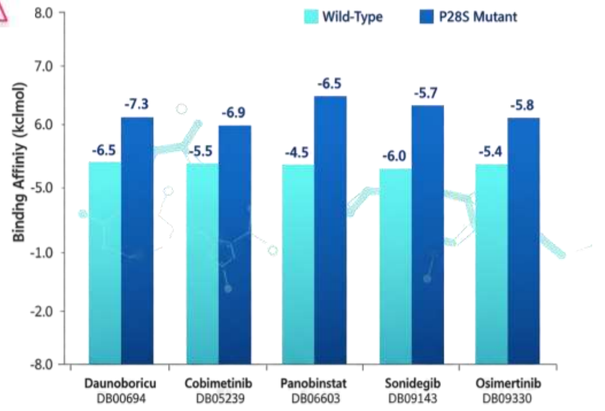


Figure 2 Docking Scores for Drugs against MUC3A Wild-Type and P258S Mutant. Increased negative affinity implies stronger binding

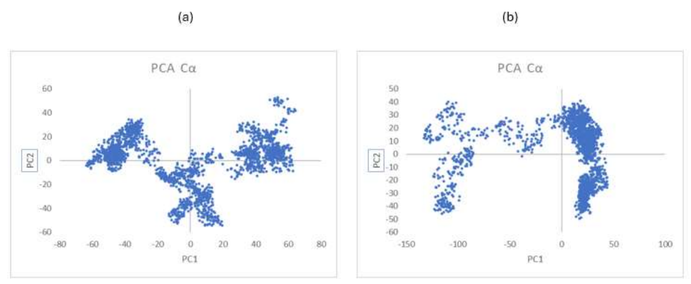


Figure 3 (a) The wild-type MUC3A protein's Principal Component Analysis (PCA) plot displays the conformational space that was investigated during the molecular dynamics (MD) simulation. (b) structural changes in the mutant MUC3A protein.

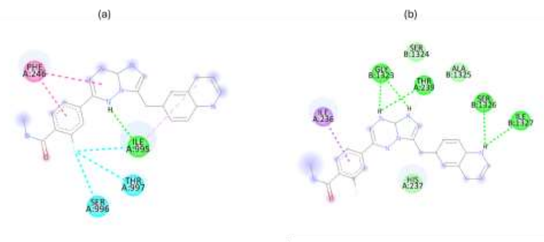


Figure 4 2D interaction of capmatinib with both mutant (b) and wild-type (a) MUC3A

MIR5195 MUTATION ALTERING TF BINDING

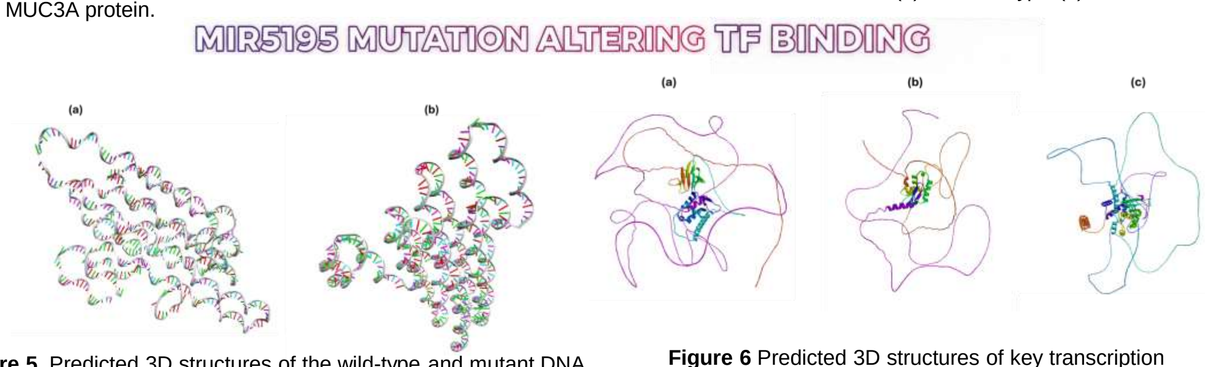


Figure 5 Predicted 3D structures of the wild-type and mutant DNA regulatory regions. (a) Wild-type DNA and (b) mutant DNA structures

Figure 6 Predicted 3D structures of key transcription factors involved in regulatory binding.

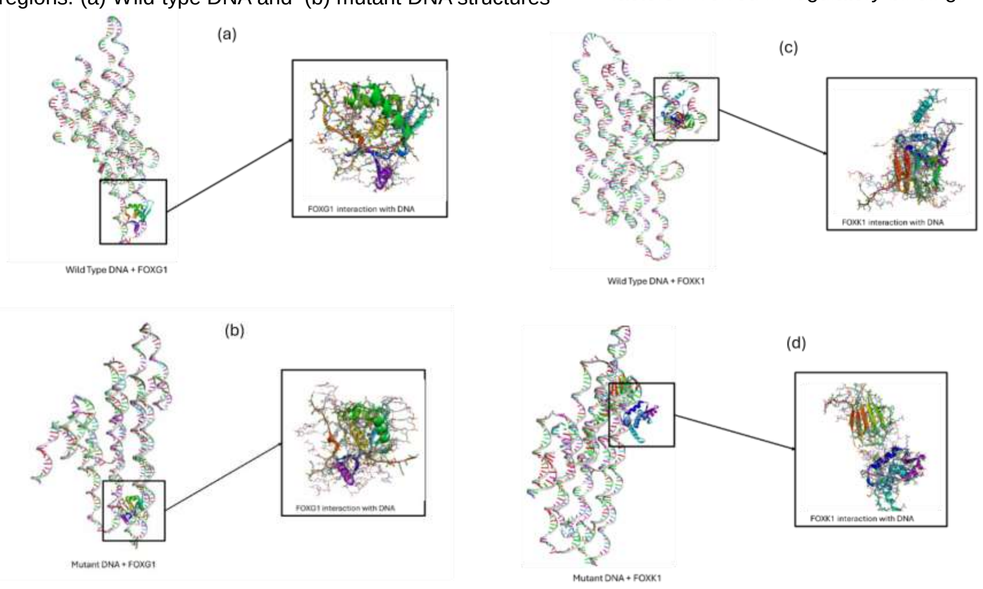


Figure 7 Docking Complexes of Wild-Type and Mutant DNA with Transcription Factors (a) Docking complex of wild-type DNA with FOXG1 protein, illustrating their interaction. (b) Docking complex of mutant DNA with FOXG1 protein, showing altered binding interactions. (c) Docking complex of wild-type DNA with FOXK1 protein, highlighting their interaction. (d) Docking complex of mutant DNA with FOXK1 protein, demonstrating changes in the binding interface and affinity. The insets show detailed views of the interactions between the DNA and transcription factors.

DISCUSSION

The MUC3A P258S mutation enhances protein flexibility and drug affinity, revealing its potential role in CML progression. Similarly, MIR5195 regulatory variants alter transcription factor binding, suggesting disrupted gene regulation in leukemic transformation

FUTURE WORK

The MUC3A P258S and MIR5195 regulatory mutations contribute to CML progression by altering protein stability and gene regulation, offering novel biomarkers for early detection and therapy. These findings support the development of personalized treatment strategies targeting mutation-driven mechanisms in advanced CML.

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