Multi-Scale Analysis of KRAS Mutations in Acute Myeloid Leukemia: Integrating Network Biology, Population Genomics, and Structural Dynamics

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Abstract

Acute myeloid leukemia (AML) is a genetically heterogeneous malignancy of hematopoietic progenitor cells characterized by impaired differentiation, clonal expansion, and bone marrow failure. AML involves dysregulation of critical signaling pathways through somatic mutations, yet systematic integration of network topology with structural mechanisms remains limited. We developed a multi-scale framework integrating protein-protein interaction networks, population-level genomics, and molecular dynamics simulations to characterize KRAS mutations in AML. Network analysis of 67 AML-associated genes identified 837 interactions forming five functional clusters, with KRAS and AKT1 emerging as consensus hub genes across twelve topological algorithms. Comprehensive TCGA-LAML profiling of 200 patient samples revealed 3,899 somatic mutations with a median of 30 per sample, dominated by missense variants (61.7%) and ageing signatures (Ti/Tv=2.34). Twenty recurrently mutated genes included NPM1 (8%), TP53 (7%), RUNX1 (6%), DNMT3A (6%), ASXL1 (6%), and KRAS (5%), with the RTK-RAS pathway most frequently altered. Notably, KRAS demonstrated 5.6-fold higher mutation frequency than AKT1, with 73 and 13 mutations, respectively. The KRAS mutations have three clinically relevant hotspots: G13D (3.32%), G12D (2.79%), and Q61H (1.57%) across the blood and bone marrow cohort. Molecular dynamics simulations revealed mechanistically distinct structural behaviours: G13D and G12D mutant proteins operate through destabilisation, while Q61H functions show a higher stable nature through hyper compactness. This integrated approach establishes network-guided target prioritization and mutation-specific therapeutic strategies for precision oncology in Acute Myeloid Leukemia.

Keywords: Acute Myeloid Leukemia; Oncogenic Mutations; KRAS Mutations; Network Biology; Molecular Dynamics Simulation.