Actionable but Overlooked: Targetable Mutations in AML

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Introduction

Mutations in genes such as KRAS and *EZH2* are well-characterized in lymphoid and solid tumors, where they play roles in tumorigenesis and serve as therapeutic targets[1,2]. Their prevalence and clinical significance in Acute Myeloid Leukemia (AML), however, are less understood. This study examines the frequency and characteristics of these mutations in AML, providing a basis for future exploration of their therapeutic potential.

Methods

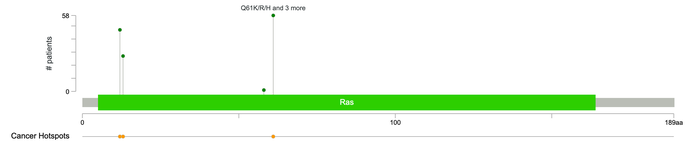
We conducted a descriptive study using data from the Therapeutically Applicable Research to Generate Effective Treatments (TARGET) Genomic Data Commons (GDC) database using cbioportal on patients with AML[3-6]. The analysis was limited to a single distinct sample per patient to avoid duplication. Mutations were categorized as driver or Variant of Unknown Significance (VUS).

Results

Among 2346 patients with AML, 2213 unique patient samples were identified. Mutation frequencies were as follows : NRAS mutations in 121 cases (5.8%) with 133 total mutations (133 driver, 0 VUS); KRAS mutations in 48 cases (2.3%) with 48 total mutations (43 driver, 5 VUS); EZH2 mutations in 10 cases (0.5%) with 11 total mutations (6 driver, 5 VUS); NF1 mutations in 9 cases (0.4%) with 10 total mutations (10 driver, 0 VUS) . Mutations with frequency >1.5% were considered significant, and all these significant mutations were somatic mutations.

Target Mutation	Altered Cases	Altered %
NRAS	121	5.80%
KRAS	48	2.30%
EZH2	10	0.50%
NF1	9	0.40%

Table 1: % of unexplored mutations in AML



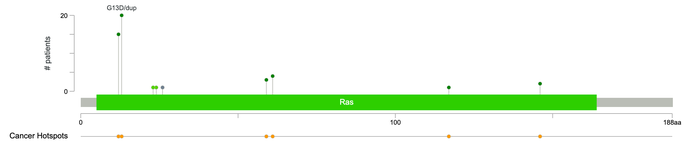


Figure 1,2. Lollipop plot showing cancer hotspots in NRAS and KRAS respectively.

Conclusion

Our findings highlight the presence of actionable mutations in AML, including *KRAS*, which is targetable with the FDA-approved inhibitor sotorasib, and *NRAS*, for which mutation-specific therapies are in development. Despite their clinical relevance, these mutations remain underexplored in AML. While MEK inhibitors have been studied in select subtypes, relapse outcomes remain poor, often driven by undruggable oncogenic pathways, as observed in our cohort. The high prevalence of these mutations supports the need for clinical trials assessing targeted therapies in the relapsed/refractory setting, offering potential new options for patients with limited treatment alternatives.

References

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