#7030

TP53/NPM1-mutated acute myeloid leukemia as a molecularly distinct disease entity.

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Background

TP53-mutated acute myeloid leukemia (AML) is a distinct disease entity associated with a dismal prognosis. This disease group is distinguishable by its low frequency of SNVs, unremarkable transcriptional signatures, and lower leukocyte and myeloblast counts compared to TP53 wild-type disease. Response to gold-standard hypomethylating agents is typically transient. NPM1 mutations in this disease subset are rare despite the fact that NPM1 has been shown to negatively regulate the tumor suppressive functions of p53.

Methods

Bone marrow, peripheral blood, or FFPE tissue samples from 10,118 patients with suspected myeloid disease were sequenced using a dual DNA/RNA 297 gene myeloid panel. Results were validated in a separate independent dataset using a 54 gene TruSight myeloid panel (N = 2463). FISH/cytogenetic data was analyzed across myeloid disease. Patients with confirmed AML (n = 460) were included in the NGS/Flow cytometry portion of this study. Statistics were performed using Fisher's exact test for categorical variables, two-tailed T-test for continuous variables, and two-tailed Mann-Whitney U for flow cytometry data.

Results

All TP53-mutated myeloid disease (n = 1282 / 10,118) was associated with fewer co-mutations except DNMT3A (13.4%; n = 172), and complex cytogenetics (36.4%; n = 134/381). TP53+/NPM1+ status across all myeloid disease was not associated with a complex karyotype (7.6% vs 38.5%; 1/13 vs. 133/368, p = 0.02). Among AML patients, NPM1+/TP53+ patients (n = 18) were more co-mutated with DNMT3A (33.3% vs. 10.3%, P = 0.01), FLT3 (33.33% vs. 2.5%, P < 0.0001), IDH1 (27.8% vs. 4.4%, P = 0.002), IDH2 (22.2% vs. 6.4%, P = 0.03); and PTPN11 (22.2% vs. 2.5%, P = 0.003) when compared to TP53+/NPM1- patients. NPM1+/TP53+ AML had more mutations in recurrently mutated genes (4.5 vs 2.1; P < 0.0001) than TP53+/NPM1- AML. TP53+/NPM1- patients had a significantly lower mean percentage of myeloblasts (25%) when compared to TP53+/NPM1+ (51%; p=0.01) and NPM1+/TP53- patients (51%, p=0.001).

Co-mutation frequency by NPM1 and TP53 status

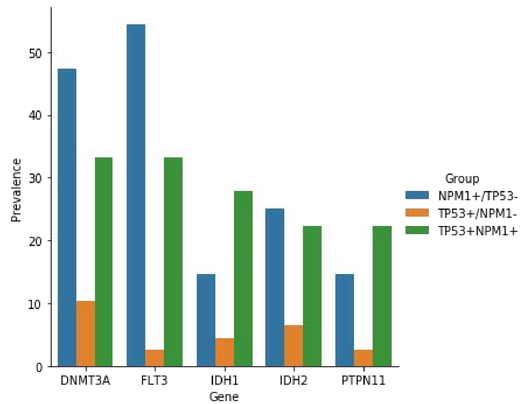


Figure 1: NPM1+/TP53+ and TP53+/NPM1- had drastically different mutation landscapes reflecting strikingly different pathophysiology. DNMT3A, FLT3, IDH1/2, and PTPN11 were all significantly more mutated in NPM1+/TP53+ patients when compared to TP53+/NPM1- patients. This phenomenon was recapitulated in the NPM1+/TP53- patient group. Conversely, DNMT3A was the only gene mutated at a frequency >10% in the TP53+/NPM1- group and these diseases were predominantly driven by cytogenetics.

Blast percentages by NPM1 and TP53 status

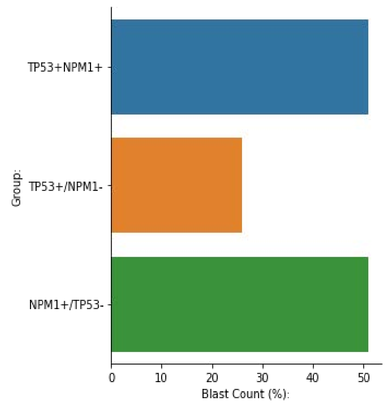


Figure 4: Mean blast percentages of different patient groups by flow cytometry. Like classic TP53-mutated disease, TP53+/NPM1- patients had a significantly lower percentage of myeloblasts (mean: 25%, median: 25%; p=0.001) when compared to NPM1+/TP53- patients (mean: 51%, median: 52%). This myeloblast signature was not present in NPM1+/TP53+ patients (p=0.01, mean: 51%, median: 48%).

Co-occurrences in TP53+/NPM1+ AML

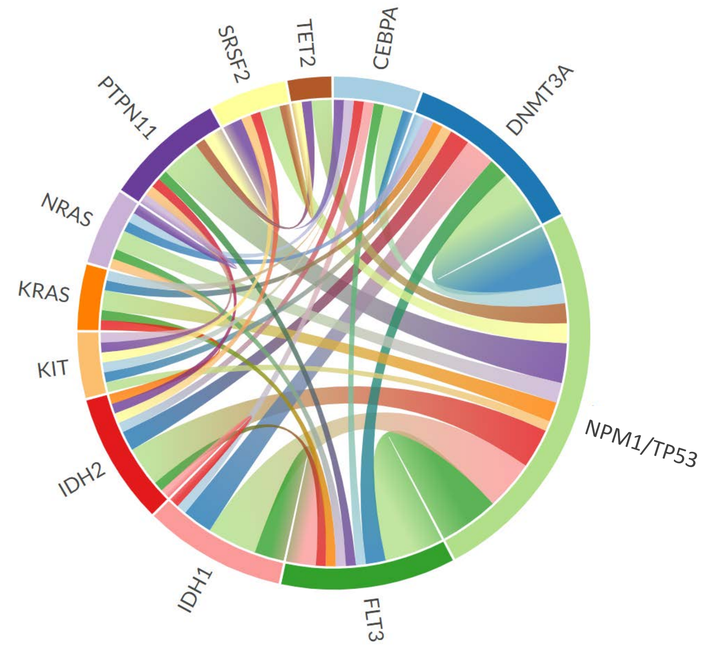
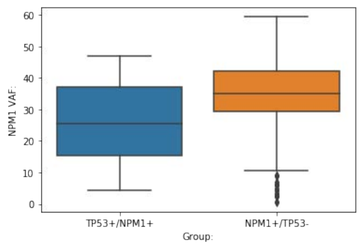


Figure 5: Chord diagram of NPM1+/TP53+ patients demonstrating an abundance of SNVs, insertions, and deletions in recurrently mutated genes and their co-occurrences with each other. Each gene is represented by a unique color, with the width of the "ribbons" denoting the number of patients with a particular molecular aberration in that gene. Colors are reversed for better visualization.

NPM1 allele frequency vs TP53 status



TP53 allele frequency vs NPM1 status

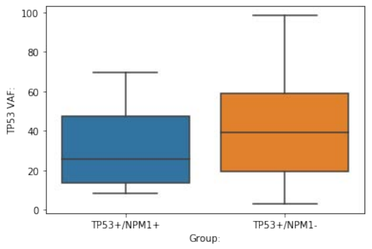


Figure2: Boxplots of NPM1 and TP53 VAF demonstrating clonal dominance and similar VAFs regardless of NPM1 or TP53 status.

SNV, insertion, and deletion burden by TP53/NPM1 status

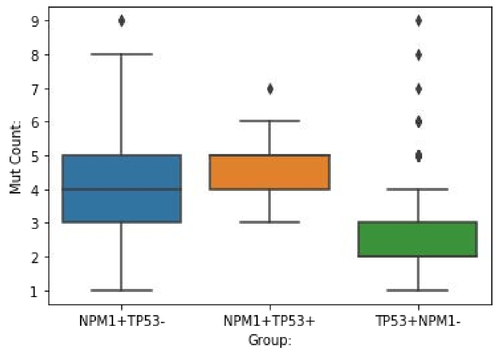


Figure 3: Boxplots demonstrating burden of protein coding mutations across patient groups. Like classic TP53-mutated disease, TP53+/NPM1- patients had a significantly lower burden of protein-coding mutations (~2 per patient) with patients with much higher burdens of mutations representing outliers. Conversely, this signature wasn't present in TP53+/NPM1+ despite their TP53-mutation status. NPM1+/TP53+ AML had more mutations in recurrently mutated genes (4.5 vs 2.1; P < 0.0001) than TP53+/NPM1- AML.

Key Points

- TP53+/NPM1+ AML harbors molecular signatures which clearly distinguish it from ordinary TP53-mutated AML.
- TP53+/NPM1+ AML is more reflective of *de novo* and NPM1+ AML.
- Our work suggests that this subset of patients may have differing therapeutic implications and clinical outcomes than classic TP53-mutated AML.
- Although TP53-mutated AML patients overall are associated with a dismal prognosis and therapy resistance, further clinical studies in those with and without NPM1 mutations are recommended to potentially identify a subset with better prognosis.