#6071

Molecular profiling of the RUNX1 RUNT domain in myeloid disorders

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Background

AML with RUNX1 mutation is a provisional entity of the WHO classification. RUNX1 variants generally consist of truncating mutations throughout the gene, as well as SNVs, insertions, and deletions in the RUNT domain. In the germline setting, these mutations may lead to familial platelet disorders and have profound implications in donor selection for allogeneic stem cell transplant. Approximately half of mutations in RUNX1 are classified as variants of unknown clinical significance (VOUS), underscoring this patient population as one with unmet clinical needs.

Methods

Bone marrow, peripheral blood, or FFPE tissue samples from 10,118 patients with suspected myeloid disease were sequenced using a 303 gene myeloid NGS panel. Among these, a total of 1209 RUNX1-mutated patients formed the cohort for this study. While pair-matched samples were not available and germline status not established, these are likely to be in the 40-60% variant allele frequency (VAF) range. Statistics were performed using Fishers exact test.

Results

Among the RUNX1-mutated patients, 277 (22.9%) had a RUNX1 variant at a subclonal VAF (<20%), 505 (41.7%), 352 (29.1%), & 75 (6.2%) had variants at VAFs of 20-39%, 40-60%, & >60%, respectively. While all truncating were classified as pathogenic, 84.3% of non-truncating RUNT domain mutations were classified as VOUS. RUNT domain mutations included 272 non-truncating and 220 truncating mutations. There were 599 (49.5%) truncating mutations throughout the entire gene. Non-truncating RUNT domain-mutated patients most frequently harbored mutations in ASXL1 (31.6%), SRSF2 (31.3%), TET2 (29.4%), STAG2 (19.1%), RAS (18.3%), & BCOR/BCORL1 (17.3%). The frequency of RUNT domain co-mutations in ASXL1 (36.8% [35] vs. 10.4% [5]; p=0.0007) and RAS family (28.4% [26] vs. 10.4% [5]; p=0.03) were significantly higher in the 40-60% VAF group compared to subclonal populations, while BCOR/BCORL1 mutations (10.5% [10] vs. 29.1% [14]; p=0.008) were significantly lower. These results were recapitulated in a cohort of VOUS only RUNT domain patients with a VAF of 40-60% compared to subclonal populations: ASXL1 (36.8% [21] vs. 22.2% [10]), RAS family (24.5% [14] vs. 10.9% [5]), and BCOR/BCORL1 (8.8% [5] vs. 31.1% [14]; p=0.005). Among patients with truncating mutations in RUNX1, mutations in ASXL1 (34.4% [44] vs 20.3% [42]; p=0.0047) and RAS family members (25.8% [33] vs. 10.1% [21]; p=0.0002) were more frequent in patients with VAFs of 40-60% when compared to subclonal populations, and mutations in BCOR/BCORL1 were similar (28.1% [36] vs. 20.7% [42]).

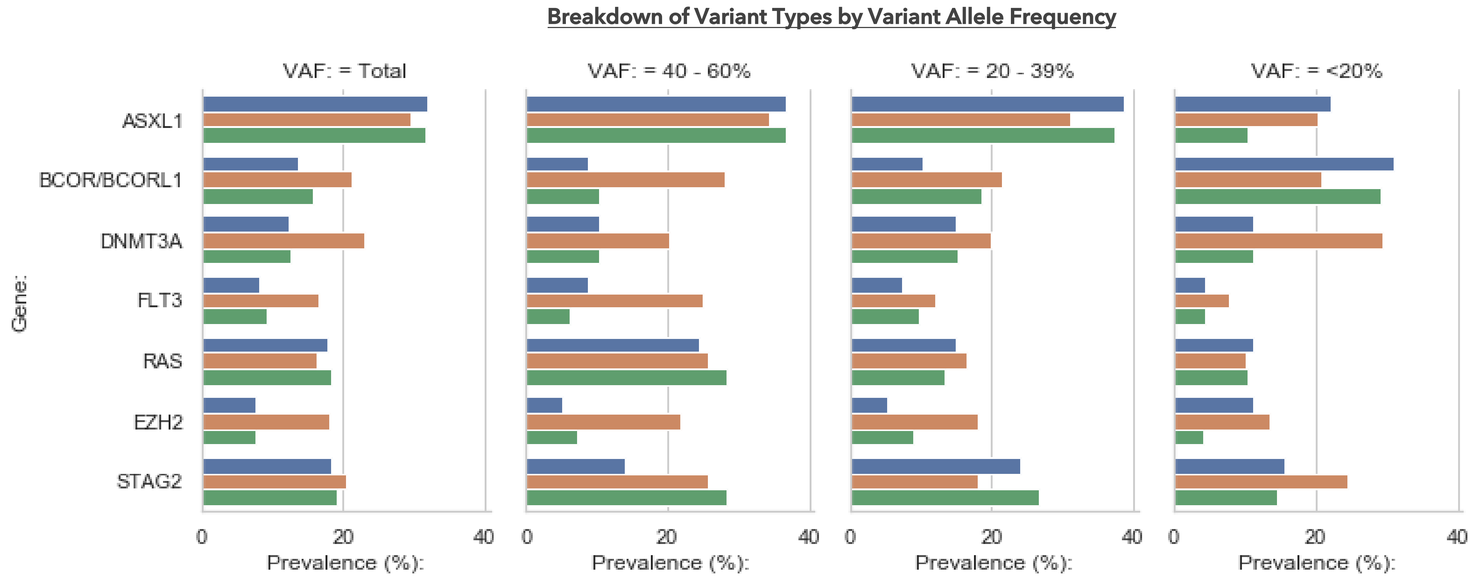

Figure 1: The prevalence of 7 recurrently mutated genes broken down by both mutation type as well as variant allele frequency (VAF = 40 - 60%; 20 - 39%; <20%). Mutations were classified as either being truncating (TRUNC), a non-truncating RUNT domain mutation (RUNT), or a non-truncating RUNT mutation classified as being a variant of unknown clinical significance (RUNT VOUS). Additionally, the cumulative prevalence of each group (VAF = Total) is provided for comparison. Figure was generated using Python 3 (Packages, Seaborn, Matplotlib, Pandas).

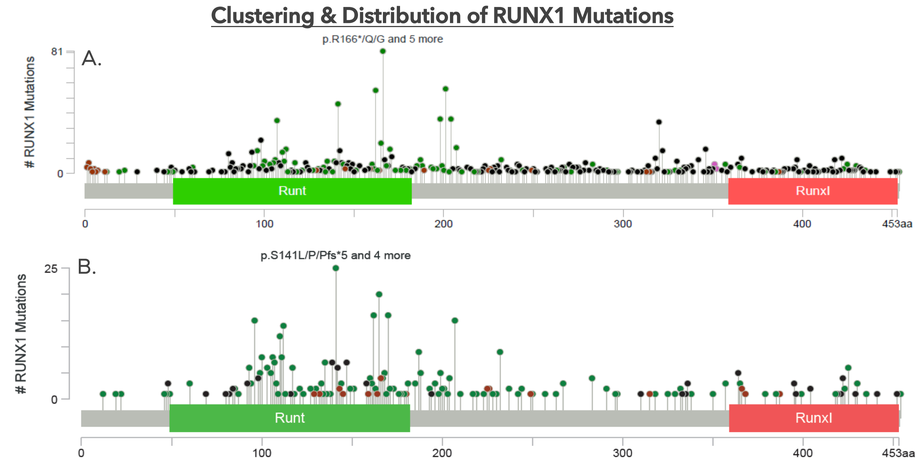

Figure 2: Lolliplot demonstrating the distribution of mutations in the RUNX1 gene of patients enrolled in this study (2A). Additionally, all variants classified as VOUS are provided in a separate visualization (2B). VOUS in the RUNT domain were analyzed separately. Missense mutations are shown in green while truncations are shown in black. Additionally inframe insertions/deletions are demonstrated in red while "other" types are shown pink. Figures were generated using CBioPortal.

Key Points

- VOUS represent a significant challenge in patient care.
- The majority of RUNX1 mutations that cluster in the RUNT domain are VOUS.
- This study demonstrates that both truncations and RUNT domain mutations harbor molecular signatures reflective of similar oncogenic mechanisms.
- These molecular signatures are also present when filtering exclusively by VOUS in the RUNT domain.
- Future mechanistic and outcome studies are needed to to better classify RUNX1 VOUS, as approx 10% - 30% of these have been suggested to be germline.