From Infancy to Young Adulthood: Exploring the Divergent Genomic Mechanisms that Drive AML

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Abstract: 548782

Background

Pediatric and young adult Acute Myeloid Leukemias (pAML and YA-AML) are uncommon, heterogenous, and a clinically challenging group of malignancies, as age ranges widely and proper therapy selection (i.e. pediatric vs. adult regimens, etc.) can be unclear. The genomics of these disorders can help understand distinct disease biology, better risk stratification, and improve outcomes

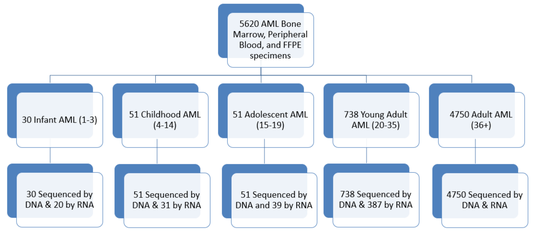


Figure 1: *Study workflow and breakdown of different AML sub cohorts by age: Infant AML (≤3) [n=30]; Childhood AML (4 – 14) [n=51]; Adolescent AML (15 – 19) [n=51]; Young Adult AML (20 – 35) [n=738]; and Adult AML (>35) [n=4750].*

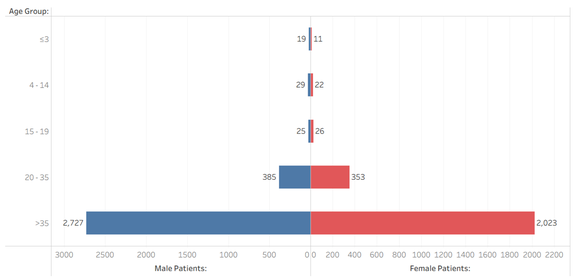


Figure 2: *Breakdown of different AML sub cohorts by age and sex: Infant AML (≤3) [n=30]; Childhood AML (4 – 14) [n=51]; Adolescent AML (15 – 19) [n=51]; Young Adult AML (20 – 35) [n=738]; and Adult AML (>35) [n=4750].*

Methods

Bone marrow, peripheral blood, or FFPE samples from 870 suspected AML patients (defined by ICD10 codes and medical history) were sequenced using a 302 gene panel to detect SNVs/indels. 466 also underwent RNA sequencing for fusion detection of 184 genes & additional DNA analysis for CNV detection of 24 genes. Only pathogenic/likely pathogenic variants were included in the analysis. AML patients were split into 4 groups based on age: Infant (≤3, n=30), Childhood (4-14, n=51), Adolescent (15-19, n=51), Young Adult (YA) (20-35, n=738). 4750 DNA/RNA sequenced adult AML patients (>35) were also included in the analysis. Statistics were performed using Fisher's exact test.

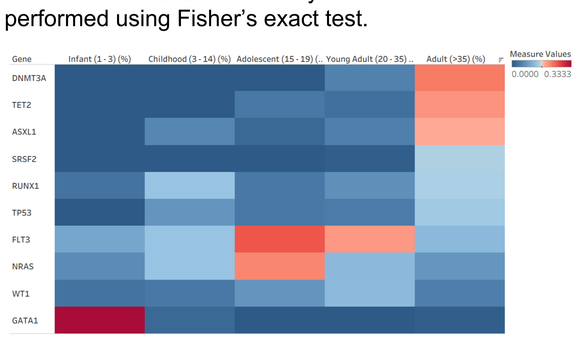


Figure 3: *Heatmap depicting the prevalence of frequently mutated pathogenic/likely pathogenic genes across all groups. Prevalence ranges from 0% (blue) to 33% (red).*

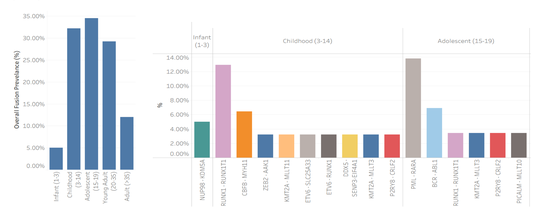
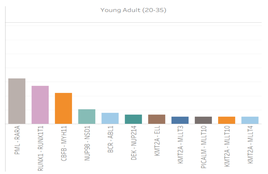


Figure 4: *Clustered bar graphs depicting overall prevalence of fusions across all groups and breakdown of specific RNA Fusions. Fusions were virtually absent in infant AML.*



Results

pAML patients (infant, childhood, & adolescent) had a high prevalence of FLT3 & NRAS variants (17.4% & 15.2%) & fusions (26.2%) while YA-AML had a high prevalence of fusions (29.2%), FLT3 (20%), NRAS (12.5%), & WT1 (12.6%) variants. Adult AML had a high prevalence of TET2 (18.4%), DNTM3A (18.3%), ASXL1 (16.8%), SRSF2 (14.8%), & TP53 (14.2%) variants, highlighting an increased prevalence of mutations associated with clonal hematopoiesis or prior chronic myeloid neoplasms. Infant AML had a higher number of GATA1 variants (33.3% vs. 0% - 2%, p<0.00001) compared to childhood, adolescent, & YA-AML; trisomy 21 was present in 90% of patients by CNV detection. Fusions were only found in 5% of infant AML (p=0.02) compared to 29.2% - 34.5% in other groups. FLT3 variants were lower in infant (10%) and childhood AML (13.7%) vs. adolescent (25.5%) & YA (20%) while NRAS variants were higher in adolescent AML (21.6% vs. 6.7% - 13.7%). Childhood AML had a higher prevalence of RUNX1 fusions (16.1% vs. 0 – 5.4%, p=0.03) & Adolescent AML had a higher prevalence of PML::RARA fusions (13.8% vs. 0% – 6.5%) compared to other groups. YA AML had a higher prevalence of WT1 variants (12.6% vs. 0% - 7.8%, p=0.02). CNV losses in IKZF1 (7p12) were more prevalent in adolescent AML (10.3% vs. 0-0.5%, p=0.002) while EZH2 CNV losses (7q36) were more prevalent in YA & childhood AML (4.7% & 3.4% vs. 0%). Upon aggregating genes by their molecular function, infant AML had a lower prevalence of variants in epigenetic genes (6.7% vs. 15.57-24.8%, p=0.02), RAS (10% vs. 23.2%-25.5%), & signaling genes (16.7% vs. 27.5% – 41.2%). Variants in DNA repair genes were more frequent among adolescent AML (13.7% vs. 3.9% - 6.7%, p=0.01).

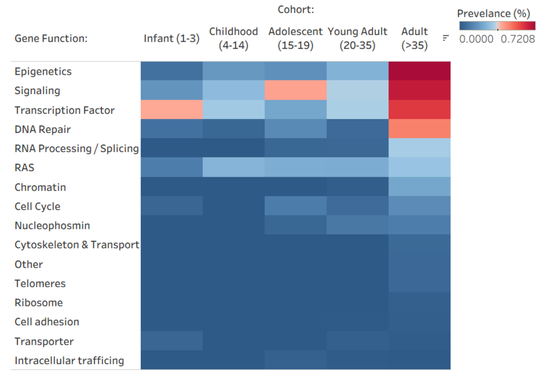


Figure 5: *Heatmap depicting the prevalence of pathogenic/likely pathogenic mutations across different genes classified by molecular function. Functional grouping was based off PANTER classification. Prevalence ranges from 0% (Blue) to 72% (Red)*

Conclusions

Infant, childhood, adolescent, & YA-AML harbor unique genetic profiles that distinguish themselves from each other and reflect divergent and evolutionarily favored mechanisms behind leukemogenesis. Understanding these genetic profiles can help better predict prognosis and help tailor more effective treatments.

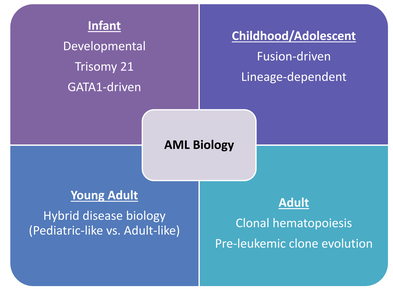


Figure 6: *Summary figure depicting major findings from the study across different AML subgroups. The hybrid disease biology of Young Adult AML may be attributed to heterogeneity, indicating that patients in this group could be further subdivided into pediatric or adult-like AML.*

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