Abstract: P442

Title: SEX DISPARITIES IN GENETIC LANDSCAPE OF ACUTE MYELOID LEUKEMIA: A COMPREHENSIVE ANALYSIS USING THE HARMONY CONSORTIUM DATASET

Abstract Type: Poster Presentation

Topic: Acute myeloid leukemia - Biology & translational research

Background:

The genetic landscape of acute myeloid leukemia (AML) is associated with differential survival outcomes. Recent studies have indicated that sex influences acquired genetic alterations, with males exhibiting increased incidence of mutations, which are more frequently annotated as adverse risk. Furthermore, the outcomes of targeted treatments can differ between sexes, underscoring the necessity of understanding sex-specific genetic landscapes.

Aims:

Our study aims to comprehensively analyse the impact of sex on genetic aberrations in AML, encompassing both single-gene mutations and clusters of genes identified by the Hierarchical Dirichlet Mixture (HDM) model.

Methods:

We used the collaborative HARMONY consortium dataset of 5244 AML patients, which has been annotated and organized by the OMOP common data model. All included patients were above 16 years of age, capturing data on the most prevalent genes and all genetic aberrations of the ELN 2022 risk classification. Differences in single genetic mutations between sexes were assessed using a chi-square test followed by a Bonferroni correction (significance threshold at $p<0.05$). For genetic clustering, the remaining missing genetic data (under 10%) was imputed using the median status of each genetic variable. The HDM model identified 15 components, consisting of families of possible combinations of genomic alterations, and estimated how frequently every component emerges in each sex. The Fasano-Franceschini test assessed differences in frequencies between sexes, with adjustments made using the Bonferroni procedure for multiple testing.

Results:

Of the included patients, 2466 (47%) were female and 2778 (53%) were male. Sex differences were observed at the single-gene level, with significantly more mutations in *ASXL1* and *SRSF2* found in men and mutations in *NPM1*, *DNMT3A* and *FLT3-ITD* genes more prevalent in females (**Figure 1A**). No difference in median age or age distribution was found between the sexes. For the different clusters of genes, the genomic driver mutation can be found in **Figure 1B**. Notably, all 15 components showed statistically significant differences in frequencies between sexes.

Summary/Conclusion:

Through the stratification of AML patients by sex, we reaffirm established knowledge concerning sex-specific single-gene mutations in AML, notably *NPM1* in females and *ASXL1* in males. Furthermore, our study illuminates distinct patterns of mutation interplay between sexes, highlighting significant sex-related disparities in AML biology. These findings emphasize the critical role of considering patients' sex in AML analyses and may explain the different outcomes observed between males and females in some studies.

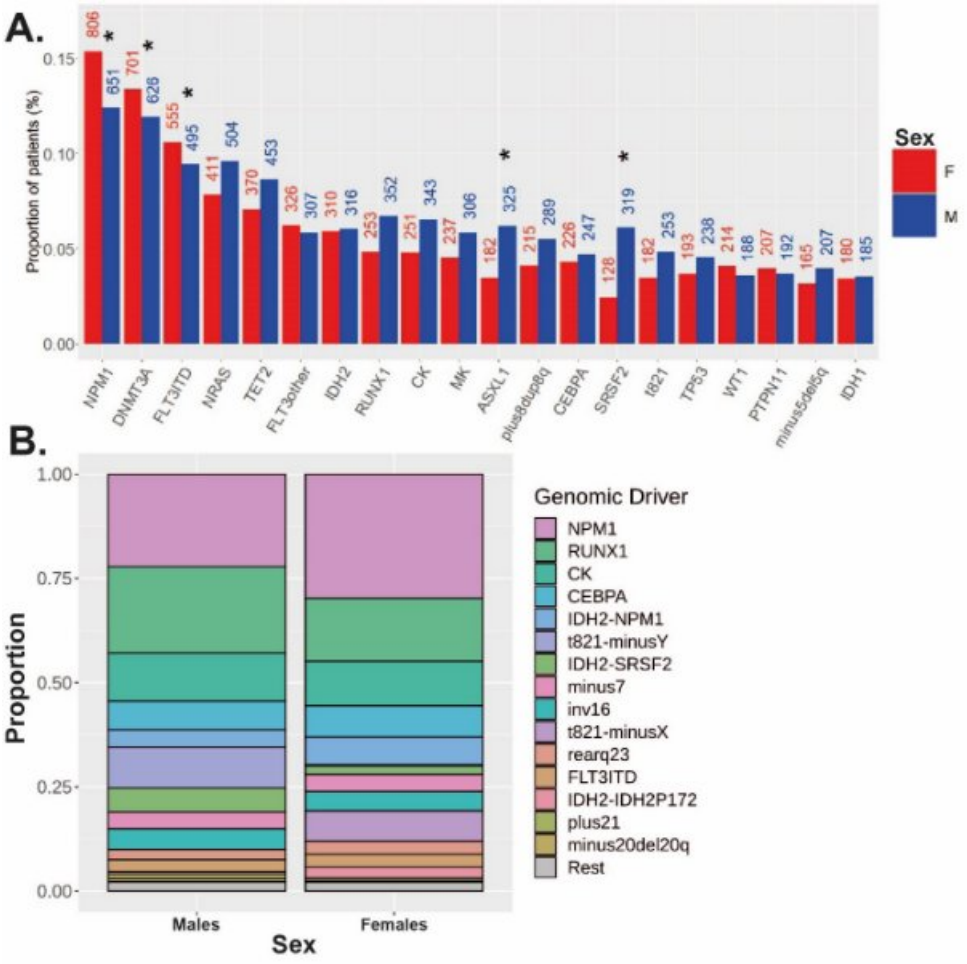

Figure 1. Differences in genetic mutations stratified by sex.(A) Top twenty genetic mutations found in a cohort of 5244 AML patients with numbers above the red bars indicating the female patient counts and in blue the male patient counts. Statistical significance is indicated with an asterisk. **(B)** The fifteen different components with their driver mutation subdivided for males and for females as proportion of the total 100%.

Keywords: Cytogenetic abnormalities, Gender, Acute myeloid leukemia