Mutation Spectrum and Risk Distribution of AML in Puerto Rican Patients Compared with International Cohorts

Ian Crespo-Orta[1], William Marrero León[2], Cristian I. Rodriguez-Arocho[3], William Caceres[1], Alexis M. Cruz-Chacon[1,3] .

1. Hematology-Oncology, San Juan City Hospital, San Juan, PR, 2. MD Anderson Cancer Center, Houston, TX, 3. Blood And Marrow Transplant-Cellular Therapy Program, Auxilio Mutuo Hospital, San Juan, PR.

Introduction

Key studies like the Cancer Genome Atlas (TCGA; NEJM 2013) and Papaemmanuil et al. (NEJM 2016) led to the European LeukemiaNet (ELN) 2017 risk classification. Along with the NCCN guidelines, these form the basis for risk-guided management and have been validated in large international groups. However, differences in AML biology across regions and ethnicities are still not well understood. For example, Puerto Rico does not have systematic genomic data, which suggests there may be a unique pattern of mutations and more cases of high-risk disease. This study uses ELN 2017, but future work should use the updated ELN 2022 framework, which improves genomic risk assessment and includes more molecular markers in clinical decisions.

Aim

To define the genomic landscape and ELN 2017 risk distribution of AML in Puerto Rican patients, and determine how they differ from international cohorts, with a particular focus on the burden of adverse-risk disease

Methods

We conducted a retrospective study of 193 patients newly diagnosed with AML at San Juan City Hospital (SJCH), a main referral center for AML in Puerto Rico, from 2020 to 2025. We used next-generation sequencing (NGS) to profile mutations, combining cytogenetics, molecular markers, and the ELN 2017 risk classification. We analyzed patient demographics, the prevalence of mutations in 27 common AML-related genes, and patterns of co-mutations, grouping results by age (<60 or ≥60 years) and gender. To compare our findings, we used global prevalence estimates and ELN 2017 risk distributions from major genomic studies, such as The Cancer Genome Atlas (TCGA; Ley et al., NEJM 2013), Papaemmanuil et al. (NEJM 2016), and validation cohorts published between 2019 and 2024. We also referenced the European LeukemiaNet (ELN) 2017 recommendations (Döhner et al., Blood 2017) and the NCCN Clinical Practice Guidelines (Version 2.2025). Additionally, we included recent large international datasets like the PETHEMA Registry (2668 adult AML patients; Cancers 2023) and a multicenter Chinese cohort (de novo and secondary AML; Int J Cancer 2024). We used the reported ranges from these validated datasets as benchmarks to compare with the SJCH cohort.

Conclusion

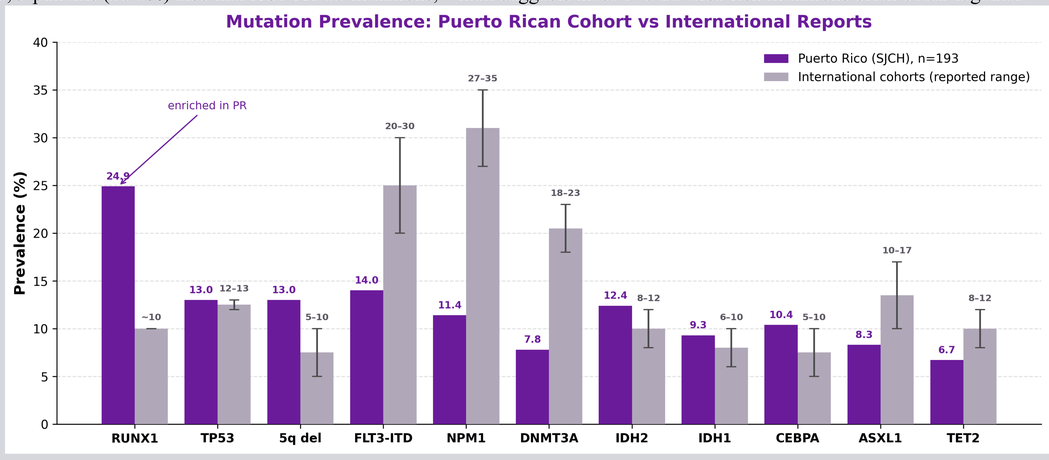
- AML patients in Puerto Rico have a different mutation profile compared to international groups.
- Mutations linked to de novo cases, like NPM1 (11.4% vs 27–35%), FLT3-ITD (14.0% vs 20%-30%), and DNMT3A (7.8% vs 18–23%), are less common. In contrast, RUNX1 (24.9% vs ~10%) and 5q deletion (13.0% vs 5–10%) appear more often.
- TP53 mutations (13.0%) are found at similar rates worldwide, but they often occur with RUNX1 (36% of TP53+ cases) and show a median VAF of 47% for TP53, marking a group with especially high risk and elevated VAF.
- The ELN 2017 risk distribution is heavily weighted toward adverse risk (51.8% vs 27–36% globally), showing that high-risk AML is more common in Puerto Rico.
- These results point to the need for more research into the genetic, environmental, and healthcare factors behind the high rate of adverse-risk AML in Puerto Rico. They also support using the updated ELN 2022 framework in future studies to improve risk assessment and treatment choices.

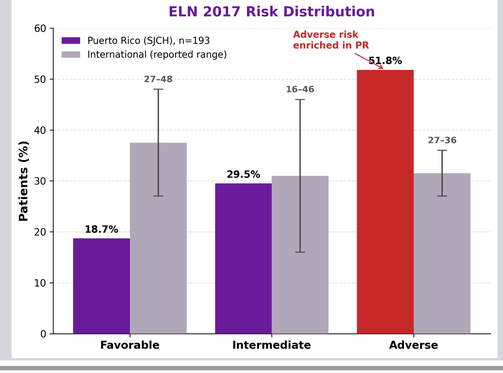
. **Table 2**. Top Co-mutations in SJCH AML Cohort.

Co-mutation	Patients (Prevalence %)
RUNX1 + 5q deletion	11 (5.7)
TP53 + 5q deletion	10 (5.2)
FLT3-ITD + NPM1	10 (5.2)
RUNX1 + TP53	9 (4.7)
RUNX1 + ASXL1	9 (4.7)

Results

- The study group included 193 AML patients with a median age of 59 years. Of these, 107 were female and 86 were male.
- When looking at age groups, patients aged 60 or older had higher rates of adverse genetic combinations, such as TP53 with 5q deletion (9.7%), RUNX1 with 5q deletion (8.6%), and RUNX1 with TP53 (7.5%). Patients younger than 60 more often had patterns linked to de novo AML, like FLT3-ITD with NPM1 (5.4%) and NPM1 with DNMT3A (3.6%).
- Analysis by gender showed that males had higher rates of adverse genetic clusters, including RUNX1 with TP53 (7.9%) and RUNX1 with 5q deletion (6.7%). Females more often had de novo-associated combinations, such as FLT3-ITD with NPM1 (5.6%) and RUNX1 with IDH1 (4.6%).
- In a closer look at TP53-mutated patients, 25 individuals (13.0% of the group) had TP53 mutations, with a median TP53 VAF of 47%.
- Of these, 9 patients (36.0%) also had RUNX1 co-mutations, which suggests these two adverse-risk mutations often occur together.





References

- Ley, T. J., Miller, C., Ding, L., Raphael, B. J., Mungall, A. J., Robertson, A., … Wilson, R. K. (2013). Genomic and epigenomic landscapes of adult de novo acute myeloid leukemia. *The New England Journal of Medicine, 368*(22), 2059–2074. https://doi.org/10.1056/NEJMoa1301689
- Papaemmanuil, E., Gerstung, M., Bullinger, L., Gaidzik, V. I., Paschka, P., Roberts, N. D., … Campbell, P. J. (2016). Genomic classification and prognosis in acute myeloid leukemia. *The New England Journal of Medicine, 374*(23), 2209–2221. https://doi.org/10.1056/NEJMoa1516192
- Döhner, H., Estey, E., Grimwade, D., Amadori, S., Appelbaum, F. R., Büchner, T., … Bloomfield, C. D. (2017). Diagnosis and management of AML in adults: 2017 ELN recommendations from an international expert panel. *Blood, 129*(4), 424–447. https://doi.org/10.1182/blood-2016-08-733196
- National Comprehensive Cancer Network. (2025, January 27). *NCCN Clinical Practice Guidelines in Oncology: Acute Myeloid Leukemia (Version 2.2025).* Retrieved from https://www.nccn.org/guidelines
- Sargas, C., Ayala, R., Larráyoz, M. J., Chillón, M. C., Carrillo-Cruz, E., Bilbao-Sieyro, C., … Sanz, M. A., on behalf of PETHEMA group. (2023). Molecular landscape and validation of new genomic classification in 2668 adult AML patients: Real life data from the PETHEMA registry. *Cancers, 15*(2), 438. https://doi.org/10.3390/cancers15020438
- Dou, X., Dan, C., Zhang, D., Zhou, H., He, R., Zhou, G., … Wang, L. (2024). Genomic mutation patterns and prognostic value in de novo and secondary acute myeloid leukemia: A multicenter study from China. *International Journal of Cancer, 155*(12), 2253–2264. https://doi.org/10.1002/ijc.35125