MOLECULAR AND CYTOGENETICS ABNORMALITIES IN ACUTE MYELOID LEUKEMIA AT PUERTO RICO

WILLIAM D. MARRERO-LEÓN, MD
Molecular and cytogenetics abnormalities in acute myeloid leukemia at Puerto Rico.

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Timeline of Genetic and Molecular Landscape in AML

Guideline

Genetic Findings of Potential Donor Origin following Hematopoietic Cell Transplantation: Recommendations on Donor Disclosure and Genetic Testing from the World Marrow Donor Association

Angharad Pryce¹, Eefke Van Eerden², Meghann Cody³, Jason Oakes³, Anna DeSalvo³, Sarah Bannon⁴, Catherine Burlton¹, Rachel Pawson⁵, Warren Fingrut⁶, Francisco Barriga⁷, Jane Ward⁸, Charlotte Ingram⁸, Michael Walsh⁶, Khaled El-Ghariani⁹, Sunday Ocheni¹⁰, Laura Machin¹¹,¹², David Allan¹³, Thilo Mengling¹⁴, Chloe Anthias¹,¹⁵,*
### 2022 ELN risk classification by genetics at initial diagnosis

<table>
<thead>
<tr>
<th>Risk category</th>
<th>Genetic abnormality</th>
</tr>
</thead>
</table>
| **Favorable** | t(8;21)(q22;q22.1)/RUNX1::RUNX1T1†, ‡  
| | inv(16)(p13.1;q22) or t(16;16)(p13.1;q22)/CBFB::MYH11†, ‡ |  
| | Mutated NPM1†, § without FLT3-ITD |  
| | bZIP in-frame mutated CEBPA† |  
| **Intermediate** | Mutated NPM1†, § with FLT3-ITD |  
| | Wild-type NPM1 with FLT3-ITD (without adverse-risk genetic lesions) |  
| | t(9;11)(p21.3;q23.3)/MLLT3::KMT2A†, ¶ |  
| | Cytogenetic and/or molecular abnormalities not classified as favorable or adverse |  
| **Adverse** | t(6;9)(p23.3;q34.1)/DEK::NUP214 |  
| | t(v;11q23.3)/KMT2A-rearranged# |  
| | t(9;22)(q34.1;q11.2)/BCR::ABL1 |  
| | t(8;16)(p11.2;p13.3)/KAT6A::CREBBP |  
| | inv(3)(q21.3q26.2)| GATA2, MECOM(EVII) |  
| | t(3q26.2;v)/MECOM(EVII)-rearranged |  
| | −5 or del(5q); −7; −17/abn(17p) |  
| | Complex karyotype, **monosomal karyotype†† |  
| | Mutated ASXL1, BCOR, EZH2, RUNX1, SF3B1, SRSF2, STAG2, U2AF1, and/or ZRSR2†† |  
| | Mutated TP53§ |  |
Patient characteristics
(age, performance status, prior exposure to chemotherapy or radiotherapy, AHD, organ function)

AML characteristics
(morphology, immunophenotye, cytogenetics, molecular NGS)

Patient eligible for intensive induction therapy

- CBF-AML
  - Inv 16, t(8;21)
- FLT3 (ITD and/or TKD) mutation
- All patients
- t-AML, AML with AHD, or AML-MRC

Patient ineligible for intensive chemotherapy

- TP53-mutated AML
- Consider clinical trials (including magrolimab/eprenetapopt or others)
- IDH1-2 mutation
- HMA + venetoclax or LDAC + venetoclax or LDAC + glasdegib
- FLT3 mutation
- FLT3 inhibitor + HMA (+/- venetoclax)

Intensive chemo + GO (CD33 ADC)

- Intensive chemo + FLT3 inhibitor
- IDH1-2 mutation
- Intermediate-risk cytogenetics
- CPX-351
- Add GO?

Add IDH1-2 inhibitor?*

Add venetoclax?*

Add GO?

Allogeneic SCT OR low-intensity therapy indefinitely OR maintenance therapy
(eg, CC-486)

Consider post-allogeneic SCT maintenance

*Under investigation
Age-Adjusted Incidence Rates by County, in Puerto Rico.
Myeloid and Monocytic Leukemia, 2015-2019

All rates are per 100,000 population.
Rates are age-adjusted to the 2000 PR Std Population (19 age groups)
Based on data released 2/2/2022
Data accessed 1/16/2024 2:19:28 PM
CYTOGENETICS AND MOLECULAR

Sorry
No Data Available
OBJECTIVE

The San Juan City Hospital-hematology oncology department is one of the major referral centers on the island for initial evaluation and management of AML.

Retrospective study was to identify the most common cytogenetic and molecular abnormalities present in our population.
METHODS

Examined the frequency of molecular markers in newly diagnosed (ND) patients with AML. Patients that were at least 18 years of age or older with cytogenetic and molecular analysis.


Demographic, bone marrow biopsy, cytogenetics, and molecular markers were obtained from electronic medical record at our institution with institutional review board approval.
METHODS

MEDICAL RECORD DATABASE
(Acute Leukemia, Acute Myeloid Leukemia, Acute Monocytic Leukemia, Acute Myeloblastic Leukemia)

697 RECORDS IDENTIFIED

INCOMPLETE, DUPLICATED, OTHER DIAGNOSIS

NO MOLECULAR STUDIES

169 RECORDS MEET CRITERIA
RESULTS

169 PATIENTS

FEMALE: 56.21%

MALE 43.79%

AGE AT DX 58.10
Regulation and differentiation of normal hematopoietic stem cells.

Mutation of RUNX1 leads to impaired hematopoiesis and ultimately leukemia.

Poor outcome observed in AML expressing RUNX1.

Germline RUNX1 mutations result in the well-described autosomal-dominant familial platelet disorder with predisposition to hematologic malignancies.

RUNX1 in 5-10% of patients at a median age of 68 years old.
Genomic Classification and Prognosis in Acute Myeloid Leukemia

<table>
<thead>
<tr>
<th>Other class-defining lesions</th>
<th>Frequency</th>
<th>Mean (CI)</th>
<th>P-value</th>
<th>blasts</th>
</tr>
</thead>
<tbody>
<tr>
<td>t(11;19), not MLLT3–MLL</td>
<td>37 (2)</td>
<td>1.4 (1.0–2.1)</td>
<td>0.06</td>
<td>0.2</td>
</tr>
<tr>
<td>ASXL1</td>
<td>70 (5)</td>
<td>1.3 (1.0–1.6)</td>
<td>0.04</td>
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<tr>
<td>ZRSR2</td>
<td>13 (1)</td>
<td>1.3 (1.0–1.7)</td>
<td>0.04</td>
<td>0.2</td>
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<tr>
<td>RUNX1</td>
<td>133 (9)</td>
<td>1.1 (0.9–1.3)</td>
<td>0.5</td>
<td>0.8</td>
</tr>
<tr>
<td>t(9;11), MLLT3–MLL</td>
<td>18 (1)</td>
<td>0.8 (0.4–1.4)</td>
<td>0.5</td>
<td>0.7</td>
</tr>
<tr>
<td>IDH2R12</td>
<td>39 (3)</td>
<td>0.8 (0.6–1.0)</td>
<td>0.07</td>
<td>0.2</td>
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<tr>
<td>t(8;21), RUNX1–RUNX1T1</td>
<td>63 (4)</td>
<td>0.7 (0.4–1.0)</td>
<td>0.03</td>
<td>0.2</td>
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<tr>
<td>Characteristic</td>
<td>Value</td>
<td></td>
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<td></td>
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<tr>
<td>NPM1</td>
<td>54/200 (27)</td>
<td></td>
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<tr>
<td>FLT3</td>
<td>56/200 (28)</td>
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<tr>
<td>DNMT3A</td>
<td>51/200 (26)</td>
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<td>IDH1 or IDH2</td>
<td>39/200 (20)</td>
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<tr>
<td>NRAS or KRAS</td>
<td>23/200 (12)</td>
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<tr>
<td>RUNX1</td>
<td>19/200 (10)</td>
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<tr>
<td>TET2</td>
<td>17/200 (8)</td>
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<td>TP53</td>
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<tr>
<td>CEBPA</td>
<td>11/200 (6)</td>
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<td>WT1</td>
<td>12/200 (6)</td>
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<tr>
<td>PTPN11</td>
<td>9/200 (4)</td>
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<tr>
<td>KIT</td>
<td>8/200 (4)</td>
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<tr>
<td>Loss of 5 or del(5q)</td>
<td>16/195 (8)</td>
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<tr>
<td>Loss of 7 or del(7q)</td>
<td>20/195 (10)</td>
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<tr>
<td>11q23</td>
<td>4/195 (4)</td>
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<tr>
<td>t(15;17)</td>
<td>18/195 (9)</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>t(8;21)</td>
<td>7/195 (4)</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>inv(16)</td>
<td>12/195 (6)</td>
<td></td>
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Clinical Outcomes and Co-Occurring Mutations in Patients with RUNX1-Mutated Acute Myeloid Leukemia

by Maliha Khan 1, Jorge Cortes 1, Tapan Kadia 1, Kiran Naqvi 1, Mark Brandt 1, Sherry Pierce 1, Keyur P. Patel 2, Gautam Borthakur 1, Farhad Ravandi 1, Marina Konopleva 1, Steven Kornblau 1, Hagop Kantarjian 1, Kapil Bhalla 1 and Courtney D. DiNardo 1,*

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High Frequency of RUNX1 Mutation in Acute Myeloid Leukemia at Puerto Rico

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Blood (2023) 142 (Supplement 1): 5985.
https://doi.org/10.1182/blood-2023-173450
• MEAN AGE: 56.08 (+/- 15.80)

• GENDER
MALE: 46.15%
FEMALE: 53.85%

VAF: 40%

RUNX1 and TP53: 19%
RUNX and complex cytogenetics: 41%
Germline Predisposition

SPECIAL REPORT | SEPTEMBER 22, 2022

Diagnosis and management of AML in adults: 2022 recommendations from an international expert panel on behalf of the ELN

Hartmut Döhner, Andrew H. Wei, Frederick R. Appelbaum, Charles Craddock, Courtney D. DiNardo, Hervé Dombret, Benjamin L. Ebert, Pierre Fenaux, Lucy A. Godley, Robert P. Hasserjian, Richard A. Larson, Ross L. Levine, Yasushi Miyazaki, Dietger Niederwieser, Gert Ossenkoppele, Christoph Röllig, Jorge Sierra, Eytan M. Stein, Martin S. Tallman, Hwei-Fang Tien, Jianxiang Wang, Agnieszka Wierzbowska, Bob Löwenberg


A variant is deemed germline if:

- it is detected in DNA derived from a tissue source not likely to undergo somatic mutation frequently and at a variant allele frequency consistent with the germline (generally 30–60%); or
- it is identified in ≥2 relatives at a variant allele frequency consistent with the germline.
CONCLUSION

- Younger patients with AML
- High incidence of RUNX1
- Higher VAF for RUNX1
- Possibility of germline mutation, need to be considered