DNMT3A AS AN EPIGENETIC SCAFFOLD IN ACUTE MYELOID LEUKEMIA- SYNERGISTIC MUTATIONAL LANDSCAPES AND THERAPEUTIC IMPLICATIONS

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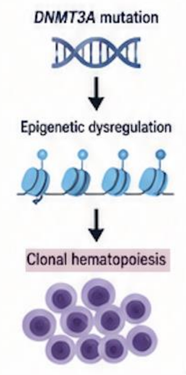
BACKGROUND

DNT3A mutations occur in -20-25% of AML and are early clonal events associated with adverse outcomes.

They frequently co-occur with driver mutations (IDH1/2, NPM1, FLT3, TP53, TET2) that influence prognosis and therapeutic response.

Next-generation sequencing (NGS) allows precise characterization of the mutational landscape and supports individualized treatment decisions.



MATERIALS AND METHODS

PATIENT COHORT

- 10 patients with AML
- Median age – 62 years
- Age range: 26-75

MOLECULAR PROFILING

32 gene somatic myeloid panel

NGS WORKFLOW

RESULTS

DNMT3A alterations

4 / 10 patients

40%

CASE 1

- 67 y.o. male
- ELN – Adverse (KMT2E(7q22), CUL1(7q36) del 57%)
- Treatment and Outcome – Aza/Ven & 7+3 (no remission), then Aza/Ven + enasidenib (remission)

CASE 2

- 75 y.o. female
- History of breast cancer
- ELN – Adverse (cytogenetic: -5, -17)
- Treatment and Outcome – Aza/Ven (no remission, the patient subsequently died)

CASE 3

- 67 y.o. male
- ELN – Intermediate
- Treatment and Outcome – Aza/Ven & 7+3 (no remission), then ivosidenib (on therapy)

CASE 4

- 57 y.o. female
- ELN – Favorable
- Treatment and Outcome – 7+3 (remission), then relapse – FLAG-Ida (remission)

	P1	P2	P3	P4	P5	P6	P7	P8	P9	P10
	Bone marrow	Bone marrow	Peripheral blood	Peripheral blood	Bone marrow	Bone marrow	Bone marrow	Peripheral blood	Bone marrow	Peripheral blood
DNMT3A	R882H 33.33%	K382Sfs*25 41.45%	V296M 88.24%	I310S 46.83%						
IDH1			R132C 38.33%				R132C 39,7%			R132H 31,9%
IDH2	R140Q 28.26%									
TET2				W954* 44.01%		N752Kfs*60 51.21%				
NPM1				W288Cfs*12 13.2%		W288Cfs*12 28,66%	W288Cfs*12 20,62%			W288Cfs*12 23,9%
TP53		S215G 63.7%								
FLT3					F594_R595 insSSSDN EYFYVDF	E598_P606dup 55,2%			I867S 14,62%	
PTPN11							S502L 42,18%			G503E 6,25%
SRSF2							P95R 47,37%			
RUNX1									R162T 40,57%	
NRAS									G12D 4,85%	
KRAS										G12D 16,27%

Pathogenic *Likely Pathogenic* *VUS*

CONCLUSION

Our findings emphasize that DNMT3A mutations serve as a critical epigenetic scaffold for secondary mutations. Comprehensive NGS profiling identifies these synergistic clusters, enabling a shift from standard "7+3" protocols to personalized, targeted combinations (e.g.,IDH inhibitors) that can overcome epigenetic block in relapsed/refractory AML.

CONTACT INFORMATION

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