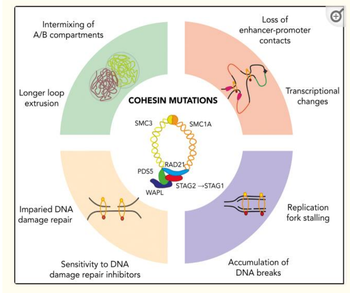
Mutational landscape and survival outcomes of patients (pts) with acute myeloid leukemia (AML) or myelodysplastic syndromes (MDS) harboring cohesin complex mutations

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Background

- Cohesin is a multisubunit protein complex that forms a ring-like structure around DNA.
- Essential for sister chromatid cohesion, chromatin organization (align & stabilize replicated chromosomes prior to cell division), transcriptional regulation, & DNA damage repair.[1]
- Core complex subunits *STAG2, RAD21, SMC1, and SMC3,* have been found to be recurrently mutated 10-20% of myeloid malignancies. [1-3]



Role of Mutations in Myeloid Malignancies

- Cytogenetic abnormalities and genetic mutations play an important role in determining outcomes in patients with acute myeloid leukemias (AML) and myelodysplastic syndromes (MDS). [4,5]
- Currently there is paucity of data about clinical outcomes in patients with AML/MDS who harbor cohesin mutations.

Purpose

To investigate the association of clinical prognostic impact of the presence of cohesion gene mutations in AML/MDS patients treated at our institution in survival, as well the implications of other associated co-occurring mutations.

Methods

- We performed a retrospective analysis in patients with AML/MDS with cohesin mutations who were treated at our center between March 2017 and August 2023.
- Approval was obtained through the UMass Institutional Review Board via protocols H00019393 ('AML Database') and H00013131 ('Blood & Marrow Banking;' NCT01174615).

Patient Characteristics (N=36)

Characteristics	Results
Age, median (range)	73 (31-84)
Male, n (%)	24 (67)
Disease, n (%)	
AML	17 (47)
MDS	19 (53)
AML, ELN 2022 risk, n/N (%)	
Favorable	2/17 (12)
Intermediate	1/17 (6)
Adverse	14/17 (82)
AML cytogenetic group, n/N (%)	
Favorable	1/17 (6)
Diploid	9/17 (53)
Intermediate	2/17 (12)
Complex/adverse	3/17 (18)
Unavailable	2/17 (12)
MDS IPSS-R, n (%)	
Very low	1 (5)
Low	5 (26)
Intermediate	6 (32)
High	3 (16)
Unavailable	4 (21)

Revised International Prognostic Scoring System (IPSS-R) for Myelodysplastic Syndrome (MDS)

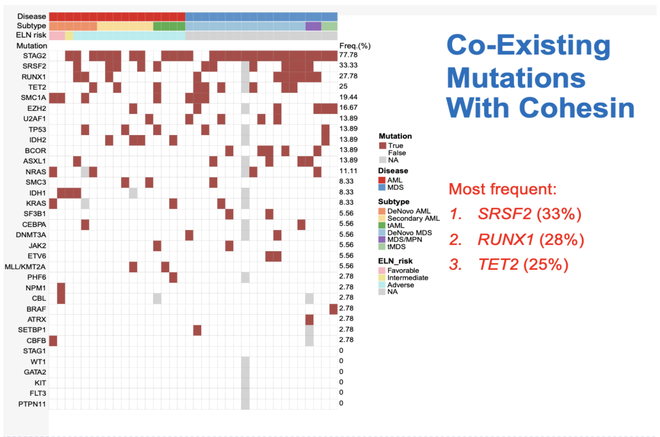
Hematopoietic Variables & Treatments

Characteristics	Results)
% Bone marrow blasts, median (range)	
AML	36 (21.5-42.5)
MDS	9 (3-8)
WBC, median (range) x10^9/L	
AML	2.1 (0.7-46.8)
MDS	3.9 (1.2-17.7)
Platelets count, median (range) x10^9/L	
AML	41 (12-305)
MDS	144 (6-635)
Treatments	
Hypomethylating agents	17 47)
Hypomethylating agents+ Venetoclax	5 (14)
Chemotherapy	7 (19)
Chemotherapy +Venetoclax	3 (8)
No treatment	4 (11)
Allogeneic Hematopoietic Cell Transplantation	7 (19)

Frequency and Distribution of Cohesin Mutations

Cohesin type	Overall Frequency (N=36)	AML (N=17)	MDS (N=19)	*P value*
***STAG2*, n (%)**	28 (78)	11 (65)	17 (89)	0.11
***SMC3*, n (%)**	3 (8)	2 (12)	1 (5)	0.6
***SMC1A*, n (%)**	7 (19)	4 (24)	3 (16)	0.7

*Co-expression of 2 cohesin mutations was observed in 3 patients.

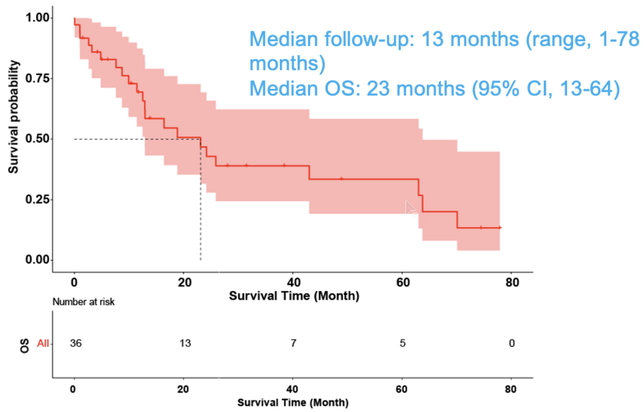


Co-Existing Mutations With Cohesin

Most frequent:

1. *SRSF2* (33%)
2. *RUNX1* (28%)
3. *TET2* (25%)

Overall Survival

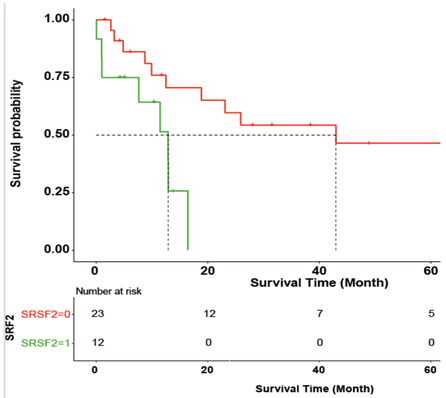


Median follow-up: 13 months (range, 1-78 months)
Median OS: 23 months (95% CI, 13-64)

Determinants of Overall Survival

Factors	Stat Method/ Median OS (months)		*P value*
Age	Continuous variable		0.19
AML vs MDS	11.5	29.5	0.31
***SRSF2* (+ vs -)**	12.9	43	0.016
***RUNX1* (+ vs -)**	11.5	25.9	0.094
***TET2* (+ vs -)**	12.9	24.2	0.9
Therapy type	HMA$ vs HMA+Ven$$ vs Chemo vs Chemo+ Ven		0.88
Allogeneic HCT	Mantel Byar Methodology[6]		0.11

• Calculated from time of diagnosis
$ HMA=Hymomethylating agent; $ $ Ven=Venetoclax



OS according to presence or absence of co-expression of *SRF2*

Median OS for *SRF2* (-) vs *SRF2* (+) was 12.9 vs 43 months, respectively (*P* = 0.016)

Conclusions

- *STAG2* mutation was the predominant mutant cohesin subunit observed in our cohort of AML/MDS patients
- The co-existence of *SRSF2* mutations with cohesin mutations was associated with inferior OS

References

1.Jann J-C and Tothova Z. Cohesion mutations in myeloid malignancies. *Blood* 2021;138:649-661.
2. Viny AD and Levine RL. Cohesin mutations in myeloid malignancies made simple. *Curr Opin Hematol* 2018;25:61-68.
3. Anthony J, Chin CV and Horsfield JA. Cohesin mutations in cancer: emerging therapeutic targets. *Int J Mol SCI* 2021;22:67-88
4.Dohner H, et al. Diagnosis and management of AML in adults: 2022 recommendations from an international expert panel on behalf of the ELN. *Blood* 2022;140:1345-1377.
5. Papaemmanuil E, et al. Genomic classification and prognosis in acute myeloid leukemia. *N Engl J Med* 2016;374:2209-2221.
6. Mantel N and Byar DP. Evaluation of response-time data involving transient states: an illustration using heart-transplant data. *J Am Stat Assoc.* 1974:69; 81-86