Characteristics and clinical outcomes of patients with myeloid malignancies and cohesin mutations

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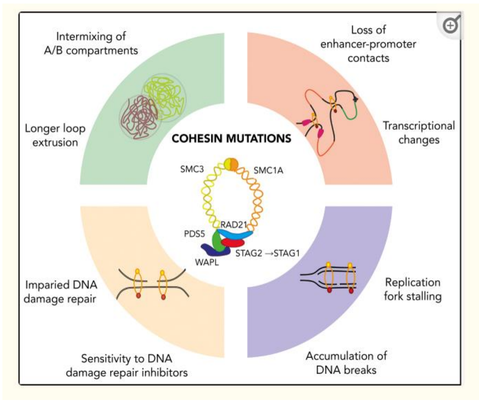
BACKGROUND

- 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

In patients with AML and MDS with next-generation sequencing at our center during 2017-2023, we assessed the landscape of cohesin mutations and the impact of co-occurring mutations on overall survival and compared outcomes between patients with cohesin mutations and those with wild-type cohesin genes.

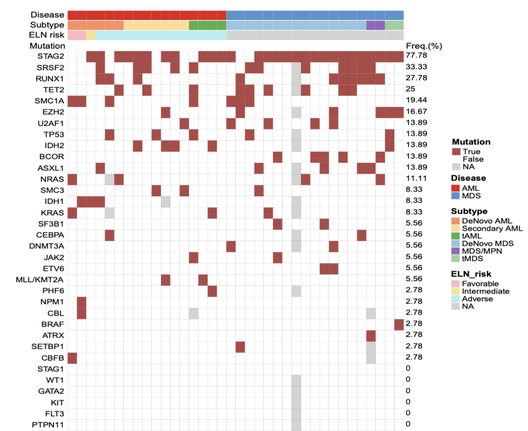
RESULTS

Patient and Treatment Characteristics

Characteristics	Cohesin-mutations cohort (n=36)	Wild-type cohort (n=47)	*P*
Age, median (IQR), y	73 (63.5-79)	63 (57-72)	0.009
Male, n (%)	24 (67)	25 (53)	0.03
Disease, n (%)			
AML	17 (47)	43 (92)	0.0005
MDS	19 (53)	4 (8)	
ELN 2022 risk (for AML), n (%)			0.2
Favorable	2 (12)	6 (14)	
Intermediate	1 (6)	9 (21)	
Adverse	14 (82)	23 (53)	
Unavailable	-	5 (12)	
AML cytogenetic group, n (%)			0.32
Favorable	1 (6)	4 (9)	
Diploid	9 (53)	11 (26)	
Intermediate	2 (12)	8 (19)	
Complex/adverse	3 (18)	16 (37)	
Unavailable	2 (12)	4 (9)	

Characteristics	Cohesin-mutations cohort (n=36)	Wild-type cohort (n=47)	*P*
IPSS-M (for MDS), n (%)			0.022
Low	2 (11)	1 (25)	
Moderate low	3 (16)	-	
Moderate high	3 (16)	-	
High	8 (42)	-	
Very high	1 (5)	3 (75)	
Not classifiable	2 (11)	-	
Induction therapy, n (%)			0.002
HMA	17 (47)	7 (15)	
HMA+ venetoclax	5 (14)	12 (26)	
Chemotherapy	7 (19)	24 (51)	
Chemotherapy+ venetoclax	3 (8)	0	
None	4 (11)	4 (9)	
FLT-3 inhibitor	0	6 (13)	
Allogeneic HCT	7 (19)	15 (32)	

Mutational distribution in the cohesin-mutations cohort according to disease type and subtype ELN, European LeukemiaNet 2022 risk category

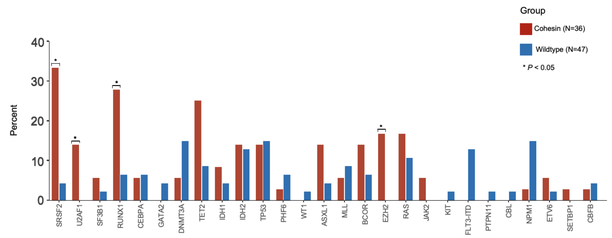


Frequency and Distribution of Cohesin Mutations

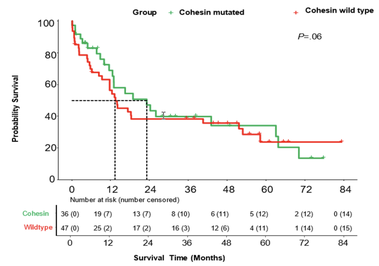
Cohesin type	Overall Frequency (N=36)	AML (N=17)	MDS (N=19)	*P value*
***STAG2*, n (%)**	**28 (78)**	**11 (65)**	**17 (89)**	**0.11**
***SMC3*, n (%)**	**3 (8)**	**2 (12)**	**1 (5)**	**0.6**
***SMC1A*, n (%)**	**7 (19)**	**4 (24)**	**3 (16)**	**0.7**

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

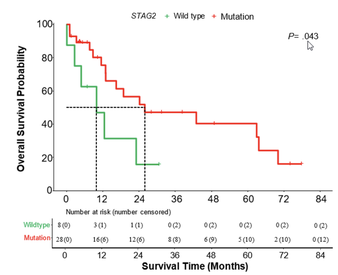
Co-occurring mutational frequency in the cohesin-mutated vs cohesin-wildtype cohorts



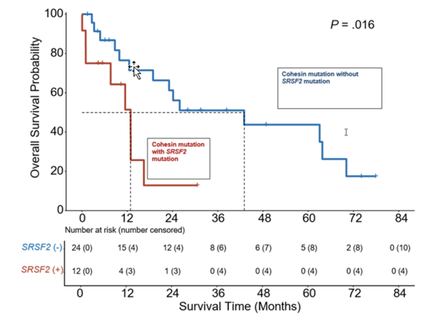
Overall survival for patients with cohesion mutations vs patients with cohesin wildtype genes



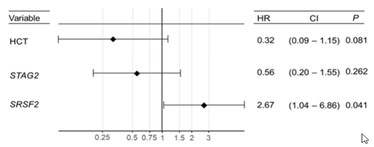
Overall survival for patients with *STAG2* mutations vs patients with only *SMC1A* or *SMC3* mutations



Overall survival for patients with cohesin mutation with and without co-existing *SRSF2* mutation



Multivariable analysis of overall survival in patients with cohesin mutations



CONCLUSIONS

- *STAG2* mutation was the predominant mutant cohesin subunit observed in our cohort of AML/MDS patients
- Myeloid neoplasms with cohesin mutations are enriched for *SRSF2*, *U2AF1, RUNX1*, *TET2*, and *EZH2* mutations
- In patients with myeloid neoplasms, the co-existence of *SRSF2* mutation with cohesin mutations is associated with inferior overall survival.
- Allogeneic HCT appears promising and must be evaluated in a larger number of patients.

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