

TO THE EDITOR:

Clinical and prognostic impact of *STAG2* mutations in myeloid neoplasms: the Mayo Clinic experience

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The stromal antigen 2 (*STAG2*) gene, located on chromosome Xq25, is a core component of the cohesin complex that functions on chromatin organization, transcriptional regulation, and postreplicative DNA repair.¹⁻³ *STAG2* mutations (*STAG2*ms) are reported in 5% to 10% of myeloid neoplasms (MNs), mostly high-risk myelodysplastic syndrome (MDS) and acute myeloid leukemia (AML).^{4,5} Although few data are available on the frequency of *STAG2*ms alone, collectively, cohesin complex mutations are present in 8% of MDS, 12% of AML, and 10% of chronic myelomonocytic leukemia cases. It is considered 1 of 8 secondary-type mutations and are specific to secondary AML (sAML).⁶ *STAG2*ms correlate with MDS response to hypomethylating agents (HMAs)^{3,5} but are linked to poor prognosis in MDS,^{3,7,8} with conflicting data on AML outcome⁹⁻¹¹ and limited data on effects of hematopoietic stem cell transplantation (HSCT).

Our single-institute retrospective study included 91 patients with *STAG2*m MN, whose charts were reviewed for clinical information after institutional review board approval. Patients were included at date of in-house *STAG2*-harboring next-generation sequencing (NGS) (performed at diagnosis or progression). Diagnosis was rendered according to World Health Organization classification^{12,13} and MDS risk stratification according to the Revised International Prognostic Scoring System.¹⁴ BlueSky Software V7.40 was used for statistical analysis.

Most patients were older (median age, 72 years) males (78%). MDS was the most common diagnosis (55%), followed by AML (29%), MDS/myeloproliferative neoplasm (MPN) overlap, and MPN. Of the MDS cases, 36 (72%) belonged to the excess blast subtype (MDS-EB) (including 17 MDS-EB1 and 19 MDS-EB2) and 23 (46%) were high or very high risk. None were of the ring sideroblast subtype (including the 8 patients carrying *SF3B1*m). Ten patients with AML (38%) had sAML, whereas 14 patients (15%) had therapy-related MN (t-MN) (including 10 and 8 who received prior chemotherapy and radiotherapy, respectively). By the European LeukemiaNet risk stratification, 18 of the AML cases were adverse risk, 7 intermediate, and 1 favorable risk. Twenty-eight patients (31%) had abnormal cytogenetics, with trisomy 8 being the most common (Table 1; supplemental Tables 2-4). None of the females had X-chromosome deletion.

The median VAF of *STAG2*ms was 50% (range, 5% to 100%) and was significantly higher in males ($P < .001$), as expected of an X-linked gene. Corrected median VAF (accounting for X chromosome) was 29.5% and 27% in males and females ($P = .5$), respectively. There was no difference in VAF between diagnostic groups ($P = .6$), MDS subtypes ($P = .7$), high and non-high-risk MDS ($P = .6$), de novo AML (dnAML) ($P = .2$), and sAML or between t-MN and de novo MN (dnMN) ($P = .1$). There was no correlation between VAF and bone marrow (BM) or peripheral blasts. Most *STAG2*ms were in the N-terminus (64%) and 15 (16%) were in the STAG domain. Within the STAG domain, there were

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Data are available on request from the corresponding author, Aref Al-Kali (alkali.aref@mayo.edu).

The full-text version of this article contains a data supplement.

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Table 1. STAG2-mutated patients' characteristics

Variable	Value
Characteristics and hematologic features of patients with STAG2m	
Total no. of patients	91
Race, n (%)	
White	85 (93)
Latino/Hispanic	4 (4)
African American	1 (1)
Other	1 (1)
Sex (male), n (%)	71 (78)
Age (range), y	72 (25-91)
Hemoglobin, median (Q1, Q3), g/dL	8.7 (7.9, 9.8)
Leukocytes, median (Q1, Q3), $\times 10^9/L$	2.8 (1.8, 6.0)
Platelets, median (Q1, Q3), $\times 10^9/L$	88 (36, 129)
BM blasts (range), %	7 (0-86)
Circulating blasts (range), %	3 (0-71)
Cytogenetics, n (%)	
Abnormal	28 (31)
Normal	59 (65)
Diagnosis, n (%)	
MDS	50 (55)
AML	26 (29)
MDS/MPN	9 (10)
MPN	3 (3)
CCUS	2 (2)
Aplastic anemia	1 (1)
t-MN	14 (15)
STAG2m characteristics	
VAF of STAG2 (range), %	50 (5-100)
Median VAF, %	
Males	59
Females	27
AML	51
MDS	50
MDS/MPN	41
MPN	31
Mutation type, n (%)	
Nonsense	49 (54)
Frameshift	33 (36)
Splice site	9 (10)
Computational pattern	
No. of comutations, median (range)	3 (0-6)
Isolated STAG2, n (%)	6 (7)
Major comutations, n (%)	
ASXL1	59 (65)
SRSF2	33 (36)
TET2	33 (36)
RUNX1	27 (30)
BCOR	18 (20)

Table 1 (continued)

Variable	Value
IDH2	16 (18)
U2AF1	12 (13)
Treatment, n (%)	
Received at least 1 line of treatment	64 (70.3)
HMA	30 (47)
HMA + VEN	17 (27)
Low-dose cytarabine + VEN	3 (5)
Chemotherapy	6 (9)
TK inhibitor	4 (6)
IDH inhibitor	1 (2)
Immunomodulator	1 (2)
Study therapy	2 (3)
HSCT, n (%)	25 (28)

	Response to therapy		
	HMA, n (%)	HMA + VEN, n (%)	Chemotherapy, n (%)*
CR	1 (3.8)	2 (11.8)	3 (50.0)
CRi	6 (23.1)	7 (41.2)	2 (33.3)
PR	0 (0)	1 (5.9)	0 (0)
HI	5 (19.2)	0 (0)	0 (0)
No response	14 (53.8)	7 (41.2)	1 (16.7)
Relapse			
Yes	3 (25)	6 (60)	2 (40)
No	9 (75)	4 (40)	3 (60)

CCUS, clonal cytopenia of unknown significance; CR, complete remission; CRi, complete remission with incomplete hematologic recovery; HI, hematologic improvement; IDH, isocitrate dehydrogenase; PR, partial response; TK inhibitor, tyrosine kinase inhibitor; VEN, venetoclax.

*Chemotherapy regimens used were 7 + 3 with or without midostaurin.

6 (p.Arg259) and 4 (p.Arg216) nonsense mutations, representing mutational hotspots (Figure 1). Nonsense mutations were the most common (54%), followed by frameshift (36%) and splice site (10%) (supplemental Table 5). There was no correlation between mutation type or site and MN classification, BM blasts, or VAF.

The median number of comutations was 3 (range, 0-6) (supplemental Table 6). The most common were ASXL1 (65%), TET2 (36%), SRSF2 (36%), RUNX1 (30%), and BCOR (20%), whereas TP53 was uncommon (1%) (supplemental Figure 1; supplemental Tables 7 and 8). There was no correlation between the number of comutations and MN classification. Higher risk MDS had more BCOR mutations ($P = .01$) and RUNX1 mutations ($P = .2$) than lower risk MDS. There was no difference in the computational pattern between dnAML and sAML or between dnMN and t-MN. t-MN cases carried fewer comutations than dnMN (2 vs 3, $P = .02$), whereas sAML cases and those that progressed to AML carried 4. No single comutation was associated with progression to AML and none of those that progressed carried KRAS mutations/ NRAS mutations. Six cases (7%) had isolated STAG2ms, including 3 MDS, 2 AML, and 1 CCUS. There was no difference in

mOS among 88 patients (after excluding CCUS and aplastic anemia) was 19.9 months (number of deaths = 39). Median 2-year survival in patients with AML was 40%. There was no difference in survival based on sex ($P = .2$) or cytogenetics ($P = .08$). There was no difference between diagnostic groups ($P = .3$), sAML and dnAML ($P = .2$), or higher and lower risk MDS ($P = .6$). Patients with t-MN had lower mOS than dnMN (9.9 vs 20.5 months, $P = .03$). Those with circulating blasts $\geq 5\%$ had lower mOS than those with $< 5\%$ (10.1 vs 21.4 months, $P = .01$). On univariate Cox regression analysis with VAF as a continuous variable, mOS worsened with increasing VAF (hazard ratio [HR], 1.01; $P = .03$). t-MN and circulating blasts $\geq 5\%$ remained significant on multivariate analysis (supplemental Table 9), whereas higher VAF worsened OS (HR, 1.01; $P = .09$). A higher VAF worsened OS in males alone with HR, 1.01 and $P = .1$. Analysis of OS against corrected VAF among all patients yielded HR, 1.02 and $P = .1$. Patients who received HSCT after NGS had longer mOS than those who without HSCT (HR, 0.4; $P = .06$; by time-dependent variable analysis). Mutations of *KRAS*, *PTPN11*, and *CBL* led to lower mOS ($P < .001$, $P < .001$, and $P = .04$, respectively), whereas *IDH2* mutations improved mOS ($P = .04$). Neither *ASXL1* mutations nor computational burden affected mOS (Figure 1; supplemental Figures 2-11).

Of 91 patients, 47 (52%) were diagnosed with MN before NGS (supplemental Figure 12), with a median time of 8.4 months from initial diagnosis to in-house NGS. Among 37 non-AML cases, 7 (19%) had progressed to AML at time of NGS. mOS did not differ between those with and without a prior diagnosis ($P = .9$). Thirty-one of 91 patients had a subsequent NGS (S-NGS). Sixteen patients (52%) continued to harbor *STAG2m* in S-NGS and had poor mOS compared with those who did not (19.9 months vs not reached, $P = .03$) (supplemental Figure 13). Where the *STAG2m* was lost on S-NGS, the median number of mutations became 2. Of 11 patients with AML who had a S-NGS, 7 had lost *STAG2m*. Four of these 7 patients had shown response to therapy, whereas the remaining 3 had not.

Our study included 91 patients, which is the largest cohort of patients with *STAG2m* MN in current literature. We found a high cooccurrence of *STAG2ms* and *ASXL1* mutations, as previously alluded to by Kon et al.^{15,16} We demonstrated the prevalence of higher risk disease among patients with *STAG2m* MDS, as previously suggested.^{4,5} Eighteen percent of MDS cases progressed to sAML, with an increased computational burden on progression, as previous studies suggest.¹⁷⁻¹⁹ It is possible that *STAG2ms*, therefore, favor transformation through induction of genetic instability and acquisition of new mutations. In our cohort, 31% patients had abnormal karyotype. Thota et al.⁵ had found that the prevalence of abnormal karyotype was similar among cohesin-mutated and wild-type MN. Our study found that karyotype did not impact survival or disease progression, which previous studies had not alluded to.

Our study also showed *STAG2ms* to be associated with poor prognosis in MN. There was possible worsening of OS with higher VAF, which may be highlighted with a larger cohort. This, combined with the lack of association between MN classification and OS, suggests an adverse impact of *STAG2ms* on survival regardless of phenotypic features. There was also no correlation of VAF with

clinical features (age, MN phenotype, and blast counts); hence, there was no clear explanation for an impact of VAF. Because none of the females had X-chromosome deletion, the impact of the loss-of-heterogeneity could not be assessed. *STAG2m* sAML had comparable clinical characteristics and survival to dnAML, unlike what others have suggested.²⁰ This supports the notion that *STAG2ms* are secondary type and define a subset of dnAML cases with worse clinical outcome, comparable to that of clinically defined sAML.⁶ Our data also suggest a positive response to HSCT among patients with *STAG2m* MN, albeit a larger sample size is needed to confirm this.

Our study is limited by the relatively small sample size, retrospective nature, patient heterogeneity, and the lack of long-term follow-up. To our knowledge, we present novel findings on the role of *STAG2ms* in MN progression. A larger cohort can provide further insight.

Contribution: B.K., A.N., and A.A.-K. planned the study, reviewed data, completed statistical analysis, and wrote the manuscript; R.H. and D.V. performed molecular analysis and reviewed the manuscript; P.N. reviewed BM slides and manuscript; P.G. performed cytogenetic analysis and reviewed the analysis; K. Bessonon coordinated NGS data collection; and N.G., K. Begna, A.T., A.M., M.P., W.J.H., M.L., M.V.S., C.A.Y., J.F., T.B., and H.B.A. reviewed the manuscript and contributed patients.

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