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POSTER ABSTRACTS

637.MYELODYSPLASTIC SYNDROMES - CLINICAL AND EPIDEMIOLOGICAL

STAG2 Somatic Mutations Are Associated with Specific Dysplastic Megakaryocytic and Myeloid Cell Features in Myelodysplastic Syndrome

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Introduction:
Although myelodysplastic neoplasms/myelodysplastic syndromes (MDS) are driven by genetic mutations, their diagnosis relies on morphologic evaluation of abnormal hematopoiesis in the bone marrow. Only a small number of genetic abnormalities define bone marrow morphologic features in MDS, such as those harboring *SF3B1* mutations and deletions of chromosome 5q. We hypothesized that there are additional genetic alterations and dysplastic morphologic features in MDS that have not been well-described in the literature. We assessed genetic morphologic associations between 50 commonly mutated genes and 10 morphologic features in a cohort of MDS bone marrows with a high degree of dysplasia. We validated and extended these findings in an independent cohort of myeloid neoplasms. *STAG2* mutations were strongly associated with specific dysplastic megakaryocytic and myeloid cell features in both cohorts.
Methods:
We reviewed bone marrow core biopsies and aspirates from 272 MDS clinical cases (2013-2014) and selected 89 for further study based on the presence of prominent dysplastic features. Each case was independently evaluated by two pathologists for the following dysplastic features: small hypolobated megakaryocytes, widely separated megakaryocyte nuclei; abnormal myeloid nuclear segmentation, myeloid hypogranulation, Auer rods; ring sideroblasts, erythroid binucleation, irregular erythrocyte nuclei, erythroid nuclear cytoplasmic dyssynchrony, and erythroid karyorrhexis. Targeted next generation sequencing was performed using a 50 gene panel comprising the most common somatic myeloid mutations. For each dysplastic feature, univariate risk analysis was used to identify genetic mutations for use in multivariable analysis. Significant associations were validated through blinded morphologic review in an independent cohort of 155 bone marrow biopsies of myeloid neoplasms, comprised of 83 myelodysplastic syndromes, 33 myelodysplastic/myeloproliferative neoplasms and 39 acute myeloid leukemias, diagnosed between 2014 and 2019 and selected for mutations identified in the initial discovery cohort (*STAG2, RUNX1, SRSF2, ASXL1* and *SETBP1*) .
Results:
Pairwise analyses demonstrated broad patterns of genetic associations with myeloid/megakaryocytic dysplasia versus erythroid dysplasia (Panel 1). In multivariable analysis, *STAG2* and *SRSF2* mutations were significantly associated with megakaryocytes with widely separated nuclei (*STAG2*, OR = 25.5, 95% CI [4.17, 493.5], $P = 0.003$; *SRSF2*, OR = 10.1, 95% CI [2.07, 75.0], $P = 0.008$). Mutations in *STAG2* and *SETBP1* were significantly associated with abnormal myeloid nuclear segmentation (*STAG2*, OR = 7.08, 95% CI [1.94, 28.0], $P = 0.003$; *SETBP1*, OR = 12.2, 95% CI [1.29, 267.4], $P = 0.04$). Furthermore, *STAG2* mutations were significantly associated with myeloid cell hypogranulation (OR = 12.7, 95% CI [3.10, 86.3], $P = 0.002$). Because this initial cohort was relatively small, which led to wide confidence intervals suggesting estimation instability, we validated

and extended these findings in an independent cohort of myeloid neoplasms. In the validation cohort (enriched for mutations in *STAG2*, *SRSF2*, and *SETBP1*), *STAG2* mutations were significantly associated with separated megakaryocyte nuclei (univariate OR = 4.18, 95% CI [1.98, 8.80], $P = 0.0002$), abnormal myeloid nuclear segmentation (univariate OR = 3.47, 95% CI [1.47, 8.22], $P = 0.008$), and myeloid cell hypogranulation (multivariable OR = 5.28, 95% CI [2.18, 13.4], $P = 0.0003$) (Panel 2). In contrast, morphologic associations with *SRSF2* and *SETBP1* mutations were not validated.

Conclusion:

STAG2 genetic alterations are strongly associated with the presence of separated megakaryocyte nuclei, abnormal myeloid nuclear segmentation and myeloid cell hypogranulation in MDS. Our data suggest that STAG2 may affect pathways involved in nuclear shape control and secondary granule formation.

Panel 1:

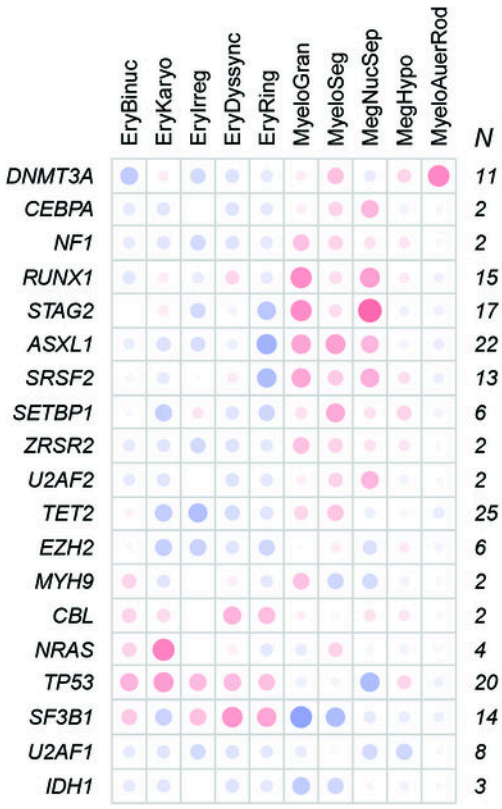
Pairwise associations between gene mutation and bone marrow morphology in MDS. *N*, number.

Panel 2:

Multivariable (black) and univariate (white) analysis in two independent cohorts showing significant gene associations with megakaryocytes with separated nuclei, abnormal myeloid nuclear segmentation, and myeloid cell hypogranulation. CI, confidence interval.

Disclosures Zon: *Amagma Therapeutics:* Consultancy, Current equity holder in private company. **Ho:** *Loxo@Lilly:* Current Employment; *Eli Lilly and Company:* Current equity holder in publicly-traded company. **Pozdnyakova:** *Sysmex:* Consultancy; *Scopio:* Consultancy. **Neuberg:** *Madrigal Pharmaceuticals:* Current equity holder in private company. **Luskin:** *Novartis:* Honoraria, Research Funding; *Pfizer:* Honoraria; *Jazz:* Honoraria; *AbbVie:* Research Funding. **Ebert:** *Exo Therapeutics:* Current equity holder in private company, Membership on an entity's Board of Directors or advisory committees; *TenSixteen Bio:* Current equity holder in private company, Membership on an entity's Board of Directors or advisory committees; *Abbvie:* Consultancy; *Neomorph Inc.:* Current equity holder in private company, Membership on an entity's Board of Directors or advisory committees; *Calico:* Research Funding; *Novartis:* Research Funding; *Skyhawk Therapeutics:* Current equity holder in private company, Membership on an entity's Board of Directors or advisory committees.

Panel 1



Panel 2

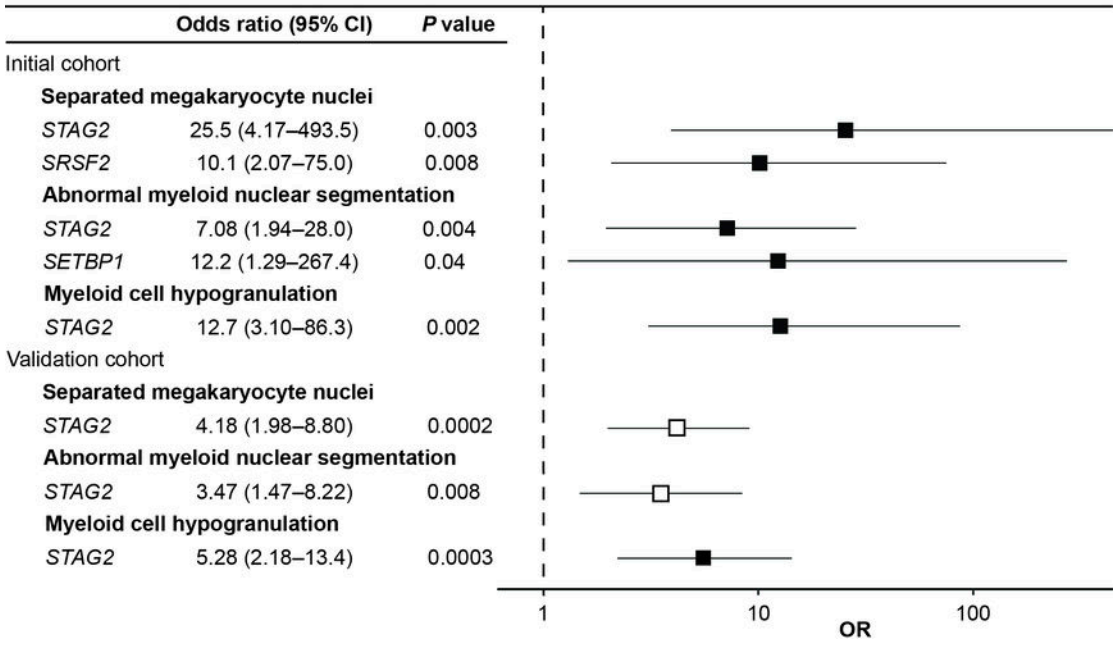


Figure 1

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