Gene Mutations in MDS Associating with Peripheral Blood Count Abnormalities

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Introduction

- Cytogenetic evaluation is the most widely used determinant of IPSS-R prognosis in patients with MDS.
- The presence of underlying gene mutations despite normal karyotype may result in worse prognosis than IPSS-R predictions from chromosome examination.
- At least one myeloid gene mutation was identified in 90% of patients with MDS, and approximately two thirds of these gene mutations were found in patients with normal karyotype [1].
- 50% of practicing hematologists and oncologists do not order cytogenetic testing [2], and even fewer order gene mutation profiling.

Hypothesis

Certain myeloid gene mutations positively associate with blood count abnormalities in patients with MDS.

Methods

Patient Specimens:
Analysis of bone marrow aspiration cells from 147 patients with morphologically and clinically confirmed MDS for genomic mutations was performed by conventional cytogenetics and targeted next generation sequencing (NGS). Mutation status was analyzed for the genes *TET2, SF3B1, ASXL1, DNMT3A, SRSF2, RUNX1, NRAS, ZRSR2, EZH2, ETV6, TP53, CBL,NPM1, JAK2, U2AF1, IDH1, KRAS, IDH2, FLT3, PTPN11,* and *SETBP1*. IPSS-R score was calculated for each patient [3].

Definitions:
•Anemia: Hgb < 10 g/dL
•Macrocytosis: MCV > 100 fl
•Thrombocytopenia: Platelets < 100x10^9/L

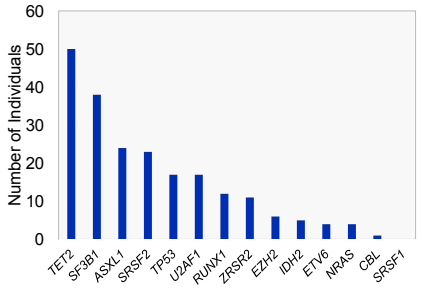
Statistical Analyses:
Associations between gene mutations and blood counts were assessed using the Kruskal-Wallis test. Adjustment to control for family-wise type I error rate (FWER) was performed using the Holm-Bonferroni (Stepdown Bonferroni) multiple testing procedure. All statistical analysis was performed using SAS version 9.3.

Results

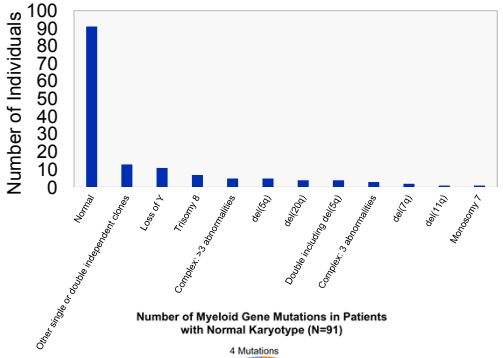
Table I. Patient Demographics.

Characteristics	N (147)	% of Cohort
Cytogenetic Risk Group		
Very Poor	5	3.4%
Poor	4	2.7%
Intermediate	22	15.0%
Good	104	70.7%
Very Good	12	8.2%
Hemoglobin		
>10 g/dL	67	45.6%
<10 g/dL	80	54.4%
Platelet Count		
>100x10(9)/L	86	58.5%
≤100x 10(9)/L	61	41.5%
ANC		
>1.8x10(9)/L	94	63.9%
<1.8x10(9)/L	53	36.1%
Bone Marrow Blasts		
≤2%	84	57.1%
>2-<5%	39	26.5%
5-10%	17	11.6%
>10%	7	4.8%
IPSS-R Category		
Very Low	32	21.8%
Low	75	51.0%
Intermediate	29	19.7%
High	5	3.4%
Very High	6	4.1%

Spectrum of Myeloid Gene Mutations



Spectrum of Karyotypes



Number of Myeloid Gene Mutations in Patients with Normal Karyotype (N=91)

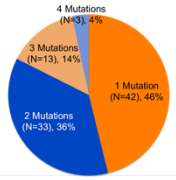


Table II. Peripheral Blood Count Associations with Genetic Mutations.

Peripheral Blood Count Presentation	Gene Mutation	P-value
Anemia	*SF3B1**	0.0017
Higher Hemoglobin	*SRSF2*	0.0051
Macrocytosis	*SF3B1**	<0.0001
	ZRSR2	0.0382
Thrombocytopenia (<100x10^9/L)	*SRSF2*	0.0148
	*TP53**	0.0005
	U2AF1	0.434
Higher Platelet Count	*SF3B1**	<0.0001
Higher Total WBC Count	*SF3B1**	<0.0001
Higher Absolute Neutrophil Count (ANC)	*SF3B1**	<0.0001
Higher Absolute Monocyte Count (AMC)	*SF3B1*	0.0122
	NRAS	0.0237
Lower % Bone Marrow Blasts	*TET2**	0.0032
Lower IPSS-R Score	*SF3B1*	0.0133
Higher IPSS-R Score	*TP53**	0.0017

* Denotes P-value significance based on the Holm-Bonferroni (Stepdown Bonferroni) multiple testing procedure.

Conclusions

- In patients with MDS, certain myeloid gene mutations significantly and specifically associated with peripheral blood count abnormalities and IPSS-R score.
- Genetic testing of bone marrow samples is warranted in MDS patients showing abnormal peripheral blood counts. Gene mutation results could be used for verifying diagnosis, determining prognosis and informing treatment.
- This study supports previous associations of
  - *SF3B1* mutation and anemia, higher platelets, higher WBC count, higher ANC, lower IPSS-R score, and higher absolute monocyte count;
  - *SRSF2* mutation and higher hemoglobin and lower platelet count;
  - *TP53* mutation and lower platelet count and higher IPSS-R score; and
  - *TET2* mutation and lower percentage of bone marrow blasts.
- Novel findings from this study included associations between
  - *SF3B1* mutation and macrocytosis,
  - *ZRSR2* mutation and macrocytosis,
  - *U2AF1* mutation and lower platelets and lower absolute monocyte count, and
  - *NRAS* mutation and higher absolute monocyte count. Further research will be needed to identify whether these associations are consistent in other cohorts.

References

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3. Greenberg, P.L., et al., *Revised international prognostic scoring system for myelodysplastic syndromes.* Blood, 2012. **120**(12): p. 2454-65.