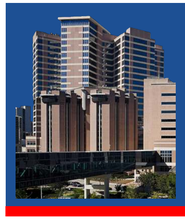

Myelodysplastic Syndromes with *EZH2* Mutations Frequently Show Multilineage Dysplasia, Chromosome 7 Alterations and Concomitant Mutations in *ASXL1, RUNX1* and *TET2*

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CONTEXT

- *EZH2* (7q36) encodes a histone methyltransferase essential for epigenetic silencing during stem cell renewal.
- *EZH2* mutation is one mechanism of abnormal *EZH2* function and is shown to be an independent predictor of survival in MDS.
- Unlike lymphomas where *EZH2* Y641 hot-spot gain-of-function mutation is frequent, MDS cases show a spectrum of mutations.
- Due to the availability of *EZH2*-targeted therapies, there is a need for precise evaluation of these mutations in larger cohorts.
- In this study, we evaluated *EZH2* mutations in MDS patients and correlated with clinical, morphologic and genetic findings.

METHODS

- We searched the institutional database for MDS patients with *EZH2* mutation.
- NGS using a 81-myeloid-gene panel was performed.
- Clinical, morphologic, cytogenetic and mutational results were reviewed.

RESULTS

- The *EZH2* mutations were most frequent in exons18 and 19.
- All cases had at least 1 concurrent gene mutation; *ASXL1* (45%), *RUNX1* (35%), *TET2* (33%) etc..(fig.2).
- By morphologic review, MLD was most frequent subtype (fig.3).
- Abnormal karyotype was frequent; majority include concurrent chromosomal 7 alterations.

RESULTS

Table1. Summary of clinical and laboratory features

Features \ MDS		+ No other mutation N = 5	+ *TP53** N = 6	+ 1 of *RUNX1* or *ASXL1* or *TET2* N = 12	+ ≥ 2 of *RUNX1*, *ASXL1*,*TET2* N = 14***	+ ≥ 3 extra mutations N = 10	Total N = 40
Gender M:F		3:2	5:1	11:1	12:1	9:1	33:7
Age - M (range)		76 (66 - 79)	64 (55 - 77)	75 (65 - 90)	74 (59 - 80)	75 (63 - 84)	74 (55 - 90)
% BM blasts		2 (1 - 9)	2.5 (0 - 13)	4 (1 - 15)	6 (1 - 15)	6.5 (1 - 11)	4 (0 - 15)
BM fibrosis - MF		1 (0 - 2)	1 (0 - 2)	1 (0 - 3)	1 (0 - 1)	1 (0 - 1)	1 (0 - 3)
BM cellularity		70 (40 - 80)	65 (15 - 90)	60 (15 - 95)	50 (10 - 95)	50 (10 - 95)	60 (10 - 95)
% Ring sideroblasts		0 (0 - 15)	1 (0 - 20)	0 (0 - 67)	0 (0 - 7)	0 (0 - 8)	0 (0 - 67)
Karyotype	Normal	1	2	4	3	2	12 (30%)
	Not-complex	4	1	7	7	5	19 (47.5%)
	Complex	0	3	1	3	2	7 (17.5%)
	+ chr 7 alteration	1	4	3	5	4	14 (35%)

Table2. Distribution of most common co-mutated genes with *EZH2*

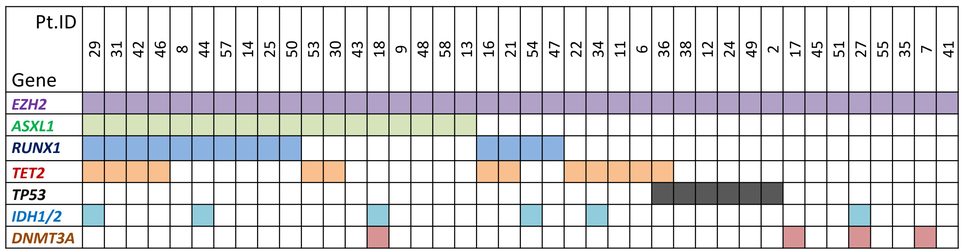


Table3. Summary of different subtypes of MDS

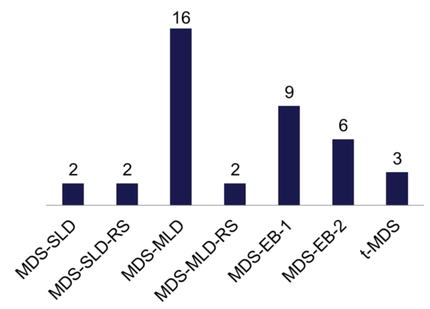
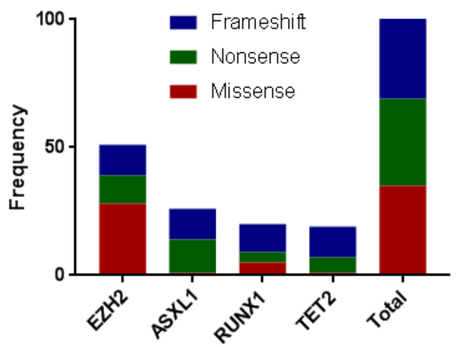


Table4. Summary of gene mutations and types



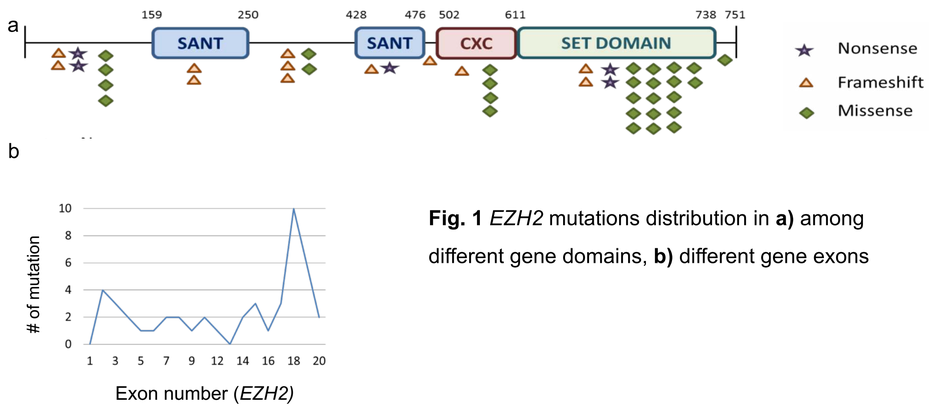


Fig. 1 *EZH2* mutations distribution in **a)** among different gene domains, **b)** different gene exons

Fig. 2 VAF for *EZH2* gene mutation

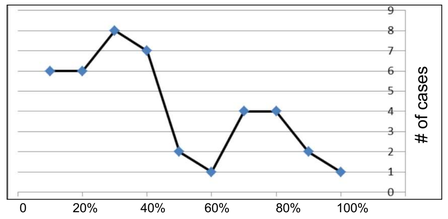
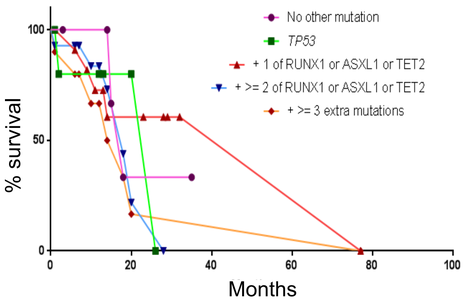


Fig.3 Overall survival in different mutational subgroups



CONCLUSIONS

- *EZH2* mutations in MDS span the entire gene.
- MDS patients with *EZH2* mutations show a male predominance, multilineage dysplasia and frequent co-mutations in *ASXL1*, *RUNX1* and *TET2.*
- Mutations between *TP53* and other (*ASXL1, RUNX1, TET2, etc..*) genes are mutually exclusive.
- *EZH2* VAF shows a clonal rather than a subclonal change in most cases.
- A high proportion (35%) has concurrent chromosome 7 alterations suggesting a tumor suppressor role.