# *STAG2*, *SRSF2* and *RUNX1* Mutations Might Define Prognosis in MDS Patients with Isolated Trisomy 8

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MDS-472

## Background

Myelodysplastic syndromes (MDS) are clonal disorders with increasing risk of leukemia transformation. Chromosomal abnormalities and somatic mutations are key pathogenic defects in MDS and play a role in progression to acute myeloid leukemia (AML)[1,2]. The Revised International Prognostic Scoring System (IPSS-R) includes cytogenetic alterations as strong prognostic factors. Specifically, isolated trisomy of chromosome 8 (isolated +8) is present in 5% of MDS and is associated with an intermediate cytogenetic risk. Interestingly, these patients show high heterogeneous clinical features[3].

Therefore, we hypothesized whether mutational profile might help to reclassify MDS with isolated +8 patients into subgroups with different outcomes.

## Objective

To evaluate the mutational landscape of isolated trisomy 8 MDS patients and to determine whether specific somatic mutations might be associated with adverse outcome of these patients.

## Materials & Methods

**MDS at diagnosis**

**400** patients **without trisomy 8**
*non +8 (control group)*

+

**79** patients with **isolated trisomy 8**
*Isolated +8*

**Next-generation sequencing analysis**
custom capture-enrichment panel (>100 genes)
*Coverage > 100x, VAF > 2%*

**Statistical analysis**
SPSS and R
*Dichotomous variables: $\chi^2$*
*Continuous variables: U-Mann Whitney*
*Survival analyses: Kaplan Meier (Log-Rank)*

## Results

### 1. PATIENTS WITH ISOLATED TRISOMY 8 MDS DISPLAY A DIFFERENTIAL MUTATIONAL LANDSCAPE

The most frequently mutated genes in isolated +8 MDS patients were *TET2*, *STAG2*, *SRSF2* and *RUNX1* (Fig.1).

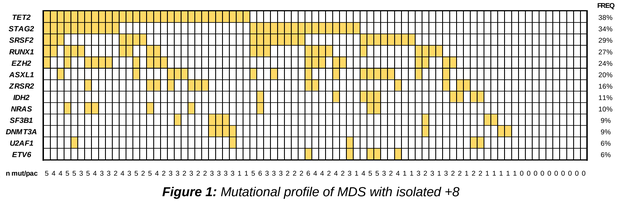



***Figure 1:*** *Mutational profile of MDS with isolated +8*

When they were compared to MDS without trisomy 8 (non +8), mutations in *STAG2, SRSF2*, *RUNX1, EZH2, ASXL1* or *ZRSR2* were more frequent in isolated +8 patients than in the control group (Fig.2). Clinical data from patients included in the study are shown in table 1.

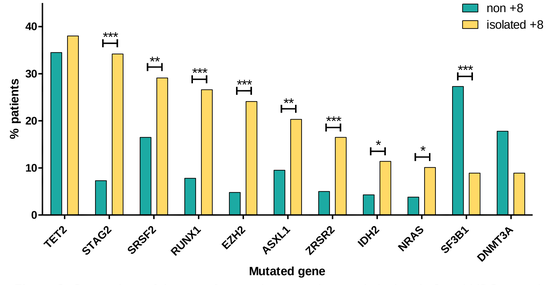



***Figure 2:*** *Comparison of the most frequently mutated genes in isolated +8 and MDS controls*

| | MDS without +8 | MDS isolated +8 |
|---|---|---|
| **Demographics** | | |
| Years (median, range) | 75 (29.4-92.2) | 77.7 (33-94) |
| Gender, n (%) | | |
| Male | 229 (58.1%) | 57 (72%) |
| Female | 165 (41.9%) | 22 (28%) |
| **2016 WHO classification, n (%)** | | |
| MDS-SLD | 16 (4.2%) | 3 (4%) |
| MDS-MLD | 115 (30.2%) | 21 (28%) |
| MDS-RS | 102 (26.8%) | 7 (9.3%) |
| MDS del(5q) | 41 (10.8%) | 0 (0%) |
| MDS-EB-1 | 51 (13.4%) | 22 (29.3%) |
| MDS-EB-2 | 53 (13.9%) | 19 (25.3%) |
| Hypoplastic MDS | 1 (0.3%) | 3 (4%) |
| **IPSS-R, n (%)** | | |
| Very low / low | 245 (72.9%) | 9 (26.5%) |
| Intermediate | 51 (15.2%) | 12 (35.3%) |
| High / very high | 40 (11.9%) | 13 (38.2%) |
| **PB and BM counts at diagnosis, median (range)** | | |
| Hemoglobin (g/dL) | 9.9 (3.8-15.3) | 9.7 (5.4-14.6) |
| Platelets (x10⁹/L) | 161 (4-1067) | 102.5 (2-520) |
| Neutrophils (x10⁹/L) | 2 (0.1-56) | 1.8 (0.2-11.8) |
| Bone marrow blasts (%) | 1.4 (0-19.9) | 4.5 (0-16) |
| Ring sideroblasts (%) | 0 (0-95) | 0 (0-72) |
| **AML progression, n (%)** | | |
| No | 261 (77.9%) | 64 (81%) |
| Yes | 74 (22.1%) | 15 (19%) |
| **Follow-up, months (range)** | 8.7 (0-245) | 7.6 (0-133.3) |

*PB:peripheral blood; BM:bone marrow*

***Table 1:*** *Clinical characteristics of patients included in the study*

### 2. SOMATIC MUTATIONS ARE ASSOCIATED TO CLINICAL FEATURES IN PATIENTS WITH MDS AND ISOLATED TRISOMY 8

The presence of somatic mutations allow the distinction of differential clinical features in patients with MDS and isolated +8. *STAG2* mutations were associated to a higher percentage of bone marrow blasts, while *SF3B1* and *TET2* correlated with lower blasts counts. In addition, both *SF3B1*$^{mut}$ and *DNMT3A*$^{mut}$ patients showed higher platelets and ring sideroblasts counts (Fig. 3).

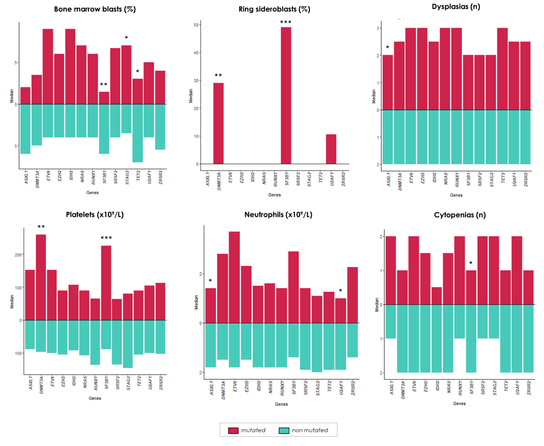



***Figure 3:*** *Clinical features for the most frequently mutated genes in isolated +8 MDS patients*

### 3. MUTATIONAL PROFILE DISTINGUISHES TWO SUBGROUPS WITH DIFFERENT OUTCOME AND TIME TO AML PROGRESSION IN ISOLATED +8 MDS

Patients with mutations in at least one of *STAG2*, *SRSF2* or *RUNX1* genes, showed a shorter overall survival compared to non-mutated (p=0.005) defining a low risk-like and a high risk-like subgroups (Fig. 4). In addition, the new high risk-like defined subgroup showed a shorter time to both AML progression and time to treatment, compared to the low risk-like.

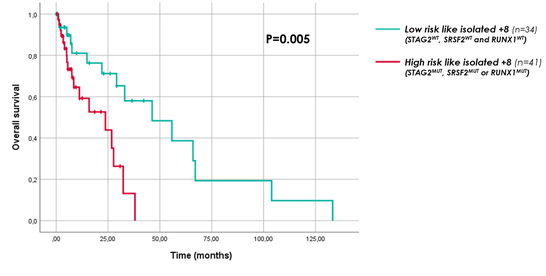



***Figure 4:*** *Overall survival of newly defined subgroups in isolated +8 MDS patients*

Multivariate analysis revealed that only *SRSF2* mutations were enough to predict shorter time to AML (p<0.001, Fig.5a). Furthermore, isolated +8 with mutations in *SRSF2* showed similar time to AML when they were compared to MDS control group with high risk IPSS-R (p=0.54), while *SRSF2*$^{WT}$ were comparable to patients with low-risk IPSS-R (p=0.84, Fig.5b).

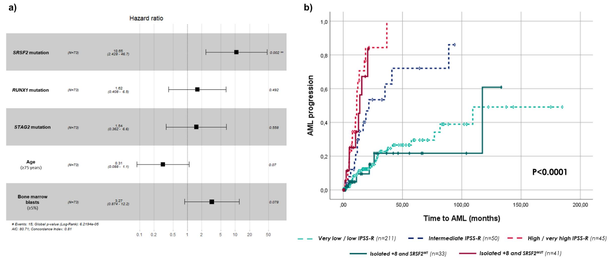



***Figure 5:*** *a) multivariate analysis of patients with MDS and isolated +8; b) Time to AML progression in isolated +8 MDS patients with SRSF2$^{mut}$ and SRSF2$^{wt}$*

## Conclusions

Patients with MDS and isolated +8 display a differential mutational landscape compared to MDS without trisomy 8. Mutations in *STAG2, SRSF2* and/or *RUNX1* might define a new high risk-like subgroup among patients with isolated +8. Mutations in these genes are useful markers for predicting adverse outcome, shorter time to HMA treatment and reclassifying MDS patients with isolated +8 in two risk subgroups. *SRSF2* is also a strong, independent marker of shorter time to leukemia transformation.

## References

1. Haferlach T, *et al. Leukemia*, 2014; 28:241-7.
2. Papaemmanuil E, *et al. Blood*, 2013; 122(22):3616-27.
3. Drevon L, *et al. Br J of Haematol*. 2018; 182:843-50.

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