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ORAL ABSTRACTS

636.MYELODYSPLASTIC SYNDROMES-BASIC AND TRANSLATIONAL

Outcome Prediction in *DDX41*-Mutant Myelodysplastic Syndromes Is Not Possible with General Disease Schemes and Requires a Dedicated Risk Scoring System

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Hypomorphic *DDX41* mutations are prototypic lesions for germline predisposition to late onset myeloid neoplasia (MN), chiefly MDS. In a recent study [1], we demonstrated that germline mutations in this gene are found in up to 5% of MDS cases and explain nearly 80% of the etiologic fraction of known MN inherited predisposition. *DDX41* mutation carriers have a ~50% lifetime risk of developing MN, which commonly accompanies the acquisition of a secondary somatic *DDX41* mutation in the contralateral allele (most commonly p.R525H) with a strong male predominance. Because of these peculiarities, risk classification assigned by currently available schemes such as the revised/molecular international prognostic scoring system (IPSS-R/M) has also been questioned, differentiating *DDX41*-mutant MDS as a distinct nosologic subentity, whereby current prognostic tools are not able to capture invariant biologic features crucial for outcome prediction. Particularly, the impact of somatic *DDX41* mutations on disease progression has not been evaluated.

In this study, we explored the applicability of current schemes used for MDS outcome prediction leveraging an international collaboration across 6 academic centers. We accrued a total of 238 MDS cases from a cohort of 409 MN patients with *DDX41* mutations with clinical-molecular annotations and relevant follow up data. For relevant comparisons, a cohort of 1212 *DDX41* wild-type (WT) MDS cases with matching annotations and follow up was used.

Overall, the median age at MDS diagnosis was 69 years (IQR 61-76) with a strong male predominance (4.4 M:F ratio). According to IPSS-R, patients clustered in very low (10%), low (17%), intermediate (34%), high (20%) and very high (18%) risk groups, whereas by IPSS-M the redistribution of risk categories was as follows: very low (7%), low (27%), moderate low (18%), moderate high (16%), high (15%), and very high (17%). After merging the moderate low/high IPSS-M categories for comparison purposes, the overall shift was 51%, with 38% up- and 62% down-staged. Notably, pairwise Log-Rank tests across IPSS-R/M risk categories resulted in non-significant survival differences in majority of subgroups, pinpointing how these commonly used schemes fail in separating *DDX41*-mutant MDS into groups of diverse prognoses. Conversely, the same analysis in the WT cohort led to a significant separation and identification of distinct prognostic categories. (**Fig1A**)

Next, we examined the reasons why *DDX41*-mutant MDS cases defy accuracy of current prognostic schemes. When looking at *DDX41* specific genomic configuration, cases with germline plus p.R525H somatic mutations showed higher bone marrow blast percentages (median 11%) vs those acquiring other secondary somatic hits (4%, p<.001) or harboring only 1 germline alteration (7%, p=.002). By dividing patients according to IPSS-R scores (lower <3.5, higher-risk >3.5), we noticed a twice

higher frequency of adverse risk MDS among patients with germline plus p.R525H mutations (p=.009). Thus, we explored whether *DDX41* specific mutational configuration may have a role in driving MDS outcomes. While no survival difference was found between cases with germline alone vs germline plus somatic configuration, the dissection of the genomic architecture of double mutants showed worse survival outcomes and faster leukemia evolution in cases carrying truncating and/or p.R525H mutations (**Fig1B**). These features still held significance in a *DDX41*-specific multivariable model for leukemia progression considering age and gender, with the best goodness of fit (Akaike Information Criterion-AIC: 131; c-index: 0.81) as compared to IPSS-R (AIC: 150, c-index: 0.71) and IPSS-M (AIC: 144, c-index: 0.73), whereas the acquisition of p.R525H mutation was the only independent predictor of survival (HR=3.9, 95% CI 1.5-9.9, p=.005).
We show that IPSS-R/M are not able to adequately assess leukemic evolution and survival outcomes in *DDX41*-mutant MDS. Indeed, germline truncating and somatic p.R525H mutations are better predictors of faster leukemic evolution and survival. Additional risk factors inherent to this MDS subentity hold a prognostic significance beyond the consideration of traditional disease-specific variables, substantiating the need for a dedicated risk scoring system. This refined prognostication approach is also a consideration for other known germline mutations with predisposition to MN.

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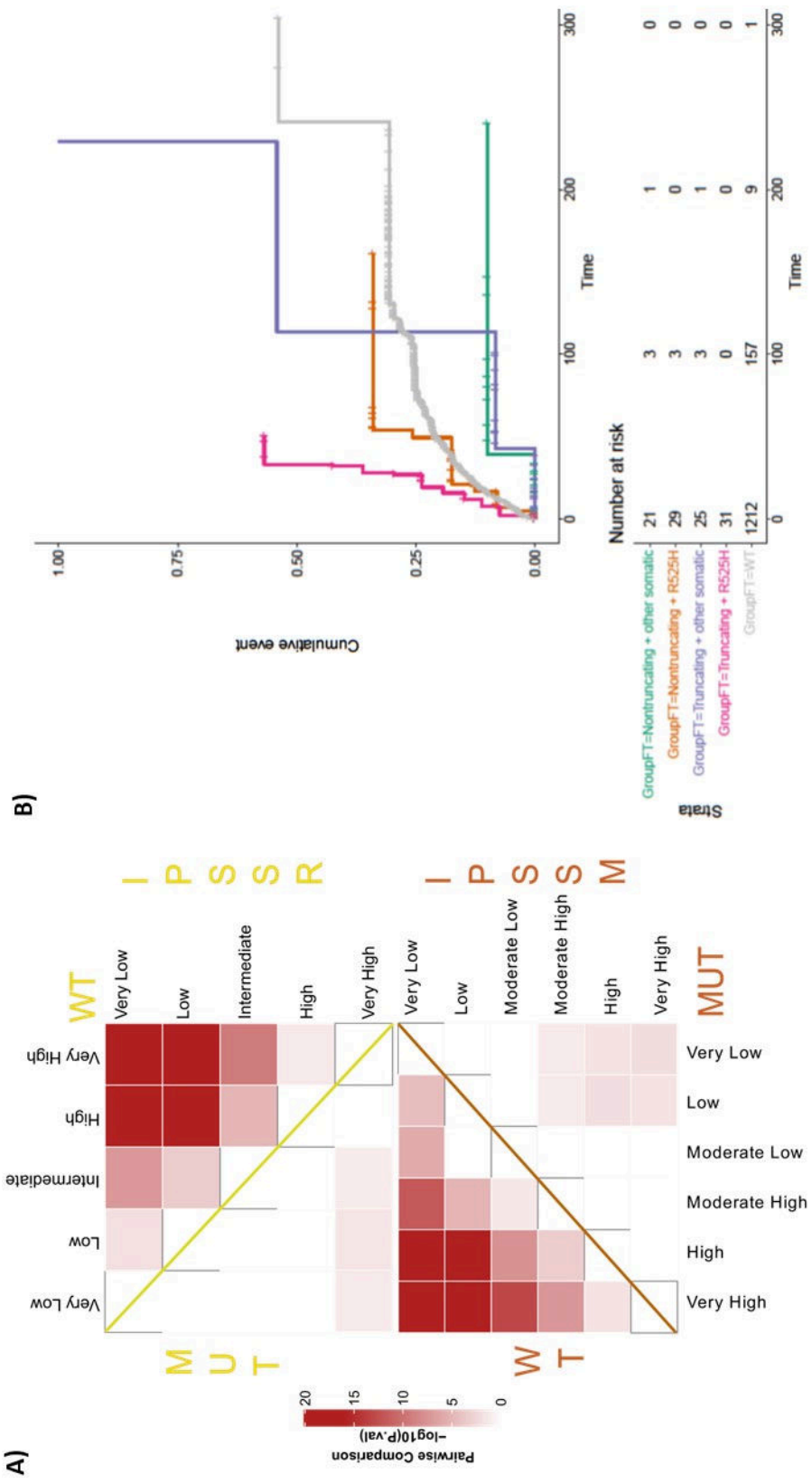

Figure 1