HIGH EXPRESSION OF NSD2 IN NON t(4;14) NEWLY-DIAGNOSED MULTIPLE MYELOMA PATIENTS MAY MIMIC t(4;14) BIOLOGY

M. Samur[1], E. Flynt[2], A. Aktas Samur[1], S. Talluri[1], D. Nandana[3], A. Hasheminasab[3], M. Kazeroun[3], V. Gamble[3], W. Baker[3], V. Sridharan[2], H. Avet-Loiseau[4], J. Corre[4], N. Munshi[1], A. Thakurta[3]

1. Dana Farber Cancer Institute, Harvard Medical School, Boston, USA, MA
2. K36 Therapeutics, Inc. Cambridge, MA, USA
3. Oxford Translational Myeloma Centre, University of Oxford, Oxford, United Kingdom
4. Unité de Genomique du Myélome, University Cancer Center of Toulouse, Toulouse, France.

22nd Annual MEETING & EXPOSITION
International Myeloma Society
September 17-20, 2025 • Toronto, Canada

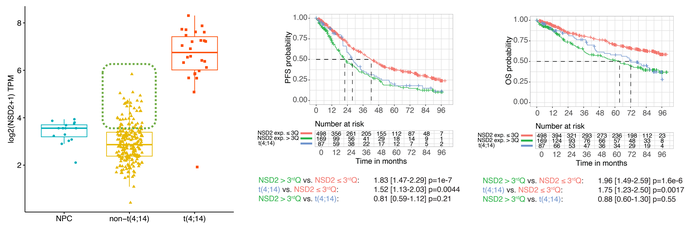
INTRODUCTION

In newly diagnosed multiple myeloma (ndMM) t(4;14) causes overexpression of the histone methyltransferase NSD2 (MMSET) which adds dimethyl groups on histone 3 lysine 36 residues leading to a gene expression program associated with poor prognosis[1,2]. Interestingly, some patients without the translocation can have high NSD2 expression. Here, we compared genomic and prognostic features between t(4;14) vs non-t(4;14) patients with high vs low NSD2 expression.

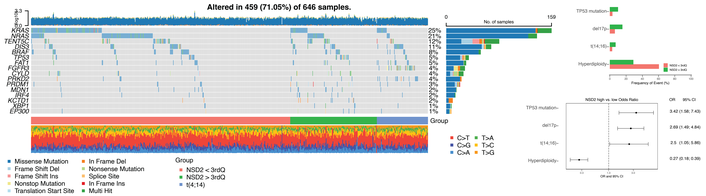
METHOD

RNA sequencing data from newly diagnosed MM patients and normal plasma cells were obtained from two independent studies conducted by the IFM and Dana-Farber Cancer Institute (DFCI). Additional RNA sequencing data from newly diagnosed MM patients were incorporated from the Multiple Myeloma Research Foundation CoMMpass study. Genomic alterations were identified from CoMMpass variant calls and compared between patient groups using Fisher's exact test to calculate odds ratios and 95% confidence intervals. Differential gene expression analysis was conducted using the DESeq2 software package. A t-distributed stochastic neighbor embedding plot was generated based on genes differentially expressed between H-NSD2 and L-NSD2 groups. Gene set enrichment analysis (GSEA) was performed to identify enriched pathways. Single-cell assay for transposase-accessible chromatin using sequencing (ATAC-seq) data were processed using the 10X Genomics Cell Ranger pipeline and ArchR. Master regulatory analysis of gene expression data was conducted using the Regulatory Transcriptional Elements (RTE) tool.

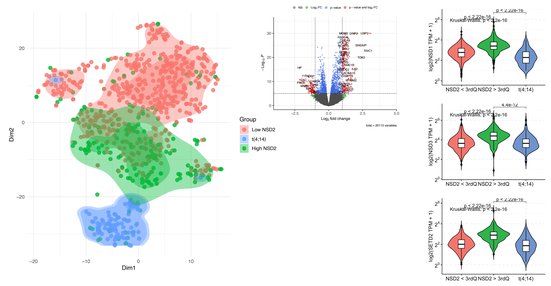
RESULTS



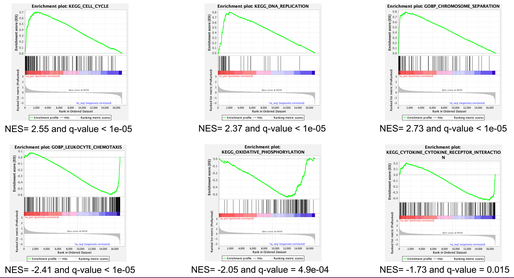
NSD2 expression is generally low in MM compared to NPC, except in patients with the t(4;14) translocation and a subset of MMs. Patients in this subset, characterized by high NSD2 expression but no detectable t(4;14) translocation, have a prognosis similar to that of patients with t(4;14).



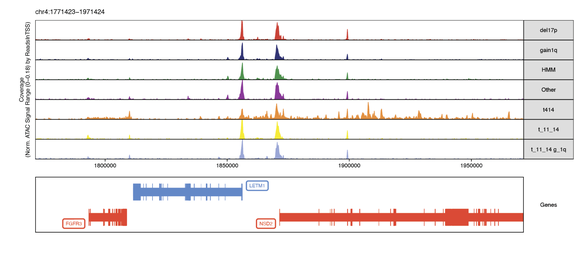
High NSD2 patients in CoMMpass had significantly higher prevalence of high-risk features eg, P53 mutations (OR=3.42 [1.58-7.43]), del17p (OR=2.69 [1.48-4.83]), and t(14;16) (OR=2.50 [1.04-5.86]) and significantly lower prevalence of hyperdiploidy (OR=0.26 [0.17-0.39]) vs. Low NSD2 patients.

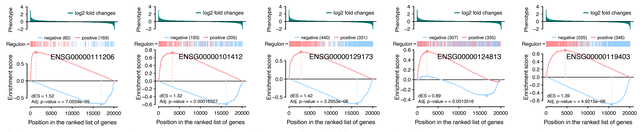


t(4;14) patients and high-NSD2 patients without t(4;14) had similar global transcriptomic profiles with each other when compared against low-NSD2 patients. Moreover, high NSD2 patients also had high expression of other H3K36 methyltransferases. We found that high NSD2 patients have increased cell cycle and replication activities, as well as decreases in OXPHOS and cytokine-receptor interactions, specifically cytokines in the CC-chemokine and CXC-chemokine families.



Single-cell ATAC sequencing from newly diagnosed MM patients identifies 3 main regulatory regions around NSD2. These regions also overlap with early, mid, and late breakpoints[4], where t(4;14) translocations are reported. While the late region overlaps with CTCF in MM cell lines, two earlier spots overlap with active promoter/enhancer signals from H3K27ac and H3K4me3. The main TF motifs identified in these two locations are E2F, MYC, HDAC2, and POLR2A.





Master regulatory analysis of differentially expressed genes between high and low NSD2 groups identified E2F, PHF19, RUNX2, and FOXM1 as key master regulators of the differentially expressed genes between high-NSD2 and low-NSD2 patients genes[3].

CONCLUSIONS

A subset of ndMM may have high expression of NSD2 independent of t(4;14) with poor clinical outcomes. The H-NSD2 group had significantly more high-risk genomic alterations with biology similar to t(4;14) group correlated with high NSD2 levels. Further ongoing analysis would elucidate the biology of high NSD2 and associated tumor genomic features and may support clinical investigation of NSD2 inhibition in the H-NSD2 MM patients.

REFERENCES

1) Chavez R, Powell DR., Lakhani K et al. Ectopic NSD2 Remodels H3K36me2 and DNA Methylation to Promote Oncogenic Gene Expression in Multiple Myeloma. Blood (2024) 144: 1359. https://doi.org/10.1182/blood-2024-210929

2) Sobh A, Encinas E, Patel A, et al. NSD2 drives t(4;14) myeloma cell dependence on adenylate kinase 2 by diverting one-carbon metabolism to the epigenome. Blood. 2024;144(3):283-295. doi:10.1182/blood.2023022859

3) Huang Z, Wu H, Chuai S, et al. NSD2 is recruited through its PHD domain to oncogenic gene loci to drive multiple myeloma. Cancer Res. 2013;73(20):6277-6288. doi:10.1158/0008-5472.CAN-13-1000

4) Stong N, Ortiz-Estévez M, Towfic F, et al. The location of the t(4;14) translocation breakpoint within the NSD2 gene identifies a subset of patients with high-risk NDMM. Blood. 2023;141(13):1574-1583. doi:10.1182/blood.2022016212

ACKNOWLEDGEMENT

CONTACT INFORMATION

If you have further questions, please contact us at:
mehmet_samur@dfci.harvard.edu and anjan.thakurta@ndorms.ox.ac.uk