Expanding the landscape: SF3B1 mutations in Lymphoid Neoplasms

K. Arora[1], S. Garg [2] , J. Grover [3], Y. Ni [4], A. Jain [4], S. Mazzoni [4], A. Singh [4]

1. Department of Internal Medicine, Cleveland Clinic Akron General, Akron, Ohio, USA
2. Anne Arundel Medical Center, Annapolis, Maryland, USA
3. Pt. BDS Institute of Health Sciences, Rohtak, Haryana, India
4. Taussig Cancer Center, Cleveland Clinic, Cleveland, Ohio, USA.

Introduction

Advancements in genetic profiling are paving the way to personalized medicine by identification of mutations across all tumor types, helping optimize therapeutic outcomes. Splicing Factor 3B subunit 1A (SF3B1), plays a significant role in preventing aberrant splicing that can lead to a distinct subtype of Myelodysplastic syndrome (MDS)[1]. While its role is partially explored in Chronic Lymphocytic Leukemia (CLL) and certain solid tumors, it remains less known in lymphoma.

Methods

We performed a retrospective analysis using publicly available datasets from Broad Institute (Nature Genetics, 2022)[2] and Diffuse Large B-Cell Lymphoma from Duke (Cell, 2017)[3], accessed via cBioPortal[4-6]**.** The analysis was limited to a single distinct sample per patient to avoid duplication. The study assessed the frequency and characteristics of SF3B1 mutations in these groups. The overall survival in the altered and unaltered groups was compared in the CLL subpopulation.

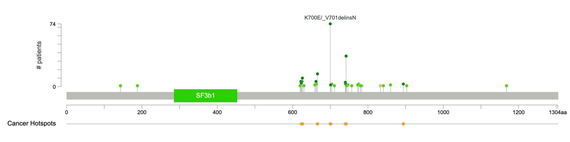


Figure 1: Lollipop plot showing mutations in CLL which are known cancer hotspots in the SF3B1 gene: Y623, N626, K666, K700, V701, G740, G742 and D894 respectively.

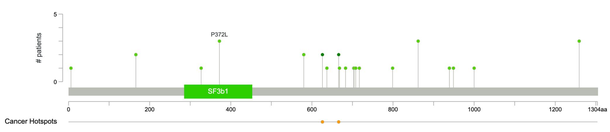


Figure 2: Lollipop plot showing mutations in DLBCL which are known cancer hotspots in the SF3B1 gene: N626S, K666E.

Results

We identified 1,142 patients with CLL and 1,001 with diffuse large B-cell lymphoma, each contributing a single sample, which were subsequently analyzed to assess the prevalence of the SF3B1 mutation. **Fifteen percent (172/1142) of CLL** samples harbored 200 somatic SF3B1 mutation with 169 driver (all missense) and 31 Variant of Uncertain Significance (VUS). In patients with **Diffuse Large B Cell Lymphoma, 2.5%** (25/1001) had 30 mutations, with 4 driver (all missense) and 26 VUS. In the CLL subpopulation, the unaltered group had better overall survival, **p=0.004**.

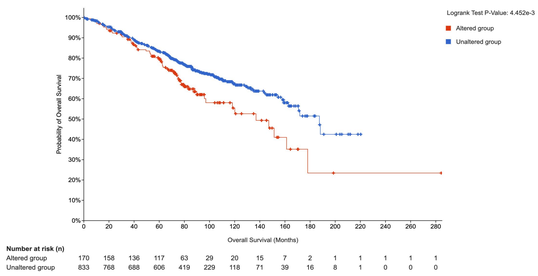


Figure 3. Kaplan–Meier curves for overall survival in the SF3B1 altered group (red, n=170) and unaltered group (blue, n=833) in CLL. The unaltered group demonstrated significantly better survival (log-rank p = 0.00445). Numbers at risk indicate patients alive and under follow-up at each time point; despite the smaller starting cohort, the altered group shows a proportionally steeper decline in survival.

Conclusion

SF3B1 mutations, while well-characterized in myeloid neoplasms, also appear in other hematologic malignancies, including chronic lymphocytic leukemia (CLL), where they may be linked to poor prognosis. Their role in non-Hodgkin lymphoma (NHL), however, remains underexplored. Our survival analysis suggests that patients with CLL and SF3B1 alterations experience proportionally worse overall survival compared with unaltered cases, underscoring their potential as an adverse prognostic biomarker, with implications for risk stratification, closer surveillance, and consideration of alternative therapeutic strategies. A key limitation of current NGS-based studies is the use of bulk mononuclear cell DNA, which obscures the myeloid vs lymphoid origin of mutations. Future research should prioritize lineage-specific analyses, such as sorted lymphocyte populations, to clarify the clinical and therapeutic relevance of SF3B1 mutations in lymphoid malignancies.

References

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