

Wahab A. Khan ^{1,2*}, Soma Roy Chakraborty³, Michelle A. Bickford ², Irma G. Domínguez Vigil ², Farzana Murad ², Jing Bao ², Devon N. Wilson², Lauren M. Wainman ², Liam L. Donnelly ^{1,2,3}, Laura J. Tafe ^{1,2}, Prabhjot Kaur ^{1,2,3}, Jeremiah X. Karrs ^{1,2,3}

1)Geisel School of Medicine, Dartmouth College, Hanover, NH 03755, USA, 2)Laboratory for Clinical Genomics and Advanced Technology (CGAT), Department of Pathology and Laboratory Medicine, Dartmouth Hitchcock Medical Center, Lebanon, NH 03756, USA, 3)Division of Hematopathology, Dartmouth Hitchcock Medical Center, Lebanon, NH USA.

External consultant: Dr. Romena Qazi, PhD, M.Phil (SKMCH)

Background & Rationale

- CLL is recurrent adult leukemia presenting with clonal CD5+ mature B cells, and a heterogeneous course [1]
- Key markers include deletion (del) chromosome 13q, trisomy 12, del(11q), del(17p)/*TP53*, IGHV status, recurrent molecular mutations
- FISH targets only 4–5 loci; karyotyping needs culture adjuvants to stimulate indolent clones
- Cryptic rearrangements and multi-hit complexity go undetected; genome-wide SV analysis is needed

Methods

- Cohort:** 50 retrospective bone marrow cases (47 CLL, 2 suspected MBL, 1 suspected MCL); 25 male/25 female; median age 63–65 years
- OGM:** Ultra-long DNA (250–300 kb) analysis of chromosomal structural variants (SV) & copy number variants (CNV) performed using Bionano Solve pipelines
- Concurrent:** FISH (13q, 11q, 17p, CEP12, IGH::*CCND1*); + hematologic malignancy NGS panel (Agilent Exome v8)
- Correlates:** IGHV status; **time to first intervention (TTFI)**

Results

41/50

cases with oncogenic-potential SVs/CNVs

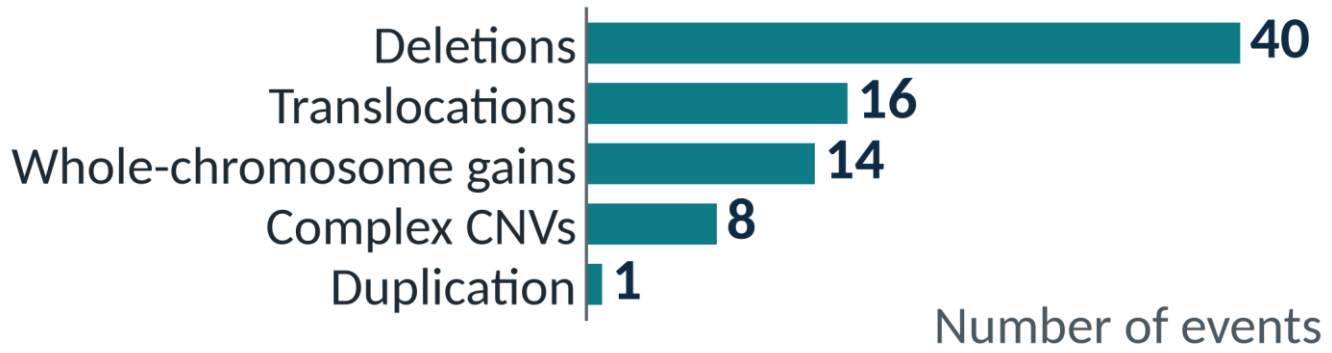
65+23

oncogenic + likely oncogenic SVs/CNVs

20%

of OGM cases with multi-hit complex SVs/CNVs

Structural variant (SV) spectrum detected by OGM



Deletion (13q) heterogeneity (most frequent abnormality)

58% without *RB1*

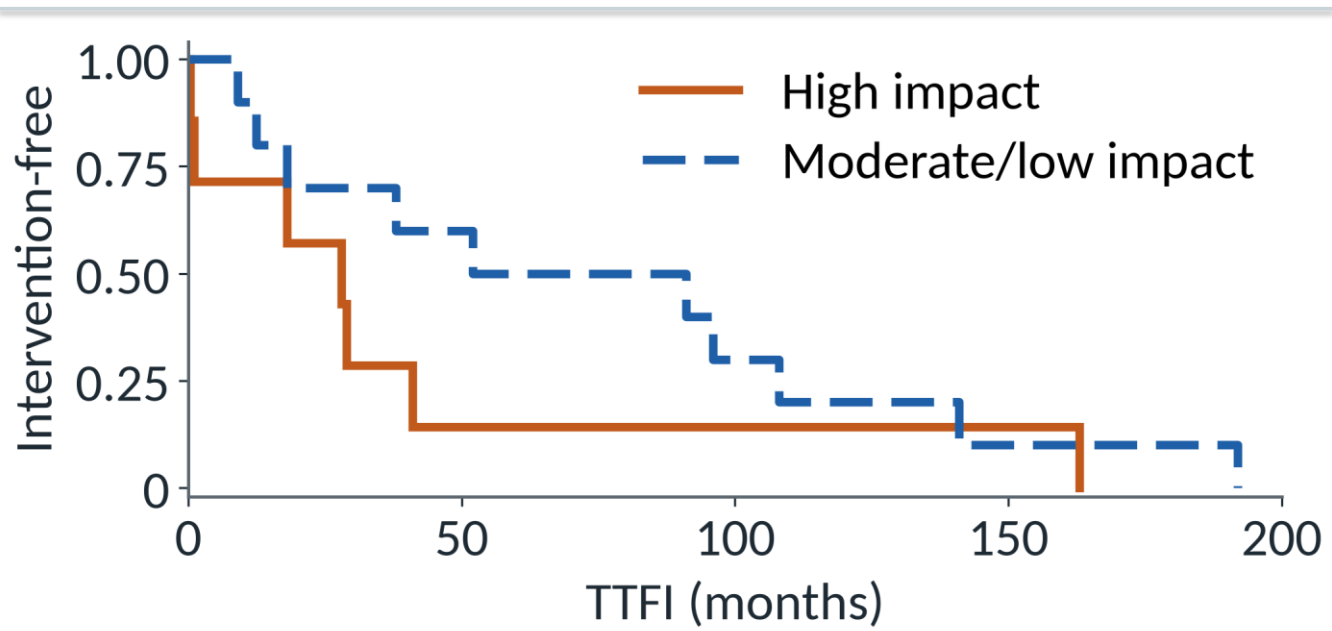
focal miR15a/miR16-1; favorable

42% *RB1*-spanning

large; often adverse

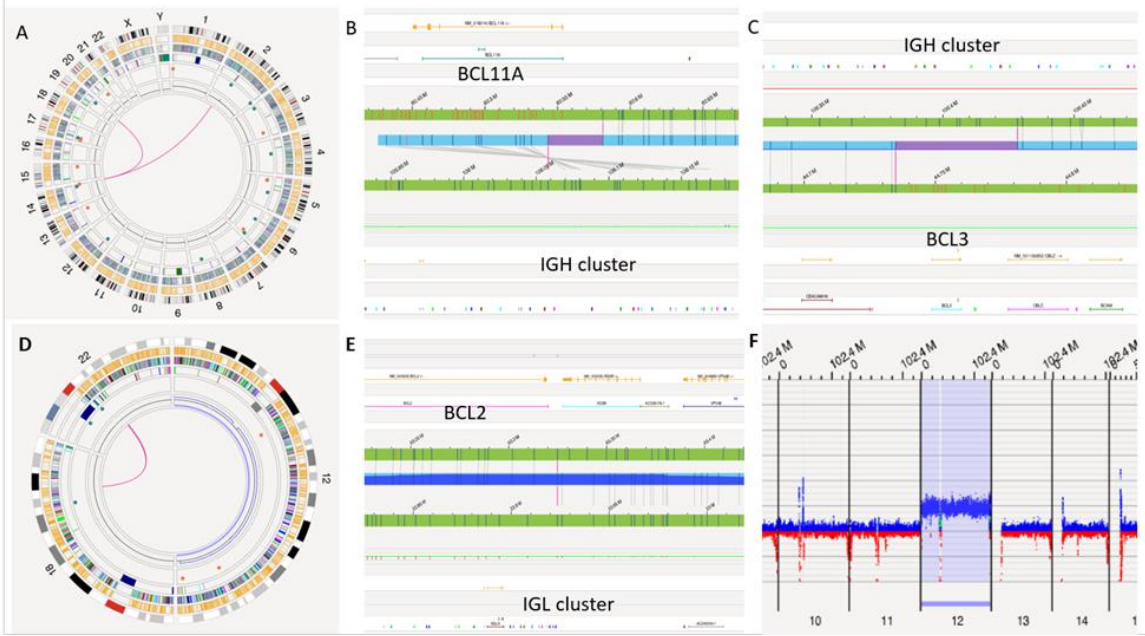
- RB1*-spanning: often with other deleterious events
- Multi-allelic 13q events (e.g., translocation + deletion): instability and shorter TTFI [2,3]

TTFI (time to first intervention) by OGM profile (17 cases)



Median TTFI 28 vs 71.5 months; U = 21.5, p ≈ 0.20
High impact: del(17p), complex CNVs, IGH translocations.
Moderate/low: focal del(13q), OGM-negative.

Cryptic rearrangements unique to OGM



- IGH::BCL2*** t(14;18) with trisomy 12: 2 cases (rare in CLL)
- IGH::BCL11A* + *IGH::BCL3***: double-IGH (1 case)
- IGL::CCND1***: 1 case re-defined as MCL
- 143 kb *ATM*-disrupting SV (*ATM::ACAT1*), unmutated IGHV, adverse [4]
- IGHV-unmutated (16/37, 43.2%): often high-impact OGM profiles

Conclusions

- OGM revealed cryptic rearrangements and multi-hit complexity covert by FISH, short read NGS, and metaphase chromosome analysis
- Lesions “isolated” by FISH were often embedded in complex CLL genomes
- High-impact OGM profiles trended toward earlier intervention
- OGM + NGS + IGHV supports more precise, individualized CLL care

Acknowledgments

We thank external Centers of Biomedical Research Excellence funding from NIGMS subaward to Dartmouth College (Center for Molecular Epidemiology) . We would like to also acknowledge support and conference visibility from Dr. Romena Qazi, PhD; external consultant in Molecular Biology

References:

[1] Marionneaux SM, et al. Lab Med. 2021;52(5):426-438; [2]Hawthorn LA, et al. Oncogene. 1993;8(6):1415-1419; [3]Xia C, et al. Genes (Basel). 2025;16(3):252; [4] Kanagal-Shamanna R, et al. Leuk Lymphoma. 2022;63(4):865-875.

Disclosures & Ethics Statement : Generative AI helped design this poster's layout and condensed text, from the authors' own slides and data. The primary author checked all content of the work presented here. This study was performed under IRB approvals; STUDY02002136 (OGM Hematolymphoid) and STUDY02003556 (quality assurance).