

Persistent mutations among serially biopsied treatment-naïve and post-relapse Waldenström macroglobulinemia

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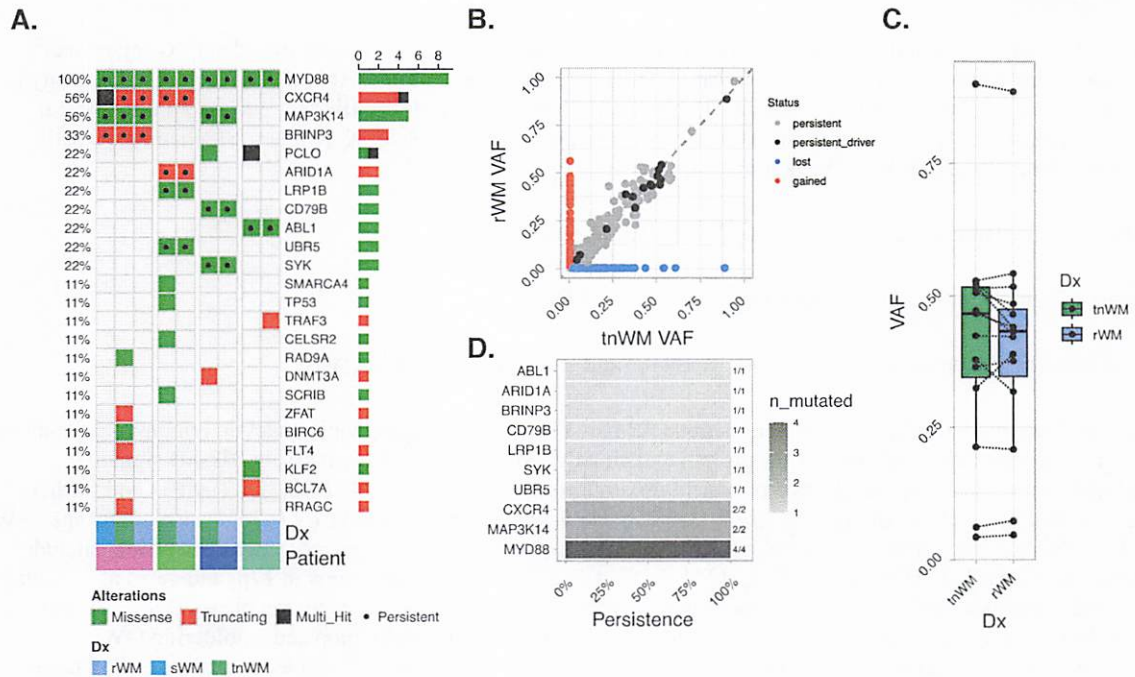
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Introduction: Waldenström macroglobulinemia (WM) is a rare indolent lymphoplasmacytic lymphoma, diagnosed by the presence of elevated serum IgM protein and clonal WM cells in the bone marrow. NF-κB signaling is a central driver of disease pathogenesis primarily driven through the mutation *MYD88*_{L265P} (~90%) and further dysregulated by deletions of 6q (*TNFAIP3*, ~25%). WHIM-like mutations in *CXCR4* (~35%) also contribute to WM biology through impairment of normal immune trafficking. Increasingly recognized genetic alterations include mutations in *ARID1A*, *MAP3K14*, *TP53*, *ATM*, *CD79A/B*, *BTK*, *KMT2D*, deletions in 17p, and gains at 3, 7, and 18. Literature provides evidence of these less frequent events in WM; however, it is not yet clear what role these alterations play in treatment resistance. Using Mayo Clinic data from serially biopsied smoldering (sWM), treatment-naïve (tnWM) and post-relapse (rWM) WM samples, we sought to characterize patterns of mutation persistence after disease recurrence and identify pro-WM mutations less frequently mutated across the disease spectrum.

Methods: Genetic data from Mayo Clinic patients with available whole-exome sequencing (WES) was collected and queried for those with serial biopsies diagnosed with tnWM and rWM, including sWM when available. Patient data was used as previously reported, abstracted from the electronic health record adhering to all IRB guidelines. WES data was processed as formerly described. In brief, bone marrow aspirate and matched peripheral-blood mononuclear cells were obtained. WM cells were enriched for using CD19+ and/or CD138+. DNA was isolated and processed on an Illumina sequencer. Reads were aligned to hg38. Somatic mutations were confirmed in a consensus fashion. Persistent mutations were defined as single-nucleotide variants or short indels observed in both pre-treatment and post-relapse biopsies from the same patient, requiring identical allele-position change. Two one-sided test with a +/-10% margin was used to assess equivalence.

Results: In total, WES profiles from four WM patients with serial collections, comprising nine observations [sWM (n=1) tnWM (n=4) and rWM (n=4)] were available for analysis. We noted persistent mutations in previously reported lymphoma driver genes *MYD88* (n=4/4), *CXCR4* (n=2/2), *MAP3K14* (n=2/2), *ARID1A* (n=1/1), *CD79B* (n=1/1), *UBR5* (n=1/1), *ABL1* (n=1/1), *SYK* (n=1/1), and *BRINP3* (n=1/1). For one patient whom all three timepoints available, a core set of driver mutations endured all stages of disease (*MYD88*, *CXCR4*, *MAP3K14*, *BRINP3*). All profiles displayed persistent driver mutations beyond *MYD88* and *CXCR4*. Among all persistent driver mutations, variant allele frequency (VAF) was statistically equivalent between tnWM and rWM (median fold-change=0.99; 90%CI=[0.94,1.04]) compared against the margin (p=0.005).

Conclusion: We observed driver mutations present prior to treatment that remained detectable at relapse with equivalent VAF, indicating driver architecture of WM is retained through disease stages. These patterns harbored mutations involved in NF-κB and BCR signaling (*MYD88*, *CXCR4*, *MAP3K14*, *CD79B*, *SYK*), chromatin remodeling (*ARID1A*), and genomic stability (*UBR5*, *ABL1*) which persisted after treatment and disease progression. In one patient with sWM this architecture was already established at precursor stage. The identification of recurrent mutations at diagnosis using WES supports evaluation of broad clinical sequencing approaches, as the diversity of pro-WM mutations extends beyond *MYD88* and *CXCR4*.



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