

Germline Variant rs116446171 Drives Malignant B cell Fate and Immune Exhaustion In Waldenström Macroglobulinemia

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Background: Waldenström macroglobulinemia (WM) is an indolent lymphoplasmacytic lymphoma that frequently evolves from IgM MGUS, yet the mechanisms driving disease progression remain poorly understood. Recent multi-omic studies have identified memory B-cell (MBC)-like and plasma cell (PC)-like differentiation states associated with distinct clinical phenotypes, but the determinants of these states remain unknown. Germline variants at 6p25.3 (rs116446171) and 14q32.13 (rs117410836) represent the strongest inherited susceptibility loci for WM, although their biological consequences are undefined. We integrated germline genetics with genomic, epigenetic, single-cell transcriptomic, and immune profiling to determine how inherited variation shapes malignant cell identity and disease evolution.

Methods: Multi-omic profiling was performed in patients with newly diagnosed IgM MGUS and WM. FACS-sorted bone marrow (BM) malignant B cells underwent targeted sequencing of the two germline risk loci and 18 recurrently mutated genes (IgM MGUS n=47; WM n=41), together with genome-wide DNA methylation profiling (IgM MGUS n=9; WM n=22). Matched CD3⁺ T cells were sequenced to confirm the somatic origin of mutations. Paired scRNA/BCR/TCR-seq was performed on unfractionated BM cells (IgM MGUS n=10; WM n=14), with multiplex cytokine profiling of BM supernatant from rs116446171-positive (n=7) and wild-type (WT; n=16) WM.

Results: rs116446171 was detected in 38% of WM compared with 19% of IgM MGUS, whereas rs117410836 was uncommon (~7%). rs116446171 carriers presented at a younger age (p=0.003), more frequently had a family history of hematologic malignancy (p=0.003), and exhibited higher serum IgM (p=0.002), M-protein (p=0.013), and serum viscosity (p=0.009). Malignant PC-like (CD138^{hi}CD27⁻) and MBC-like (CD138⁻CD27^{hi}) populations shared highly concordant somatic mutations, supporting a common clonal origin. However, *CXCR4* mutations were preferentially enriched in the MBC-like compartment, suggesting phenotypic plasticity across malignant states. Notably, rs116446171-positive tumors were enriched for an MBC-like state, whereas WT tumors showed greater PC-like differentiation. The variant also frequently co-occurred with *IRF4* (p=0.025), *KMT2D* (p=0.023), and *TP53* (p=0.043) alterations.

Genome-wide methylation profiling identified a B-cell-restricted epigenetic program in rs116446171-positive tumors characterized by widespread hypermethylation, repression of PC differentiation genes including *IRF4* ($p=0.02$), and preservation of MBC regulators such as *BACH2* ($p<0.01$).

Single-cell analysis confirmed expansion of MBC-like cells with contraction of PC-like populations in rs116446171-positive tumors ($FDR=0.001$). Trajectory analysis further demonstrated preferential occupancy of terminal MBC-like states in variant-positive tumors, whereas WT tumors progressed toward PC-like states. This differentiation bias was accompanied by suppression of antigen presentation and immune-response pathways in variant-positive malignant cells ($FC>2$, $FDR<0.05$). Immune profiling revealed expansion of exhausted $CD8^+$ cytotoxic T cells (CTL exh; $FDR=0.001$) in rs116446171-positive tumors, whereas WT tumors were enriched for $CD4^+$ T effector memory, central memory, naïve and T follicular helper populations (all $FDR=0.001$). TCR-seq identified $CD8^+$ CTL exh cells as the only expanded clonotype in rs116446171-positive tumors. These clones were enriched for immune regulatory (*CCR5*, *CCL4*) and antigen presentation (*HLA-DRB5*, *HLA-DQA1*) genes, with increased *KDM5D* expression ($FC>2$, $FDR<0.05$), defining a distinct immune state. CellChat demonstrated stronger interactions between malignant cells and $CD8^+$ CTL exh cells ($p=0.002$), characterized by increased MHCI-CD8 signaling, reduced MHCII-CD4 interactions, and selective activation of the inhibitory CD70-CD27 axis. BM supernatant from rs116446171 carriers also contained higher levels of immunosuppressive cytokines, including IL-8, IL-5, and IL-2.

Conclusion: Germline rs116446171 establishes a mechanistic link between inherited susceptibility, malignant B-cell differentiation and immune dysfunction in WM. The variant promotes an MBC-like epigenetic and transcriptional program, impairs PC differentiation, and fosters an exhausted immune microenvironment associated with clinically aggressive WM. These findings identify rs116446171 as a candidate biomarker for molecular risk stratification and a potential target for early therapeutic intervention.

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