Mutational Landscape of WM revealed through Whole Genome Sequencing

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Background: Waldenstrom's Macroglobulinemia (WM) is an IgM secreting lymphoplasmacytic lymphoma. The genetic basis for this disease remains to be clarified.

Methods: We performed whole genome sequencing (WGS) using $CD19^+$ selected bone marrow lymphoplasmacytic cells (LPC) from 30 WM patients. For 10 of these patients, paired $CD19^+$ depleted peripheral blood samples were used for WGS as normal controls.

Results: The most common somatic variants identified and validated by Sanger sequencing included MYD88 L265P, an activating mutation for IRAK/TRAF6/NFKB and MAPK signaling, which was observed in 27/30 (90%) patients; the C-terminal domain of CXCR4, which included mutations associated with WHIM syndrome and confer constitutive CXCR4 signaling resulting from dysfunctional receptor endocytosis, a finding observed in 8/30 (27%) patients, and ARID1A (5/30; 17%), a tumor suppressor gene. Less common somatic variants were also identified in MUC16 (4/30; 13%), TRAF2 (3/30; 10%), TRRAP (3/30; 10%) and MYBBP1A (2/30; 7%).

Conclusions: Using WGS and confirmatory Sanger sequencing, we have identified several somatic variants with oncogenic function, the most common of which include MYD88 L265P, the C-terminal domain of CXCR4, and ARID1A.