The genomic landscape of Waldenström's Macroglobulinemia defined by whole genome sequencing.

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We employed whole genome sequencing (WGS) utilizing tumor derived DNA from 30 patients, which included paired germline/tumor sequencing for 10 patients. Genes observed affected by validated somatic mutations included *MYD88*, *CXCR4*, *ARID1A*, CD79B, TP53, MLL2, and MYBBP1A. We further validated CXCR4 and MYD88 in 175 WM patients revealing a mutation rate for MYD88 and CXCR4 of 90% and 29% respectively and observed statistically significant differences in clinical presentation and overall survival based on these genotypes. Some of these clinical differences were also noted between patients with frame-shift vs. nonsense c-terminal tail mutations in CXCR4. WGS also delineated somatic copy number alterations (CNA) and structural variants in the 10 paired WGS patients. CNA findings were validated in independent expansion cohorts of 30 WM patients. Validated gene losses due to CNAs involved *PRDM2* (93%), *BTG1* (87%), *HIVEP2* (77%), *MKLN1 (77%), PLEKHG1* (70%), *LYN* (60%), *ARID1B* (50%), and *FOXP1* (37%). Losses in *PLEKHG1, HIVEP2, ARID1B,* and *BCLAF1* constituted the most common deletions within chromosome 6. Moreover, CNVs and acquired uniparental disomies were found opposite the aforementioned somatic genic mutations 11 times in our 30 patient WGS cohort making them effectively homozygous. While no recurrent translocations were observed, in 2 patients deletions in 6q corresponded with translocation events. These studies evidence highly recurring somatic events, and provide a genomic basis for understanding the pathogenesis of WM.