



The 65th ASH Annual Meeting Abstracts

POSTER ABSTRACTS

654.MGUS, AMYLOIDOSIS AND OTHER NON-MYELOMA PLASMA CELL DYSCRASIAS: CLINICAL AND EPIDEMIOLOGICAL**Mutational Landscape of Bone Marrow CD19 and CD138 Cells in Waldenström Macroglobulinemia (WM) and IgM Monoclonal Gammopathy of Undetermined Significance (IgM MGUS)**

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Background

Waldenström's Macroglobulinemia (WM) is an incurable B-cell neoplasm characterized by serum monoclonal immunoglobulin M (IgM) and clonal lymphoplasmacytic cells infiltrating the bone marrow (BM). Smoldering WM (sWM) is the asymptomatic/indolent form with a high risk of progressing to symptomatic WM requiring treatment whereas IgM monoclonal gammopathy of undetermined significance (IgM MGUS) is an early precursor stage of WM. Despite recurrent and activating mutations, including *MYD88*, *CXCR4*, *ARID1A*, *KMT2D*, and *CD79B* have been identified, the genetic basis for WM and the risk of progression of IgM MGUS to WM remain to be fully elucidated.

Methods

Based on the mutational profiling of WM and our previous wide transcriptome analyses on BM CD19+ and CD138+ cells of patients with WM and IgM MGUS, we decided to investigate the mutation status of these patients as follows: WM (n=10), sWM (n=7), and IgM MGUS (n=5), by performing high throughput targeted AmpliSeq next generation sequencing on 117 target genes potentially involved in B-cell lymphomagenesis and in the risk of progression of IgM MGUS to WM (Trojani A. et al. *Cancers*, 2021).

Results

We identified genetic aberrations in multiple genes, including previously described classic mutations in *MYD88* (L260P alias L265P) found in 82.3% (14/17) of WM/sWM patients and in 60% (3/5) of IgM MGUS subjects. The *CXCR4* mutation (S338Ter) was detected in 23.5% of CD19+ cells of WM patients, whereas it was absent in IgM MGUS subjects.

Interestingly, we also identified new mutated genes, including *WNK2* somatic mutations affecting 47% of WM patients, for which a recurrent allelic variant (V1635Ter) was observed, and *BCL9* with a recurrent frameshift variant (P516Lfs) identified in 29.4% of WM patients exclusively in the CD19 cell fraction. The *BCL9* (P516Lfs) variant was also detected in the B cells of one IgM MGUS patient.

Moreover, sequencing evaluation revealed recurrently frameshift or missense mutations involving *NFKB2* (L473Afs), *PTPN13* (P1546Tfs), *CARD11* (S622del), *KMT2C* (I823T), and *ATM* in WM and IgM MGUS patients (Figure 1). Of interest, *KMT2C* (also known as *MLL3*) exhibited a somatic hypermutated phenotype in both CD19+ and CD138+ cells of WM and IgM MGUS samples. The *KMT2C* mutations were not mutually exclusive with those involving *KMT2D* in our cohort of patients.

Conclusion

The present genomic analysis revealed new insights into the mutational landscape of Waldenström Macroglobulinemia, providing evidence of the recurrence of some variants in subjects with IgM MGUS as well. Notably, we uncovered new genetic mutations with somatic variants recurrently observed ($n \geq 3$) in *KMT2C*, *WNK2*, *BCL9*, *PTPN13*, *CARD11* and *NFKB2* genes. These recurring somatic events provide a genomic basis for future research and a better understanding of the WM pathogenesis as well as the risk of transformation of IgM MGUS to WM.

Disclosures No relevant conflicts of interest to declare.

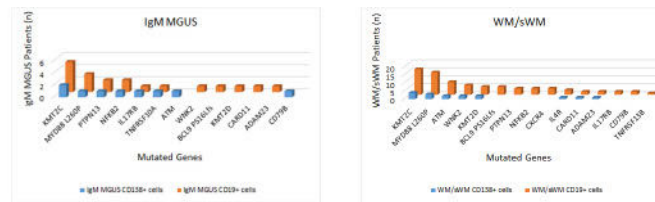


Figure 1 Mutational landscape of IgM MGUS (left) and WM/sWM (right) patients analyzed by high-throughput targeted sequencing on CD19+ (orange) and CD138+ (blue) cells.

Figure 1

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