What is the genomic landscape of CXCR4 mutations in WM?

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Introduction: Whole-genome sequencing has revealed *MYD88* L265P and *CXCR4* mutations (*CXCR4^{mut}*) as the most prevalent somatic mutations in Waldenstrom's macroglobulinemia (WM). CXCR4 is a G-protein-coupled receptor that promotes migration and activation of several pathways including RAS, Akt and NFKB. *CXCR4* mutation has proved to be of critical importance in WM, in part due to its role as a mechanism of resistance to several agents. We have therefore sought to unravel the different aspects of *CXCR4* mutations in WM.

Experimental Design. Bone marrow samples of 98 patients with WM were analyzed. Tumoral DNA was extracted following CD19 B cell selection. We have scanned the 2 coding exons of *CXCR4* in WM using deep next generation sequencing and sanger sequencing, and correlated with SNP array landscape. Mutational spectrum of 8 candidate genes involved in Toll Like Receptor, RAS and B Cell Receptor (BCR) pathway along with *MYD88L265P, CD79A* (ITAM domain)*, CD79B*(ITAM domain)*, CARD11* (exon 5-9)*, N RAS* (exon 2-3)*, K RAS* (exons 2-3)*, BRAF6* (exon 15)*, PTEN*(exon 5-7)*,* was also analysed in an integrative study.

Results. We found all mutations to be heterozygous, somatic and located in the C-terminal domain of CXCR4 in 25% of the WM. Sub clonal *CXCR4* mutations identified using NGS were identified in 4/14 cases. Among the 17 variants, 12 new variants were identified in WM. The most frequent mutation was the *CXCR4 C1013G (S338X)* mutation (5/98*)* followed by *CXCR4C1013A (S338X)* (3/98). *CXCR4* mutations led to a truncated receptor protein associated with a higher expression of CXCR4. *CXCR4* mutations pertain to the same clone as to *MYD88* L265P mutations, but were mutually exclusive to *CD79A / CD79B* mutations (BCR pathway). We identified a genomic signature in *CXCR4^{mut}* WM traducing a more complex genome. *CXCR4* mutations were also associated with gain of chromosome 4, gain of Xq and deletion 6q.

Conclusions. Our study panned out new *CXCR4* mutations in WM, and identified a specific signature associated to *CXCR4^{mut}*, characterized with complex genomic aberrations among MYD88L265P WM. Our results suggest the existence of various genomic subgroups in WM.