Large-Scale Genome-Wide Association Study Illuminates Disease Aetiology for Waldenström Macroglobulinemia and Lymphoplasmacytic Lymphoma

Family history is a strong risk factor for Waldenström macroglobulinemia (WM)/ lymphoplasmacytic lymphoma (LPL). We previously identified two rare variants at 6p25.3 and 14q32.13 that were significantly associated with an increased risk of WM/LPL. However, the genetic basis for WM/LPL predisposition remains largely unknown. Here, we discuss new findings from the largest genome-wide association study (GWAS) of WM/LPL, including 1,707 cases and 58,328 controls with replication in four independent cohorts (570 cases and 771,770 controls). A total of twelve germline genetic variants were discovered to be associated with WM/LPL risk and replicated ($P< 5 \times 10^{-8}$). Interestingly, four of the discovered variants showed strong associations with WM/LPL risk with odds ratios greater than 10. Enrichment was observed for regulatory elements in CD19+ B-cells, and gene-based and colocalization analyses identified several potential biological pathways, including B-cell development and immune function. These findings provide deeper insight into disease aetiology and may be useful in identifying individuals at higher risk and suggesting new drug targets for treatment.