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Genomic predisposition to Waldenström macroglobulinemia

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Family history of Waldenström macroglobulinemia (WM), lymphoplasmacytic lymphoma (LPL), or related lymphoproliferative disorder is strongly associated with WM/LPL risk, and the estimated heritability is high; however, the genetic basis for WM predisposition remains unknown. Germline mutations in the somatic driver mutation, *MYD88* p.L265P, have not been observed, indicating that *MYD88* is unlikely to function as a WM predisposition gene. Early promising findings by linkage analysis suggested rare deleterious gene variants might contribute to WM susceptibility. Following extensive investigations in WM families using whole exome sequencing, however, no single gene mutations accounting for WM susceptibility in multiple WM families have been conclusively reported to date. Given these results, a polygenic model underlying WM predisposition provides one alternative hypothesis to explain WM heritability. To discover genetic loci for WM/LPL susceptibility, we performed a two-stage genome-wide association study (GWAS) of WM/LPL in over 500 WM/LPL cases and 4300 controls of European ancestry, leveraging a family-based oversampling approach in the discovery followed by replication in an independent, predominantly nonfamilial, cohort. In the discovery stage, we genotyped 217 unrelated WM cases (40% familial) and 3,798 controls. Following quality control filtering, the data were imputed using the Haplotype Reference Consortium panel and analyzed using logistic regression. Eleven promising loci ($P<5.0 \times 10^{-7}$) were selected for replication in a cohort of 313 WM/LPL cases (~8% familial) and 564 controls. Two novel loci were convincingly replicated in stage 2 and reached genome-wide significance in the combined analysis of both stages: 6p25.3 (rs116446171, near *EXOC2* and *IRF4*; OR=21.14, 95% CI: 14.40-31.03, $P=1.36 \times 10^{-54}$) and 14q32.13 (rs117410836, near *TCL1*; OR=4.90, 95% CI: 3.45-6.96, $P=8.75 \times 10^{-19}$). Both risk alleles are observed at a low frequency among controls and occur in excess in affected cases within families. *In silico* data suggest that rs116446171 may have functional importance, and in functional studies we demonstrated increased reporter transcription and proliferation in cells transduced with the 6p25.3 risk allele. Although further studies are needed to fully elucidate underlying biological mechanisms, together these loci explain 4% of the familial risk and provide insights into genetic susceptibility to this malignancy in the general population.