Family studies in Waldenström macroglobulinemia

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The U.S. National Cancer Institute (NCI) began accruing Waldenström macroglobulinemia (WM) families in 1976. In 2000, we intensified our accrual efforts and established a Familial WM Registry. We have since conducted a series of clinical, epidemiological and genetic studies in families characterized by at least two members with WM or one case of WM accompanied by at least one case of a related B-cell disorder. Efforts have focused on 1) refining the clinical and laboratory phenotype associated with familial WM; 2) understanding the genetic and environmental determinants that predispose to WM in families; and 3) risk prediction. Using whole-genome linkage analysis, we identified potential susceptibility loci on chromosomes 1 and 4. Using a family-based candidate gene association approach, we identified SNPs in several genes that were associated with development of WM. These results suggest genetic heterogeneity underlying WM susceptibility. The advent of whole-genome and whole-exome sequencing technology has permitted intensive study to follow-up earlier linkage and association analyses geared toward identifying WM susceptibility genes. In addition, genome-wide association studies (GWAS) provide opportunities to investigate common genes with small effect size. Our group has also conducted population-based registry studies to both confirm and extend the findings from our family studies. Our familial WM registry now contains nearly 150 multiple-case families from the U.S. and Canada, and improvements in technology have opened the Registry to international participation; it therefore represents a rich resource for genetic and other studies. This presentation will outline recent findings from our familial and population-based studies in WM.