Familial predisposition to Waldenström macroglobulinemia (WM): studies of WM susceptibility in high-risk families

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Understanding familial predisposition for Waldenström macroglobulinemia (WM) is desirable to i) improve understanding of pathogenetic pathways; ii) estimate risk; and iii) develop screening and prevention strategies. Cancer predisposition, or susceptibility, may be due to either genetic and/or environmental factors. In addition, monoclonal gammopathy of undetermined significance (MGUS) has been long recognized as a precursor disorder for multiple myeloma. There is growing evidence that WM may also have an associated precursor disorder, IgM MGUS. We are interested in understanding the role of IgM MGUS as a marker for susceptibility to WM and as a precursor disorder that may progress to WM. We have studied familial WM based on families that have at least 2 members with WM or a related B-cell disorder and thus may be enriched for predisposing factor(s) to WM. We have studied these families from three perspectives. 1) Genetic. We used DNA from a subset of 11 WM families to perform whole-genome linkage analysis. Linkage analysis suggests that at least four different chromosomal regions (on chromosomes 1, 3, 4 and 6) may contribute to WM susceptibility. We also used DNA from 71 familial WM patients and 107 unrelated individuals to perform candidate gene association studies. These association studies also revealed several genes that may contribute small effects toward WM susceptibility. These results were suggestive, and confirmatory studies are ongoing. 2) Personal Medical History and Environment. We used a self-administered questionnaire to gather information about medical conditions and environmental exposures of interest from all study participants. We compared 103 patients with WM to 242 of their unaffected

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relatives, adjusting for age, sex and familial clustering (that is, taking into account that members of a single family are likely to share certain features). Certain medical conditions (e.g., a personal history of an autoimmune disorder) and environmental exposures (e.g., pesticides) are significantly associated with risk of developing WM. 3) Precursor disorders. In preliminary cross-sectional studies of first-degree relatives of WM patients from 27 families, relatives of WM patients expressed a variety of immunoglobulin (Ig) patterns. IgM MGUS occurred most frequently (n=20, 14.3%), but other Ig patterns, including small-volume IgM MGUS (n=12, 8.6%), polyclonal Ig elevations (n=13, 9.3%), and hypo Ig (n=8, 5.7%) were also seen. In some families, no unusual Ig patterns were found. Our longitudinal studies demonstrated that some of these patterns, notably IgM MGUS and IgM polyclonal gammopathy, can evolve to WM or non-Hodgkin lymphoma in some patients. Based on these data, we propose that disordered immune regulation, manifest as a variety of immune abnormalities, may represent a generalized precursor, or susceptible, state. IgM MGUS may arise as either a primary manifestation of this susceptibility or in response to the influence of additional genetic and/or environmental factors, and may in turn predict progression to WM. Large collaborative studies are needed to confirm and extend these findings.