# Familial Waldenström Macroglobulinemia

## Families Informing Populations

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**KEYWORDS**

• Waldenström macroglobulinemia • Family studies • Cancer predisposition
• Environmental factors • Genetic susceptibility

**KEY POINTS**

- Family studies in Waldenström macroglobulinemia (WM) have provided the seminal observations leading to many aspects of the current understanding of WM susceptibility.
- The clinical phenotype of familial WM is broad; WM and lymphoplasmacytic lymphoma (LPL) coaggregate with other B-cell lymphoproliferative malignancies, immunoglobulin abnormalities, in vitro lymphocyte functional abnormalities, and autoimmune conditions.
- Immunoglobulin M (IgM) abnormalities are common within WM families and merit further evaluation, because they may eventually provide a basis for screening and prevention.
- A family history of WM/LPL has prognostic implications for WM patients.
- Family studies have provided evidence supporting not only genetic but also environmental factors contributing to WM predisposition; accumulating evidence supports the hypothesis that WM predisposition is complex and may reflect substantial genetic heterogeneity, an as-yet unrecognized common environmental exposure, and/or gene-environment interactions.

### INTRODUCTION

Family studies are uniquely positioned to answer specific questions related to the cause and manifestations of Waldenström macroglobulinemia (WM) and have also frequently provided the initial observations that lead to definitive large-scale population studies with broadly applicable results. As such, family studies have occupied a

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pivotal role in WM research. The familial occurrence of WM in 2 brothers was first reported more than 50 years ago.[1] Familial clusters have subsequently been the subject of dedicated case reports[2–8] or embedded within larger family studies.[9–13] **Table 1** summarizes the most important studies of families published to date, some including extensive literature surveys.[14]

## THE FAMILIAL WALDENSTRÖM MACROGLOBULINEMIA PHENOTYPE

Family studies first suggested that predisposition to WM encompasses a broader clinical phenotype than the occurrence of WM alone. The realization that the familial WM phenotype is complex was a critical observation, because characterizing the clinical phenotype may aid investigations of predisposition mechanisms by more precisely identifying at-risk individuals. Furthermore, from a clinical standpoint, familiality may have implications for screening, diagnosis, surveillance, and outcomes. Likewise, identification of modifiable environmental risk factors would be particularly useful for prevention strategies. Until better treatments and/or prevention strategies are developed for WM, identification of genetic factors mediating susceptibility may have limited practical clinical utility. Meanwhile, however, family studies also provide opportunities to study the natural history and pathophysiology of these disorders, which is also of value for nonfamilial cases.

### *Waldenström Macroglobulinemia Coaggregates with Related B-Cell Disorders*

Family studies provided the initial suggestion that predisposition to WM includes susceptibility to related B-cell diseases, observing that WM sometimes clusters with other B-cell lymphoproliferative disorders (LPD), including chronic lymphocytic leukemia (CLL), other subtypes of non-Hodgkin lymphoma (NHL), and possibly multiple myeloma (MM), as well as with monoclonal gammopathy of undetermined significance (MGUS).[15–18] Ascertainment strategy and definitions critically influenced these studies' design and results.

Building on clues provided by families, population-based studies evaluated coaggregation of WM with other B-cell LPD. Because WM is a subset of lymphoplasmacytic lymphoma (LPL), population studies typically include both in order to increase power and to account for possible misclassification. These investigations confirmed that first-degree relatives of WM/LPL patients also have significantly increased risk of developing other B-cell malignancies, including CLL and NHL, but not HL or MM.[19,20] As illustrated in **Table 2**, the data supporting coaggregation are remarkably similar irrespective of the proband's diagnosis. Increased risk was also observed for MGUS, but immunoglobulin isotype data were unavailable. In contrast, other Scandinavian studies identified families containing both immunoglobulin G (IgG)/IgA and IgM disorders,[21,22] or increased risk of MM in certain inheritance patterns,[23] although the ascertainment scheme may have accounted for some of these results.

Conventional case-control studies have provided additional evidence supporting coaggregation of WM and other hematolymphoid diseases, including an international study that found a 64% increased risk for developing WM/LPL in individuals with a first-degree relative diagnosed with a hematologic malignancy.[24] Moreover, WM patients in a large single-center series reported a high prevalence (18.7%) of either WM or another B-cell disorder in first-degree relatives.[25] Taken together, WM definitely coaggregates with B-cell lymphoid disorders, whereas coaggregation of IgG/IgA and IgM disorders in the same family may occur. The relationship of MM to familial WM remains to be clarified. These data apply to predominantly white, northern European populations. Similar studies have not yet been conducted in other demographic groups.