Familial predisposition to monoclonal gammopathy of unknown significance, Waldenström’s macroglobulinaemia and multiple myeloma.

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The medical literature contains reports of around 130 families with two or more cases of MM, MGUS or WM. The co-occurrence of IgM and IgG/IgA disorders in the same family has been noted in some families. Compared with MM families, those with WM are more likely to show involvement of several family members and have cases in different generations. Anticipation has been noted. An Icelandic family with multiple cases of MGUS, WM and lymphoma in the same sibship was first described in 1978. Subsequently, one case of MM occurred in the next generation (1983) and two further cases of MGUS have been detected (in 1990 and 2006). In vivo testing of peripheral blood lymphocytes from 35 family members revealed increased production of IgG, IgA and IgM in response to PWM in ten subjects. These family members were referred to as hyper-responders (HR). Some of them had previously been found to have raised seIgM, a feature also reported for other WM families. Further studies revealed enhanced B-cell survival after mitogen stimulation which was found to be associated with prolonged expression of Bcl-2. A population-based cancer-registry study of 218 MM patients identified eight families with two cases of MM and/or MGUS and >1 additional case of a haematological malignancy. Comparison with the Icelandic Cancer Registry revealed 22 further cases of lymphoproliferative disorders in these families and 9 new cases of monoclonal gammopathy were detected by screening 350 family members. Further testing of selected clusters has confirmed previously identified HR in the originally described family as well as detecting new cases. Only two HR were found in the other families but testing is still in progress. The study of the natural history of diseases, including hereditary predisposition, is particularly important when trying to understand the pathogenesis of rare disorders. Such studies have already provided good support for the notion that MM and WM are in the majority of cases preceded by MGUS. It can be expected that further studies will help to identify the genetic background(s) and biology predisposing to the emergence of a single, persistent clone of immunoglobulin-producing cells.