Exome sequencing reveals recurrent germline variants in patients with familial Waldenström macroglobulinemia.

Roccaro AM, Sacco A, Shi J, Chiarini M, Perilla-Glen A, Manier S, Glavey S, Aljawai Y, Mishima Y, Kawano Y, Moschetta M, Correll M, Improgo MR, Brown JR, Imberti L, Rossi G, Castillo JJ, Treon SP, Freedman ML, Van Allen EM, Hide W, Hiller E, Rainville I, Ghobrial IM

Familial aggregation of Waldenström macroglobulinemia (WM) cases, and the clustering of B-cell lymphoproliferative disorders among first-degree relatives of WM patients, has been reported. Nevertheless, the possible contribution of inherited susceptibility to familial WM remains unrevealed. We performed whole exome sequencing on germ line DNA obtained from 4 family members in which coinheritance for WM was documented in 3 of them, and screened additional independent 246 cases by using gene-specific mutation sequencing. Among the shared germ line variants, LAPTM5(c403t) and HCLS1(g496a) were the most recurrent, being present in 3/3 affected members of the index family, detected in 8% of the unrelated familial cases, and present in 0.5% of the nonfamilial cases and in <0.05 of a control population. LAPTM5 and HCLS1 appeared as relevant WM candidate genes that characterized familial WM individuals and were also functionally relevant to the tumor clone. These findings highlight potentially novel contributors for the genetic predisposition to familial WM and indicate that LAPTM5(c403t) and HCLS1(g496a) may represent predisposition alleles in patients with familial WM.