

An updated review of immunoglobulin heavy and light chain gene analysis in Waldenström Macroglobulinaemia

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Background

In 2016, we previously performed immunoglobulin heavy chain gene (IGHV) analysis in a cohort of 34 Waldenström Macroglobulinaemia (WM) patients and combined this with 5 of the largest published datasets at the time. We have now extended our cohort and incorporated immunoglobulin light chain gene (IGLV) analysis to investigate immunogenetic features and clinical associations in WM patients.

Methods

We performed a retrospective analysis of 77 WM patients, diagnosed according to IWWM & BSH guidelines, to investigate the IGHV gene and the corresponding IGLV gene. Sanger sequencing was performed on complementary DNA or genomic DNA samples extracted from bone marrow aspirates or in one case peripheral blood. Statistical analysis was performed in IBM SPSS Statistics (v31).

Results

We were able to obtain 77 productive IGHV sequences and at present 43 productive IGLV sequences with 35/77 patients having a corresponding productive IGHV and IGLV for the same time point. The kappa light chain was utilised by 79% of patients. Genes of the IGHV3 subtype and IGKV1 subtype are the most frequently utilised in 70% and 37% of rearrangements respectively and no statistically significant association was demonstrated between IGHV and IGLV gene subtypes ($p=0.094$). Analysis of paired IGHV and IGLV gene usage demonstrated substantial repertoire diversity, with all 35 evaluable IGHV/IGLV combinations being unique.

IGHV and IGLV germline identity percentages were positively correlated (Spearman's $\rho=0.554$; $p<0.001$), indicating that patients with highly mutated IGHV genes also possess highly mutated IGLV genes (figure 1). However, paired analysis demonstrated significantly lower germline identity in the heavy chain compared to the light chain (median 93.54% vs 96.49%; $p<0.001$), indicating a greater degree of somatic hypermutation (SHM) within the IGHV repertoire. This finding was independently observed in both kappa-chain cohorts ($p<0.001$) and lambda-chain cohorts ($p=0.028$). No significant differences in time to first treatment (TTFT) ($p=0.725$) or overall survival (OS) ($p=0.121$) were observed between kappa- and lambda-chain expressing patients.

Within the IGHV cohort, IGHV3-23 was the most utilised gene ($n=15$). Patients expressing IGHV3-23 exhibited significantly lower IGHV germline identity compared with patients using other IGHV3 genes (median 91.58% vs 93.30%; $p<0.001$) and all other IGHV genes (median 93.40%, $p<0.001$), consistent with a greater degree of somatic hypermutation within the IGHV3-23 subgroup. The previously noted association with IGHV3-23 and TTFT is no longer upheld in the current dataset. No significant differences in TTFT or OS was observed in relation to combined IGHV/MYD88 status.

A significant association was observed between IGHV and *MYD88*^{L265P} mutation status ($p=0.002$). All IGHV-unmutated ($>98\%$ identity) cases were *MYD88* wild-type ($n=3$), while 90.1% (64/71) of IGHV-mutated ($\leq 97\%$ identity) cases carried a *MYD88*^{L265P} mutation.

Conclusion

Significant relationships were identified between IGHV and IGLV mutation frequencies. IGHV and IGLV germline identity were positively correlated, although IGHV genes demonstrated significantly greater SHM than IGLV genes. IGHV mutation status was strongly associated with *MYD88*^{L265P} mutation status. As expected, 96% of cases demonstrated SHM in keeping with the putative malignant transformation of post-germinal centre B-cells. All IGHV-unmutated cases were restricted to the *MYD88* wild-type cohort, potentially suggesting a different cell of origin with implications on B-cell biology and further investigation of these cases is warranted.

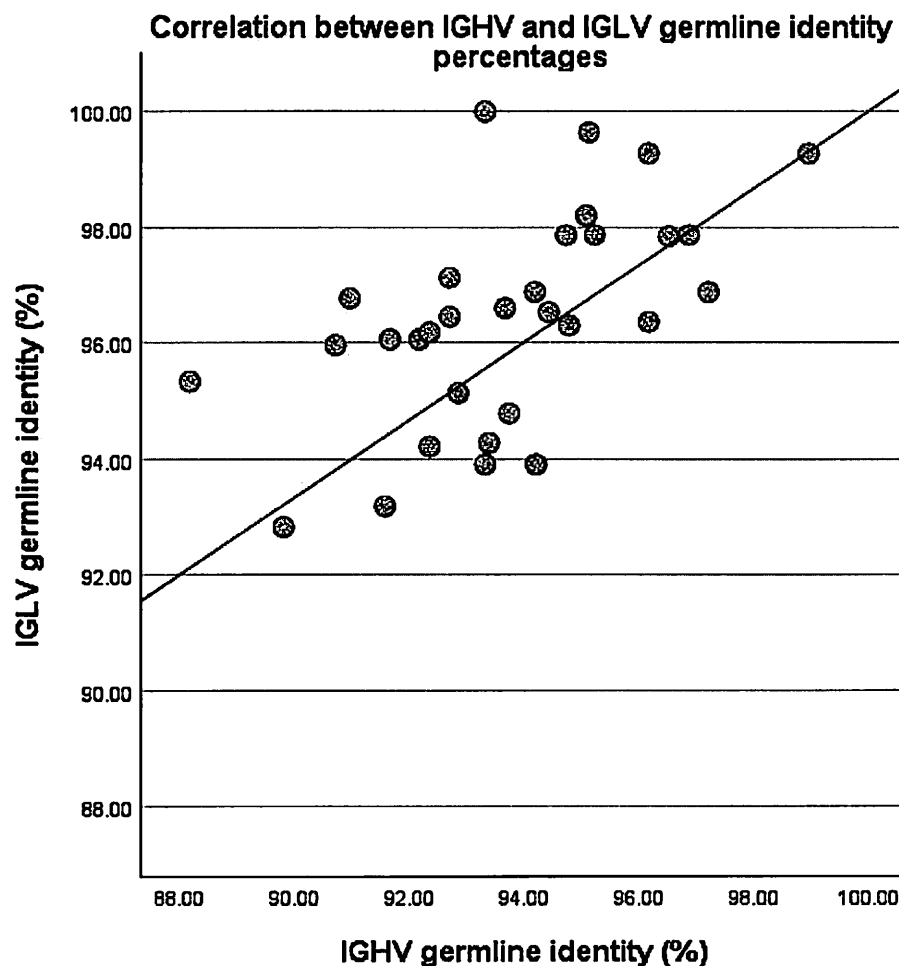


Figure 1

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