[ABSTRACT WM3.13]

Genomic mutations in the April/Taci/Traf pathway in Waldenstrom's Macroglobulinemia (wm)

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Introduction: IgA and IgG hypogammaglobulinemia are a common finding in patients with WM with 74% and 63% of patients in our studies exhibiting IgA and IgG levels respectively below the lower limit of normal. An extension of this study looking at the impact of therapy on IgA and IgG levels concluded that disease reduction or even attainment of a CR failed to improved IgA and IgG levels in statistically significant manner. These results provided the impetus to look for a genetic link between WM and hypogammaglobulinemia and we subsequently uncovered novel germ line mutations in the Blys/April receptor Taci (TNFRSF13B) in 6 of the 29 (21%) patients studied and these correlated with IgG and IgA hypogammaglobulinemia ($p < 0.0001$ for both). To expand on these findings we have now sequenced the entire length of Taci including introns and the 2kb 5¢ and 3¢ flanking regions as well as the upstream and down stream genes April, Blys, Traf2, and Traf5. Materials and Methods: DNA from the BCWM1 cell line and CD19+ selected bone marrow cells from 22 patients with WM were used for genomic sequencing studies. Results No notable genomic variants were observed in Blys and Traf5 in this population. Novel variants were discovered in the first exon of April in 4/17 (23%) of the samples studied and in 2/22 (9%) of the Traf2 samples in exons 5-6. A region of increased homozygosity was also noted 1.5kb upstream of Taci. Conclusions: These studies clearly demonstrate an unusually high frequency of mutations and abnormalities in the April-Taci-Traf2 pathway. Taci mutations have already been associated with hypogammaglobulinemia and common variable immunodeficiency (CVID) while CVID itself has been associated with increased rates of lymphoma. While the current numbers are too small for rigorous statistical analysis with clinical data, further studies are underway at our institution to expand these results through further sequencing of additional WM patient samples, healthy donor samples, and samples from extended families of patients with WM.