## Familial monoclonal gammopathy: phenotypic and genotypic associations.

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We have previously described the familial occurrence of mononclonal gammopathies in eight Icelandic families, five of these including IgM and IgG/A disorders. In one of these families a B cell phenotype was discovered, manifesting as enhanced production of immunolglobulins in response to stimulation by poke-weed mitogen (PWM). Family members showing this phenotype are referred to as hyper-responders (HR). Subsequently HR were discovered in three other families. Using an *in vitro* model of the germinal centre (GC) reaction we found, to our initial surprise, that the HR phenotype was not elicited. Subsequently we have found that PWM stimulation does not stimulate expression of CD40L on T cells and a recent publication suggests that PWM stimulates B cells via TLR activation by microbial contaminants. The GC model is based on activation through CD40L and IL-4. The HR phenotype is thus associated with non-antigen T-cell independent B cell activation.

In order to analyse somatic genetic events in B cells we performed array-based comparative genomic sequencing (CGH), on isolated peripheral-blood B-cells and neutrophils from the same sample. This revealed the expected deletions at Ig-gene loci as well as random changes throughout the genome, reflecting off-target AID activity. Remarkably, these random variations were significantly less marked in HR compared with related or unrelated controls. This implies that B cell from HR are less exposed to the GC environment.

At the germ- line level we have demonstrated a strong association between three linked single-nucleotide polymorphisms in intron3 in the *HAS1* gene with the HR phenotype. These polymorphisms lead to formation of aberrant splice variants of HAS1 that may affect mitotic spindle stability, motility and, by extrapolation, cell polarization.

Three features have thus been identified that distinguish HR from non-affected members in the same families and unrelated controls. Two of these relate to B-cell physiology; limited acquired random genetic variation and enhanced response to non-specific stimulation. The third is a germ-line genetic polymorphism. The aberrations in B-cell biology may indicate a tendency to bypass the germinal centre reaction. It remains to be determined whether and how the genotypic variant is associated with the phenotypic characteristics.