Association of CLEC16A with human common variable immunodeficiency disorder and role in murine B cells.

Common variable immunodeficiency disorder (CVID) is the most common symptomatic primary immunodeficiency in adults, characterized by B-cell abnormalities and inadequate antibody response. CVID patients have considerable autoimmune comorbidity and we therefore hypothesized that genetic susceptibility to CVID may overlap with autoimmune disorders. Here, in the largest genetic study performed in CVID to date, we compare 778 CVID cases with 10,999 controls across 123,127 single-nucleotide polymorphisms (SNPs) on the Immunochip. We identify the first non-HLA genome-wide significant risk locus at CLEC16A (rs17806056,
P=2.0 × 10(-9)) and confirm the previously reported human leukocyte antigen (HLA) associations on chromosome 6p21 (rs1049225, P=4.8 × 10(-16)). Clec16a knockdown (KD) mice showed reduced number of B cells and elevated IgM levels compared with controls, suggesting that CLEC16A may be involved in immune regulatory pathways of relevance to CVID. In conclusion, the CLEC16A associations in CVID represent the first robust evidence of non-HLA associations in this immunodeficiency condition.