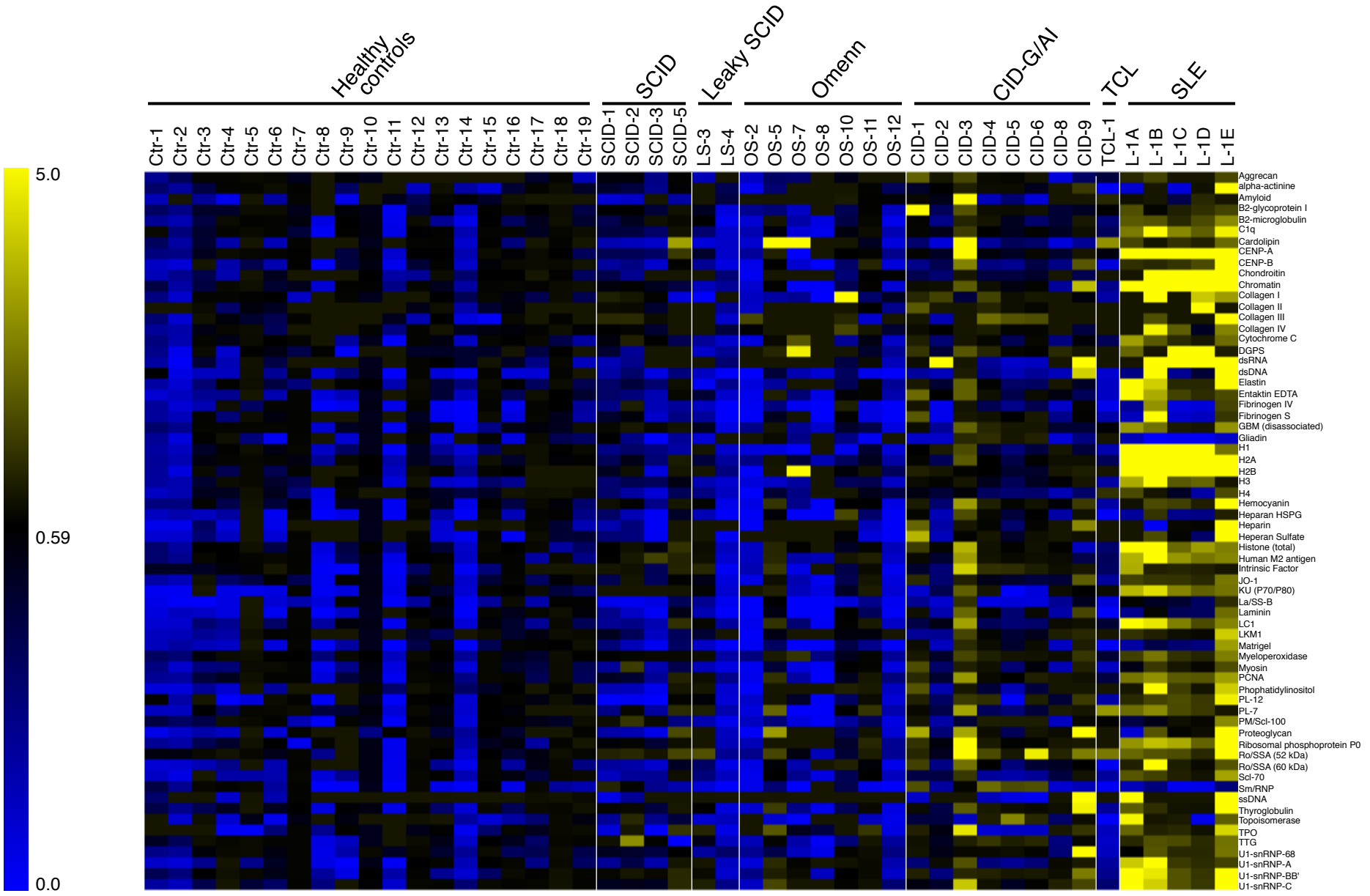
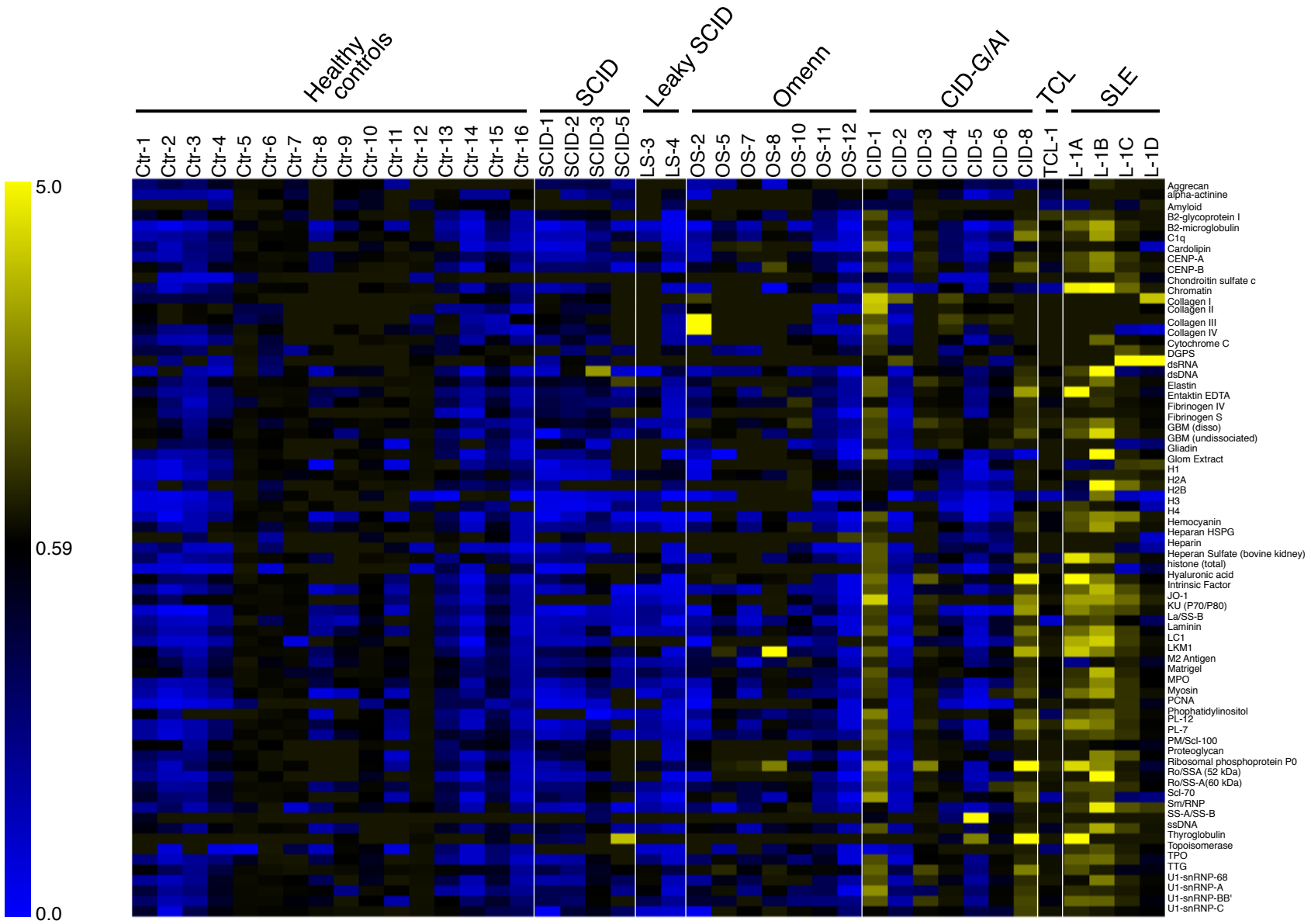
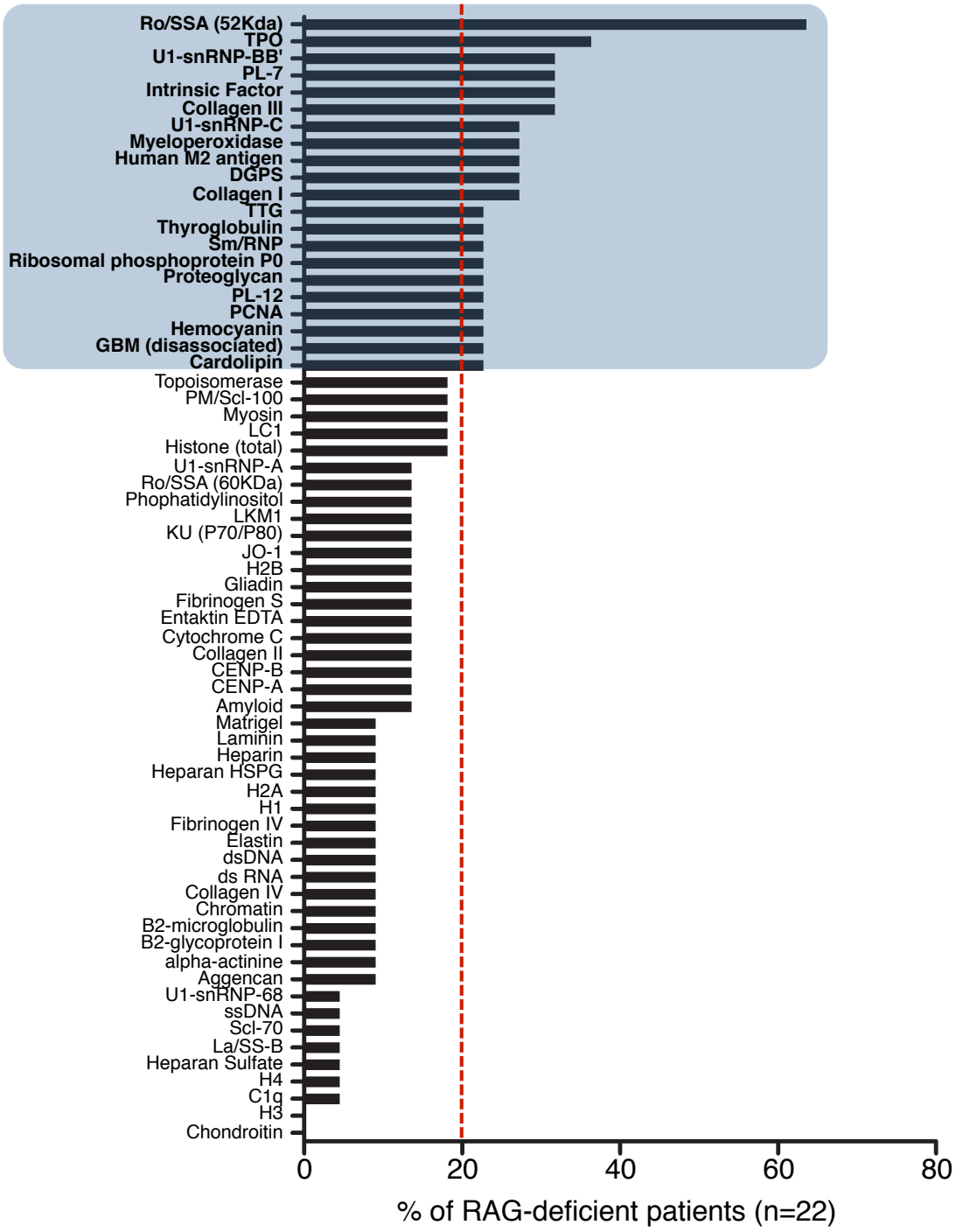


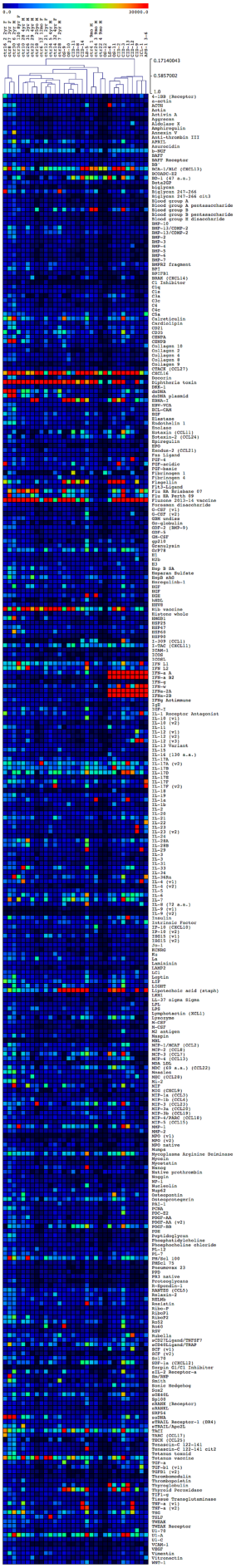
Supplementary Figure 1. Heatmap of autoantibody microarray detecting immunoglobulin (Ig)G reactivity to 66 autoantigens in RAG-deficient patients (n=22) and controls (n=19). RAG-deficient patients (n=22) are grouped by phenotype on the x axis (SCID n=4; LS n=2; OS n=7; CID-G/AI n=8; TCL n=1) along with healthy controls (Ctr) (n=19) and a patient with systemic lupus erythematosus as positive control (SLE L-1 to 5; measured on five separate arrays). Autoantigens are listed on the y axis in alphabetic order. The relative autoantibody reactivity values (described in the Methods section) are depicted in color using Multi Experiment Viewer software 3 (MeV). The intensity of reactivity is indicated according to a scale bar ranging between 0 to 5 (blue to yellow, with midpoint value of 0.59 in black).



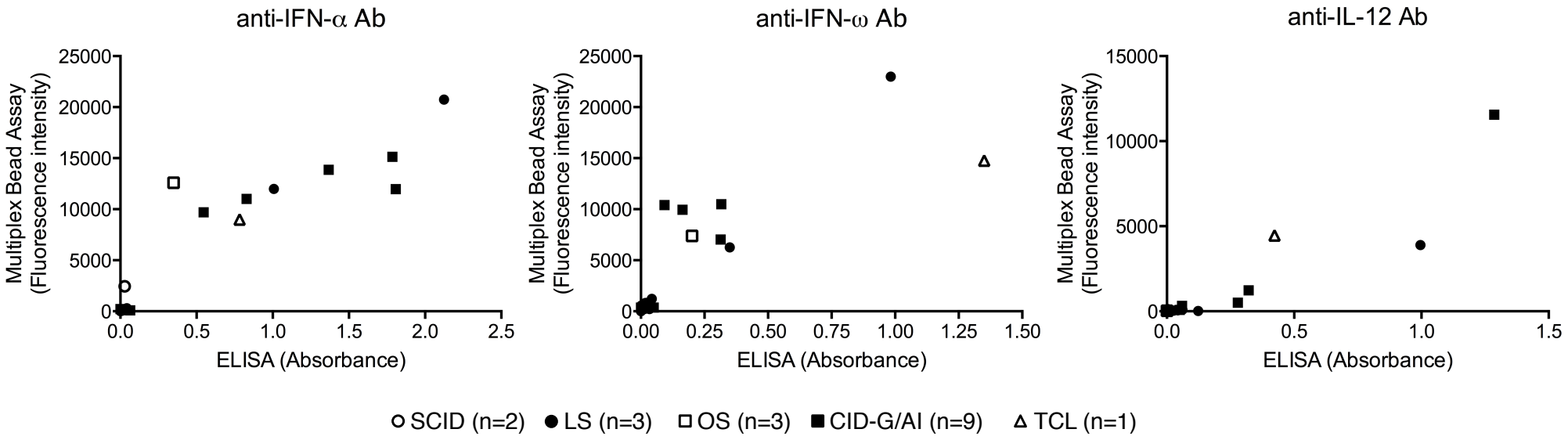
Supplementary Figure 2. Heatmap of autoantibody microarray detecting immunoglobulin (Ig)M reactivity to 70 autoantigens in RAG-deficient patients (n=21) and controls (n=16). RAG-deficient patients (n=21) are grouped by phenotype on the x axis (SCID n=4; LS n=2; OS n=7; CID-G/AI n=7; TCL n=1), along with healthy controls (Ctr) (n=16) and a patient with systemic lupus erythematosus as positive control (SLE L-1A-D; measured on four separate arrays). Autoantigens are listed on the y axis in alphabetic order. The relative autoantibody reactivity values (described in the Methods section) are depicted in color, using Multi Experiment Viewer software 3 (MeV). The intensity of reactivity is indicated according to a scale bar ranging between 0 to 5 (blue to yellow, with midpoint value of 0.59 in black).



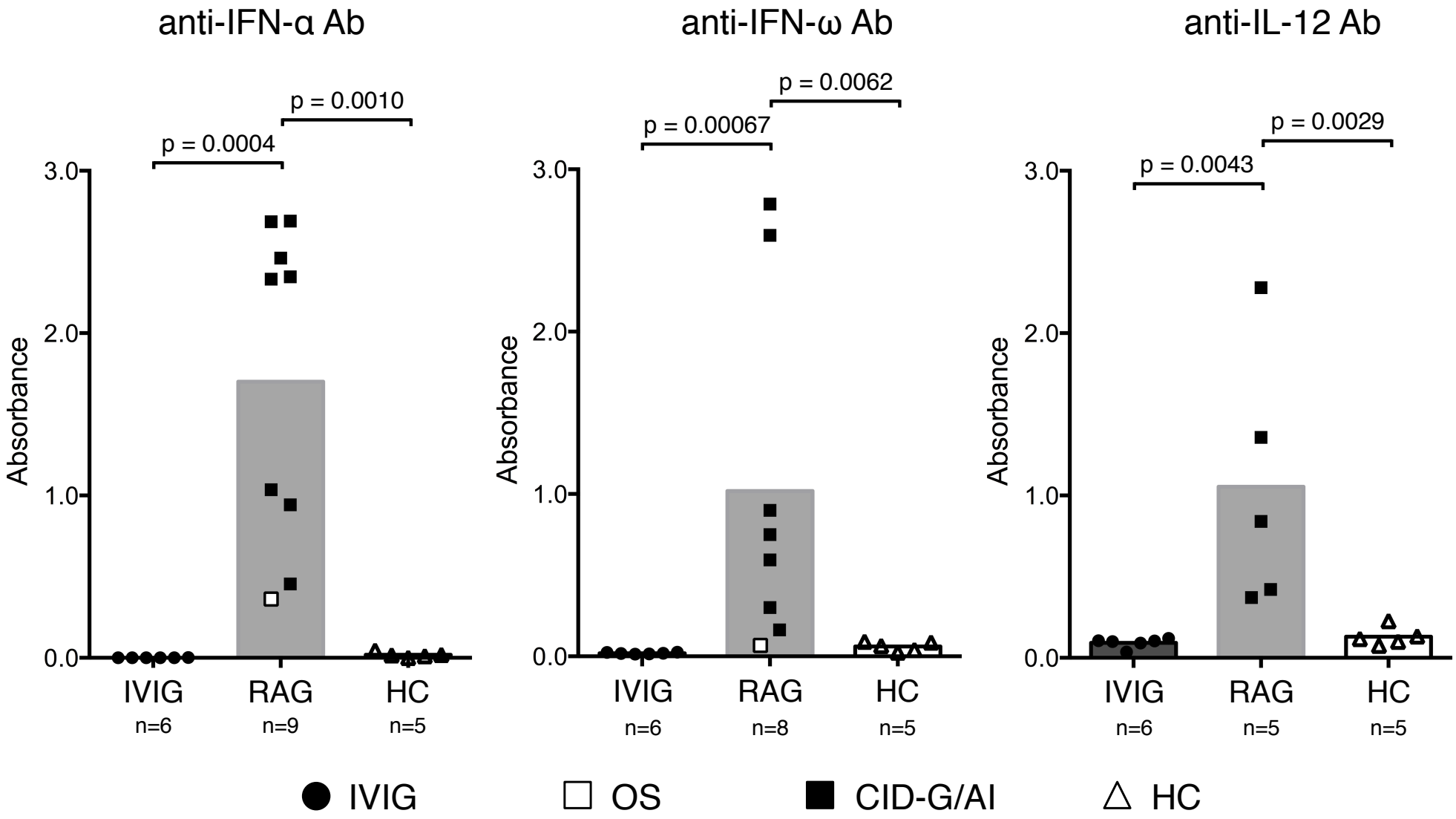
Supplementary Figure 3. Frequency of individual autoantibodies in multi-reactive RAG-deficient patients. A panel of antibodies to "common" autoantigens (n=21) (highlighted in grey) was identified, and defined as being present in at least 20% of RAG-deficient patients. The 20% cut-off level is marked with dashed line, and "common" autoantigens are highlighted in bold.



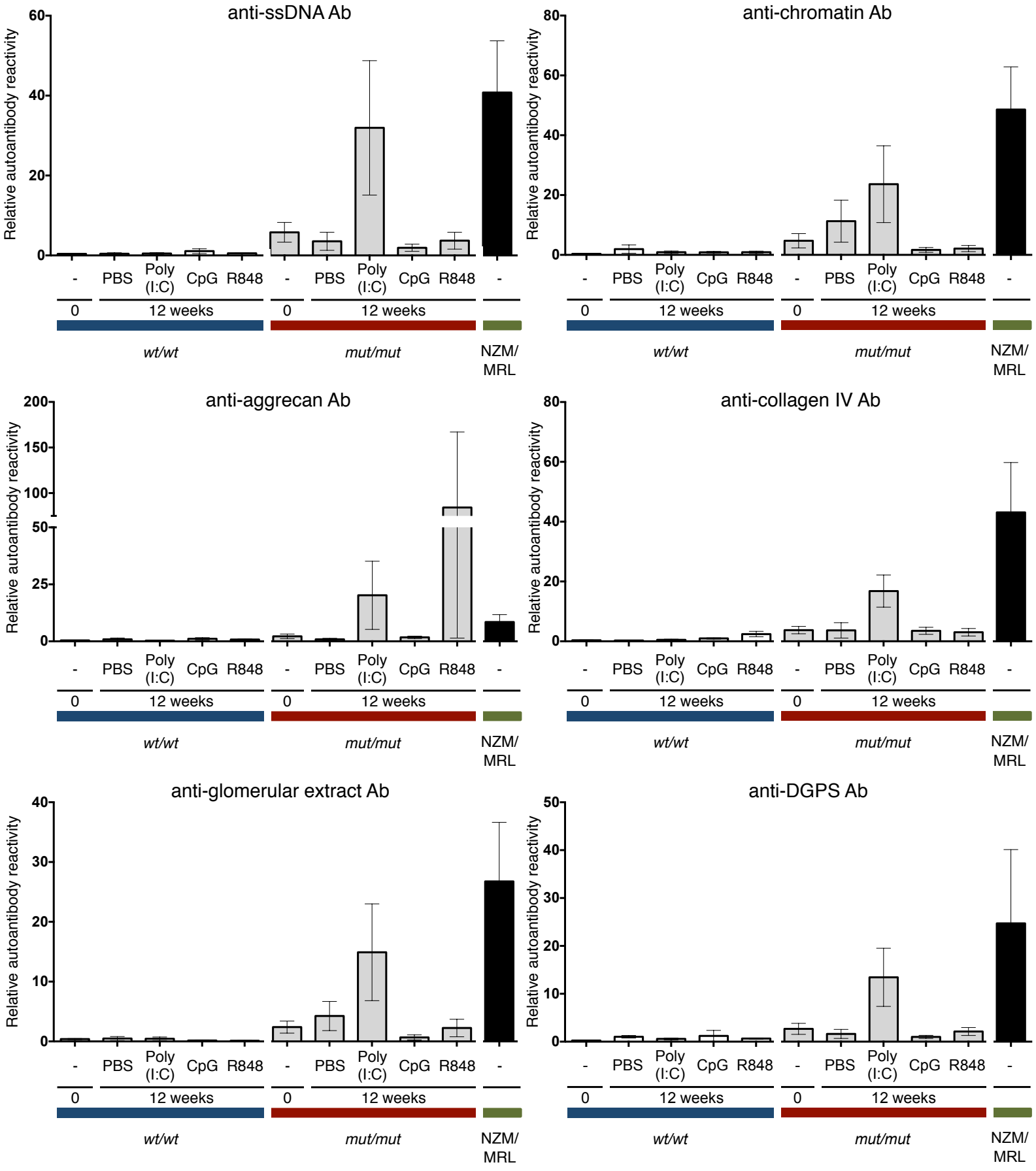
Supplementary Figure 4. Cytokine, chemokine and protein autoantibody microarray profiling in RAG-deficient patients and healthy controls. Heat map representation of autoantibody reactivity of plasma from 16 healthy controls (Ctr), 14 RAG-deficient patients [Omenn (OS) n=3; Leaky-SCID (LS) n=2; CID with granulomas and autoimmunity (CID) n=8; idiopathic CD4+ T cell lymphopenia (TCL) n=1], and 1 patient with autoimmune polyendocrine syndrome type 1 (APS-1). Autoantigens are listed on the y axis in alphabetic order. Patients and controls were clustered according to the reactivity observed. Values of Relative Autoantibody Reactivity (described in the Methods section) are depicted in color using Multi Experiment Viewer software 3 (MeV), according to a scale bar ranging between 0 to 30,000 (blue to red).



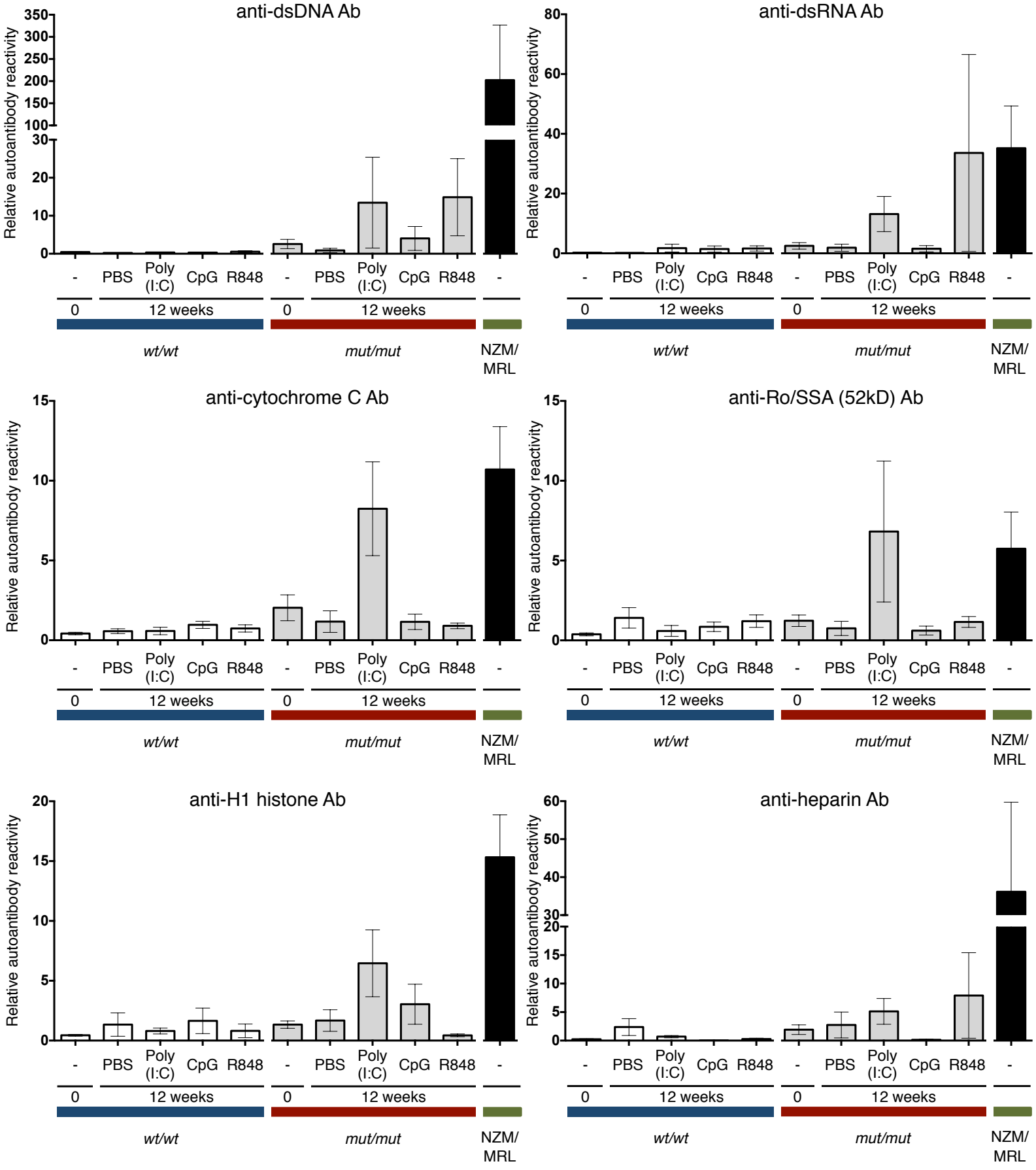
Supplementary Figure 5. Correlation of cytokine autoantibodies levels detected by ELISA and bioplex methods. Arbitrary ELISA Unit (ELISA) and Fluorescence Intensities (FI) (bioplex) in samples from a cohort of RAG-deficient patients: SCID, n=2 (open circle); Leaky SCID, n=3 (filled circle); Omenn syndrome (OS), n=3 (open square); CID with granulomas and autoimmunity (CID-G/AI), n=9 (filled squares); idiopathic CD4+ T cell lymphopenia (TCL), n=1 (open triangle). Statistical significance of the correlation was not tested as the data did not follow a continuous distribution.



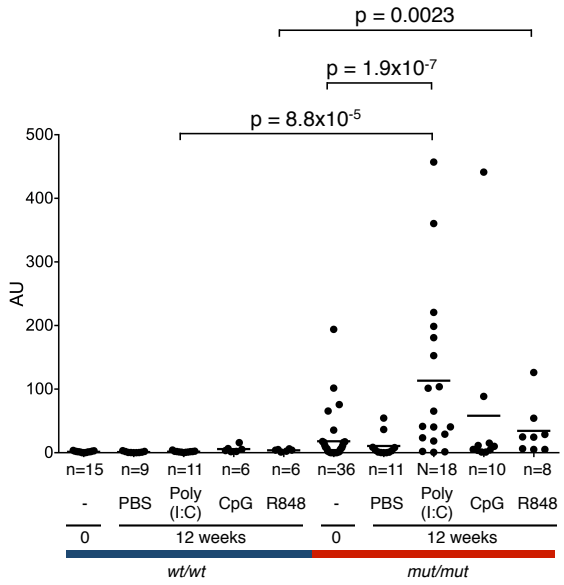
Supplementary Figure 6. Levels of antibodies to IFN-α, IFN-ω and IL-12 in commercial IVIG preparations diluted to 600 mg/dl (n=6), in anti-cytokine autoantibody (ACA)-positive RAG-deficient patients (OS: open square, and CID-G/AI: filled square) as positive controls, and in healthy controls (HC, n=5), as determined by ELISA. Absorbance was measured at 450 nm. Using Wilcoxon rank sum test, significantly different levels of anti-IFN-a, anti-IFN-ω and anti-IL-12 were detected in the three groups analyzed (IVIG, RAG, and HC).



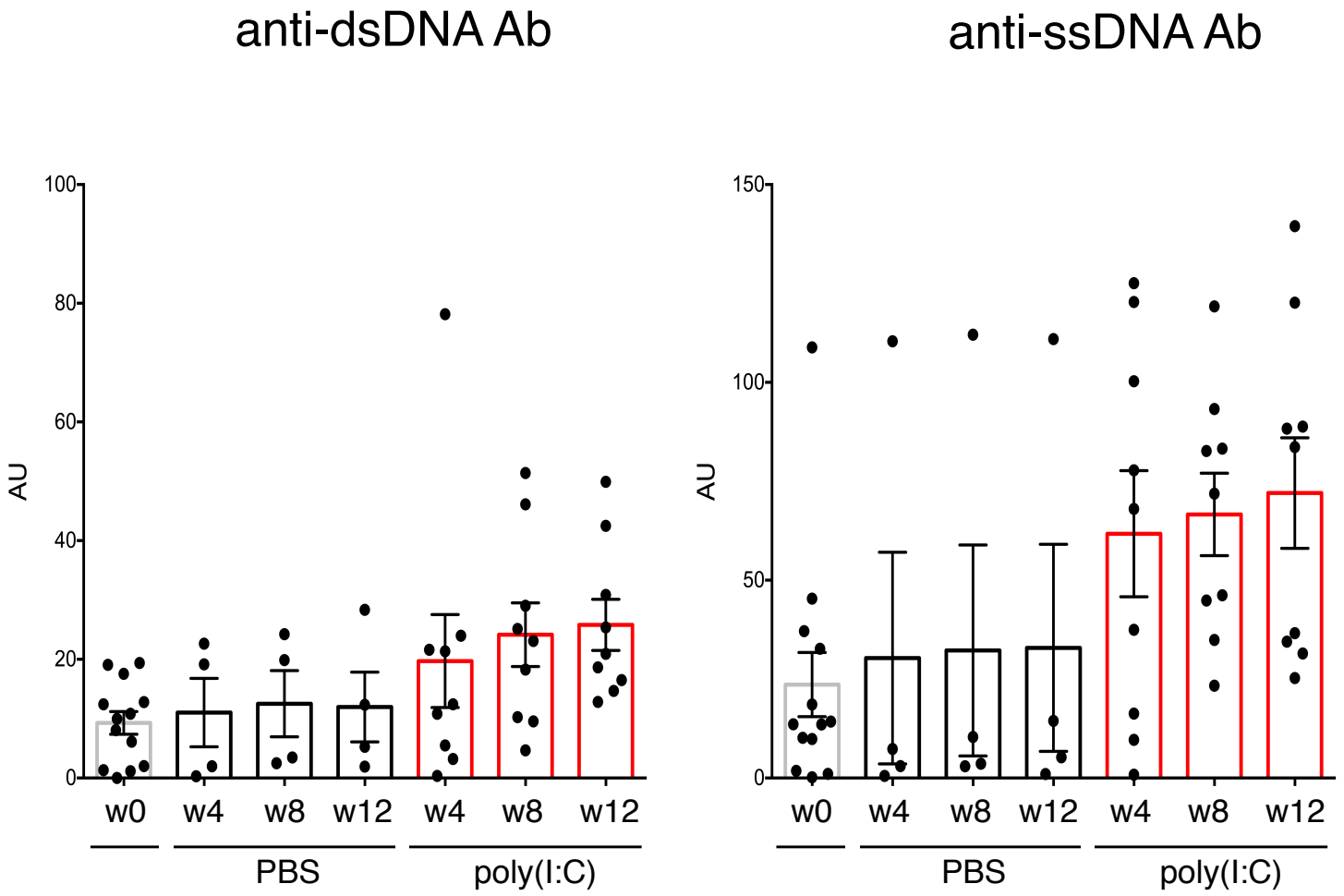
Supplementary Figure 7 (A) Relative reactivity of autoantibodies to selected target antigens (ssDNA, chromatin, aggrecan, collagen VI, glomerular extract, DGPS) in *wt/wt* and *mut/mut* mice at baseline (*wt/wt* n=13, *mut/mut* n=15) and after 12 weeks of weekly *i.p.* injection of poly(I:C) (*wt/wt* n=5, *mut/mut* n=8), CpG (*wt/wt* n=3, *mut/mut* n=9), R848 (*wt/wt* n=3, *mut/mut* n=8) and PBS (*wt/wt* n=4, *mut/mut* n=4). Plasma pooled from lupus-prone NZM/MRL mice (n=6) served as a positive control.



Supplementary Figure 7 (B) Relative reactivity of autoantibodies to selected target antigens (dsDNA, dsRNA, cytochrome C, Ro/SSA (52kd), H1 histone, heparin) in *wt/wt* and *mut/mut* mice at baseline (*wt/wt* n=13, *mut/mut* n=15) and after 12 weeks of weekly *i.p.* injection of poly(I:C) (*wt/wt* n=5, *mut/mut* n=8), CpG (*wt/wt* n=3, *mut/mut* n=9), R848 (*wt/wt* n=3, *mut/mut* n=8) and PBS (*wt/wt* n=4, *mut/mut* n=4). Plasma pooled from lupus-prone NZM/MRL mice (n=6) served as a positive control.



Supplementary Figure 8. Validation of single-stranded DNA (ssDNA) antibodies by ELISA. Plasma samples were diluted 200-fold. Wilcoxon test with Holm's correction was used to compare results in *wt/wt* and *mut/mut* mice at baseline (week 0) and for each of the treatments, as well as to compare each of the four treatments to week 0 separately in *wt/wt* and in *mut/mut* mice. Significant differences between groups are highlighted. Results from 3 separate experiments were pooled.



Supplementary Figure 9. Anti-ss/dsDNA autoantibodies in *mut/mut* mice treated with weekly low-dose *i.p.* injection of poly(I:C) (n=9) and PBS (n=4) as a control. Autoantibody levels to ssDNA and dsDNA were measured at 0, 4, 8 and 12 weeks (w0, w4, w8, w12) and visualized as Arbitrary ELISA Unit (AU). There was no obvious increase at intermediate time points (week 4 to week 8) compared to week 12, in either PBS or in poly(I:C)-treated mice. Results from three separate experiments are shown. Boxes and bars represent mean value ± standard error mean.