

## Supplementary Figure Legends

**Supplementary Figure S1. Gating strategy and PI3K signaling in B-cell subpopulations** (A) Gating Strategy for CD21<sup>pos</sup> in one representative HD and CD21<sup>low</sup> and CD21<sup>pos</sup> in one representative CVID patient after gating on CD19<sup>pos</sup>CD21<sup>pos/low</sup> and CD27<sup>neg</sup>IgM<sup>pos</sup> naïve B cells. (B) Statistics of the MFI of pAkt, pmTOR and pS6 unstimulated and after anti-IgM stimulation in CD21<sup>pos</sup> B cells from HD, CD21<sup>pos</sup> and CD21<sup>low</sup> B cells from CVID patients (pAkt, HD n=8, CVID n=9; pmTOR, HD n=13, CVID n=13; pS6, HD n=13, CVID n=13). (C) Statistical analysis of the MFI of pS6 unstimulated and after anti-IgM stimulation for 16 hours in CD21<sup>pos</sup> B cells from HD (n=4) and CD21<sup>pos</sup> and CD21<sup>low</sup> B cells from CVID patients (n=4) and ratio of the MFI stimulated and unstimulated.

**Supplementary Figure S2. Expression of PI3K signaling components** Heat map of selected genes involved in PI3K signaling in B cells as determined by RNAseq in CD21<sup>pos</sup> B cells from HD (n=2), CD21<sup>pos</sup>(n=3) and CD21<sup>low</sup> B cells (n=2) from CVID patients. Fold changes (FC) between the different subpopulations as indicated. Stars indicate significant differences.

**Supplementary Figure S3. Upregulation of GLUT1 in B-cell subpopulations** (A) Representative histogram overlays for GLUT1 in CD21<sup>pos</sup> B cells from HD, CD21<sup>pos</sup> and CD21<sup>low</sup> B cells from CVID patients without stimulation or after stimulation with anti-IgM for 40 hours. (B) Ratio of the MFI of GLUT1 after anti-IgM stimulation and unstimulated as described in (A) in CD21<sup>pos</sup> B cells from HD (n=3), CD21<sup>pos</sup> (n=3) and CD21<sup>low</sup> (n=3) B cells from CVID patients.

**Supplementary Figure S4. Correlation of PI3K signaling with proportions of CD21<sup>low</sup> B cells and manifestations of immune dysregulation in CVID** (A) Correlation of the proportions of CD21<sup>low</sup> B cells of B cells and ratios of pmTOR (n=15) and pS6 (n=26) in CD21<sup>pos</sup> B cells from CVID patients. (B) Statistical analysis of the ratio of pAkt, pmTOR and pS6 stimulated and unstimulated after grouping of patients according to non-infectious manifestations (AI=autoimmunity, AC= autoimmune cytopenia, LP=lymphoproliferation, G=granuloma or Spl=splenomegaly).

**Supplementary Figure S5. pAKT, pmTOR and pS6 in APDS patients** (A) Histogram overlays of pAkt, pmTOR and pS6 in CD21<sup>pos</sup> B cells from three APDS1 patients and two APDS2 patients (green) with the corresponding daily controls (black) unstimulated (normal lines) and after anti-IgM Stimulation (bold lines). Numbers indicate the MFI of the signaling protein under the respective condition.