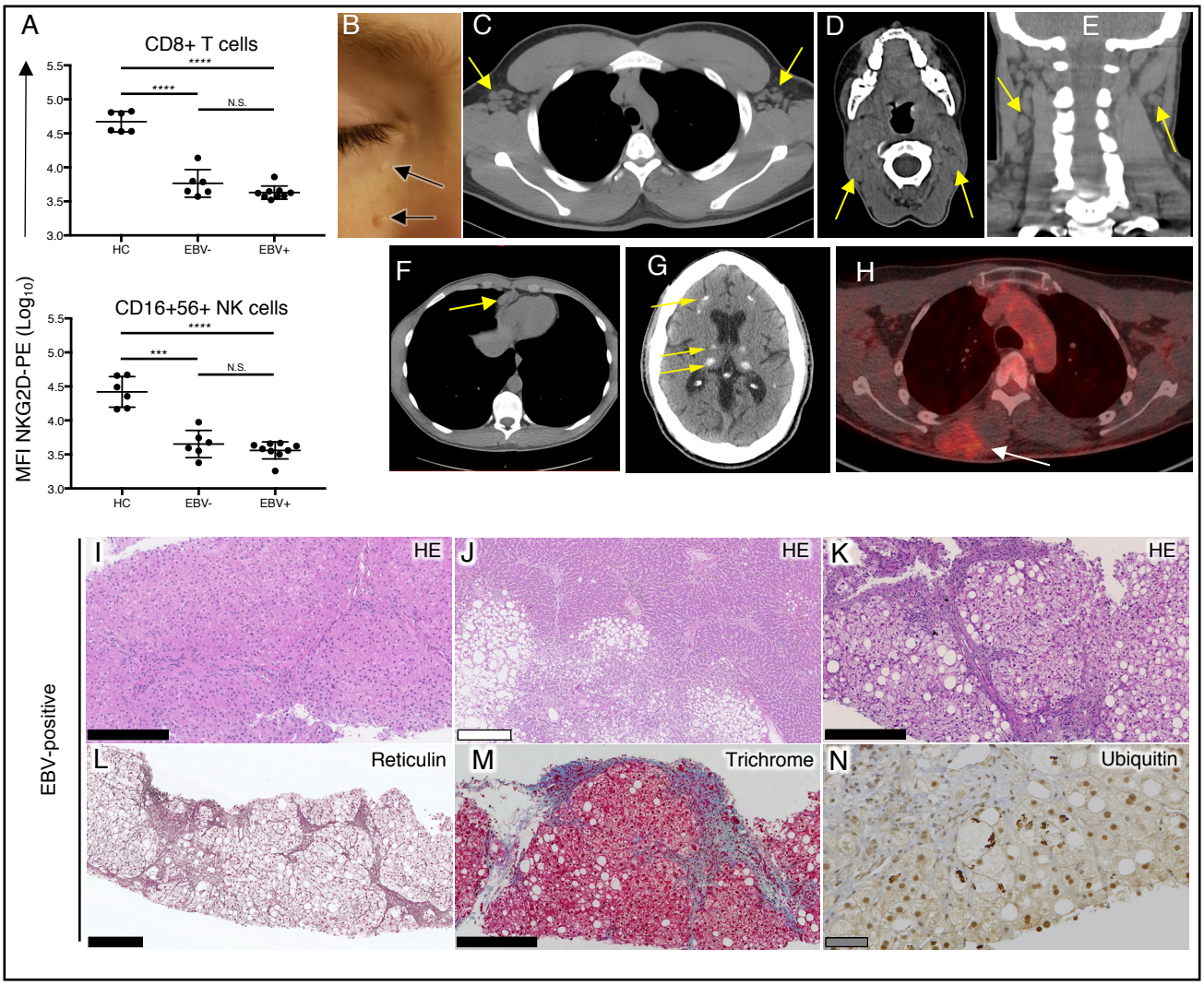
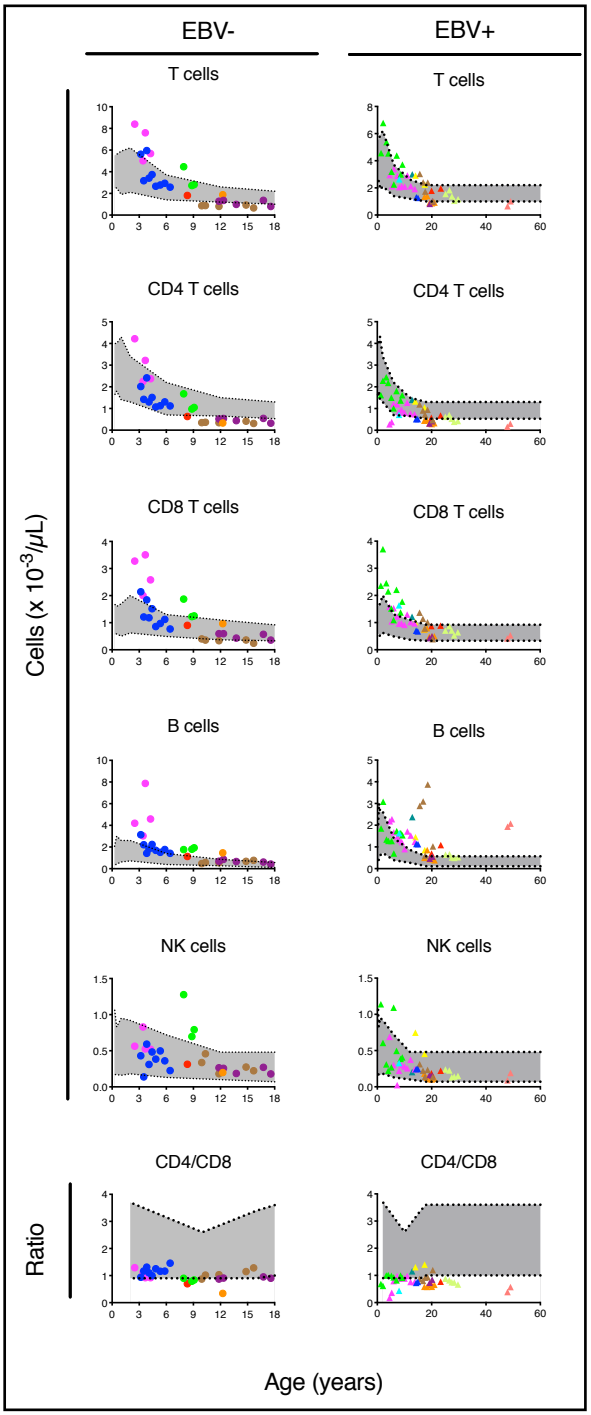
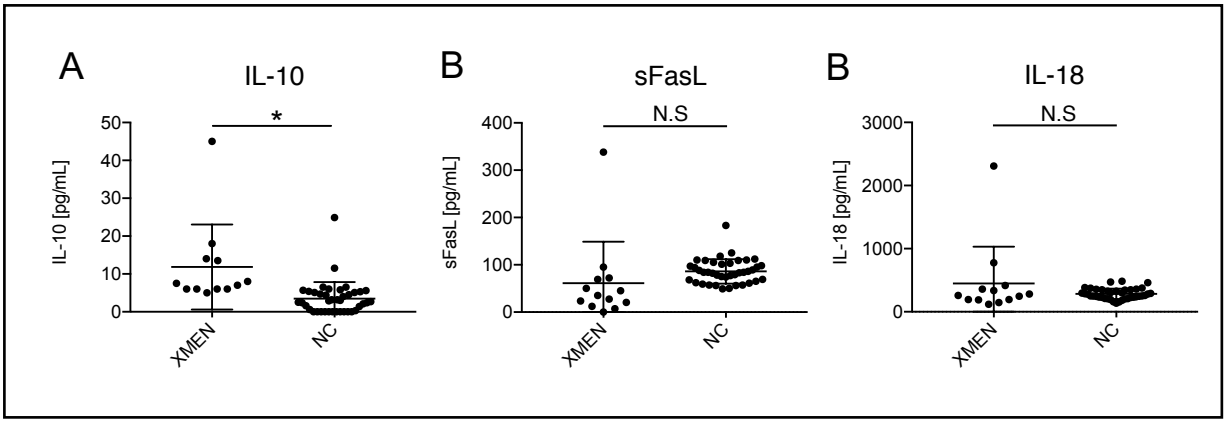



Supplementary figure 1




Supplementary figure 2

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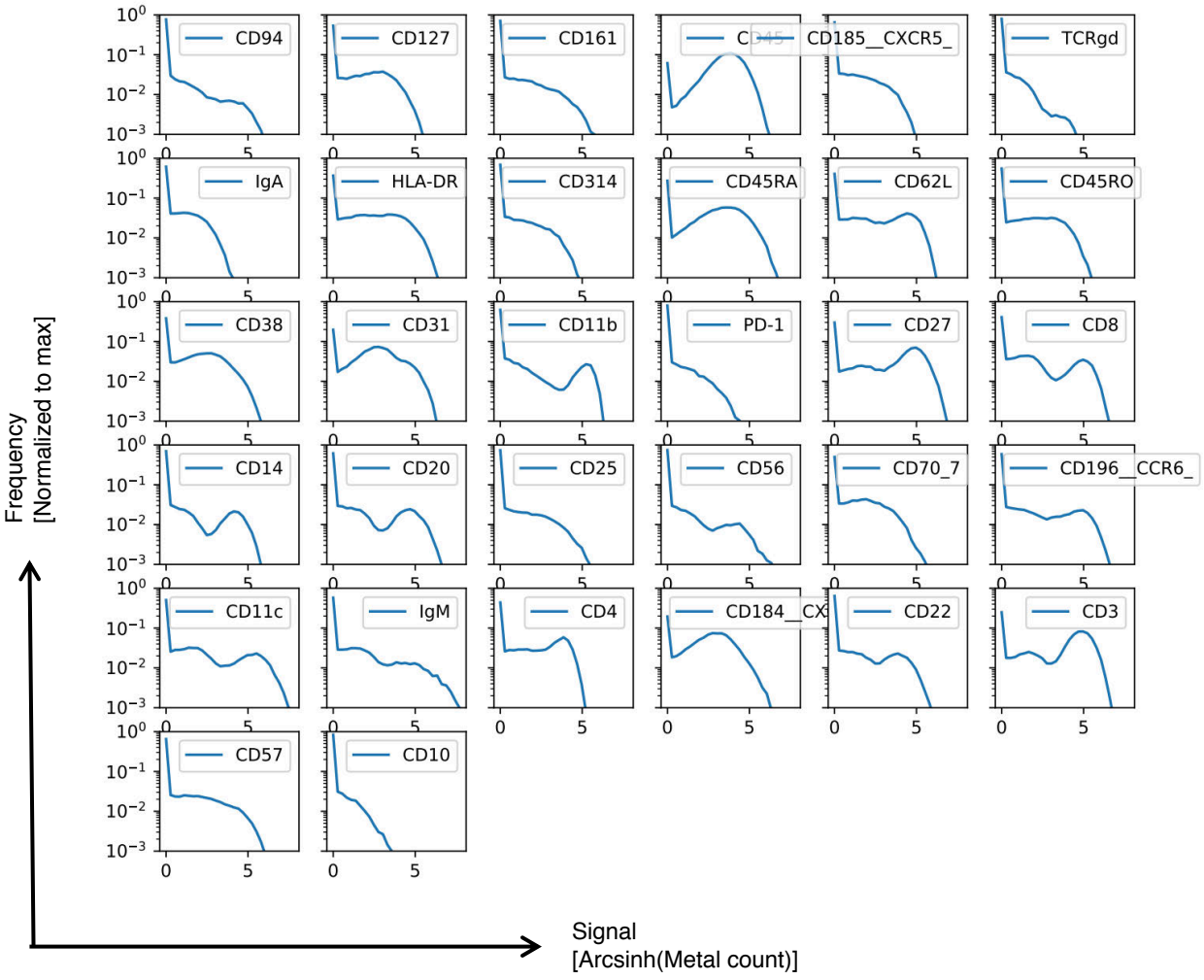


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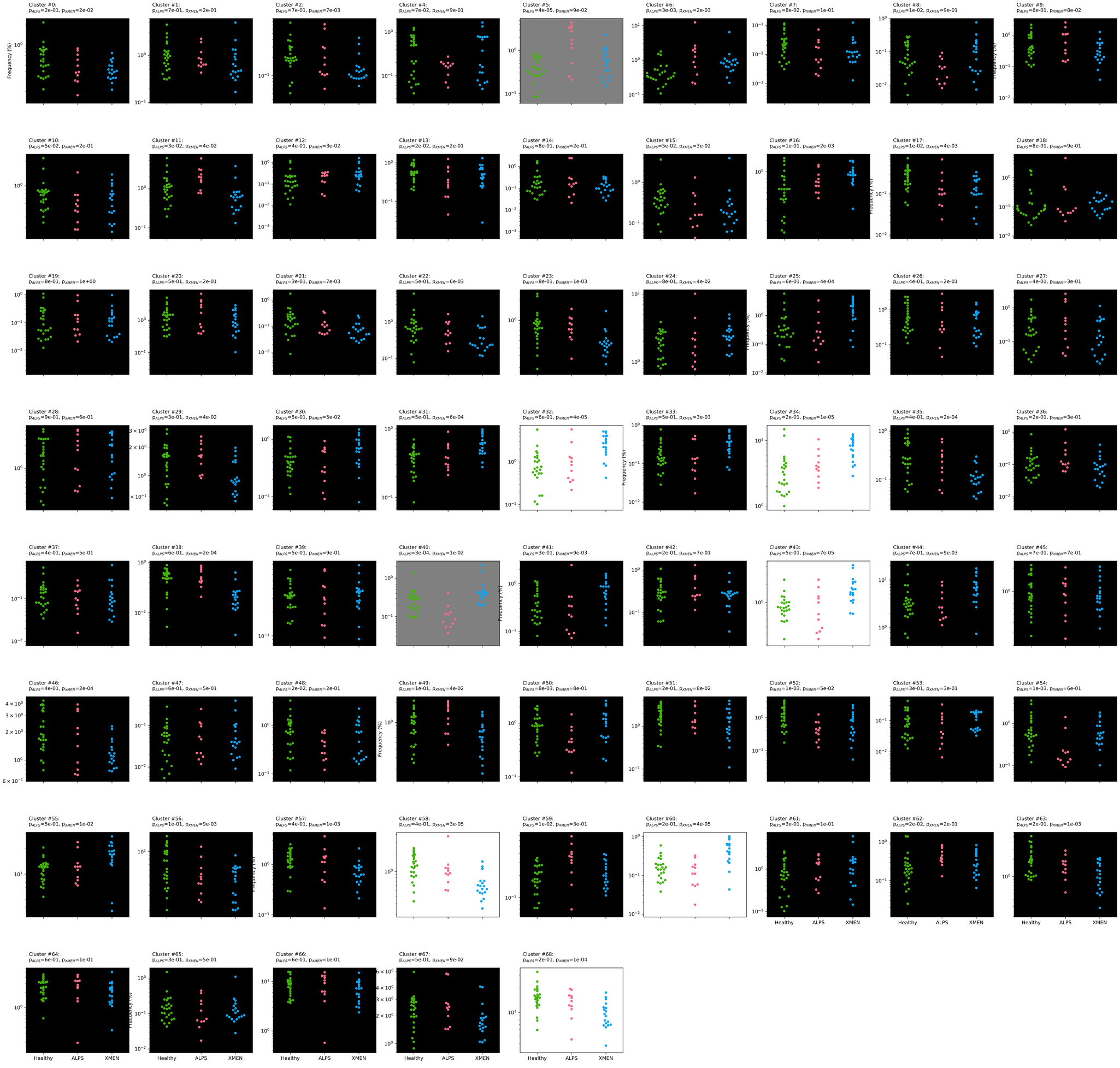
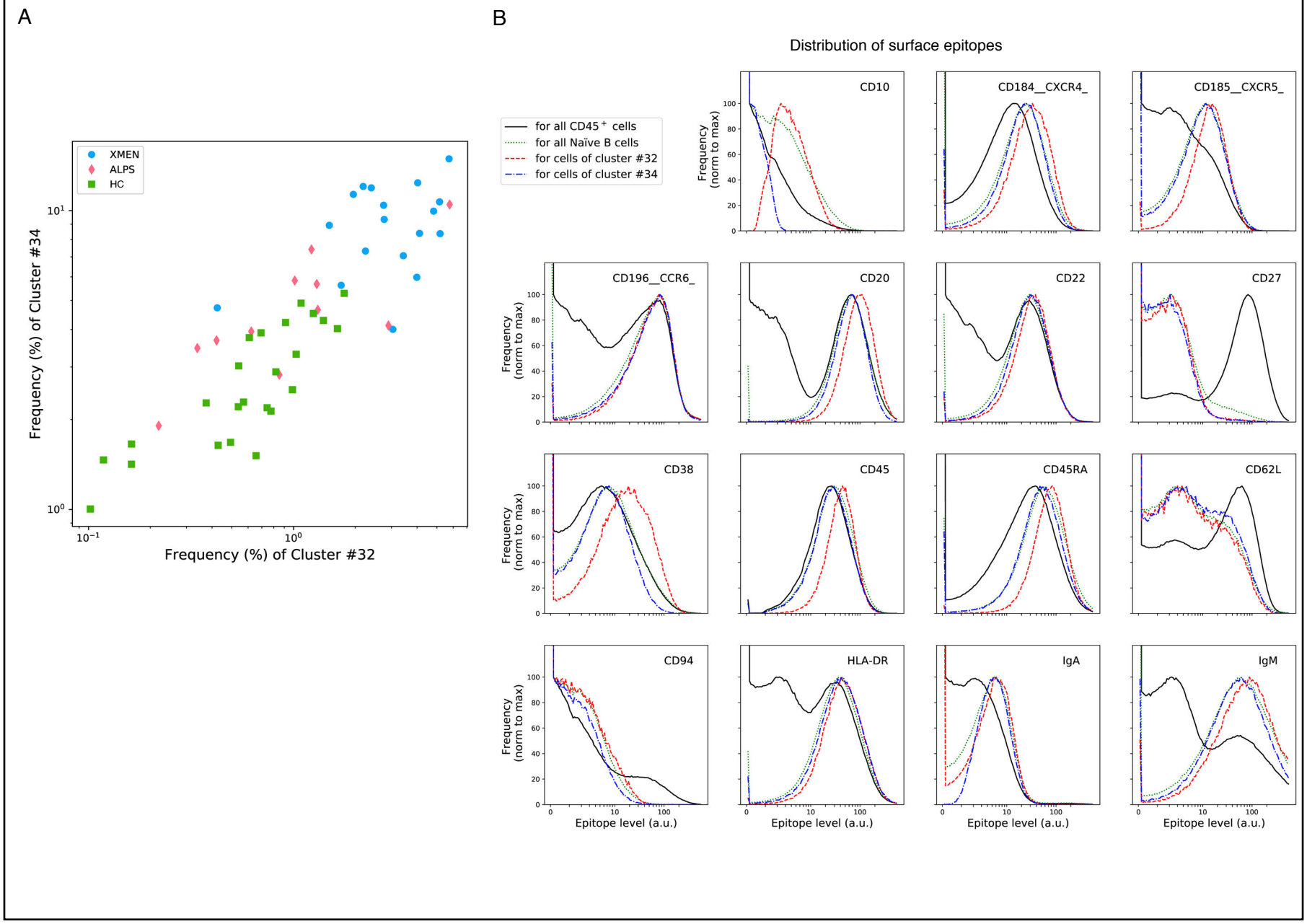
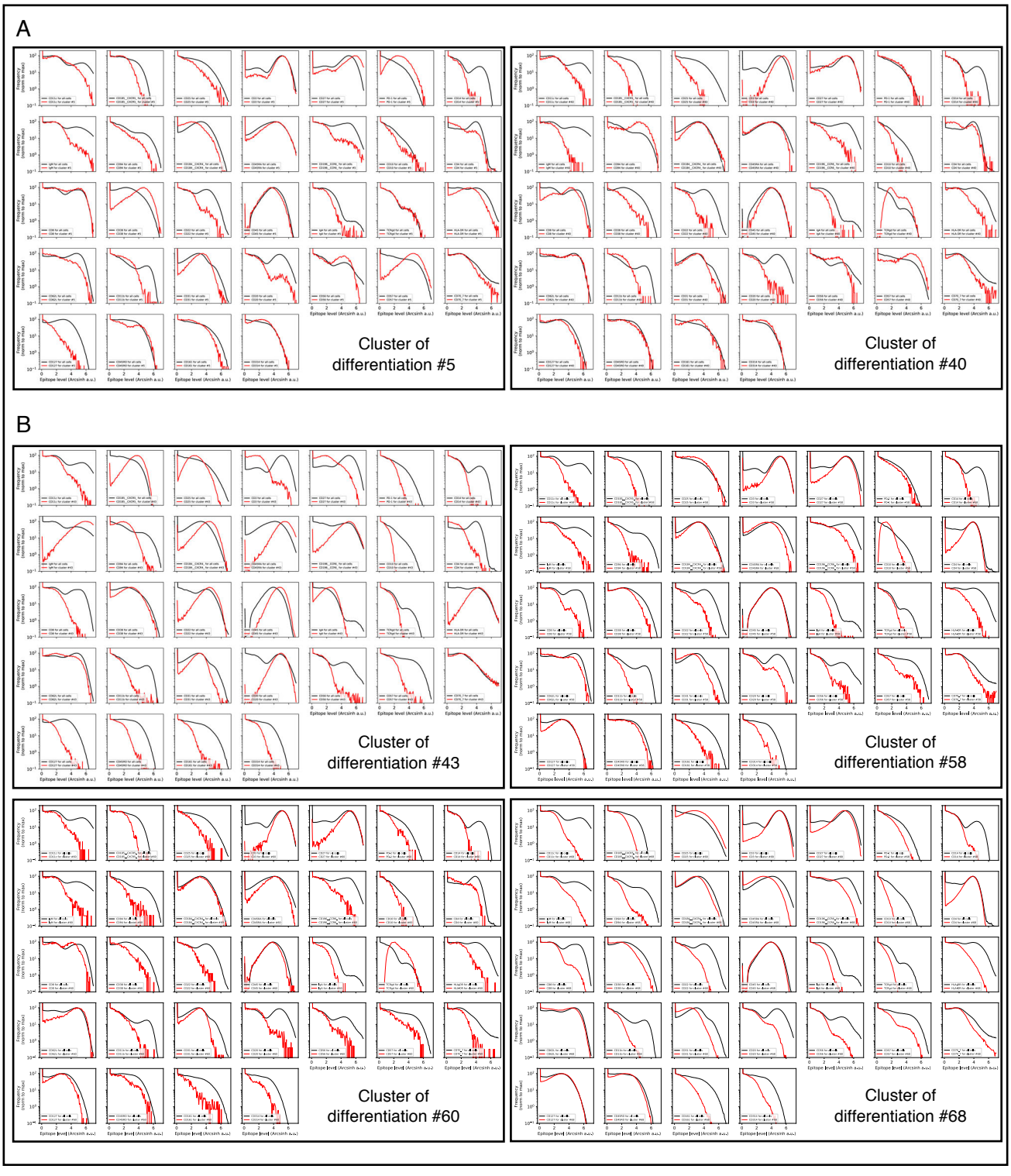


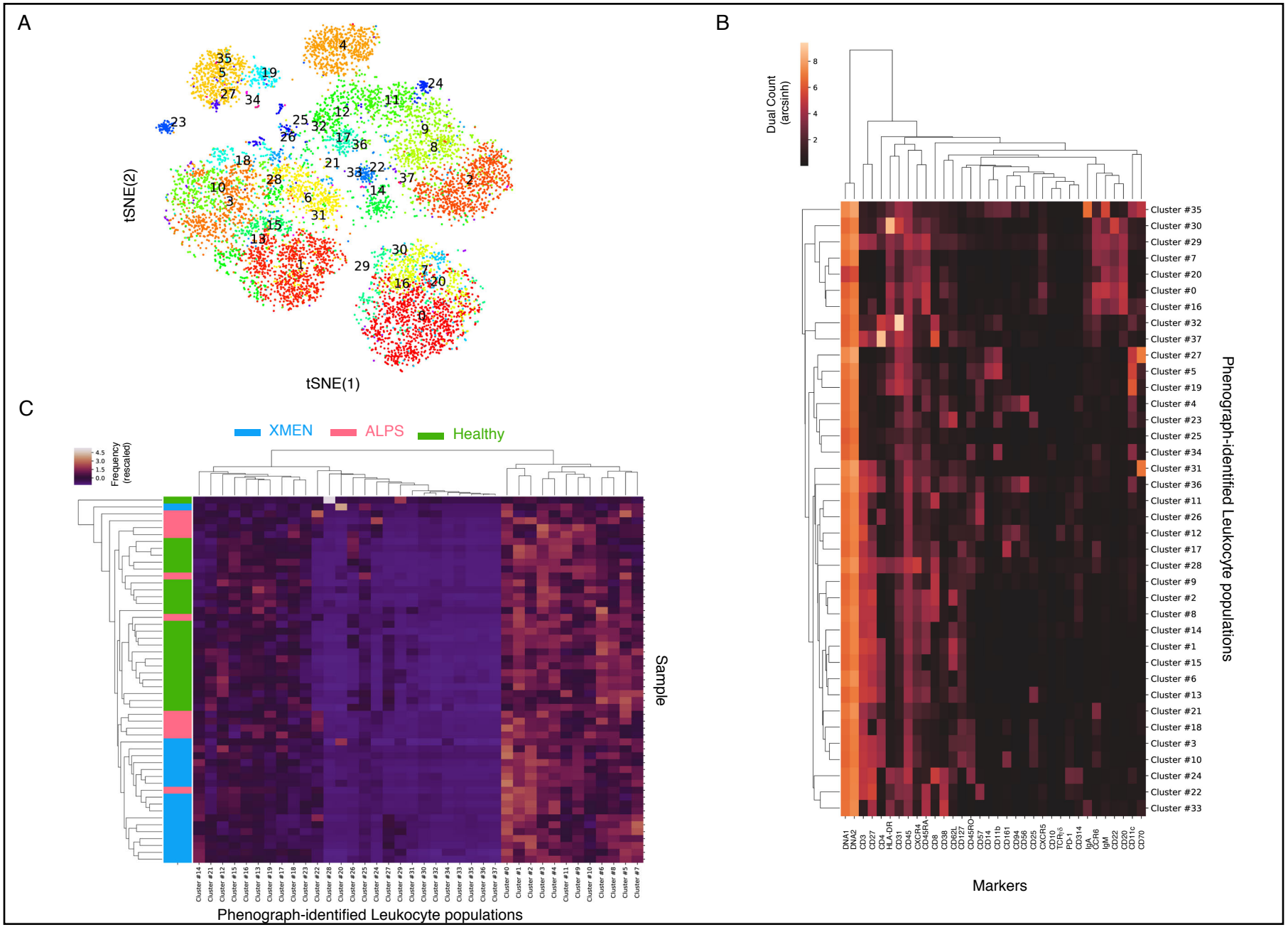

Supplementary figure 5



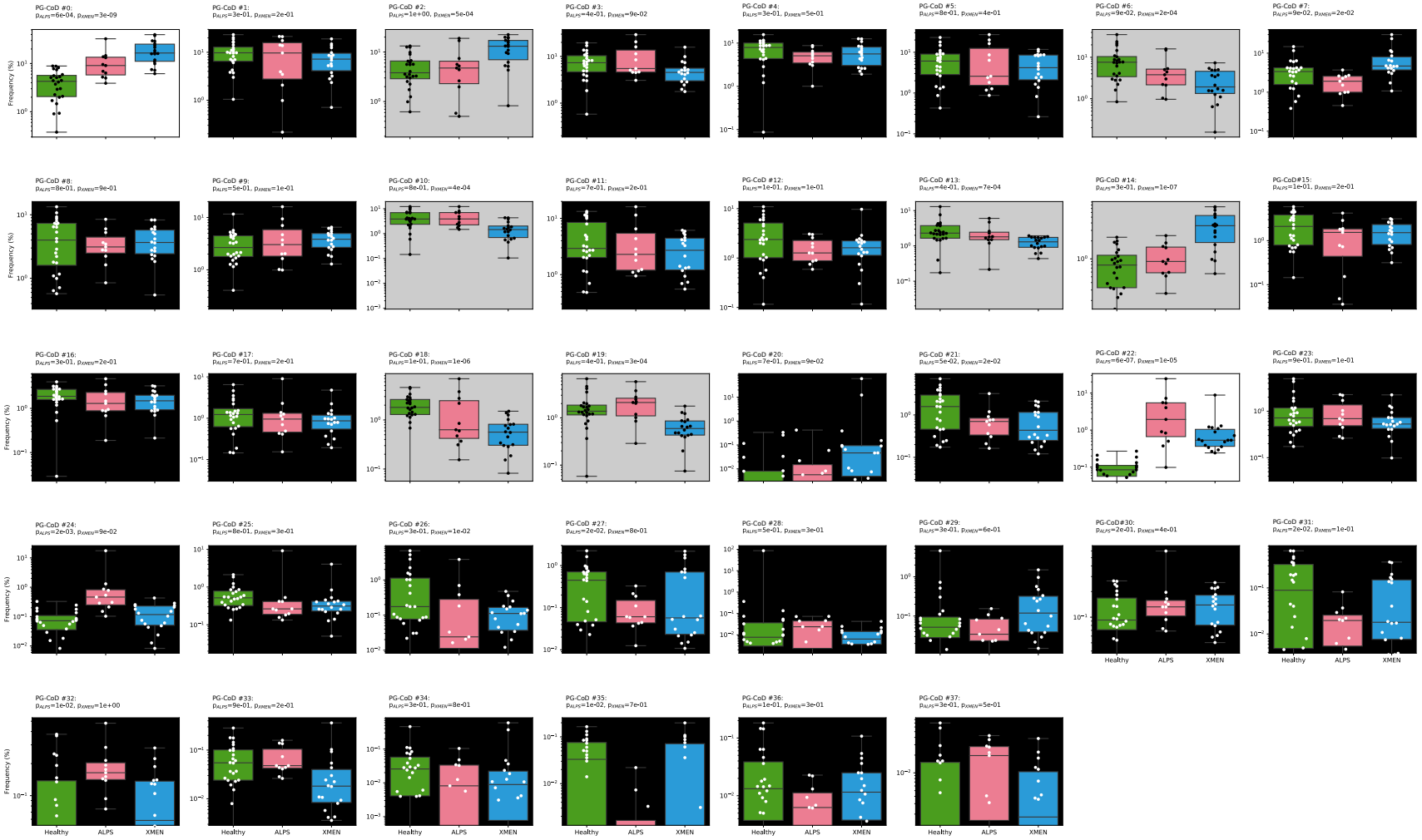

Supplementary Figure 6



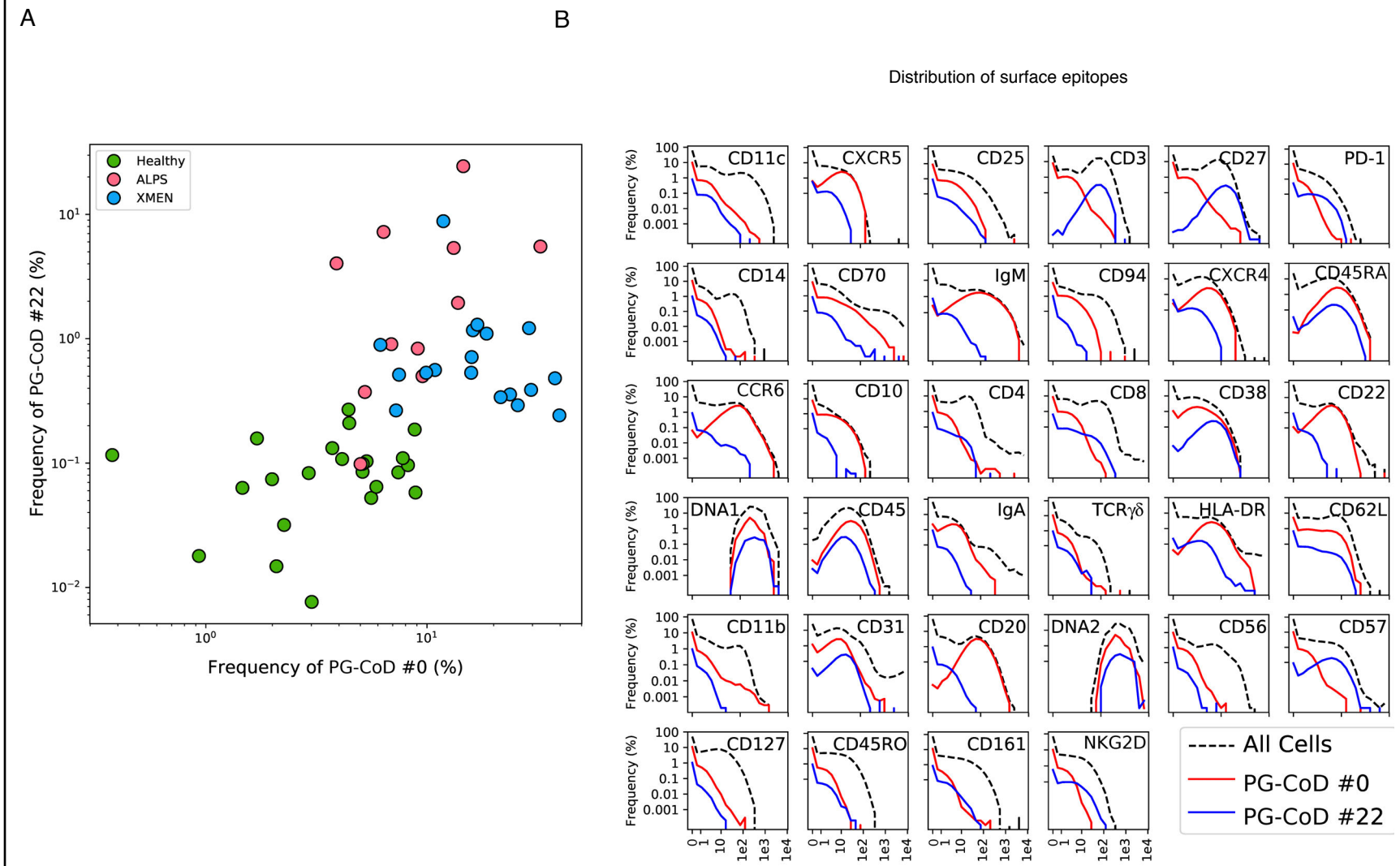

Supplementary figure 7



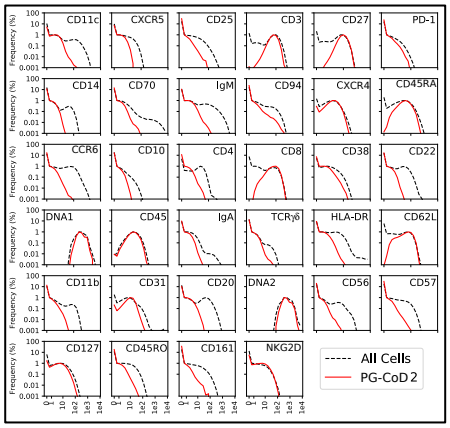

Supplementary Figure 8

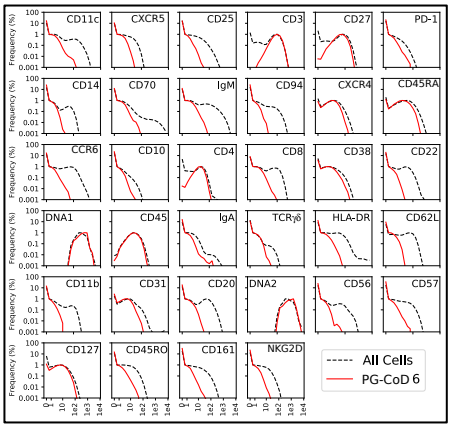


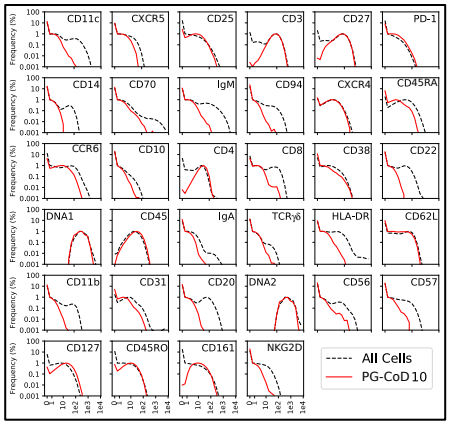

Supplementary Figure 9

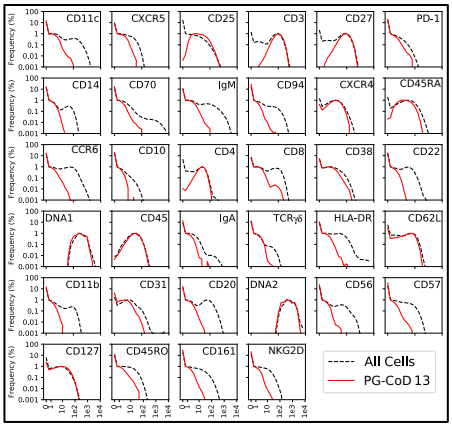


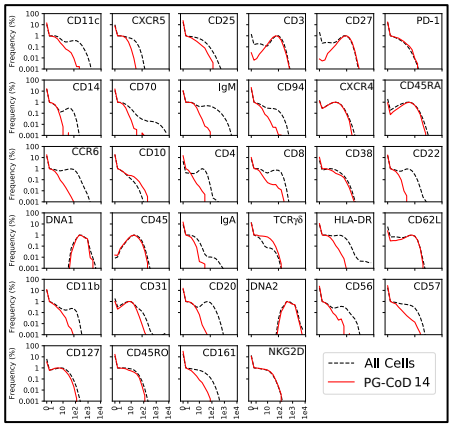

Supplementary Figure 10

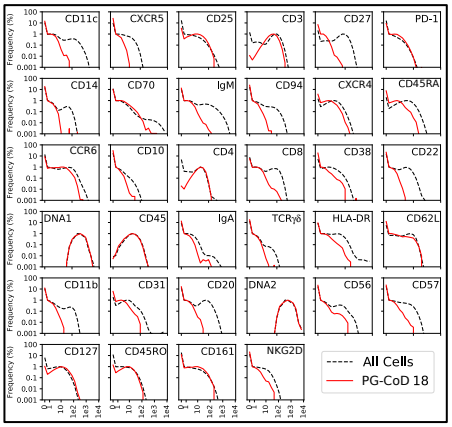


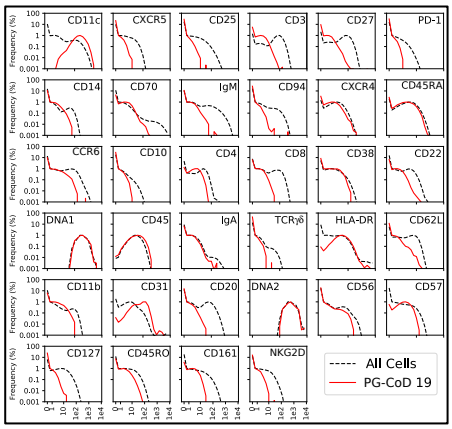



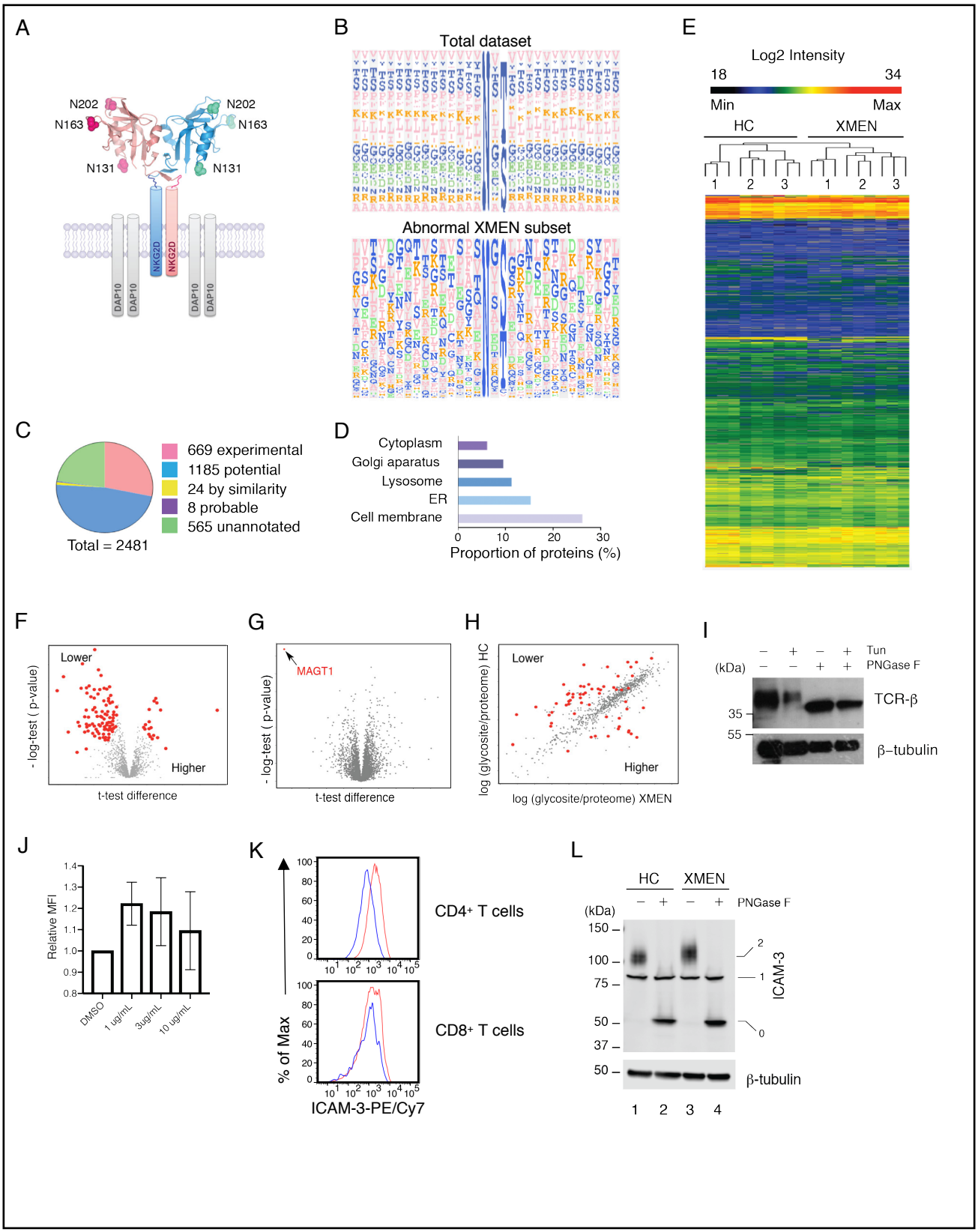



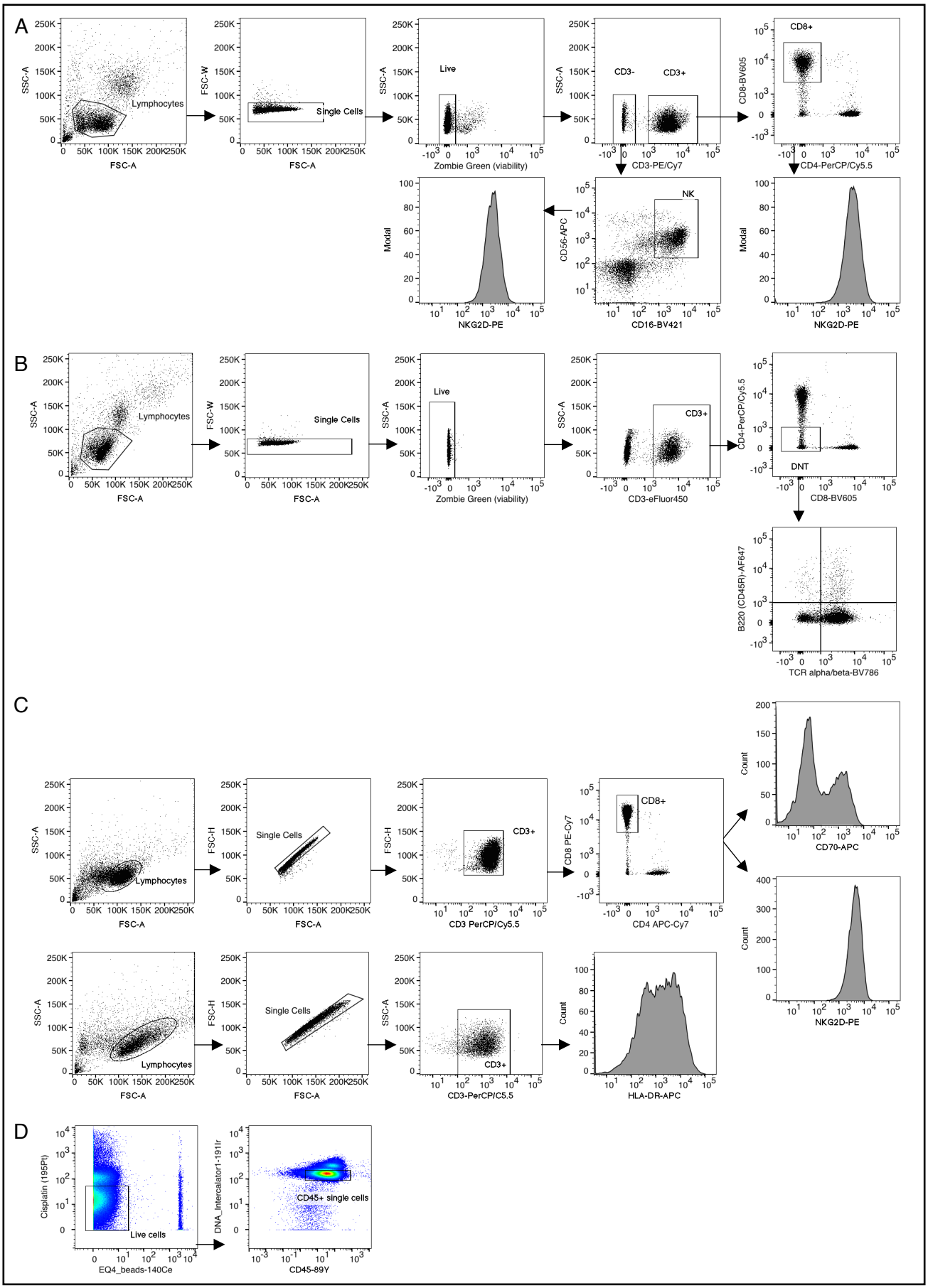




Supplementary figure 11




Supplementary figure 12




Supplementary figure 13

**Supplementary Figure 1: Imaging and pathological findings in XMEN disease.** (**A**), Quantification of log NKG2D MFI on $CD8^+$ T cells **(top)** and $CD16^+CD56^+$ NK cells **(bottom)** of 6 healthy controls (HC), 6 EBV-naïve (EBV-), and 9 EBV-positive (EBV+) XMEN patients. Data are expressed as mean ± standard deviation. ****$P < 0.0001$ by ordinary one-way ANOVA with Tukey's multiple comparisons test. N.S., not statistically significant. (**B**) Facial molluscum contagiosum lesions (black arrows) in an EBV-naïve patient. (**C**) CT scan of the chest showing bilateral axillary lymphadenopathy (yellow arrows) in an EBV-infected patient. Contrast-enhanced CT scans showing cervical lymphadenopathy (yellow arrows) in an EBV-naïve (**D**) and an EBV-infected (**E**) patient. (**F**) Contrast-enhanced CT scan showing a large mediastinal lymph node (yellow arrow) in an EBV-naïve patient. (**G**) CT scan of the brain from same patient shown in figure 1L demonstrating multifocal calcifications (yellow arrows) in the bilateral frontal lobes, thalami, and basal ganglia. (**H**) FDG PET-CT scan showing a mildly hypermetabolic subcutaneous mass, identified on biopsy as liposarcoma, in the right upper chest wall posteriorly (white arrow). Images (**I-N**) depict histopathological findings from liver biopsies of EBV-infected patients. (**I**) Hematoxylin and eosin (HE) stains showing mild portal chronic inflammatory infiltrate, foci of lobular inflammation, and minimal steatosis in EBV-infected patient; (**J**) focal fatty change and mild periportal fibrosis in liver autopsy of patient deceased from EBV-lymphoproliferative disease; and (**K**) liver biopsy from patient with persistent EBV viremia depicting moderate steatosis, frequent foci of lobular inflammation, and marked glycogenosis. Reticulin (**L**) and Masson's trichrome (**M**) staining of a liver biopsy from same $EBV^+$ XMEN patient showing prominent ballooning injury and bridging fibrosis. (**N**) Numerous Mallory bodies are evident by immunoperoxidase staining for ubiquitin.

**Supplementary Figure 2: Lymphocyte subsets in EBV-naïve and EBV-infected XMEN patients:** Lymphocyte immunophenotyping of peripheral blood cells from 7 EBV-naïve (-) and 12 EBV-infected (+) XMEN patients is shown according to age. Normal ranges for age are shown in gray and represent the $10^{th}$ to $90^{th}$ percentiles based on published data(1). Patients are listed according to their assigned family letter, followed by their patient number: EBV-naïve (●): **H.1**, **J.1**, **J.2**, **L.1**, **L.2**, **M.1**, **M.2**; and EBV-infected (▲): **A.1**, **A2**, **D.1**, **E.1**, **G.1**, **G.2**, **I.2**, **M.1***, **N.1**, and **O.1**. *Refers to values after developing EBV infection.

**Supplementary Figure 3: ALPS biomarkers in XMEN disease.** Comparison of serum IL-10 (**A**), sFasL (**B**), and IL-18 (**C**) levels in pg/mL between 13 XMEN patients and 40 normal controls (NC). For individuals with >1 determination, a median value is shown. *$P < 0.05$ by mixed model analysis. N.S. not statistically significant.

**Supplementary Figure 4: CyTOF signals for markers.** Smoothed densities of signal expression (Arcsin-transformed) versus frequency of 32 lineage markers as indicated.

**Supplementary Figure 5: Comparison of the relative abundance of 69 clusters of differentiation between HC, ALPS, and XMEN.** Bonferroni-corrected t-test analysis for each of the 69 (0-68) clusters of differentiation identified comparing the corresponding relative abundance of cells from HC (green), ALPS patients (magenta), and XMEN patients (blue). A white background is used for clusters for which there is a statistically significant difference between XMEN and both HC and ALPS; a gray background for those with a statistically significant difference between ALPS and both HC and XMEN. A black background is used for

clusters with no statistically significant difference between samples. The respective *P* value for comparisons between either ALPS or XMEN with healthy controls are shown for each cluster.

**Supplementary Figure 6: Distinct clusters of differentiation for XMEN patients. (A)** Frequency of cluster of differentiation (CoD) # 32 on the X axis and CoD #34 on the Y axis for XMEN (blue), ALPS (magenta), and healthy controls (HC) (green). (**B**) Histograms for surface marker expression as indicated in all lymphocytes ($CD45^+$), all naïve B-cells ($CD20^+CD27^-$), CoD #32, and CoD #34 are shown in black, green, red, and blue, respectively.

**Supplementary Figure 7: Cell markers for statistically different clusters of differentiation.** Histograms for surface marker expression as indicated in all peripheral blood mononuclear cells (black) and within the respective cluster of differentiation (CoD) (red). (**A**) Cell markers for CoD where ALPS samples were statistically different from both XMEN and HC (CoD #5 and #40). (**B**) Cell markers for four of the CoD where XMEN samples were statistically different from both ALPS and HC (CoD #43, #58, #60, and #68). The "all cells" group is the same for all panels.

**Supplementary Figure 8: High-dimensional clustering analysis of mass spectrometry data using Phenograph confirms distinctive immune subsets for XMEN compared to healthy controls and ALPS.** (A) Two-dimensional projection of the 38 Phenograph-identified clusters of differentiation (PG-CoD) on CyTOF data acquired from PBMCs of XMEN (n=18), ALPS (n=11), and healthy controls (n=24) as visualized by t-SNE. (B) Dendrogram showing these PG-CoD based on their abundance of surface epitopes. (C) Dendrogram for the frequencies of these PG-CoD based on unsupervised grouping showing the clustering of XMEN patients (blue), ALPS patients (magenta), and healthy controls (green). Each row refers to one individual sample.

**Supplementary Figure 9: Comparison of the relative abundance of 38 Phenogragh-identified clusters of differentiation (PG-CoD) between HC, ALPS, and XMEN.** Bonferroni-corrected t-test analysis for each of the 38 (0-37) clusters of differentiation identified by Phenograph, comparing the corresponding relative abundance of cells from HC (green), ALPS patients (magenta), and XMEN patients (blue). A white background is used for clusters for which there is a statistically significant difference for both XMEN and ALPS compared with HC; a gray background for those with a statistically significant difference only between XMEN and HC. A black background is used for clusters with no statistically significant difference between samples. The respective *p* value (9e-4 cutoff) for comparisons between CoD frequencies for either ALPS or XMEN compared with healthy controls are shown for each cluster.

**Supplementary Figure 10: Distinct Phenograph-identified clusters of differentiation (PG-CoD) for XMEN patients. (A)** Frequency of PG-CoD # 0 on the X axis and PG-CoD #22 on the Y axis for XMEN (blue), ALPS (magenta), and healthy controls (HC) (green). (**B**) Histograms for surface marker expression as indicated in all cells, PG-CoD #0 and PG-CoD #22 are shown in black, red, and blue, respectively.

**Supplementary Figure 11: Cell markers for statistically different Phenograph-identified clusters of differentiation (PG-CoD).** Histograms for surface marker expression as indicated in all peripheral blood mononuclear cells (black) and within the respective cluster PG-CoDo (red). The "all cells" group is the same for all panels.

**Supplementary Figure 12: Selective glycosylation defects in lymphocytes from patients with XMEN disease.** (**A**) Schematic of NKG2D and its co-receptor DAP10 with the predicted stoichiometry and NLG sites. (**B**) Motif analysis of the collated NxS/T glycosites identified from glycoproteomics analysis for the complete dataset **(top)** and proteins differentially glycosylated between healthy controls (HC) and XMEN **(bottom)**. The height of each symbol indicates relative frequency of each amino acid at that position. (**C**) Annotation of these proteins in proteomic databases. (**D**) The cellular location of the proteins from which the peptides were derived. (**E**) Unsupervised heat map of the entire N-linked glycoproteome analysis of 3 HC and 3 XMEN patients. (**F**) Volcano plot of the log test *P* value (Y axis) vs. the t-test difference (X axis) of glycopeptide abundance (**F**) and protein abundance (**G**) with MAGT1 labelled (red). (**H**) Log (glycosite/proteome) for HC (Y axis) vs. XMEN (X axis) showing underglycosylated proteins to the upper left (Lower) and overglycosylated proteins to the lower right (Higher). (**I**) Immunoblot of TCR-β and β-tubulin in T cells with (+) or without (-) PNGase F treatment after incubation with (+) or without (-) 10 μg/ml tunicamycin (Tun) for 48 hours. (**J**) Flow cytometry analysis showing mean fluorescent intensity (MFI) quantification of TCR-β on T cells treated with tunicamycin for 48 hours relative to the DMSO-treated control. (**K)** Flow cytometry histogram of ICAM-3 on $CD4^+$ **(top)** and $CD8^+$ **(bottom)** T cells from HC (blue) and XMEN (red). (**L**) Immunoblot of ICAM-3 and β-tubulin in T cells from HC and XMEN. Fully-glycosylated (2), non-specific (1), and unglycosylated (0) bands are indicated. Results shown in (I), (K), and (L) are representative of three independent repeats.

**Supplementary Figure 13: Flow and mass cytometry gating strategies.** (**A**) Flow cytometry gating strategy to select $CD3^+$ T cells, $CD3^+CD8^+$ T cells, and $CD16^+CD56^+$ NK cells from peripheral blood mononuclear cells (PBMCs). Histograms showing the mean fluorescent intensity (MFI) for NKG2D on gated $CD8^+$ T cells and $CD16^+CD56^+$ NK cells are shown. A variation of this gating strategy was used to evaluate surface expression of ICAM3 on $CD4^+$ and $CD8^+$ T cells. (**B**) Flow cytometry gating strategy to select $CD4^-CD8^-$ DNT cells, $TCR\alpha\beta^+$ DNT cells, and $B220^+TCR\alpha\beta^+$DNT cells from PBMCs. (**C**) Flow cytometry gating strategy to determine the MFI of CD70 and NKG2D from $CD8^+$ T cell blasts **(top)** and HLA-DR from $CD3^+$ T cells **(bottom)**. A similar gating strategy or variations of that was used to assess surface expression of CD5, CD28, and TCRαβ on T cell blasts (not shown). (**D**) Gating strategy for mass cytometry.

## References


1. Shearer WT, Rosenblatt HM, Gelman RS, Oyomopito R, Plaeger S, Stiehm ER, et al. Lymphocyte subsets in healthy children from birth through 18 years of age: the Pediatric AIDS Clinical Trials Group P1009 study. *J Allergy Clin Immunol.* 2003;112(5):973-80.

**Supplementary Table 1: XMEN Patients with clinical and laboratory features**

| Clinical manifestations | Patients | Frequency |
|---|---|---|
| Recurrent ear and sinopulmonary infections | A.1, A.2, A.3, G.1, I.2, J.1, J.2, L.1, L.2, M.1, M.2, N.1, O.1, P.1, Q.1, R.1 | 70% (16/23) |
| Chronic lymphadenopathy | A.1, A.3, B.1*, D.1, E.1, G.1, G.2, H.1, J.2, K.2, M.1, M.2, N.1, P.1, R.1 | 65% (15/23) |
| Splenomegaly | A.1, B.1*, D.1, E.1, G.2, K.1, K.2, P.1, R.1 | 39% (9/23) |
| Lymphoma/LPD | B.1, D.1, E.1, I.2, K.2, M.2, N.1, P.1†, R.1 | 39% (9/23) |
| Molluscum contagiosum | A.2, E.1, K.1, K.2, L.1, L.2, M.1, M.2 | 35% (8/23) |
| Recurrent mouth sores | G.1, G.2, I.2, J.2, K.1, K.2, L.1, M.2 | 35% (8/23) |
| Severe autoimmune cytopenias (grade 4) | A.1, D.1, H.1, I.2, K.1, N.1, O.1, R.1 | 35% (8/23) |
| Skin Warts or Condylomata acuminata | A.1, A.3, E.1, G.1, J.2, M.2, O.1 | 30% (7/23) |
| Guillain-Barré syndrome | B.1*, M.2, N.1, R.1 | 17% (4/23) |
| HSV infection | A.1, A.2, E.1‡, N.1 | 13% (3/23) |
| Other autoimmune | A.1 (alopecia partialis), J.1 (episcleritis), R.1 (Autoimmune hepatitis (1)) | 13% (3/23) |
| Pericardial and/or pulmonary effusions | B.1, N.1 | 9% (2/23) |
| EBV-negative malignancy | I.2 | 4% (1/23) |
| **Laboratory and imaging findings** | | |
| Transient elevation of liver enzymes | A.1, A.2, A.3, B.1*, D.1, E.1, G.1, G.2, H.1, I.2, J.1, J.2, K.1, K.2, L.1, L.2, M.1, M.2, N.1, O.1, P.1, Q.1,R.1 | 100% (23/23) ¶ |
| Low NKG2D surface expression on NK and CD8 T cells | A.1, A.2, A.3, B.1, D.1, E.1, G.1, G.2, H.1, I.2, J.1, J.2, K.1, K.2, L.1, L.2, M.1, M.2, N.1, O.1, P.1, Q.1, R.1 | 100% (23/23) |
| Elevated B cells | A.1, A.2, A.3, D.1, E.1, G.1, G.2, H.1, I.2, J.1, J.2, K.1, K.2, L.1, L.2, M.1, M.2, N.1, O.1, P.1, Q.1, R.1 | 95% (22/23) |
| Elevated αβDNT cells | A.1, A.2, A.3, D.1, E.1, G.1, G.2, H.1, J.1, J.2, K.1, K.2, L.1, L.2, M.1, M2, O.1, P.1 , R.1 | 95% (19/20) |

| | | |
|---|---|---|
| Low IgA | A.1, A.2, A,3, D.1, E.1, G.1, G.2, I.2, J.1, J.2, K.1, K.2, L.2, M.1, M.2, N.1, O.1, P.1 | 78% (18/23) |
| Low CD4/CD8 ratio | A.1, A.2, A.3, D.1, E.1, G.1, H.1§, I.2, J.1, J.2, K.1, K.2, L.1, L.2, M.1, M.2, N.1, R.1 | 78% (18/23) |
| Low IgG | A.1, A.2, A.3, D.1, E.1, I.2, J.1, J.2, K.1, K.2, L.1, L.2, M.1, M.2, N.1, O.1, P.1 | 74% (17/23) |
| Persistently elevated EBV-viremia | A.1, A.2, A.3, B.1, D.1, E.1, G.1, G.2, I.2, K.1, K.2, M.1#, M.2#, N.1, O.1, Q.1, R.1 | 74% (17/23) |
| Thrombocytopenia | A.1, A.2, B.1*, D.1, E.1, H.1, I.2, K.1, K.2, L.2, M.1, M.2, N.1, O.1, P.1, R.1 | 70% (16/23) |
| Transient neutropenia | A.1, A.2, B.1*, D.1, E.1, H.1, I.2, K.1, K.2, L.1, M.1, M.2, N.1, P.1 | 61% (14/23) |
| Transient elevations of CPK | A.1, A.2, E.1, G.1, G.2, I.2, J.1, J.2, M.1, M.2, O.1 | 52% (11/21) |
| Cave septum pellucidum | A.1, A2. E.1, D.1 | 50% (4/8) |
| CD4 lymphopenia | A.1, A.2, B.1*, E.1, L.1, M.1, M.2, O.1, P.1, R.1 | 44% (10/23) |
| Central nervous system abnormalities | B.1 and N.1 (brain atrophy greater than expected for age), E.1 (small areas of brain leukomalacia and gliosis consistent with history of PRES), Q.1 (cerebrum, cerebellum, brainstem, and spinal atrophy with calcifications in the basal ganglia and thalami) | 17% (4/23) |

EBV-naïve and EBV-infected patients are shown in red and black respectively. Patients in blue were followed for several years before and after EBV-infection. * In the setting of acute lymphoma. † EBER-negative mediastinal mass comprised of atypical lymphohistiocytic proliferation of uncertain malignant potential. ‡ Due to chemotherapy, not accounted for frequency determination. § Variable. ¶ One patient (P.1) had elevated liver enzymes only once out of multiple determinations. # EBV-naïve at time of XMEN diagnosis. PRES: Posterior reversible encephalopathy syndrome.

**Supplementary table 2: Laboratory results**

| Patient | A.1 | A.2 | A.3 | B.1‡‡ | D.1 | E.1 | G.1 | G.2 | H.1 | I.2 | J.1 | J.2 | K.1 | K.2 | L.1 | L.2 | M.1 | M.2 | N.1 | O.1 | P.1 | Q.1 | R.1 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Hemoglobin (g/dL) | 10.9-14.8 | 11.2-14.6 | 12.9 | 9.7¶ | 3.7-13.4 | 13-15 | 12.9-14 | 13.9-14.9 | 4.4-13.6 | 11-17.2 | 11.1-12.8 | 11.9-14.3 | 4.8-13.9 | 13.8-14.3 | 11.3-13.2 | 11-14.2 | 13.1-14.1 | 12.9-13.9 | 3.1-12.5 | 14.2-15.4 | 8.5-13.5 | 14.6-16.8 | 3.2** |
| Platelet count (161-347 K/uL) | 47-436 | 111-386 | 164 | 7-111‡ | 133-205 | 88-147 | 226-233 | 174-276 | 108-400 | 38-92 | 224-304 | 221-276 | 33-169 | 116-137 | 214-286 | 179-368 | 140-190 | 111-150 | 4-316 | 168-233 | 111-939 | 186-210 | 5** |
| Neutrophils absolute (k/uL) | 0.41-36.33 | 0.5-4.13 | 3.24 | 4.2¶ | 1.15-3.47 | 1.31-2.74 | 3.14-3.19 | 2.94-3.85 | 0.79-3.13 | 1.18-2.26 | 2.45-4.09 |  | 0.1-5.2 | 1.55-3.16 | 1.26-5.59 | 1.54-7.69 | 1.31-3.43 | 1.31-2.15 | 0.71-12.87 | 1.84-2.9 | 0.2-10.9 | 1.95-2.16 | 2.5-6.5 |
| CD4/CD8 (1.11-5.17) | 0.17-1.1 | 0.82-1.13 | 1.03 | 3.7-8.5‡ | 0.86-1.24 | 0.54-0.71 | 0.66-0.77 | 1.3-1.4 | 0.94-1.46 | 0.69-0.84 | 0.92-1.29 | 0.79-1.02 | 0.44 | 0.73 | 0.34-0.36 | 0.79-1.02 | 0.73-0.95 | 0.87-1.29 | 0.57 | 1.7 | 1.7 | 1.18 | 0.39-0.72 |
| T cells (cells/uL) | 1253-3389 | 1562-6786 | 1468 | 175-318‡ | 1245-3028 | 695-1405 | 1792-1955 | 2244-2911 | 2578-5618 | 524-1900 | 5010-8397 | 1266-4461 | 2633 | 1264-1308 | 1399-2104 | 10900-1955 | 724-1351 | 665-927 | 648-1126 | 3000 | 1,158 | 1963 | 897-2000 |
| CD4 T cells (cells/uL) | 272-1309 | 741-2443 | 655 | 138-277‡ | 521-1190 | 244-459 | 577-683 | 1047-1326 | 1070-2416 | 202-710 | 2249-4218 | 501-1675 | 711 | 509-514 | 280-364 | 412-734 | 296-520 | 310-415 | 162-394 | 1401 | 674 | 1004 | 351-543 |
| CD8 T cells (cells/uL) | 545-1580 | 653-3706 | 637 | 25-37‡ | 581-1364 | 380-794 | 870-889 | 749-1016 | 767-2141 | 273-868 | 2002-3505 | 564-1870 | 1635 | 676-702 | 725-1048 | 488-909 | 358-596 | 241-401 | 416-674 | 1215 | 395 | 878 | 490-1380 |
| B cells (cells/uL) | 688-2279 | 717-1727 | 1307 | 40-74‡ | 502-4088 | 369-709 | 692-1086 | 852-1448 | 1420-3138 | 375-758 | 3025-7869 | 1214-1928 | 1635 | 1136 | 1182-1553 | 901-1286 | 360-862 | 468-767 | 745-2073 | 2106-2321 | 952 | 2716 | 890-1776 |
| NK cells (cells/uL) | 155-689 | 144-1139 | 209 | 2-23‡ | 98-355 | 60-196 | 187-222 | 454-747 | 138-498 | 50-302 | 520-845 | 122-1277 | 328 | 244 | 118-377 | 142-313 | 155-264 | 182-458 | 89-486 | 203 | 222 | 291 | 140-240 |
| NKT cells (cells/uL) | 31-255 | 89-402 | 263 | 5‡ | 46-268 | 27-134 | 312-540 | 229-288 | 50-558 | 41-87 | 291-726 | 76-340 | 92 | 96 | 250-401 | 134-369 | 30-136 | 23-34 | 144 | N/A |  | N/A | N/A |
| CD4+CD45RA+CD31+ T cells (cells/uL and %) | 310 (10.5%) | 978 (17.4%) | 233 (7.8%) | N/A | N/A | 57-80 (4.1-4.7%) | 95 (2.9%) | 178 (5%) | 714 (14.9) | N/A | 1312-1880 (11.8-15.2%) |  | 208 (4.5%) | 190 (7.1%) | 53-65 (1.5-2.1%) | 260-292 (8.1-10.3%) | 138-200 (11.1-11.6) | N/A | N/A | N/A | N/A | 6.80% | N/A |
| αβDNT cells (cells/uL and %) |  |  | 90 (3%) | N/A | 151 (3.2%) | 34-42 (1.9-2.5%) | 186 (5.7%) | 85 (2.4%) | 380-1089 (8.2-13.8%) | N/A | 488-542 (3.4-5.6%) | 89-199 (2.8-3.6%) | 120 (2.6%) | 38 (1.4%) | 84-104 (2.6-2.9%) | 44-56 (1.5-1.8%) | 31-45 (2.5-2.9%) | N/A | N/A | 40 (1.3%) | 69 (4.2%) | 1.10% | 32 (3.2%) |
| IgG (716-1711 mg/dL) | 654-2460* | 277-1450* | 452 | 734 | 427-1690* | 525-927* | 1297-1401 | 1069-1264 | 902-1161 | 387-2240* | 563-868* | 537-1295* | 570 | 334-540 | 543-608 | 759-1188 | 490-1052 | 752-960 | 518-691* | 656-1338* | 529-796* | 776-952 | 880-1650 |
| IgA (47-249 mg/dL) | 47-165 | <7-16 | 106 | 128 | 33-84 | 35-54 | 59-61 | 40-59 | 26-62 | 22-42 | 16-23 | 32-48 | 30 | 64-73 | 70-76 | 20-29 | 31-52 | 29-45 | 26-33 | 56-73 | 23 | 82-105 | 50-75 |
| IgM (15-188 mg/dL) | 52-150 | 22-94 | 31 | 14 | 43-89 | 51-86 | 135-170 | 207-241 | 137-206 | 27-63 | 11-20 | 187-265 | 119 | 159-167 | 95-114 | 87-97 | 169-244 | 250-369 | 20-36 | 105-151 | 83 | 133-181 | 52-145 |
| EBV PCR (Log10 IU/mL) | 4.29-5.85 | <2.40-5.28 | 3.33 | Positive | <2.4-3.98 | 3.48-5.34 | 3.87-4.17 | 4.24-4.31 | Negative | 4.08-4.82 | Negative | Negative | 4.16 | 4.85-5.47 | Negative | Negative | Negative- | Negative- | 2.91-3.69 | 5.92† | Negative | 3.58 | Positive |
| CMV PCR ($10^6$ copies/mL) | Negative | Negative | Negative | Negative | Negative | Negative | Negative | Negative | Negative | Negative | Negative | Negative | Negative | Negative | Negative | Negative | Negative | Negative | Negative | Negative | Negative | Negative | 150-600‡ |
| ALT (5-30 U/L) | 30-141 | 24-71 | 60 | 79¶ | 32-204 | 26-104 | 36-49 | 26-137 | 22-61 | 45-380 | 29-53 | 55-171 | 148 | 28-33 | 22-190 | 24-47 | 23-95 | 34-74 | 27-35 | 40-531 | 11-84 | 85-137 | 418 |
| AST (0-40 U/L) | 25-80 | 24-85 | 33 | 74¶ | 27-225 | 20-62 | 36 | 24-61 | 27-35 | 34-207 | 38-52 | 42-61 | 115 | 34-42 | 27-126 | 36-55 | 18-58 | 26-57 | 23-30 | 33-237 | 24-74 | 39-47 | 526 |
| CPK (0-174 U/L) | 75-201 | 73-226 | 159 | 7-69 | 55-157 | 241-1351 | 689-828 | 267-318 | 71-91 | 375-1041 | 180-313 | 102-183 | 104 | 54 | 121-150 | 121 | 125-2684 | 104-644 | 36-196 | 382 | N/A | 115 | 86 |
| Vitamin B12 (193-982 pg/mL) | N/A | 316 | 926 | 518 | 670 | N/A | N/A | N/A | 966 | 573 | N/A | 540 | 907 | 455 | N/A | 626 | N/A | N/A | N/A | 617 | N/A | N/A | 156 |
| Serum magnesium (0.66-1.07 mmol/L)§ | 0.69-0.97 | 0.67-1 | 0.82 | 0.74-1.07 | 0.56-0.8# | 0.81-0.86 | 0.86-0.87 | 0.86-0.9 | 0.8-0.88 | 0.85-1.01 | 0.86-0.89 | 0.88 | 0.83 | 0.83-0.88 | 0.76-0.82 | 0.78-0.92 | 0.77-0.98 | 0.72-0.86 | 0.99 | N/A | N/A | 0.85-0.86 | 0.89 mmol/L |
| Ionized magnesium (0.44-0.59 mmol/L)§ | 0.49 | 0.55 | 0.58 | N/A | 0.4--0.57# | 0.46-0.49 | 0.55 | 0.55 | 0.52-0.53 | 0.48-0.7 | 0.53 | 0.51 | 0.51 | 0.51 | 0.47 | 0.49-0.52 | 0.51-0.56 | N/A | 0.52 | N/A | N/A | 0.57 | N/A |
| RICD | Impaired | Impaired | Impaired | N/A | Impaired | Normal | Impaired | Impaired | Impaired | Impaired | Normal | N/A | N/A | N/A | N/A | N/A | N/A | N/A | Impaired | N/A | N/A | Impaired | N/A |
| Fas-Kill assay | Normal | Normal | Normal | N/A | Normal | Normal | Normal | Normal | Normal | Normal | Normal | N/A | N/A | N/A | N/A | N/A | N/A | N/A | Normal | N/A | N/A | Normal | Normal |

Units and where appropriate reference ranges are shown in parenthesis. * Includes values on Ig replacement therapy. † Calculated from copies/mL. ‡ Patient on chemotherapy. §Prior to Mg2+ supplementation. #Patient with diabetes insipidus, includes values on magnesium supplementation. ¶ Prior to starting chemotherapy for lymphoma and HSCT. ** Lowest value. ‡‡ Diagnosed post-mortem.

**Supplementary Table 3: Genotypes of XMEN patients**

| *MAGT1* Mutation | Family (patients) |
|---|---|
| c.859_997del139, p.N287X | A (1-3)*, F(1,2)* |
| c.409C>T, p.R137X | B (1), D (1), L (1,2), O (1) |
| c.236G>A, p.W79X | C (1) |
| c.598_598delC, p.R200GfsX13 | E (1) |
| c.774_774delT, p.F258LfsX5 | G (1,2) |
| c.991C>T, p.R331X | H (1) |
| c.712C>T, R238X | I (1,2) |
| c. 110G>A, p.W37X | J (1,2) |
| Partial gene deletion exons 3-10 | K (1,2) |
| c.901-902insAA, p.T301KfsX14 | M (1,2) |
| Partial gene deletion introns 1-8 | N (1) |
| c.223C>T, p.Q75X | P(1) |
| c.414C>A, pY138X | Q(1) |
| c.555dup, pY186IfsX2 | R(1) † |

*MAGT1* NCBI Reference Sequence: NM_032121.5. Patients are listed according to their family letter, followed by their patient number (Patient A-1, Patient B-1, etc.). *Families A and F have different genomic mutations, but they both result in the same c.DNA and protein alterations (Family A:g.46668_46677del 10, Family F: g.46604G>T). †Reference (1).

**Supplementary table 4: Liver disease in XMEN**

| Patient | EBV in blood | EBER | Transfusions (PRBCs) | Hemosiderin deposits in liver | Hepatosteatosis | Ballooning injury | Inflammation pattern | CK7 | Fibrosis | Other |
|---|---|---|---|---|---|---|---|---|---|---|
| B.1 | Positive | N/A | Yes | Yes | Yes | No | N/A | Yes | Periportal | Congestion + periportal fibrosis; cholangiolar, hepatocellular, cannicular cholestasis. |
| A.1 | Positive | Negative | No | No | Minimal | No | Portal + Lobular | No | No | |
| I.2 | Positive | Negative | Yes | Mild hepatocellular( zone 2 + 3), moderate reticuloendothelial. | | No | None | N/A | No | |
| D.1 | Positive | N/A | Yes | No | Moderate | Prominent | Foci of lobular; mid portal - associated with mild focal piecemeal-like necrosis | N/A | Bridging | Marked glycogenosis. Comorbidity: morbid obesity. |
| L.1 | Negative | Negative | No | N/A | No | No | Minimal: portal and sinusoidal along zone 1 | N/A | Mils peri-portal - lymphocytess and macrophages | Diffuse glycogenosis. |
| O.1 | Positive | N/A | Yes | No | Minimal | No | Minimal: portal areas; rare lobular. | No | Peri-portal trapping and mild ductular reaction | |
| Q.1* | Positive | N/A | No | Hepatocytes and kupffer cells | No | No | N/A | N/A | None | |
| R.1† | Positive | N/A | Yes | N/A | Moderate | Prominent | Rare foci of lobular inflammation. Mild portal chronic inflammatory infiltrate associated with mild, focal piecemeal-like necrosis. | N/A | Bridging | No Mallory bodies and negative for ubiquitin. |

PRBCs: packed red blood cells. *Biopsy specimen not available at NIH (outside report). †NIH pathology report of previously published case (1).

**Supplementary Table 5: Non-malignant lymphoid histopathological findings**

| Patient | Tissue | EBER | Pathology |
|---|---|---|---|
| A.1 | Tonsils and adenoids | + | Follicular hyperplasia with increased number of EBV-positive cells. |
| D.1 | Cervical and inguinal lymph nodes | + | Follicular hyperplasia and Inguinal atypical lymphoid proliferation. |
| G.2 | Inguinal lymph node | + | Reactive lymphoid hyperplasia and increased cells positive for Epstein-Barr virus. |
| | Small intestinal mucosa | + | Terminal ileum mucosa with reactive mucosal lymphoid follicles. |
| J.2 | Cervical lymph node | − | Reactive lymphoid hyperplasia with Castleman changes and focal follicular lysis. |
| | Adenoids | − | Reactive lymphoid hyperplasia |
| P.1 | Mediastinal mass | − | Atypical lymphoid tissue comprised of small lymphocytes, and scattered histiocytes/dendritic cells with a polyclonal TCR/BCR rearrangement. |

**Supplementary Table 6: Cancer Predisposition in XMEN disease**

| ID | Age at cancer diagnosis | Current age | Type | EBV viremia | EBER (tumor) |
|---|---|---|---|---|---|
| B.1 | 45 | 45† | Lymphoma | + | N/A |
| D.1 | 12 | 20† | EBV-positive LPD of the hypothalamus* | + | + |
| F.1 | 17, 22 | 23† | Classical Hodgkin lymphoma | + | N/A |
| E.1 | 7, 13 | 22 | Burkitt's lymphoma | + | + |
| I.2 | 13<br>27 | 31 | EBV-positive LPD of the palate*<br>Liposarcoma | + | +<br>- |
| I.1(2) | 57 | 57 | Diffuse large B-cell lymphoma | + | N/A |
| K.2 | 15 | 15 | Classical Hodgkin lymphoma | + | + |
| M.2* | 16 | 18 | EBV-positive LPD* | + | + |
| N.1 | 29 | 49 | Classical Hodgkin lymphoma | + | N/A |
| R.1 (1) | 15 | 18† | Classical Hodgkin lymphoma | + | - |
| Ref.(3) | 5 | N/A | Kaposi sarcoma | + | N/A |

N/A not available. *Given the severity of the disease EBV-positive lymphoproliferative disease (LPD) is included in this table. † Age at death. Reference (Ref.).

## Supplementary Table 7: Mass cytometry staining panel

| Metal | Epitope | Clone | Serial # | Lot # |
|---|---|---|---|---|
| 089Y | CD45 | HI30 | 3089003B | 2291710 |
| 116Cd | CD70-Biotin & Streptavidin-Qdot 655 | 113-16 | 355114 & Q10121MP | NA |
| 141Pr | CD196 (CCR6) | G034E3 | 3141003A | 831717 |
| 143Nd | HLA-DR | L243 | 3143013B | 1711719 |
| 144Nd | CD31 | WM59 | 3143013B | 1711719 |
| 145Nd | CD4 | RPA-T4 | 3145001B | 3391705 |
| 146Nd | CD8 | RPA-T8 | 3146001B | 1671716 |
| 147Sm | CD20 | 2H7 | 3147001B | 3081607 |
| 148Nd | IgA | Polyclonal | 3148007B | 2481401 |
| 149Sm | CD56 | NCAM16.2 | 3149021B | 3331703 |
| 151Eu | CD14 | M5E2 | 3151009B | 2351604 |
| 152Sm | TCRγδ | 11F2 | 3152008B | 1531708 |
| 153Eu | CD62L | DREG-56 | 3153004B | 1351720 |
| 154Sm | CD3 | UCHT1 | 3154003B | 1351723 |
| 155Gd | CD27 | L128 | 3155001B | 1031712 |
| 156Gd | CD184/CXCR4 | 12G5 | 3156029B | 471708 |
| 158Gd | CD10 | HI10a | 3158011B | 1131612 |
| 159Tb | CD22 | HIB22 | 3159005B | 3001407 |
| 162Dy | CD11c | Bu15 | 3162005B | 1671707 |
| 163Dy | CD57 | HCD57 | 3163022B | 2671603 |
| 164Dy | CD161 | HP-3G10 | 3164009B | 3271610 |
| 165Ho | CD45RO | UCHL1 | 3165011B | 1421721 |
| 166Er | CD314/NKG2D | ON72 | 3166016B | 91703 |
| 167Er | CD38 | HIT2 | 3167001B | 1731804 |
| 169Tm | CD25 | 2A3 | 3169003B | 1931713 |
| 170Er | CD45RA | HI100 | 3170010B | 3521705 |
| 171Yb | CD185/CXCR5 | 51505 | 3171006B | 471707 |
| 172Yb | IgM | MHM-88 | 3172004B | 1671708 |
| 174Yb | CD94 | HP-3D9 | 3174015B | 2181508 |
| 175Lu | CD279/PD-1 | EH12.2H7 | 3175017B | 3391708 |
| 176Yb | CD127 | A019D5 | 3176008B | 1671712 |
| 191Ir | DNA1 | - | 201192A | NA |
| 193Ir | DNA2 | - | 201192A | NA |
| 195Pt | Cisplatin | - | 201198 | NA |
| 209Bi | CD11b | ICRF44 | 3209003B | 831723 |

All metal-tagged reagents were from Fluidigm, the biotinylated anti-human CD70 antibody was from BioLegend, and the Qdot-655 Streptavidin Conjugate was from Thermo Fisher.

# Supplementary Table 8: Abnormally glycosylated proteins in XMEN

## Overglycosylated Proteins

| Protein ID | Protein Name | Function | Diseases |
|---|---|---|---|
| **EMB*** | Embigin | Transmembrane glycoprotein, of the immunoglobulin superfamily, involved in motoneuron outgrowth and formation of neuromuscular junctions. This is a putative chaperone for the cell surface transporter MCT2 DOI: 10.1074/jbc.M411950200 | No known diseases |
| **SLC1A4*** | Neutral Amino Acid Transporter (Solute Carrier Family 1 Member 4) | Sodium dependent transporter of serine, cysteine, threonine and alanine | Spastic tetraplegia, thin corpus callosum, and progressive microcephaly https://doi.org/10.1111/cge.12605 |
| **HLA-DQB1*** | Major Histocompatibility Complex, Class II, DQ Beta-1 | Binds peptides derived from endocytosed antigens. Presents antigen peptides on surface of cell for CD4 T cell recognition. | Celiac disease (susceptibility to) https://doi.org/10.1086/338453 Variant Creutzfeldt-Jakob Disease (resistance to) https://doi.org/10.1038/35104694 Multiple sclerosis (susceptibility to) https://doi.org/10.1093/hmg/7.8.1235 |
| **SLC12A2*** | Sodium/Potassium/Chloride Transporter (Solute Carrier Family 12, Member 2 | Electrically silent transporter system. Mediates sodium and chloride reabsorption. Plays a vital role in the regulation of ionic balance and cell volume. | No known diseases |
| **CEACAM1** | Carcinoembryonic Antigen-Related Cell Adhesion Molecule 1 | Cell adhesion protein that mediates homophilic cell adhesion in a calcium independent manner | Linked to insulin uptake in obesity and non-alcoholic fatty liver disease. https://doi.org/10.3389/fendo.2017.00008 |
| **CEACAM6** | Carcinoembryonic Antigen-Related Cell Adhesion Molecule 6 | Cell surface glycoprotein involved in cell adhesion and tumor progression | No known diseases |
| **TSPAN31*** | Tetraspanin 31 | Also known as a Sarcoma Amplified Sequence (SAS). Family of proteins that are transmembrane with tumor-associated and hematopoietic cell proteins | No known diseases |
| **SPPL2A** | Signal Peptide Peptidase-Like 2A | Intramembrane cleaving aspartate protease which functions in CD74, FASLG, ITM2B and TNF processing | Susceptibility to mycobacterial disease https://doi.org/10.1038/s41590-018-0178-z |
| **ICAM3** | Intercellular Adhesion Molecule 3 | Leukocyte adhesion molecule that binds LFA-1, integrin alpha-D/beta-2 and contributes to apoptotic neutrophil phagocytosis by macrophages | No known diseases |
| **C10orf54** | V-type Immunoglobulin Domain-Containing Suppressor of T-Cell Activation | Receptor involved in inhibition of T-cell response | No known diseases |
| **ITGAM** | Integrin Alpha-M | Used in adhesion of monocytes, macrophages and granulocytes, as well as the uptake of complement-coated particles | Systemic lupus erythematous (association with susceptibility to) https://doi.org/10.1093/hmg/ddp118 |
| **CD101** | Immunoglobulin Superfamily Member | Inhibits T-cell proliferation induced by CD3 through inhibition of IL2 and expression of IL2RA on activated T-cells | Point mutations increase susceptibility to Type 1 Diabetes https://dx.doi.org/10.1111%2Fjdi.12586 and increased risk of HIV infection https://dx.doi.org/10.1371%2Fjournal.ppat.1006703 |
| **TMEM87A*** | Transmembrane Protein 87A | Retrograde transport from endosomes to trans-Golgi network | No known diseases |
| **PKD2** | Polycistin 2 | Cation channel in fluid-flow mechanosensation of primary cilium of renal epithelium. K+ channel with Ca+2 permeability and limited Na+ permeability | Polycystic kidney disease 2 http://dx.doi.org/10.1126/science.272.5266.1339 |
| **ITGA5** | Integrin Alpha-5 | Receptor for fibronectin and fibrinogen; involved in cell adhesion. | No known diseases |
| **P2RY10** | Putative P2Y Purinoceptor 10 | Receptor for G-protein coupled purines | No known diseases |

## Underglycosylated Proteins

| Protein ID | Protein Name | Function | Diseases |
|---|---|---|---|
| **GPR171** | Probable G Protein-Coupled Receptor 171 | Orphan receptor | No known diseases |
| **HLA-E** | HLA Class I Histocompatibility Antigen, Alpha Chain E | Binds signal sequences of HLA-A, -B, -C and -G molecules | Association with type 1 diabetes, Behcet's disease and pemphigus vulgaris https://doi.org/10.1111/exd.12077 |
| **CLAR** | Calreticulin | Calcium binding chaperon in the endoplasmic reticulum; involved in maternal gene expression regulation | Myelofibrosis (somatic) and Thrombycythemia (somatic) https://doi.org/10.1056/NEJMoa1311347 |
| **CERS5** | Ceramide Synthase 5 | Dihydroceramide synthase that catalyzes the acylation of sphingosine to form dihydroceramide | No known diseases |
| **ST3GAL1** | CMP-N-Acetylaneuraminate-Beta-Galactosamide-Alpha-2,3-Sialtransferase 1 | Synthesizes the sequence found on sugar chains O-linked to threonine and serine and as the terminal sequence on some gangliosides | No known diseases |
| **SLCO3A1** | Solute Carrier Organic Anion Transporter Family Member 3A1 | Na+ independent transporter of prostaglandins E1 and E2, thyroxine, deltrophin II, BQ-123 and vasopressin | No known diseases |
| **RCN1** | Reticulocalbin 1 | Regulates calcium dependent activities in the ER lumen/post-ER compartment | No known diseases |
| **HSP90B1** | Endoplasmin (Heat Shock Protein 90) | Molecular chaperone that is involved in proper folding of Toll-like receptors | No known diseases |
| **MAN2A1** | Alpha Mannosidase 2 | Catalyzes the commitment step in the biosynthesis of complex N-glycans | Contributes to inflammatory bowel disease https://doi.org/10.1247/csf.17022 |
| **TM2D1** | TM2 Domain-Containing Protein 1 | Participates in amyloid-beta-induced apoptosis | No known diseases |
| **SLC7A1** | High Affinity Cationic Amino Acid Transporter 1 | Transporter of cationic amino acids in non-hepatic tissues | No known diseases |
| **ATG9A** | Autophagy-Related Protein 9A | Functions in autophagy and cytoplasm to vacuole transport vesicle formation | ATG9A shows immunoreactivity in ALS-like mice https://doi.org/10.5115/acb.2014.47.2.101 |
| **CD28** | T-Cell-Specific Surface Glycoprotein CD28 | T-cell activation, cell proliferation, cytokine production, especially IL4 and IL10, and promotion of T-cell survival | Mutations can contribute to T cell lymphomas https://doi.org/10.1016/j.cellimm.2017.07.002 |
| **KLRK1** | NKG2-D Type II Integral Membrane Protein | Activating and costimulatory receptor involved in immunosurveillance which acts on NK cells and TCR in CD8+ T-cells | No known diseases |

| | | | |
|---|---|---|---|
| **CD6** | T-cell Differentiation Antigen CD6 | Cell adhesion molecule that regulates T-cell responses through mediation of cell-cell contacts | No known diseases |
| **EDEM1** | ER Degradation-Enhancing Alpha-Mannosidase-Like Protein 1 | Targets degradation of misfolded glycoproteins from the calnexin cycle in the endoplasmic reticulum | No known diseases |
| **CDS2** | Phosphatidate Cytidylyltransferase 2 | Synthesizes CDP-diacylglycerol, an important precursor to phospholipids | No known diseases |
| **ALG9** | Alpha-1,2-Mannosyltransferase ALG 9 | Catalyzes the transfer of mannose to lipid-linked oligosaccharides | Congenital disorder of glycosylation (type II) https://doi.org/10.1086/422367 Gillessen-Kaesbach-Nishimura syndrome https://doi.org/10.1038/ejhg.2015.91 |
| **TRAC** | T Cell Receptor Alpha Constant | Constant region of alpha chain of T cell receptor | Immunodeficiency 7 (TCR-alpha/beta deficient) https://doi.org/10.1172/JCI41931 |
| **PON2** | Serum Paraoxonase/Arylesterase 2 | Hydrolyzes lactones and aromatic carboxylic acid esters and reduces mildly oxidized LDL | Coronary artery disease (susceptibility to) https://doi.org/10.1086/301669 |
| **C1GALT1C1** | C1GALT1-Specific Chaperone 1 | Chaperone for C1GALT1 that is required for generation of a common O-glycan precursor | Tn polyagglutination syndrome (somatic) https://doi.org/10.1038/4371252a |
| **PLAUR** | Urokinase Plasminogen Activator Surface Receptor | Localizes and promotes plasmin formation by signal transduction of U-PA | Linked to polyautoimmunity https://doi.org/10.1016/j.jaut.2016.05.003 |
| **LY75** | Lymphocyte Antigen 75 | Endocytic receptor that directs captured antigens from the extracellular space; reduces proliferation of B lymphocytes | Association to inflammatory bowel disease https://doi.org/10.1155/2016/6485343 |
| **P2RY8** | P2Y Purinoceptor 8 | Receptor of purines coupled to G-proteins | Association with B cell lymphomas https://doi.org/10.1016/j.jmoldx.2016.03.004 |
| **SLC4A7** | Sodium Bicarbonate Cotransporter 3 | Regulates intracellular pH through co-transporting sodium and bicarbonate | Associated with hypertension https://doi.org/10.1093/hmg/ddu478 |
| **ERMP1** | Endoplasmic Reticulum Metallopeptidase 1 | Organization of somatic cells and oocytes in ovaries | No known diseases |
| **TPST2** | Protein-Tyrosine Sulfotransferase 2 | Catalyzes O-sulfation of tyrosine residues | No known diseases |
| **ANO9** | Anoctamin 9 | Calcium dependent scramblase | No known diseases |
| **PPIB** | Peptidyl-Prolyl cis-trans Isomerase B | Assists protein folding by isomerizing proline imidic peptide bonds | Osteogenesis imperfecta (type IX) https://doi.org/10.1093/hmg/ddr037 |
| **CHST11** | Carbohydrate Sulfotransferase 11 | Adds sulfate to chondroitin, the predominant proteoglycan in cartilage | In frame 15nt deletion caused hand/foot malformation and malignant lymphoproliferative disease http://dx.doi.org/10.1136/jmedgenet-2017-105003 SNPs linked to osteoarthritis https://doi.org/10.1371/journal.pone.0159024 |
| **ASAH1** | Acid Ceramidase | Hydrolyzes sphingolipid ceramide | Farber lipogranulomatosis https://doi.org/10.1074/jbc.271.51.33110 Spinal muscular atrophy with progressive myoclonic epilepsy https://doi.org/10.1016/j.ajhg.2012.05.001 |
| **GPR55** | G-Protein Coupled Receptor 55 | Receptor for L-alpha-lysophosphatidylinositol, triggering Ca+2 release and playing a role in hyperplasia associated with inflammation and neuropathic pain | Knockout in mice leads to age-related ventricular dysfunction and impaired adrenoceptor-mediated inotropic responses https://doi.org/10.1371/journal.pone.0108999 |
| **LMBRD1** | Probable Lysosomal Cobalamin Transporter | Exports cobalamin from lysosomes | Methylmalonic aciduria and homocystinuria (cblF type) https://doi.org/10.1038/ng.294 |
| **SLC12A9** | Solute Carrier Family 12 Member 9 | Inhibitor of SLC12A1, a sodium and chloride transporter | No known diseases |
| **LNPEP** | Leucyl-Cystinyl Aminopeptidase | Degrades oxytocin, vasopressin and angiotensin and may inactivate neural proteins in the brain | Association with psoriasis https://doi.org/10.1038/jid.2013.317 And autism https://doi.org/10.1007/s12264-017-0120-7 |
| **GDPD5** | Glycerophosphodiester Phosphodiesterase Domain-Containing Protein 5 | Promotes differentiation of motor neurons | No known diseases |
| **PTGER4** | Prostaglandin E2 Receptor EP4 Subtype | Receptor for prostaglandin E2 coupled to G-proteins that relaxes smooth muscle | Associated with Crohn's disease https://doi.org/10.1007/s00384-014-1881-3 |
| **IL17RA** | Interleukin-17 Receptor A | Receptor of IL-17 which induces proinflammatory cytokine expression | Immunodeficiency 51 https://dx.doi.org/10.1126%2Fscience.1200439 |
| **ITPR2** | Inositol 1,4,5-Triphosphate Receptor Type 2 | Involved in the release of intracellular calcium via inositol 1,4,5-triphosphate signaling | Anhidrosis (isolated, with normal sweat glands) https://doi.org/10.1172/JCI70720 |
| **CLCN5** | H(+)/Cl(-) Exchange Transporter 5 | Antiporter involved in the acidification of the endosome lumen | Dent disease, Hypophosphatemic rickets and Nephrolithiasis (type I) https://doi.org/10.1038/379445a0 Proteinuria (low molecular weight, with hypercalciuric nephrocalcinosis) https://doi.org/10.1172/JCI119262 |
| **TMEM181** | Transmembrane Protein 181 | G-protein coupled receptor that responds to cytolethal distending toxin from bacteria | Association with dental caries https://doi.org/10.1186/s12903-018-0559-6 |
| **CLEC2B** | C-Type Lectin Domain Family 2 Member B | Initiates cross talk between myeloid and NK cells through NKp80 binding, and is involved in the activation of platelets | CLEC2B deletion causes lymphatic insufficiency in mice https://doi.org/10.1182/blood-2016-04-636415 |
| **CERS2** | Ceramide Synthase | Synthesize sphingolipids | Deletion aggravates colitis in mice https://doi.org/10.1007/s00018-017-2518-9 |
| **PLXNA3** | Plexin 3A | Receptor for signaling that regulates cytoskeletal morphology and plays a role in axon guidance in developing neurons | Association with multiple sclerosis https://doi.org/10.1007/s12017-017-8443-0 |
| **S1PR4** | Sphingosine 1-Phosphate Receptor 4 | Receptor for sphingosine 1-phosphate (S1P), which is involved in cell migration of lymphocytes | No known diseases |
| **PTGDR2** | Prostaglandin D2 Receptor 2 | G-Protein Coupled Receptor whose activation mediates immune regulation and inflammatory response | No known diseases |
| **LGALS3BP** | Galectin-3-Binding Protein | Promotes cell adhesion through integrin | No known diseases |
| **NPC1** | NPC Intracellular Cholesterol Transporter 1 | Exports cholesterol from the endosomal/lysosomal compartment to the ER and plasma membrane | Niemann-Pick disease (type C1 and type D) http://dx.doi.org/10.1126/science.277.5323.228 |
| **SLC23A2** | Solute Carrier Family 23 Member 2 | Sodium and Ascorbate (Vitamin C) cotransporter | No known diseases |
| **ABCA2** | ATP-Binding Cassette Sub-Family A Member 2 | Probable transporter in macrophage lipid metabolism and neural development | Association with Alzheimer's Disease https://doi.org/10.1016/j.nbd.2004.09.011 |
| **GALNT4** | Polypeptide N-Acetylgalactosaminyltransferase 4 | Catalyzes a step in O-linked oligosaccharide biosynthesis | No known diseases |
| **B4GALT3** | Beta-1,4-Galactosyltransferase 3 | Responsible for N-linked oligosaccharide synthesis for many glycoproteins | A potential association to Hutchinson-Gilford Progeria https://doi.org/10.1002/ajmg.10753 |
| **JMJD8** | JmjC Domain Containing Protein 8 | No known function | No known diseases |

| | | | |
|---|---|---|---|
| **CLEC12A** | C-Type Lectin Domain Family 12 Member A | Receptor involved in signaling cascades, especially involving MAP kinases | No known diseases |
| **SYPL1** | Synaptophysin-Like Protein 1 | Maintenance of vesicle structure | No known diseases |
| **GPR112** | Adhesion G-Protein Receptor G4 | Orphan receptor | No known diseases |
| **SLC22A5** | Solute Carrier Family 22 Member 5 | Sodium carnitine cotransporter | Carnitine deficiency (systemic primary) https://doi.org/10.1038/5030 |

* Peptides are both overglycosylated and underglycosylated, at different sites.

Information was found using the UniProt database (https://www.uniprot.org/), the Online Mendelian Inheritance in Man (OMIM) database (https://www.omim.org/), and PubMed (https://www.ncbi.nlm.nih.gov/pubmed/).

**Supplementary Table 9: Transferrin and apolipoprotein CIII isoform analysis**

| **Transferrin*** | Normal range | A.1 | A.2 | A.3 | E.1 | H1 | J.1 | L.1 | L.2 | N1 | Q.1 |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Mono-Oligosaccharide/Di-Oligosaccharide | ≤ 0.06 | 0.18 | 0.16 | 0.14 | 0.18 | 0.17 | 0.16 | 0.16 | 0.16 | 0.13 | 0.15 |
| A-Oligosaccharide /Di-Oligosaccharide | ≤ 0.011 | 0.005 | 0.009 | 0.008 | 0.006 | 0.003 | 0.004 | 0.005 | 0.005 | 0.12 | 0.009 |
| Tri-sialo/Di-Oligosaccharide | ≤ 0.05 | 0.05 | 0.06 | 0.06 | 0.03 | 0.06 | 0.05 | 0.04 | 0.08 | 0.05 | 0.06 |
| **Apolipoprotein CIII**** Apo CIII-1/CIII-2 | ≤ 2.9 | 3.33 | 2.63 | 2.19 | 2.43 | 2.69 | 2.11 | 2.20 | 4.52 | 1.61 | 1.72 |
| Apo CIII-0/Apo CIII-2 | ≤ 0.48 | 1.01 | 0.8 | 0.39 | 0.34 | 0.66 | 0.75 | 0.52 | 0.78 | 0.17 | 0.33 |

***** Mass spectrometry; reflects N-linked glycosylation
******Reflects O-linked glycosylation

**Supplementary Table 10: Comparison of XMEN and ALPS**

| | XMEN | ALPS-FAS |
|---|---|---|
| **Clinical findings** | | |
| Sex | Male | Male/Female |
| Non-malignant lymphadenopathy and/or splenomegaly | Mild/moderate | Significant |
| Autoimmune cytopenias | May be present | Frequent |
| Recurrent sinopulmonary infections | Yes | No |
| Severe molluscum contagiosum | Common | May be seen with immunosuppressive treatment |
| Family history | Maternal male relatives | Positive except for ALPS-sFAS |
| Increased susceptibility to lymphoma | Predominantly EBV+ | Hodgkin and non-Hodgkin lymphoma |
| **Serum Ig** | Normal or Low IgA and IgG | High |
| **Lymphocyte subsets** | | |
| NKG2D | Low | Normal |
| B cells | Elevated | Normal |
| CD4/CD8 ratio | Low | Normal |
| alpha-beta DNT cells | High | High |
| CD45R(B220)$^{+}$αβ DNT cells | Normal | High |
| **Persistent EBV viremia** | Yes (except for EBV-naïve individuals) | Rare |
| **Biomarkers** | | |
| sFasL | Predominantly Low/normal | High (>200 pg/mL) |
| IL-10 | Variable | High (>20 pg/mL) |
| IL-18 | Variable | High (>500 pg/mL) |
| Vitamin B12 | Normal | High (>1500 ng/L) |
| Elevated liver transaminases | Yes | No (except in case of autoimmune hepatitis) |
| CPK | High/normal | Normal |
| **Functional assays** | | |
| Defective FAS apoptosis | No | Yes |
| Defective RICD | Yes | Yes (mild) |
| **Genetics** | | |
| Affected gene | *MAGT1* | *FAS* (germline or somatic)* |
| Inheritance | X-linked | Autosomal dominant with incomplete penetrance. Rarely, autosomal recessive due to heterozygous or homozygous mutations. |

*Mutations in genes encoding *FASL*, *FADD*, and *CASP10* also cause ALPS termed ALPS-FASL, ALPS-FADD, and ALPS-CASP10, respectively (not discussed here).

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