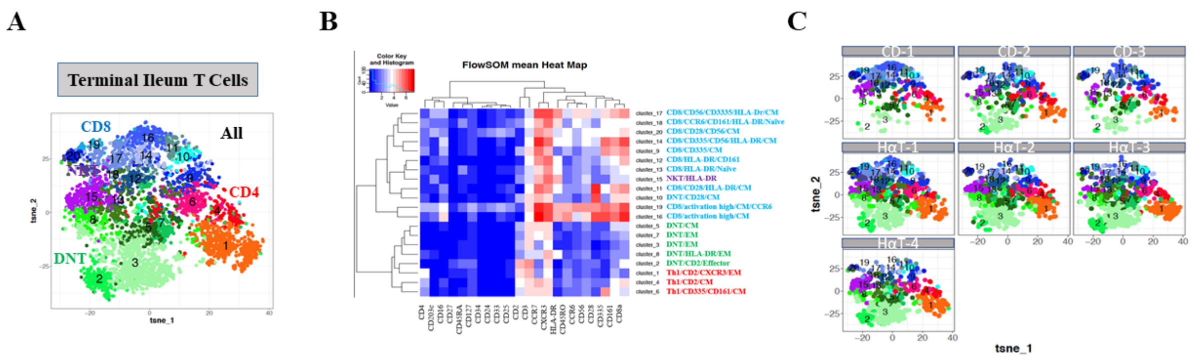
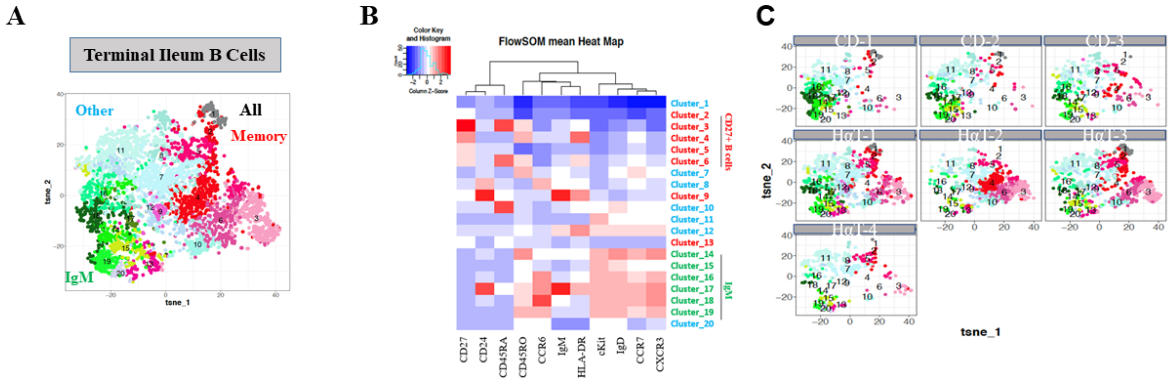
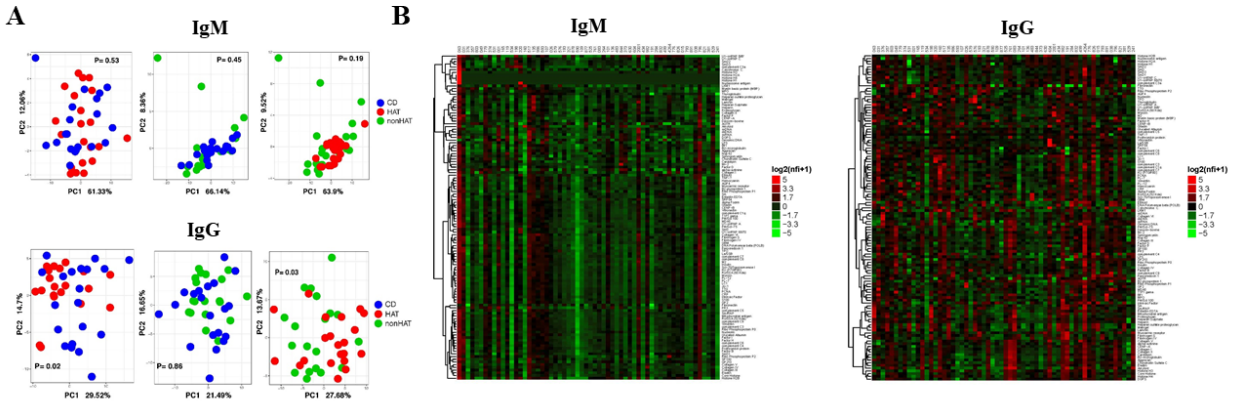

A
Terminal Ileum T Cells
CD8
All
CD4
DNT
tsne_1
tsne_2
B
FlowSOM mean Heat Map
Color Key and Histogram
cluster_17 CD8/CD56/CD3335/HLA-Dr/CM
cluster_18 CD8/CCR6/CD161/HLA-DR/Naïve
cluster_20 CD8/CD28/CD56/CM
cluster_14 CD8/CD335/CD56/HLA-DR/CM
cluster_9 CD8/CD335/CM
cluster_12 CD8/HLA-DR/CD161
cluster_13 CD8/HLA-DR/Naïve
cluster_15 NKT/HLA-DR
cluster_11 CD8/CD28/HLA-DR/CM
cluster_10 DNT/CD28/CM
cluster_19 CD8/activation high/CM/CCR6
cluster_16 CD8/activation high/CM
cluster_5 DNT/CM
cluster_7 DNT/EM
cluster_3 DNT/EM
cluster_8 DNT/HLA-DR/EM
cluster_2 DNT/CD2/Effector
cluster_1 Th1/CD2/CXCR3/EM
cluster_4 Th1/CD2/CM
cluster_6 Th1/CD335/CD161/CM
C
CD-1
CD-2
CD-3
tsne_1
tsne_2


A
Terminal Ileum B Cells
Other
All
Memory
IgM
tsne_2
tsne_1
B
Color Key and Histogram
Count
Column Z-Score
FlowSOM mean Heat Map
Cluster_1
Cluster_2
Cluster_3
Cluster_4
Cluster_5
Cluster_6
Cluster_7
Cluster_8
Cluster_9
Cluster_10
Cluster_11
Cluster_12
Cluster_13
Cluster_14
Cluster_15
Cluster_16
Cluster_17
Cluster_18
Cluster_19
Cluster_20
CD27+ B cells
IgM
CD27
CD24
CD45RA
CD45RO
CCR6
IgM
HLA-DR
cKit
IgD
CCR7
CXCR3
C
CD1
CD2
CD3
Hrd1
Hrd2
Hrd3
tsne_2
tsne_1


A
IgM
P= 0.53
P= 0.45
P= 0.19
PC2 12.06%
PC2 8.16%
PC2 9.52%
PC1 61.33%
PC1 66.14%
PC1 63.0%
CD
HAT
nonHAT
IgG
P= 0.02
P= 0.86
P= 0.03
PC2 14.7%
PC2 16.65%
PC2 13.67%
PC1 29.52%
PC1 21.49%
PC1 27.68%
B
IgM
IgG
log2(nfi+1)
5
3.3
1.7
0
−1.7
−3.3
−5

Supplemental Table 4. Basal Serum Tryptase, Tryptase Copy Number Variants and Mast Cell Numbers by Participants

Number of Participants	Sex	Year of Birth	BST (ng/mL)	Tryptase Alpha Copy Number	Tryptase Beta Copy Number	Mast Cells/HPF
1.	M	2001	14.0	2	3	30
2.	F	1974	15.0	2	3	27
3.	F	1959	23.0	2	3	102
4.	F	1956	13.0	3	2	54
5.	F	1975	12.0	3	2	39
6.	F	1964	9.9	3	2	42
7.	F	1981	22.0	2	3	72
8.	F	1995	10.5	3	2	60
9.	F	1965	18.0	2	3	40
10.	F	1944	31.0	2	3	63
11.	F	1975	20.6	2	3	35
12.	F	1946	14.6	2	3	25
13.	F	1983	13.4	3	2	35
14.	F	1993	9.2	3	2	47
15.	M	2001	10.8	2	3	32
16.	M	1941	26.5	2	3	56
17.	M	2004	15.0	2	3	45
18.	F	1981	21.0	2	3	45
19.	F	1980	13.0	2	3	21
20.	M	2002	16.0	2	3	45
21.	F	1982	8.1	3	2	23

Supplemental Table 1. Summary of HαT-Associated Clinical Features

Characteristics, N = 21 individuals	
Mean age, years ± SD	**41** ± 19.4
Female sex, N (%)	**16** (76)
Male sex, N (%)	**5** (24)
Clinical GI Symptoms	
GERD, N (%)	**4/21** (19.05)
Abdominal Pain, N (%)	**19/21** (90.48)
Diarrhea, N (%)	**13/21** (61.90)
Constipation, N (%)	**9/21** (42.86)
Food Sensitivity, N (%)	**5/21** (23.81)
GI Dysmotility, N (%)	**4/21** (14.29)
Nocturnal awakening due to abdominal pain or diarrhea, N (%)	**21/21** (100)
Laboratory Findings, Median (IQR)	
BST ng/mL	**14** (10.9 - 20.8)
GI small intestinal MCs*	**40** (33.5 – 52.0)

Abbreviations: GERD, gastroesophageal reflux disease; GI, gastrointestinal; IQR, interquartile range; BST, basal serum tryptase; MCs, mast cells.

Autoimmune Disorders, N (%) – 12/21 (57.14)

*Refer to Figure 2A.

Supplemental Table 2. Antibody and Metal List

Metal	General Panel	Clone	Source
147	CD45RO	UCHL1	Harvard Core
151	CD2	TS1/8	Fluidigm
153	CD45RA	HI100	Harvard Core
154	CD33	WM53	Harvard Core
165	Mast-cell_tryptase	AA1	Harvard Core, custom conj.
175	IgD	IA6-2	Harvard Core
191	DNA1	N/A	Fluidigm
193	DNA2	N/A	Fluidigm
148	CD28	CD28.2	Harvard Core
152	CD14	M5E2	Harvard Core
141	ckit	104D2	Harvard Core, Self Conj.
142	CD19	HIB19	Harvard Core
143	HLA-DR	L243	Fluidigm
144	CD64	10.1	Harvard Core
145	CD16	3G8	Harvard Core
149	CD25	2A3	Fluidigm
155	CD27	L128	Fluidigm
158	CD3	UCHT1	Harvard Core
159	CD11c	Bu15	Harvard Core
164	CD161	HP-3G10	Harvard Core
166	CD24	ML5	Harvard Core
168	CCR6	G034E3	Harvard Core
170	CCR7	G043H7	Harvard Core
172	IgM	MHM-88	Harvard Core
174	CD4	OKT4	Harvard Core
161	CD203c	NP4D6	Harvard Core, self conj.
146	CD8a	RPA-T8	Harvard Core
150	FCeR1	AER-37 (CRA-1)	Fluidigm
162	CD56	HCD56	Harvard Core
163	CXCR3	G025H7	Fluidigm
171	CD127	A019D5	Harvard Core
173	CD335	9E2	Harvard Core, self conj.
115	CD34	581	Harvard Core, self conj.
89	CD45	HI30	Fluidigm

Supplemental Table 3. GI Significance of Antigen Production (IgG) in Individuals with HαT, CD, and Non-HαT

Antibody	Presence in HαT patients	Presence in CD patients	Presence in non-HαT patients	Gastrointestinal Reference
Liver/Kidney Microsomal Type I (LKM1)	10/21	5/20	5/19	Autoimmune hepatitis. Targets the enzyme, CYP2D6, found primarily in liver cells.
Gliadin	9/21	4/20	4/19	Gliadin is protein component of gluten. May indicate gluten-sensitive enteropathies. Gliadin alters barrier properties of intestinal epithelial cells.
SP100	8/21	5/20	4/19	Associated with primary biliary cirrhosis. Targets SP100 nuclear antigen.
Intrinsic Factor (IF)	7/21	8/20	6/19	IF protein is produced by parietal cells in the stomach. Presence of antibodies often leads to autoimmune induced anemia secondary to inability to absorb vitamin cobalamin.
Scl-70/Topoisomerase I	6/21	8/20	6/19	Mainly in systemic scleroderma and found in patients with connective tissue disease.
Tissue Transglutaminase (TTG)	6/21	9/20	5/19	Autoantigen of Celiac Disease. Marker for intestinal barrier defects.
Lipopolysaccharide (LPS)	5/21	6/20	5/19	Contributes to systemic inflammation and impacts the intestinal barrier. Elevated in Inflammatory Bowel Disease.
Amyloid	5/21	8/20	8/19	Demonstrated in intestinal epithelial cells, can impact absorption and secretion. Commonly studied in CNS and Alzheimer's Disease.
Collagen IV	2/21	5/20	4/19	Collagen IV is a major constituent of basement membranes. Useful in detecting loss of parts of basement membrane in carcinomas.

Supplementary Figure legends

Supplemental Figure 1. Terminal ileum T cells phenotype differs between HαT and quiescent CD. tSNE plots of automated clustering by FlowSOM for leukocytes in HαT and CD (All) **(Panel A)**. CD4 (clusters: 1,4,6), CD8 (clusters: 9-14, 16-20), and DNT (clusters: 2,3,5,7,8). Cluster identity is determined by marker expression of the heatmap in **Panel B**. **Panel B.** Heatmap of indicated antibody expression in the clusters and the associated phenotype of the cells in each cluster. **Panel C.** tSNE maps of patients with CD and individuals with HαT that are associated with **Panel A**.

Supplemental Figure 2. Terminal ileum B cells phenotype reveal expanded CD27^{+} memory B cells in HαT. tSNE plots of automated clustering by FlowSOM for leukocytes in HαT and CD (All) (Panel A). Memory B cells (clusters: 2-6, 9 and 13), IgM B cells (clusters: 14-19). Panel B. Heatmap of indicated antibody expression in the clusters and the associated phenotype of the cells in each cluster. Panel C. tSNE maps of patients with CD and individuals with HαT that are associated with Panel A.

Supplemental Figure 3. Panel A. Principal Component Analysis (PCA) array of IgM and IgG in non-HαT, HαT, and quiescent CD individuals. Panel B. Heatmap indicating antibody expression in non-HαT, HαT, and quiescent CD. Note: Race and ethnicity were accounted for in the analysis, and removing these variables had no effect on the result.